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P251. The Role of Midbrain Endogenous Opioids in Affect and Motivation

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Background: The preponderance of mental illness in the United States results in tens of millions of dollars in healthcare costs. While many neuropsychiatric conditions can be dissociated based on the presence or absence of specific features, a common theme across mental illnesses is the dysregulation of affective or motivated behaviors. The serotonergic system in the midbrain dorsal raphe nucleus is widely regarded to be an important hub for mediating these types of behaviors. However, the opioidergic system, which is also highly expressed within dorsal raphe nucleus and known to powerfully modulate motivated behaviors, has received significantly less attention. Recent work in our lab has shown that mu opioid receptor expressing projections to the nucleus accumbens medial shell mediate mu opioid driven increases in reward consumption. Notably, these projections are predominately not serotonergic. While these results identified a novel circuit for opioid-mediated reward behaviors, further characterization of the circuit remains incomplete. In parallel with the mu opioid receptor circuit, we are also investing the role of endogenous enkephalin peptide in dorsal raphe nucleus. Despite the high expression of enkephalin within this region, very little is known about its role in appetitive or aversive behaviors.

Methods: For the dorsal raphe to nucleus accumbens circuit project, viral and non-viral retrograde tracing techniques are being used in conjunction with immunohistochemical or fluorescent in situ hybridization approaches to map and co-label the projection (expected $n = 8$ brains, 3 slices per brain/sex). In situ experiments are using a hi-plex approach, in which we are able to label the same slide with up to 12 different probes of interest. We are also using vGlut2-FlpO x vGAT-cre mice to simultaneously image and recording non-overlapping projections using dual-color fiber photometry with GCaMP and RCaMP (expected $n = 12$ mice/sex). For the endogenous enkephalin project, we are using CRISPR-Cas9 mediated knockdown to disrupt enkephalin production, and measuring consequent changes in a variety of appetitive and aversive behaviors (expected $n = 12$ mice/sex). These behaviors include: taste preference/avoidance, thermal and mechanical allodynia, odor preference/avoidance, and social interaction. All behavioral tests will be counterbalanced when possible, with several days between each test. When possible, mice are tested within subjects. For all projects, male and female mice are being used.

Results: Results so far indicate that while the majority of accumbens projecting dorsal raphe nucleus neurons are serotonergic, a large minority arise from lateral subregions. Ongoing work is quantifying these expression patterns. For the enkephalin peptide project, loss of enkephalin results in a profound allodynic phenotype with mechanical sensation after a mild inflammatory intervention ($F(1, 26) = 13.51$, $p = 0.0011$; $t(8, 20) = 5.531$, $p = < 0.0001$; Cre- males = 4, cre- females = 4, cre+ males = 16, cre+ females = 4). Ongoing work is testing mice on additional behavioral models.

Conclusions: Our results corroborate a previously unreported lateralized dorsal raphe input to the nucleus accumbens shell on which mu opioid receptors act to modulate reward consumption. Further work will continue to characterize the circuit using dual color-fiber photometry. We also show that loss of enkephalin peptide in dorsal raphe dramatically shifts behavioral responses to aversive stimuli such as during mechanosensation. Ongoing work is testing how other behavioral phenotypes are affected by loss of enkephalin peptide.

Keywords: Mu Opioid Receptor, Enkephalin, Dorsal Raphe, Nucleus Accumbens Shell, Incentive Motivation

Disclosure: Nothing to disclose.

P252. Quantitative Electroencephalography Demonstrates Differential Diagnostic and Severity-Based Connectivity Changes in Adolescents With Major Depressive Disorder

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Background: The early recognition, accurate diagnosis, and prognostic determination in youth with Major Depressive Disorder (MDD) is challenging. Imprecise nosology and overlapping presentations are particularly difficult in childhood (Mendelson and Tandon, 2016). As a result, there is an unmet need for evidence-based biomarkers in childhood MDD.

We previously reported in a pilot biomarker study that identified quantitative electroencephalogram (qEEG) coherence as a possible predictive biomarker for MDD in youth (McVoy et al., 2022). However, conclusions able to be drawn from this study were limited due to varied comorbidity, possible medication effects, and a small sample. We now present the initial baseline results for a larger prospective longitudinal, sample of medication-naïve (pre-treatment), comorbidity-free patients with MDD vs healthy controls (HCs), where we investigate qEEG coherence measures as a predictor of both MDD diagnosis and severity.

McVoy M, Chumachenko S, Briggs F, et al. A Predictive Biomarker Model Using Quantitative Electroencephalography in Adolescent Major Depressive Disorder. J Child Adolesc Psychopharmacol 2022;32(9):460–466; https://doi.org/10.1089/cap.2022.0041.

Mendelson T and Tandon SD. Prevention of Depression in Childhood and Adolescence. Child Adolesc Psychiatr Clin N Am 2016;25(2):201–218; https://doi.org/10.1016/j.chc.2015.11.005.

Methods: 28 MDD youth, age 14-17 (F = 24 M = 4) and 26 age and gender matched healthy controls, age 14-17 (F = 19 M = 7) received a baseline resting EEG as part of a longitudinal study of EEG in the treatment of MDD youth. MDD inclusion criteria included a confirmed MDD diagnosis and score ≥ 40 on the Children's Depression Rating Scale (CDRS), and not currently taking any psychiatric medication. Exclusion criteria included current or past bipolar disorder, psychotic disorder, post-traumatic stress disorder, attention deficit hyperactivity disorder, any past or current neurologic disorders (including brain surgeries, implanted shunts, meningitis or seizure disorder). HCs exclusion criteria were any lifetime DSM-IV or -5 psychiatric diagnoses or first or 2nd degree relatives with mood disorder or psychosis and neurologic disorders.

EEGs were recorded using a 32-channel enhanced version of the International 10–20 System of Electrode Placement. Coherence between dyads in all regions of the brain was calculated for each of the four frequency bands (alpha, beta, theta, and delta) and compared between MDD youth and HC.

For the initial MDD vs HC classifier development ("phase 1"), a two-stage framework was used to construct a predictive biosignature for MDD by the dyad measures, and outcome defined as MDD status. For subsequent predictive modeling of MDD severity in youth with MDD ("phase 2"), a similar framework was used, with outcome defined as inverse rank normalized CDRS scores. In the first stage (data reduction), regression models (logistic regression in phase 1, and linear regression in phase 2) were used to examine bivariate associations between each dyad measure and outcome. In the second stage (predictive modelling), a multivariable regression model including significant dyads associated at $p < 0.05$ was constructed. Predictors not associated with the outcome in the multivariate models were sequentially removed, retaining associated ones at $p < 0.1$. Finally, the final model was constructed from remaining dyads plus sex and age (receiver-operating characteristic curve (ROC) in phase 1, multiple regression in phase 2).

Results: Mean age of youth was 15.36 (SD = 1.16), N = 54, 79% female, on no psychiatric medication.

Within the initial new sample predictive modeling, 8 coherence dyads were significantly predictive of MDD: T7P7 (alpha, beta), P8O2 (alpha, beta, theta), F1P7 (beta), FzCz (delta), and CzPz (beta), and all lower coherence in MDD except CzPz. After data reduction, only 4 coherence dyads remained (T7P7 beta, FzCz delta, P8O2 alpha, and CzPz beta, with all except CzPz lower coherence in MDD vs HC), for a final 6-factor model ROC of 0.80 (CI 0.79-0.81).

For the novel MDD severity modeling, 3 coherence dyads were significantly predictive (F3C3 delta and theta), and CzPz (delta), and with 2 dyads remaining after data reduction (F3C3 Theta and CzPz delta coherence, both notably increasing in coherence with increasing MDD severity), for a final 4-factor R-squared of 12% (8% of this for the two coherence dyads).

Conclusions: We demonstrate a replication of our previous findings that qEEG coherence is decreased in youth with MDD compared with HC in an expanded, comorbidity-free, treatment-naïve sample of MDD youth. We show decreased qEEG coherence in patients with MDD versus HCs, but conversely increasing coherence in distinct coherence dyad measures with increasing depression severity, hinting at potential discrete pathways in MDD initiation and progression. Notably, two dyad locations empirically replicated between the two studies (P8O2 and CzPz) for MDD predictive modeling, hinting at potential consistent localization within default mode network which could strengthen a hypothesis of dysregulation in behavioral inhibition pathways leading to initial development of MDD. These findings show promise for the ongoing follow-up longitudinal investigations within this comorbidity-free, treatment naïve sample that could show how these findings endure or progress over treatment and symptom severity.

Keywords: Quantitative Electroencephalography (qEEG), Adolescent Depression, EEG Biomarkers

Disclosure: Nothing to disclose.

P253. Behavioral Variability in Response to Chronic Stress and Morphine in C57BL/6J, DBA/2J, and Their BXD Progeny

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Background: Drug addiction is a multifactorial disease in which genetic predispositions and environmental stress exposure constitute major risk factors for the early onset, escalation, and relapse of addictive behaviors. While it is well known that both social and non-social stressors play a key role in drug addiction, the genetic factors that make specific individuals particularly sensitive to stress and, thereby, more vulnerable to becoming addicted are unknown. In an effort to map a complex set of G x E interactions—specifically Gene x Chronic Stress—here we employed tools of system genetics: BXD recombinant inbred mice in addition to the parental C57BL/6J and DBA/2J lines. In the present study, we investigated such gene-stress interactions in the context of morphine exposure.

Methods: We utilized the BXD5, BXD8, BXD14, BXD22, BXD29 and BXD32 and their parental mouse lines, C57BL/6J and DBA/2J. We used the chronic social defeat stress (CSDS) and the chronic variable stress (CVS) paradigms known to induce individual behavioral stress outcomes to capture measures of anxiety, anhedonia, and depressive-like behaviors in mice. Following CSDS, we assessed social behaviors, reward sensitivity, and approach/avoidance behaviors in both male and female mice were tested. We then performed morphine place preference monitoring to test the sensitivity to morphine following social and non-social stress exposure.

Results: We first identified heterogeneous behavioral responses to CSDS amongst the BXDs and parental mouse lines (ANOVA, $F(15,231) = 4.232$, $p < 0.001$). We also observed that DBA/2J and BXD22 male and female mice are more susceptible to chronic social stress exposure than C57BL/6J mice, as evidenced by stronger social avoidance and anxiety-like behaviors (t-tests, $t = 2.515$, $p = 0.01$; $t = 3.983$, $p < 0.001$). Further, we observed sexual dimorphisms in response to CSDS amongst the BXD5, BXD8, BXD14, BXD29, and BXD32 lines (ANOVA, $F(15,231) = 21.97$, $p < 0.001$). Additionally, to investigate the interaction between genetic characteristics and vulnerability to prolonged exposure to non-social stressors, we exposed C57BL/6J, DBA/2J, and BXD8,

BXD22, BXD29 male and female mice to the chronic variable stress paradigm (CVS). We observed that DBA/2J female mice are more sensitive to the CVS when compared to the C57BL/6J female mice (i.e., a strong decrease of sucrose preference) (ANOVA, $F(9,141) = 9.49$, $p < 0.01$). Confirming the stress vulnerability of the BXD22 observed following CSDS, the BXD22 male and female mice, after CVS, displayed a higher level of anxiety than C57BL/6J (t-tests, $t = 2.293$, $p = 0.04$; $t = 2.293$, $p = 0.002$). Interestingly, while the BXD29 behaved like C57BL/6J after CSDS, both BXD29 female and male mice developed higher anxiety profiles following CVS when compared to the C57BL/6J (t-tests, $t = 4.807$, $p < 0.001$). Finally, we identified that DBA/2J and C57BL/6J mice pre-exposed to CSDS displayed differences in morphine sensitivity (TWO-WAY ANOVA, $F(2.42) = 20.14$, $p < 0.0001$; paired-side $t = 4.886$ $p < 0.001$, unpaired-side $t = 4.047$ $p = 0.007$).

Conclusions: Our results support the hypothesis that genetic markers and predispositions to stress responses may control sensitivity to drugs and, in fine, regulate drug addiction. Characterization of the genetic, neurobiological, social, and environmental factors that mediate the risk of drug addiction will fundamentally improve our understanding of individual variations in responses to drug of abuse and provide highly useful information for the development of new treatment strategies.

Keywords: Gene-Environment Interaction, Chronic Social and Non-Social Stress, Morphine Sensitivity, Sex-Specificity, BXD Mouse Lines

Disclosure: Nothing to disclose.

P254. Melanopsin-Driven Pupil Responses and Vulnerability to Mania

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Background: Bipolar disorders (BD) typically emerge between ages 18 and 22, however it has been challenging to identify biomarkers for mania/hypomania that would help identify at-risk young people. Circadian dysregulation is a chronic feature of BD that could be driven by altered sensitivity of the circadian photoentrainment system. The post-illumination pupil response (PIPR) measures the responsivity of melanopsin-containing retinal ganglion cells and captures the sensitivity of the photoentrainment pathway projecting from the retina to the circadian clock. We examined whether altered responsivity of the circadian photoentrainment pathway, via the PIPR, was associated with symptoms of mania/hypomania vs depression.

Methods: This preliminary analysis included 37 participants aged 18-24yr ($M = 22.47$, $SD = 1.58$, 26 female) without BD but recruited across a range of none/low-to-high lifetime subthreshold mania symptoms (Mood Spectrum Measure-Lifetime Version; MOODS). The MOODS assesses the lifetime incidence of manic and depressive symptoms, traits, and behaviors. During a 24-hour lab visit, past-week clinician-rated severity of mania (Young Mania Rating Scale; YMRS) and depression (Hamilton Depression Rating Scale; HRSD) was assessed, and participants completed PIPR assessments in the morning and afternoon. We calculated the Net difference between pupil response to 1-second red and blue light pulses at 3 post-stimulus intervals: 6 seconds (PIPR-6), 10-30 seconds (PIPR-20), and 10-40 seconds (PIPR-30). The morning and afternoon PIPR values were averaged due to no significant effect of testing time. Robust regression models evaluated associations between PIPR and a) lifetime MOODS mania and depression scores and b) past-week mania (YMRS) and depression (HRSD) severity. All models covaried for age, sex, acute pupil diameter minimum to blue light, and mood symptoms.

Results: Greater lifetime subthreshold mania symptoms were associated with higher PIPR-6 ($\beta 6 = 0.398$, $p = 0.007$), PIPR-20 ($\beta 20 = 0.445$, $p = 0.002$), and PIPR-30 ($\beta 30 = 0.385$, $p = 0.019$). Lifetime subthreshold-syndromal depression symptoms were not associated with any Net PIPR metrics ($\beta 6 = -0.09$, $p = 0.532$; $\beta 20 = -0.142$, $p = 0.379$; $\beta 30 = -0.348$, $p = 0.239$). PIPR metrics were not significantly associated with past-week clinician-rated mania and depression severity (all p-values>0.3).

Conclusions: Elevated melanopsin-driven pupil responsivity was specifically associated with greater lifetime subthreshold mania symptoms in young adults, independent of lifetime depression and current mood symptoms. Thus, PIPR could be a promising biomarker of mania/hypomania vulnerability and contribute to the profound circadian dysregulation characteristic of BD. Data collection is ongoing in this longitudinal study.

Keywords: Bipolar Disorder, Melanopsin, Circadian Rhythm

Disclosure: Nothing to disclose.

P255. Continuous Theta Burst Stimulation to the Right Dlpfc Adaptively Modifies Approach-Avoidance Motivation Responses Associated With Dysregulated Social Behavior: Evidence From a Preliminary TMS Study

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Background: Social avoidance behavior (SAB) is an important, trandsdiagnostic factor shared across internalizing disorders, but is largely resistant to current evidence-based treatments (Bech, 2005). Therefore, novel approaches are needed to better characterize and remediate the mechanisms underlying SAB. Social behaviors such as SAB are guided by approach-avoidance (AA) motivational responses to affective facial expressions that frequently vary in social reward (e.g., 50%Happy), social threat (e.g., 50%Angry), or social reward-threat conflict (e.g., 50%Happy + 50%Angry; Barret, et al., 2019). Previous work demonstrates that SAB is selectively associated with dysregulated modulation AA motivational responses and right dorsolateral prefrontal cortex (dlPFC) reactivity to varying social reward-threat conflict (Evans, Esterman, and Britton, 2023). However, it remains unclear if the right dlPFC plays a causal role in modulating AA motivational processes to social reward-threat conflict, which is relevant to understanding the neural mechanisms underlying SAB. Previous research demonstrates that inhibitory neuromodulation of the right dlPFC increases reward sensitivity during non-social AA motivational conflict (Chrysikou, Gorey, and Aupperle, 2017), which may provide a promising neural target for novel therapeutics (Rolle et al., 2022). Together, these results are consistent with our previous work demonstrating SAB-related dysfunction in AA motivation and right dlPFC reactivity to social reward-threat conflict. Therefore, we hypothesized that inhibitory continuous theta burst stimulation (cTBS) to the right dlPFC would adaptively modulate the sensitivity of AA motivational responses in response to social reward-threat conflict, which may be useful for normalizing social reward sensitivity underlying SAB.

Methods: A pilot sample of healthy adults ($n = 5$; 4 Females) completed an fMRI baseline session to identify personalized right dlPFC stimulation targets and completed the Social Approach-Avoidance Paradigm (SAAP) immediately following cTBS or sham TMS. In the SAAP, emotional facial expresions are parametrically morphed in 25% increments to create varying degrees of social

reward (e.g., 50%Happy), social threat (e.g., 50%Angry), or social reward-threat conflict (e.g., 50%Happy + 50%Angry). On each trial in the SAAP, participants are presented with a facial expression and separately rate subjective motivation to approach and avoid the individual. We used polynomial fit indices to quantify modulation of AA motivational responses as a function of social signals (e.g., the linear slope across 0%Happy, 25%Happy, 50% Happy, 75%Happy, and 100%Happy).

To identify personalized right dlPFC targets for each participant, we transformed a SAB-relevant right dlPFC region into native space, which was identified in previous fMRI research using the SAAP (Evans, Esterman, and Britton, 2023). Next, in a single-blind, cross-over design, participants completed the SAAP immediately after receiving 600 pulses of either active cTBS or sham TMS at 80% of resting motor threshold. We conducted cTBS and sham stimulation sessions in a counterbalanced order with a 1-week washout period. Given our small sample size, we primarily report effect sizes along with non-parametric Wilcoxon signed-rank tests to compare modulation of AA motivational following cTBS and sham stimulation.

Results: Demonstrating expected SAAP task effects, participants exhibited modulation of AA motivation as a function of social reward, social threat, and social reward-threat conflict (all ps < 0.001). Compared to sham TMS, cTBS to the right dlPFC adaptively modified AA motivation as a function of social reward-threat conflict with a medium-large effect size ($d = 0.69$, $Z = 2.02$, $p = 0.04$). Specifically, participants exhibited stronger increases in approach motivation and stronger decreases in avoidance motivation as social reward signals increased in intensity relative to co-occurring social threat signals. Demonstrating specificity of TMS-related effects, cTBS did not significantly modify AA motivation as a function of either social reward in isolation ($d = 0.41$, $Z = 1.21$, $p = 0.23$) or social threat in isolation ($d = 0.22$, $Z = 0.67$, $p = 0.50$).

Conclusions: In this pilot study, sham-controlled cTBS over personalized right dlPFC targets adaptively modified AA motivational responses to varying degrees of co-occurring social reward and social threat (i.e., social reward-threat conflict), but not varying degrees of social reward or social threat in isolation. Although larger samples are necessary to replicate these preliminary findings, these results align with previous neuromodulation research on AA motivational responses to non-social reward-threat conflict (Knoch, et al., 2006; Obeso et al., 2021). Thus, the present preliminary results dovetail with these previous findings by suggesting that inhibitory cTBS to the right dlPFC increases approach motivation in response to social reward-threat conflict. As noted previously, SAB is selectively associated with dysregulated modulation of AA motivational responses to social reward-threat conflict. As a result, inhibitory cTBS to the right dlPFC may offer a promising method to remediate dysregulation of AA motivational responses that contribute to SAB, which is largely resistant to current evidence-based treatments.

Keywords: Neurostimulation, Social Behavior, Facial Emotion Processing, Dorsolateral Prefrontal Cortex (DLPFC), Theta-Burst Stimulation

Disclosure: Nothing to disclose.

P256. Biotyping of Neuroanatomical Signatures by Machine Learning of Brain MRI Data in Treatment-Resistant Depression

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Background: One-third of patients with major depression disorder (MDD) do not respond to pharmacotherapy and psychotherapy, known as treatment-resistant depression (TRD). Repetitive transcranial magnetic stimulation (rTMS) has increasingly been applied for TRD in recent years. However, more than 60% of patients with TRD do not respond to rTMS treatment adequately (Róbert, et al. 2023). Thus, biomarker-based subtyping (i.e., biotyping) can elucidate mechanisms and treatment predictors for TRD. In such a situation, multivariate pattern analysis using biological data has recently emerged but mostly ignored heterogeneous features of brain disease. Thus, we specifically employed a heterogeneity through discriminative analysis (HYDRA) method (Varol et al., 2017) to subtype the TRD group based solely on neuroanatomical characteristics. HYDRA, a semi-supervised clustering method, considers clinical heterogeneity when determining boundaries between controls and patients, enabling the discovery of patient-specific subgroups. Hence, the present study aimed to classify the biotypes of TRD and explore their relationship with clinical characteristics as well as treatment response to rTMS.

Methods: This study was approved by the ethical committee at Keio University School of Medicine and the Keio Certified Review Board. All participants provided written informed consent. Eligible participants were aged ≥18 with a DSM-5 diagnosis of MDD, experiencing moderate or more depressive symptoms (Montgomery Åsberg Depression Rating Scale (MADRS) score ≥18), despite the adequate treatment of antidepressants. All patients with TRD received rTMS treatment to the bilateral dorsolateral prefrontal cortex. Treatment response was defined as a change in MADRS scores from baseline to last treatment of 50% or more, while remission was defined as a MADRS score of 10 or less at the time of final treatment. The MRI data were obtained from the randomized rTMS trial conducted at Keio University Hospital between 2018 and 2023. MRI images were acquired at baseline using a 3T MRI with a 32-channel head coil (Siemens Prisma) in accordance with the Human Connectome Project (HCP) protocol. T1- and T2-weighted images underwent preprocessing with the structural preprocessing in HCP pipelines (released by Washington University in St. Louis, U.S.A.) including HCP-adjusted processing with FreeSurfer 6, finally resulting in the selection of 160 ROIs (68 bilateral cortical volumes, 68 white matter (WM) volumes, and 24 other subcortical volumes) for the HYDRA clustering. Fifty healthy controls (HCs) and 103 TRDs with successful preprocessing were included in HYDRA with three covariates: age, sex, and total intracranial volume. We employed HYDRA on volumetric ROI metrics to identify subtypes. The optimal number of TRD clusters based on the highest adjusted rand index (ARI) was selected. Cortical volume differences between TRD biotypes and HCs were analyzed using Permutation Analysis of Linear Models (FMRIB Software Library, version 6.0.5) with vertex-wise analysis (corrected p-value < 0.05). WM and other subcortical volumes were compared to HCs in the ROI under false discovery rate (FDR) correction. To explore the relationship between baseline clinical data and TRD biotypes, we employed NeuroMiner (version 1.1, Koutsouleris, 2022) for machine learning using a nested cross-validation design (10-fold outer loop; 10 inner loop with five shuffled permutations; L1-regularized support vector machine classifier). Model evaluation was performed with balanced accuracy (BAC), the average of sensitivity and specificity.

Results: HYDRA identified two optimal clusters (ARI max, 0.694, $K = 2$) referred to as TRD1 and TRD2. Volumetric vertex-wise analysis revealed that TRD1 exhibited smaller volume than HCs in the left precentral, left medial orbitofrontal, right lateral orbitofrontal, right postcentral, and right middle temporal cortex ($p < 0.05$). Conversely, TRD2 showed a larger volume than HCs in the left precuneus, left postcentral, right pericalcarine, and right supramarginal cortex ($p < 0.05$). Additionally, when comparing TRD1 to HC regarding WM and other subcortical volumes, only the left accumbens showed a significant volume decrease in TRD1. The comparisons of clinical data between TRD1 and TRD2 did not

reveal significant differences. There was no significant difference in response or remission rates following rTMS treatment between TRD1 and TRD2. The prediction of TRD1 and TRD2 using clinical variables showed a BAC of 52.4%.

Conclusions: The strength of this study lies in HYDRA's focus on neuroanatomical heterogeneity, revealing two distinct TRD biotypes: one with increased brain volume and the other with decreased brain volume. HYDRA's ability to biotype based on key depression-related regions, such as the precuneus cortex, orbitofrontal cortex, and nucleus accumbens, aligns with prior studies and offers insight into biologically clustered illness. Given that the ability to make accurate predictions of the biotypes was limited using clinical characteristics, future research is needed to combine biotyping with multiple imaging modalities to elucidate the biological mechanisms underlying each biotype we found in this study and to refine the prediction of the treatment response to rTMS.

Keywords: Machine Learning Clustering, Treatment-Resistant Depression, Repetitive Transcranial Magnetic Stimulation (rTMS), Structural MRI

Disclosure: Nothing to disclose.

P257. Exploring the Effects of Real-Time Biofeedback Training With 7-Tesla MRI for Depression

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Background: Depression is significant public health problem but current treatments fail at relieving symptoms for many patients. Motivational deficits are a core feature of depression and are mediated dopaminergic projections from the ventral tegmental area (VTA), a tiny midbrain region that has been largely inaccessible with traditional 3-Tesla MRI.

Methods: We have developed an ultra-high field 7-Tesla real-time biofeedback protocol for VTA activity self-regulation, via a randomized, sham-controlled trial. So far $N = 20$ have been randomized to Active VTA or Sham biofeedback. The 7T-MRI session includes baseline, three training runs, and a transfer-test run. During training, participants use various cognitive strategies to generate a heightened state of motivation (motivate trials). Participants in the Active group observe their VTA activity, whereas participants in the Sham group view yoked control activity. ANOVA was used to compare VTA activation (motivate>rest) at baseline and test with terms for Active or Sham interventions and depression/control groups. All participants also completed clinician-administered and self-reported symptom surveys at baseline and following biofeedback training.

Results: In this preliminary sample from an ongoing study, there was a main effect of intervention ($F(1) = 5.0854$, $p = 0.0385$), whereby VTA activity increased over time in the Active compared to Sham group. There was also a significant intervention x group interaction ($F(1) = 4.60$, $p = 0.048$), whereby control participants showed a larger increase in VTA activity compared to participants with depression. All participants showed a reduction in depression symptoms over time (baseline to 24hrs follow-up, $F = 10.67$, $p = 0.005$), regardless of intervention group. All up-to-date results will be presented.

Conclusions: This is a preliminary analysis of an ongoing clinical trial. Early findings suggest the efficacy of 7T RT-BF with motivational strategies in upregulating the VTA across individuals. Further investigation will determine whether this translates to specific clinical or behavioral improvements in participants with depression.

Keywords: Depression, Ultra-high Field MRI, Neurofeedback, Ventral Tegmental Area

Disclosure: Nothing to disclose.

P258. Dysregulated Connectivity Among Insula, Postcentral Gyrus, and Precuneus and its Association With Suicide Risk

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Background: Suicide is a serious public health concern in the US, underscoring the need for objective markers of the suicidal behaviors. Existing research suggests a connection between aggressive impulsivity and suicidal behaviors, with potential links to reduced brain function in regions relevant to sensory regulation and decision-making, such as prefrontal cortex, precuneus, and insula. However, limited knowledge is available on the association between the impulsive aggression, suicidal behavior, and brain regions responsible for the sensory and emotional regulation, specifically when considering the temporal dynamics of the suicidal behavior. This study examined whether trait-like aggression and impulsivity, along with task-oriented impulsivity measures, could moderate resting-state magnetoencephalographic (MEG) power and effective connectivity.

Methods: The ongoing research initially recruited 121 participants in three groups: Individuals with recent suicidal crisis (High Risk; HR; $n = 14$), individuals with a history of suicide attempts except for last year (Low Risk; LR; $n = 41$), and individuals without a history of suicidal behaviors (Control; CL; $n = 66$). Impulsivity was assessed through two measurements: trait impulsivity, measured using the Barratt Impulsiveness Scale (BIS), and risk-taking impulsivity, evaluated using the Balloon Analogue Rating Task (BART). Additionally, trait-like aggression was measured using the Buss-Perry Aggression Scale (BPA). One or 2 8-minute, eyes-closed resting-state scans were collected for each participant, and data were source-localized using a linearly constrained minimum variance beamforming algorithm. Linear mixed effects models were employed to examine whether HRs differed from LRs and CLs in oscillating power in the delta (2-4Hz), theta (4-8Hz), alpha (9-14Hz), beta (15-29Hz), and gamma (30-58Hz) frequencies, focusing on regions-of-interest (ROIs) implicated in sensory regulation and decision-making, such as the prefrontal cortex, precuneus, insula, and post-central gyrus. Additionally, the study explored the interaction between the resting-state MEG power and aggressive impulsivity measures in those ROIs. To investigate the directional connectivity between ROIs, we performed an effective connectivity analysis using dynamic causal modeling (DCM) in SPM12. The analysis probed the estimated glutamatergic and GABAergic extrinsic connectivity between ROIs.

Results: The study did not find a significant difference in MEG power between the HR group, LR group, and CL group. However, within the HR group, participants with higher trait-like aggression and impulsivity scores showed an inverse relationship between attentional BIS and BAS scores and MEG power in various bandwidths, including delta (precuneus), theta (supra marginal gyrus), alpha (angular gyrus, middle frontal, and inferior parietal gyri), beta (precuneus and inferior frontal gyrus), and gamma (postcentral gyrus), with voxel-based corrected $ps < .05$. Parametric empirical Bayesian analysis revealed that compared to LR and CL groups, HR participants showed downregulated bidirectional AMPA-mediated connectivity between the precuneus (PRE) and insula (INS) and upregulated AMPA-mediated feedback from

the postcentral gyrus (PCG) to the INS, posterior probability (posteriorp) > .95. Additionally, within the HR group, individuals with higher BIS scores exhibited downregulated AMPA feedback from PCG to INS, and those with higher BART scores displayed upregulated AMPA feedback between PCG and INS, along with downregulated AMPA feedforward connectivity from INS to PRE, when compared to LR and CL groups, posteriorps > .95.

Conclusions: The results indicate dysregulated glutamatergic connectivity in brain regions related to sensory and decision-making, which is linked to suicidal risk, particularly when considering various measures of impulsivity and the timing of suicidal behaviors. The study suggests that the glutamatergic-mediated sensory and emotion-regulation processes may serve as significant markers of suicide risk, which can be evaluated in future longitudinal studies.

Keywords: Suicide, Magnetoencephalography, Dynamic Causal Modeling, Somatosensory Processing, Default Mode Network (DMN)

Disclosure: Nothing to disclose.

P259. Dominance Status Buffers Against Neurochemical and Behavioral Responses to Nonsocial Stressors

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Background: Dominance status has extensive effects on physical and mental health. There has been recent interest in understanding neural mechanisms that mediate winning/losing in social competitions, and in how winning/losing relates to general stress vulnerability/resilience. The prelimbic region (PL) of the medial prefrontal cortex has been implicated in (i) driving effortful behavior during winning experiences and (ii) translating competitive success to novel social contests. Here we explored in rats whether repeated winning experiences produced later resistance against the typical sequelae of a nonsocial stressor (uncontrollable tailshock). Additionally, we determined whether corticostriatal circuitry (PL and the dorsomedial striatum, DMS) is involved in the development of sustained winning.

Methods: We used a modified version of the warm spot test (WST) for rats, in which a triad competes for sole occupancy of a warm spot on a cold cage floor. To establish dominance status, triads of Sprague Dawley rats were given daily sessions of 20-min warm spot competitions. Occupancy time of the spot for each triad subject was calculated and expressed as a percentage of the total time the warm spot was occupied. Competition behavioral measures included 1) pushes initiated; 2) resistance bouts; and 3) retreats. EXP1: Adult male and female rats were given daily warm spot competitions (n = 8 triads/sex). EXP2: Cannula were implanted bilaterally in either PL or DMS (n = 7-8 male triads). EXP3: Following WST, subjects received a single session of uncontrollable tailshock and a juvenile social interaction test 24 h later (n = 8-10/group). EXP4: Following WST, stress-induced serotonin (5-HT) levels in the dorsal raphe nucleus (DRN) were assessed with in vivo microdialysis (n = 5-9/group). EXP5: Following WST, stress-induced endocrine and central immune responses were measured with ELISA and quantitative real time PCR (n = 7-9/group).

Results: EXP1: A greater proportion of males (87.5%) than females (62.5%) showed stable dominance, defined as the top rank position for at least 5 out of the 7 competitions. EXP2: To examine the role of the corticostriatal system in the development of stable winning in males, winners in the initial warm spot session received intra-PL muscimol, intra-DMS AP5, or vehicle in the respective regions. Both PL inactivation and DMS NMDA blockade decreased occupation time (p's < 0.01), and this loss of dominance was evident throughout the remaining drug-free sessions (drug: p's < 0.05, repeated-measures ANOVA). EXP3: Prior history of repeated winning completely blocked the social avoidance produced by uncontrollable stress. Importantly, the impact was specific to repeated winning, not losing (stress x rank: $F_{2,47} = 4.351$, $p = 0.02$; ANOVA). EXP4: Repeated winning also blunted the tailshock-induction of dorsal raphe 5-HT efflux (group: $F_{3,23} = 5.358$, $p = 0.006$; repeated-measures ANOVA). In contrast, pre-existing rank did not impact stress-induced increases in serum CORT nor hypothalamic immune markers (EXP4: p's > 0.05; ANOVA).

Conclusions: The current set of experiments led to two primary findings. First, the development of stable dominance involves corticostriatal structures (both PL and DMS), and second, once established, competitive success buffers against the typical neurochemical and behavioral sequelae of a nonsocial stressor. We also observed that stress-induced endocrine and neuroimmune outcomes were unaffected by pre-existing rank, suggesting boundary conditions to the stress-buffering effects of dominance. Given that dominance is implicated in positive health outcomes, the involvement of corticostriatal structures may represent a circuit-level endophenotype in the production of resilience.

Keywords: Medial Prefrontal Cortex, Stress Resilience, Social Dominance, Serotonin

Disclosure: Nothing to disclose.

P260. Low-Intensity Focused Ultrasound of White Matter Tracts in the Anterior Limb of the Internal Capsule Decreases Connectivity Between Thalamus and Orbitofrontal/Subgenual Cortices in Participants With Major Depression

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Background: This preregistered pilot study (NCT05697172) investigates the impact of low intensity focused ultrasound (LIFU) targeted at the right anterior limb of the internal capsule (rALIC), a well-established psychosurgical target for treatment-resistant depression [1-4] due to involvement in neural circuits important for mood related processing. We used individualized probabilistic tractography to define individual thalamo-orbitofrontal and thalamo-anterior cingulate tracts traversing the rALIC to target these white matter tracts with LIFU. We examined the effects of LIFU on regional functional connectivity, emotional behavior, and peripheral autonomic activity, measured by heart rate variability (HRV), compared with sham sonication.

Methods: In this double-blind (participant and rater), cross-over study, 10 participants (7 females, mean age 36 ± 9 years) diagnosed with Major Depressive Disorder (MDD) received both active and sham LIFU sessions using a Sonic Concepts NeuroFUS Pro® device. Sessions were spaced two weeks apart and the sequence of active or sham treatments was randomized. LIFU was administered following a theta burst pattern as previously described [5] (500 kHz transducer, 80 seconds, 10% duty cycle), achieving an estimated tissue ISPPA of 2.26 Watt/cm2. For sham procedures, a Sorbothane® membrane was placed between the transducer and scalp to attenuate acoustic energy. Each session began with the participants completing the Brief State Rumination Inventory (BRSI) and Positive and Negative Affect Schedule (PANAS) state assessments, followed by a 5-minute pre-stimulus HRV recording, the 80-second LIFU active or sham stimulus, a

5-minute post-stimulus HRV recording, and a repeat of the BRSI and PANAS assessments. Subjects also underwent an MRI session including a 6-minute resting-state functional scan after each LIFU session.

Functional connectivity (ROI-to-ROI of bilateral 48 ROIs located at the thalami and orbitofrontal or anterior cingulate cortices; 1128 connections) was analyzed with SPM-CONN toolbox [6]. ROI-to-ROI connectivity was compared between active and sham LIFU sessions. Cluster-level inferences based on permutation tests were applied (Spatial Pairwise Clustering [7]). Frequency-domain HRV, BSRI, and PANAS scores were evaluated with linear mixed effect models (Session: active vs. sham, Time: pre vs. post, and Session-by-Time interaction).

Results: Participants tolerated the application of LIFU to the rALIC well, with no detectable changes in neurological signs or DWI, FLAIR, or T2 MRI sequences. The correct detection rate for both active and sham sessions in the sample was 60% ($X2[1] = 0.20$, $p = 0.65$), indicating successful blinding. There were no significant Session-by-Time interactions for clinical measures. However, there were two clusters of decreased functional connectivity following the active LIFU session compared to the sham session. Cluster 1 consisted of reduced functional connectivity between the right thalamus and bilateral subgenual anterior cingulate cortex (sgACC; Cluster mass index = 253.01, p-FDR = 0.02, Cohen's d = -1.28), and Cluster 2 consisted of decreased functional connectivity between the left thalamus and bilateral sgACC, as well as bilateral ventral caudate, and between the left thalamus and the right medial orbitofrontal gyrus (Cluster mass index = 205.60, p-FDR = 0.04, Cohen's d = -0.77). There was a significant Session-by-Time interaction in LF/HF HRV ($F\ [1,27] = 4.24$, $p = 0.049$), with a specific increase in LF/HF observed following the sham session ($t\ [27] = -2.55$, $p = 0.02$, Cohen's d = 0.81), a change not seen following the active LIFU session ($t\ [27] = 0.36$, $p = 0.72$, Cohen's d = 0.11).

Conclusions: This preliminary analysis shows that LIFU applied to white matter tracts that are part of a large-scale circuit critical to symptom formation in major depression [1] produces measurable functional changes in such a circuit. In addition, there was a subtle but significant change in cardiac sympatho-vagal balance possibly related to increased arousal in response to sham but not LIFU stimulation. These findings show proof-of-principle that LIFU has neuromodulatory effects when applied to white matter tracts. If confirmed in larger samples, these preliminary findings suggest LIFU can be developed as a neuromodulatory approach for personalized, symptom-specific neuromodulation targets.

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Keywords: Depression, Focused Ultrasound, Non-Invasive Neuromodulation, Functional Connectivity, Negative Affect

Disclosure: Nothing to disclose.

P261. Brain Encoding of Perceived Control as a Prospective Predictor of Improvement in Quality of Life and its Relationship With Perceived Stress

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Background: The perception of control has been strongly related to mental health and well-being. Specifically, the lack of perceived control over events has been associated with learned helplessness and been found to predict depression and anxiety disorders (Pryce et al. 2011). In addition, rodent studies have demonstrated a protective effect of perceived controllability against stressors, which involved the ventromedial prefrontal cortex (VMPFC) (Maier 2015). However, it is unknown whether brain reactivity to perceived control and its protective effect against stress can predict improvement in quality of life. Here, we aimed to investigate the brain underpinnings of controllability in humans, for both present and future opportunities for control. Furthermore, we hypothesized that increased brain responsiveness to control would prospectively predict greater improvements in life satisfaction and that this association would be mediated by reductions in perceived stress.

Methods: Healthy female participants ($N = 40$, ages: 25.9 ± 3.5) completed the Value of Control task (VOC) (Wang and Delgado 2019) in a 3T fMRI scanner. The VOC measures an individual's preference for control and examines two types of neural encoding of controllability - present and future. (i) Present control: in this condition, participants chose if they want to have control and play the game, or have the computer play the game for them. (ii) Future control: participants chose between two options that differ in their rewards but do not differ in their controllability, where half of the trials indicate future control (i.e., the participant will play the game) and half of the trials indicate no future control (i.e., the computer will play the game). After the VOC, participants rated in the scanner how much they liked having control in the game and how much they believed they could earn rewards in both options (control, uncontrollable). An additional computational metric - the "Point of Equivalence" - was derived to capture how much a participant values controllability over receiving rewards (Wang and Delgado 2019). To prospectively evaluate quality of life and perceived stress, participants filled out the Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q) (Endicott et al. 1993) and the Perceived Stress Scale (PSS) (Cohen et al. 1983) at baseline prior to the fMRI scan as well as at a 6-month follow-up visit. fMRI data were preprocessed using fMRIprep (Esteban et al. 2019), and individual- and group-level analyses were conducted in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) to identify brain regions that were reactive to perceived control. A statistical threshold of voxel-level $p < 0.001$, FDR cluster correction at $p = 0.05$ was applied. In the next step, elastic-net algorithm was used to select predictors of

quality of life among the brain regions which showed significant activation to control. The best brain predictor was identified and included in a following mediation model to test whether a change in perceived stress (PSS at 6-month follow-up relative to baseline) mediated the relationship between brain activation to perceived control and change in life satisfaction (Q-LES-Q at 6-month follow-up relative to baseline). Elastic-net was implemented using Glmnet (http://hastie.su.domains/glmnet_matlab/) (Qian et al. 2013). Mediation analysis was performed using SPSS PROCESS macro (Hayes 2013) and the significance of the indirect effect was tested using bootstrapped 95% confidence intervals with 10,000 resamples.

Results: Controllability influenced liking to play the game but did not affect the perceived likelihood of earning rewards (interaction effect: $F(1,38) = 6.61$, $p = 0.014$). As captured by the Point of Equivalence, most participants did not prefer having control over receiving rewards ($t(36) = 1.93$, $p = 0.061$). For both present and future control (control>uncontrollable), increased brain reactivity was found for the bilateral putamen, insula, thalamus, mid-cingulate, and motor cortex (all $p < 0.05$ FDR cluster corrected for multiple comparisons). In contrast, the VMPFC and the posterior cingulate cortex (PCC) showed stronger reactivity when there was no future control (future uncontrollable>control) and the left dorsolateral PFC (DLPFC), left ventrolateral PFC (VLPFC), and PCC showed stronger reactivity when choosing not to have control (present uncontrollable>control) (all $p < 0.05$ FDR cluster corrected). The right putamen, left thalamus, left VLPFC, and left DLPFC were selected by elastic-net as prospective predictors of changes in life satisfaction, with the right putamen identified as the best predictor (correlation between predicted and observed scores: $r(35) = 0.63$ $p < 10\text{-}4$). Notably, the effect of right putamen reactivity to control on improvement in life satisfaction was mediated by perceived stress (standardized indirect effect = 0.197, SE(boot) = 0.094, 95% CI = [0.036, 0.399]).

Conclusions: We demonstrated a widespread brain circuit associated with perceived control that partially overlapped with the reward circuit (i.e., the striatum and VMPFC). In addition, our findings indicate the involvement of central nodes of the default mode network (PCC and VMPFC) in the encoding of control. Importantly, our findings suggest that neural responsiveness to perceived control may have clinical utility as a potential marker of improvement in life satisfaction.

Keywords: Functional MRI (fMRI), Perceived Control, Perceived Stress, Quality of Life, Prediction

Disclosure: Nothing to disclose.

P262. The COVID19 Pandemic Disrupts Associations Between Neural Network Connectivity and Affective and Anxiety Symptoms in Young Adults

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Background: The COVID19 pandemic has significantly impacted mental health, with a significant worsening of depression and anxiety. This provides an opportunity to identify neural mechanisms underlying depression and anxiety development during widespread stress, with implications for longer-term mental health. Yet, it remains unknown how the pandemic influenced neural networks supporting key cognitive processes, including reward, central executive, salience and ventral attention networks (RNet, CEN, SN, VAN). This cross-sectional, naturalistic study examined how depression and anxiety were associated with functional connectivity (FC) among these networks before and during the pandemic.

Methods: 79 young adults (53F/26M) completed a monetary reward fMRI task and clinician-rated measures of depression and anxiety (Hamilton Rating Scales for Depression and Anxiety [HRSD, HAMA]). COVID19 group was defined by study completion before ($n = 28$) and during ($n = 51$) the pandemic. fMRI data were preprocessed using fMRIPrep 20.2.6 and first-level analyses were completed in SPM12. We examined network FC using seed regions overlapping with activation to reward expectancy (RE) and prediction error (RPE): ventral striatum (VS;RNet), dorsal anterior cingulate cortex (dACC;RNet/SN) and left ventrolateral prefrontal cortex (vlPFC;RNet/VAN); and the interaction between COVID19 group and clinician-rated symptoms on network FC. In SPM12, six between group wholebrain models were performed for FC analyses based on reward condition and seed region (2 conditions: RPE, RE; 3 seeds: VS, left vlPFC, dACC). Models were corrected for age, sex assigned at birth, diagnosis, IQ, psychotropic medication use, and lifetime trauma (pFWE <0.05).

Results: Participants scanned during the pandemic reported higher anxiety($t = -4.41$, $p < 0.001$) and depression($t = -4.01$, $p < 0.001$). There was an interaction between depression and COVID19 group for FC between RNet/SN and the right inferior parietal lobule(IPL) during RPE (pFWE < 0.05), where greater depression was associated with higher dACC-right IPL FC during RPE prior to the pandemic, but there was a nonsignificant relationship between depression and dACC-right IPL FC to RPE during the pandemic. There was an interaction between anxiety and COVID19 group for FC between RNet/VAN and the right inferior temporal gyrus(ITG) during RPE (pFWE < 0.05), where greater anxiety was associated with higher left vlPFC-right ITG FC to RPE prior to the pandemic, but there was a nonsignificant relationship between anxiety and left vlPFC-right ITG FC to RPE during the pandemic. Lastly, there was an interaction between clinician-rated anxiety and COVID19 group for FC between RNet/SN the left caudal vlPFC and the left IPL during RE (pFWE < 0.05), where greater anxiety was associated with higher dACC-left caudal vlPFC FC and higher dACC-left IPL FC during RE prior to the pandemic, but there was a nonsignificant relationship between clinician-rated anxiety and dACC -caudal vlPFC and dACC- left IPL FC during the pandemic.

Conclusions: Relationships among neural network FC and depression and anxiety were decoupled during the pandemic, where previously observed relationships between higher neural network FC and greater-severity depression and anxiety were lost during the pandemic. The impact of pandemic-related stressors on the brain might reflect a critical role of global stress in altering neural network-symptom relationships. These findings can increase understanding of the influence of major stressors on neural mechanisms underlying mental ill-health.

Keywords: Reward Neural Circuitry, COVID-19 Pandemic, Depression, Anxiety, Neural Connectivity

Disclosure: Nothing to disclose.

P263. Preliminary Evidence of Brain-State Dependent Effects of TMS Over the Prefrontal Cortex on Approach/Avoidance Behavior in Adults

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Background: Major depressive disorder (MDD) is a widespread mental disorder and the leading cause of suicide worldwide. It is

characterized by multidimensional abnormalities in cognition and behavior, including altered approach/avoidance behavior towards emotional stimuli. One in three patients with MDD does not respond to pharmacological and psychotherapeutic interventions. Transcranial magnetic stimulation (TMS) is FDA approved for treatment-resistant MDD. Novel forms of TMS such as intermittent theta-burst stimulation provide relief for 40-60% of treatment-resistant patients following brief daily interventions over several weeks. Nevertheless, the sources of variability in treatment outcomes following theta-burst stimulation need to be understood. One likely cause for variability is the brain state during the TMS intervention. Neural states vary at a millisecond resolution, thus posing a major neurotechnological challenge. One way to characterize the brain state is by recording neural oscillations using electroencephalography (EEG). Local oscillations reciprocally reflect and affect neural populations because they periodically de- or hyper- polarize neural membranes. A key oscillation in the left prefrontal cortex, an anatomical target for TMS in MDD, is a theta rhythm. To explore the prefrontal brain state as a putative factor in the TMS efficacy, one would need to synchronize a TMS delivery to an exact phase of a patient-specific theta rhythm as captured in real-time using a closed-loop neuromodulation approach. Here we achieve this in healthy adults while they perform a computerized approach/avoidance task (AAT). AAT significantly predicts future depressive episodes, conventional treatment outcomes, relapse, and chronicity of MDD in adults.

Methods: This is a registered (NCT05416138), double-blinded study in healthy adults currently ongoing at the University of Minnesota with the approval of the local IRB. The preliminary results here are obtained from the first five participants ($n = 5$). Before the TMS experiment, a structural magnetic resonance image is collected to power an individualized TMS coil location using Neuronavigation (Brainsight, Rogue Research). During each session, an ongoing EEG is recorded by a 64-channel active system (ActiChamp, BrainProducts). It is analyzed in real-time to extract and forward predict the prefrontal theta phase (electrode F3, frequency 3-7 Hz) using Bayesian Temporal Prediction. In a predefined randomized order, peaks or troughs of the prefrontal theta are detected and stimulated. TMS is delivered by MagPro X100 with MagOption (MagVenture). For stimulation, we used a single theta-burst pulse sequence (3 pulses during 50 ms) at a target theta phase (peak or trough). The TMS coil location was set to the left DLPFC (MNI -38, 44, 26). The approach/avoidance task (AAT) is administered concurrently with TMS. In AAT, human faces expressing happy, neutral, or angry emotions from the validated Chicago face database are shown on the screen. Participants use a joystick to pull towards themselves (– approach) or push away (– avoid) the emotional stimuli. During a congruent condition, a volunteer approaches happy faces and avoids angry faces. The instruction is the opposite during an incongruent condition. TMS is delivered in synchrony with the face presentation. Each participant first performed 10 minutes of AAT for training purposes, then another 10 min to establish a baseline performance. Finally, AAT with concurrent brain-state-controlled TMS at either peaks or troughs of ongoing prefrontal theta was performed (280 trials in total). For data analysis, all reaction times outliers (>2 s) and incorrect responses were removed. The primary biomarker of the task is "positive approach tendency," estimated as the double-difference scores of reaction time in four conditions: (avoid happy - approach happy) - (avoid angry - approach angry).

Results: As expected, at baseline, volunteers were faster during the congruent condition overall (for positive and negative stimuli) than during the incongruent condition overall (12 ± 17 ms, median ± sem) with a positive approach tendency (29 ± 33 ms). This typical behavior was "flattened," e.g., without an apparent congruency effect, during the closed-loop theta-burst TMS over the prefrontal theta peaks. Overall congruent vs. incongruent reaction time difference was reversed (-30 ± 40 ms) and positive approach tendency was diminished (13 ± 64 ms). Stimulation at the prefrontal theta troughs had the opposite effect of promoting a larger congruent effect (46 ± 30 ms) and stronger positive approach tendency (81 ± 70 ms). We estimated the preliminary effect size of Hedges' $g = 0.73$ for TMS over the theta troughs vs. peaks.

Conclusions: Although preliminary, the differential effects of theta-burst TMS over the prefrontal cortex during opposite phases of the ongoing theta activity (a proxy for a prefrontal brain state) align with the hypothesis that the brain state plays a vital role in TMS treatment. These data further agree with the recent findings that ongoing motor cortex rhythms significantly affect TMS-motor evoked potentials. If confirmed, our results will provide a theoretical foundation for a brain-state controlled theta-burst stimulation in MDD, promising to significantly reduce the variability of treatment outcomes and improve therapeutic efficacy.

Keywords: TMS, Theta-Burst Stimulation, Closed-Loop Stimulation, Approach/Avoidance

Disclosure: University of Minnesota: Patent (Self), StimPhase LLC: Stock / Equity (Self)

P264. Proxy Measures of Neuroplasticity Demonstrate No Deficiency of Cortical Excitability in Major Depression and Reveal a Distinct Role for Sleep Slow-Wave Activity in the Regulation of Synaptic Homeostasis

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Background: One function of sleep has been posited to be the regulation of synaptic homeostasis. Specifically, sleep slow-wave activity (SWA) has been implicated in the downscaling of synaptic strength. Because major depressive disorder (MDD) has been postulated to be a disorder of impaired and deficient neuroplasticity, this could suggest that manipulating SWA in MDD could improve functioning by increasing synaptic strength. Therefore, the aim of the present study was to examine the impact of experimental disruption of SWA on two proxy measures of synaptic strength and plasticity: cortical excitability and peripheral brain-derived neurotrophic factor (BDNF).

Methods: 34 individuals (13 M) with MDD and 20 healthy controls (10 M) were recruited. Auditory stimulation was utilized to disrupt slow-wave sleep on one of two overnight sleep laboratory visits (Baseline, SWD) separated by one week. Following each overnight visit, plasma BDNF was assessed, and motor evoked potentials (MEP) generated from transcranial magnetic stimulation (TMS) were measured as a proxy measure of cortical excitability. Repeated measures ANOVA was used to examine levels of plasma BDNF and change in MEP amplitude following SWD with condition (Baseline, SWD) as the within-subject factor and group (HC, MDD) as the between-subjects factor. Post-hoc paired t-tests were used to examine within-group changes.

Results: At baseline, individuals with MDD and healthy controls demonstrated similar cortical excitability and plasma BDNF levels. Following slow-wave disruption, individuals with MDD demonstrated a significantly different pattern than HC, $F(1,21) = 4.58$, $p = .04$, with a significant increase in cortical excitability relative to baseline sleep, $t(21) = -2.14$, $p = .04$. Individuals with MDD also showed a descriptive increase in plasma BDNF, $t(23) = -1.62$, $p = .06$. HC showed no changes in cortical excitability or plasma BDNF.

Conclusions: Our results indicate that slow-wave disruption is associated with increases in proxy measures of synaptic strength in individuals with MDD and provides preliminary evidence that

the presence of SWA is associated with synaptic downscaling in MDD. The data from the TMS paradigm may also suggest that observed neuroplasticity impairments in MDD may be due to excessive cortical excitability rather than deficient cortical excitability, as has been previously suggested.

Keywords: Major Depressive Disorder, Slow-Wave Activity, Neuroplasticity

Disclosure: Nothing to disclose.

P265. The Activation of Serotonin Neurons in the Median Raphe Nucleus Induces Negative Emotion-Related Facial Expressions in Mice

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Background: Our previous study demonstrated that anxiety- and fear-related behavior, assessed through elevated plus maze and fear conditioning tests, respectively, is facilitated by serotonin neurons in the median raphe nucleus (MRN). Nonetheless, drawing a direct causal link between the neuronal activity of serotonin neurons in the MRN and negative emotions remains to be determined due to the relatively long time gap between experimental manipulations and the subsequent evaluation of behavioral changes in these tests. This temporal gap leaves room for the influence of learning or planning processes on test performance.

Methods: To address this concern, I employed optogenetic stimulation to activate serotonin neurons specifically in the MRN and promptly assessed the mice's responses. Five to seven transgenic mice that selectively expressed channelrhodopsin-2 (ChR2) in the serotonin neurons were used for each experiment. Approximately equal numbers of mice of both sexes were used. I surgically implanted an optical fiber into the median raphe nucleus to enable the emission of blue light from an LED device. This light activation served to stimulate ChR2 and consequently increase the activity of serotonin neurons. Alterations in facial expressions were recorded using a high-resolution camera. We employed image analysis based on Histogram of Oriented Gradients (HOG) features to assess changes in facial expression before and after the activation of serotonin neurons.

Results: My findings revealed that the activation of MRN serotonin neurons alone resulted in significant alterations in facial expressions, even without any external environmental stimuli. Remarkably, the facial expressions induced by MRN activation bore similar to those elicited by aversive stimuli, such as a loud tone or a tail shock.

Conclusions: These results collectively suggest that heightened activity of serotonin neurons in the MRN plays a mediating role in aversive responses.

Keywords: 5-HT, Reward, Aversion, Facial Expression Analysis

Disclosure: Nothing to disclose.

P266. Identification of Anti-Depressive Effects of Electroconvulsive Stimulation-Related Genes in Hippocampal Astrocytes

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Background: Electroconvulsive therapy (ECT) has superior efficacy and rapid response to pharmacotherapy and is often used for treatment-refractory depression. However, the action mechanism of ECT remains unclear. In addition, a clinical setting-associated behavioral model for ECT, in which depression-like behaviors are recovered by electroconvulsive stimulation (ECS), has not been established yet. Therefore, we first established a clinical setting-associated behavioral model of ECT with corticosterone (CORT)-administrated mice, a common mice model of depression, and ECS. Recent studies suggest the potential role of astrocytes in the pathophysiology of depression. Therefore, as a next step, we isolated hippocampal astrocytes from our mice model of ECT and performed RNA-seq with isolated astrocytes-derived RNA to identify anti-depressive effect of ECS-related genes in hippocampal astrocytes.

Methods: 35μg/mL aqueous solution of corticosterone was administrated to six-week-old male C57BL/6J mice by ad libitum feeding for four weeks. ECS was performed under anesthesia at 30 mA, 1000 Hz, 1 sec via an ear clip. According to clinical practice, ECS was administrated once a day and 3 times a week for two weeks. After the course of ECS, sucrose preference test (SPT) and novel environment feeding suppression test (NSFT) were performed to evaluate depression-like behaviors. After these behavioral tests, the hippocampus was dissected from the mice brain. The hippocampal astrocytes were isolated with FACS-based method. RNA-seq was performed with the isolated hippocampal astrocytes-derived RNA.

Results: Both of chronic CORT-induced depressive-like behaviors and reduction in the number of hippocampal astrocytes were ameliorated by ECS. Using this model, we investigated changes in gene expression in hippocampal astrocytes that are altered in a mouse model of depression and restored by ECS. Our results demonstrate that ECS reversed the altered gene expression pattern induced by chronic CORT administration. Furthermore, we identified SGK1 as a gene that is reciprocally regulated by CORT and ECS in hippocampal astrocytes.

Conclusions: Here we have established a clinical setting-associated mice model of ECT. Using this model, we identified SGK1 as a potential key regulator of anti-depressive effect of ECT via hippocampal astrocytes. Our present findings are expected to contribute to the elucidation of the action mechanisms of ECT.

Keywords: Major Depression, Electroconvulsive Therapy, Hippocampus, Astrocyte, Glucocorticoids

Disclosure: Nothing to disclose.

P267. Causal Role of Cross-Frequency Coupling for Effort-Based Decision-Making in Patients With Major Depressive Disorders

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Background: Anhedonia is a debilitating symptom that is common in major depressive disorder. Many interventions fail to ameliorate symptoms of anhedonia and severe anhedonia predicts treatment resistance. To address this need, novel forms of non-invasive brain stimulation can be developed that target the neural circuitry that underlies anhedonia symptoms. In our previous study, we found that those suffering from anhedonia showed reduced willingness to exert effort to obtain rewards and reduced prefrontal control over the motor cortex during decision-making. We designed a follow-up study that delivered non-invasive brain stimulation during task performance to investigate target engagement of these behavioral and neural constructs.

Methods: In a preregistered randomized clinical trial (NCT05084924), we administered transcranial alternating current stimulation (tACS) in 35 participants with major depressive disorder as they performed a reward-based decision-making task. In the task, participants chose to perform a more physically demanding task for a chance at winning more money, or a less demanding task for less money. In our previous experiment, one-third of our participants selected the harder task nearly every time (>85% of trials) and were excluded from analysis. Thus, we developed a version of the expenditure of effort for reward task that rapidly escalated physical difficulty after successful performance of the harder task (Extra-EEfRT). After acquiring baseline performance and titrating task difficulty, participants received cross-frequency tACS designed to synchronize prefrontal and motor cortex. The target signal, delta-beta coupling, was derived from our previous experiment that found the phase of delta oscillations (1-4 Hz) in prefrontal cortex was coupled to the amplitude of beta oscillations (15-25 Hz) in the motor cortex. As an active control, we delivered tACS using a waveform that mimicked theta-gamma coupling (5 Hz to 50 Hz), another coupling pattern often observed in memory tasks. Finally, we delivered placebo stimulation that mimicked the sensations of receiving tACS.

Results: As in our previous experiment, we found increased delta-beta coupling between prefrontal and bilateral motor cortex ($k > = 3$, $p < 0.05$) during decision-making. The hand used for the task alternated between blocks. An individual differences analysis revealed a positive relationship between choosing the hard task and delta-beta coupling strength with the motor cortex for the relevant hand ($k > = 3$, $p < 0.05$). Contrary to prediction, anhedonia symptoms were positively correlated with delta-beta coupling strength ($k > = 3$, $p < 0.05$) and the percent of trial that participants chose the hard task ($r(28) = 0.375$, $p = 0.041$). An exploratory analysis revealed that participants with a high fail rate showed a significant positive correlation with anhedonia symptom severity ($r(13) = 0.592$, $p = 0.020$), which was not present in those with a low fail rate ($r(13) = -0.032$, $p = 0.909$). These findings suggest that participants with anhedonia did not modify behavior in the face of persistent failure, consistent with previous literature suggesting a reduced ability to updated strategy based on feedback. Relative to the placebo group, delta-beta tACS to the left hemisphere produced a trend-level decrease in the overall choice to perform the hard task ($t(21) = -1.884$, $p = 0.073$, $d = 0.818$), and was significantly decreased when using the hand contralateral to tACS ($t(21) = -2.190$, $p = 0.040$, $d = 0.971$). Follow-up analysis revealed that participants that received delta-beta tACS, relative to the placebo group, chose the hard task less often following trials in which they did not receive a reward ($t(21) = -2.804$, $p = 0.011$, $d = 1.176$) and more dynamically changed their decision based on the reward of the previous trial ($t(21) = 2.297$, $p = 0.032$, $d = 0.958$). This change in decision dynamics from delta-beta tACS was also significantly different from tACS at the control frequency, theta-gamma, ($t(21) = -2.691$, $p = 0.014$, $d = 1.129$).

Conclusions: Altogether, our study discovered that participants with anhedonia exhibited rigid decision-making, perseverating on a decision that resulted in failure. After receiving tACS at a frequency designed to improve connectivity between prefrontal cortex and motor cortex, participants showed more dynamic decision-making in which they chose to conserve their physical energy after a reward loss. These findings provide evidence that delta-beta coupling plays a causal role in the decision-making process, and further suggests that delta-beta tACS could serve as a novel intervention for symptoms of anhedonia.

Keywords: Major Depressive Disorder (MDD), Transcranial Current Stimulation, Electroencephalography (EEG), Anhedonia, EEG Connectivity

Disclosure: Nothing to disclose.

P268. Chronic Corticosterone Impairs Effortful Motivation and Risky Decision-Making in Mice

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Background: Major depressive disorder (MDD) is the second-most common psychiatric disorder among US adults, affecting around a third of the population and creating the greatest burden of psychiatric care. Existing treatments for MDD fail to fully treat the disorder, necessitating the development of novel treatments. Cross-species paradigms enable high throughput testing of candidate treatments and may result in targeted treatments crossing the species barrier into clinical applications. Elevated corticosterone (CORT) is observed in people with MDD, and can be modeled by administering chronic CORT to mice in drinking water. We tested the impact of chronic elevated CORT on cross-species depression-relevant behaviors, including reduced effortful motivation as measured by a progressive ratio breakpoint task (PRBT) and impaired risky decision-making as measured by the Iowa gambling task (IGT).

Methods: Female and male C57BL/6J mice ($n = 30$, 50% female) were trained and baseline performance assessed in the PRBT and IGT. After baseline matching based on performance, half were given drinking water with CORT (35 ug/mL) and 4.5 mg/mL beta-cyclodextrin and half drinking water with 4.5 mg/mL beta-cyclodextrin. After three weeks, mice were retested in each task and in addition were assessed for changes in exploratory behavior using the behavioral pattern monitor (BPM). CORT treatment conditions were not altered during testing.

Mice were purchased from Jackson laboratories and maintained in a dedicated animal facility approved by the American Association for Accreditation of Laboratory Animal Care (AAALAC). All procedures were approved by the University of California San Diego Animal Care and Use Committee and adhered to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Chronic CORT reduced effortful motivation in mice via reduced breakpoint ($F(1,27) = 6.7$, $p < 0.05$), with no sex*CORT interaction observed. These data are consistent with our prior findings in humans that individuals with mild to moderate depression (QIDS rating scale) exhibited reduced breakpoint compared to healthy participants. Chronic CORT-treated mice also showed a reduced difference score in the IGT ($F(1,28) = 4.5$, $p < 0.05$), indicating impaired risky decision-making consistent with people with MDD. CORT-treated mice exhibited elevated punishment time ($F(1,28) = 4.5$, $p < 0.05$), and showed inappropriate responding during punishments ($F(1,28) = 5.9$, $p < 0.05$), indicative of the negative impact of such poor risky decision-making. No sex*CORT interaction was seen in the IGT. Importantly, these depression-relevant changes in performance were not impacted by CORT effects on exploration or general activity as neither measure was affected in the BPM activity, nor was any sex*CORT observed in the BPM.

Conclusions: Overall, chronic elevated CORT resulted in a depression-like behavioral profile in mice comparable to behaviors seen in humans with MDD. Specifically, chronic CORT impacted effortful motivation as measured by reduced breakpoint in PRBT and impaired risky decision-making as measured by reduced difference score in IGT, resulting in increased punishment-related behaviors. Neither total trials nor BPM activity was affected, suggesting that CORT-induced changes in effort and risky choices were not due to any sedative or maladaptive physical effects of CORT. With such depression-relevant manipulations and

behavioral outcomes, future studies can determine putative mechanisms and test potential therapies with direct predictable outcomes for patient populations.

Keywords: Chronic Corticosterone, Major Depressive Disorder (MDD), Risky Decision-Making, Translational Animal Models

Disclosure: Nothing to disclose.

P269. Understanding the Mechanisms of How a Ketogenic Diet Might Treat Bipolar Disorder

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Background: Bipolar disorder is a common and debilitating mood disorder. It affects a person's mood, concentration and energy levels, and it is characterized by aberrant GABAergic and dopaminergic signaling, as well as mitochondrial dysfunction and oxidative stress. There is recent interest in the ketogenic diet as a treatment for bipolar disorder with small case study reports of efficacy. However, the neurobiological mechanisms by which ketone bodies might ameliorate symptoms of bipolar disorder are yet to be determined. Here we investigate whether a ketogenic diet rescues manic-like behavior in ClockΔ19 mice, a mouse model with features similar to bipolar mania, and whether it leads to changes in gene expression in the ventral tegmental area (VTA).

Methods: To investigate the effects of ketogenic diet on behavior, homozygous ClockΔ19 and wild type (WT) male and female mice ($n = 5$-10/treatment, sex, genotype group) were treated with regular chow or a ketogenic diet AIN-76A-Modifled (Bio-Serv S3666) for two weeks and then throughout behavioral testing. The behavior testing battery consisted of the following tests: locomotor activity, open field, dark/light box, elevated plus maze and forced swim test. Following testing, mice were sacrificed, brains were rapidly extracted and flash frozen; punches from the VTA were taken and RNA isolated with RNeasy Plus Micro Kits (Qiagen) followed by CDNA synthesis (Invitrogen) for quantitative PCR analysis.

To examine main effects of treatment (ketogenic diet), genotype and interactions for behavioral and molecular experiments, two-way ANOVA was used, followed by Tukey's post hoc analysis.

Results: Our results show that the ketogenic diet normalized the abnormally high novelty seeking behavior in female ClockΔ19 mice, with no effect in the males in the light dark box. However, in the elevated plus maze, only male ClockΔ19 mice ($p < 0.05$) showed decreased time spent in the open arms following the ketogenic diet. In comparison the diet produced an antidepressant-like response in both males ($p < 0.001$) and females ($p < 0.05$) in the forced swim test. Interestingly ketogenic diet increased locomotor activity in female ClockΔ19 mice ($p < 0.05$) and male WT mice ($p < 0.05$). No differences were observed in the time spent in the center in the open field test following the diet. In addition, we found that ketogenic diet led to a large, significant decrease in tyrosine hydroxylase (a rate-limiting enzyme in dopamine synthesis) expression in ClockΔ19 mice ($p < 0.01$), suggesting that the diet might reduce their aberrant hyper dopaminergic transmission.

Conclusions: Our findings suggest that the ketogenic diet affects mouse behavior relevant to bipolar disorder and may reduce the hyper dopaminergic transmission in the VTA of ClockΔ19 mice.

Keywords: Bipolar Disorder, Ketogenic Diet, Ventral Tegmental Area (VTA)

Disclosure: Nothing to disclose.

P270. Normalized Attention Via Better Inhibitory Control in People With Bipolar Disorder That Use Cannabis

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Background: People with bipolar disorder (BD) exhibit poor response inhibition, driving worse attentional capacity, which likely contributes to poor psychosocial function and worse illness progression. Cannabis exposure can further impair inhibitory control and attention; however, despite the potential for compounding negative impacts of BD and cannabis use on these cognitive functions, people with BD engage in cannabis use more than any other drug, with 70% reporting cannabis use. People with BD actually report that their cannabis use ameliorates their cognitive symptoms, such as racing thoughts which could indicate failure of inhibitory control. To quantify these claims, we assessed the impact of chronic cannabis use on inhibitory control and attention in both people with BD and healthy comparison participants using the cross-species 5-choice continuous performance test (5C-CPT).

Methods: We recruited euthymic people with BD(+) and healthy comparison participants (BD-), that use cannabis (C+) or do not use cannabis (C-). Participants completed a standardized cannabis use survey including data on cannabinoid type (Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD)) and cannabis use frequency. Sustained attention and inhibitory control were assessed using the 5C-CPT, requiring people to respond to target stimuli, but inhibit from responding to rarer non-target stimuli. D prime was the primary outcome to measure attention, or sensitivity to appropriate responding (high target responding; hit rate vs. low non-target responding; false alarm rate), and false alarm rate was the primary outcome measure for inhibitory control. We performed analyses on d prime and false alarm rate using a 2X2 ANOVA with BD and cannabis use as between-subjects factors. Our main analyses compared 4 diagnostic groups: BD-/C- ($n = 21$), BD-/C+($n = 20$), BD+/C- ($n = 12$) and BD+/C+ ($n = 21$). There was no significant difference in gender distribution between groups; however, participants who reported cannabis use were significantly younger than non-users thus age was included as a covariate. We also assessed the effects of self-reported cannabis use frequency (no use, moderate use and heavy use) and self-reported cannabinoid type (no use, THC only and THC+CBD) on d prime.

Results: As predicted, people with BD+ that did not use cannabis (C-) exhibited significantly worse attention (d prime; $F(1,79) = 4.6$; $p = 0.034$; $ES = 0.055$), driven by a trend in poorer inhibitory control (false alarm rate; $F(1,79) = 3.6$; $p = 0.055$; $ES = 0.044$), relative to non-cannabis using healthy comparison participants (BD-/C-). We also observed a significant main effect of cannabis use on d prime ($F(1,79) = 4.47$, $p = 0.038$, $ES = 0.054$). Given the reports of improved cognitive function in people with BD who use cannabis, we sought to determine whether cannabis had a differential effect on attention and inhibitory control in BD+ compared to BD- participants. BD+/C- participants exhibited significantly worse attention compared to BD+/C+ ($F(1,79) = 5.97$; $p = 0.017$, $ES = 0.070$), however there was no significant difference in attention between the corresponding BD- groups. These findings appeared to be driven by significantly lower false alarm rates in the BD+/C+ compared to BD+/C- $F(1,79) = 6.44$; $p = 0.013$; $ES = 0.075$). Subsequent analyses revealed a significant effect of cannabis use frequency such that moderate, but not heavy use, was associated with better attention ($F(2,77) = 3.9$; $p = 0.024$; $ES = 0.092$) and inhibitory control ($F(2,77) = 3.13$;

$p = 0.050$; ES = 0.075). Additionally, there was moderate interaction effect between cannabinoid type and BD on d prime ($F(2,73) = 2.97$; $p = 0.058$; ES = 0.075). In BD+ participants, d prime was significantly higher in the THC-only using group compared to the no use group ($p < 0.05$); there was also a trend of higher d prime in the THC+CBD-using group relative to no use group ($p < 0.1$). There were no significant differences in d prime between cannabinoid type groups in the BD- groups.

Conclusions: Consistent with self-report reasons for use, people with BD that use cannabis (BD+/C+) exhibited better sustained attention and inhibitory control than their non-cannabis using counterparts (BD+/C-). While the latter group (BD+C-) performed worse than healthy non-using participants (BD-/C-) on the 5C-CPT, supporting the clinical sensitivity of the 5C-CPT, this difference was attenuated in those using cannabis (BD+/C+). This ameliorative effect of cannabis use on deficient attention/inhibitory control in people with BD was particularly seen in people with BD that report moderate cannabis use and primarily those that use THC, not the combination of THC and CBD. These data indicate that specific cannabis use patterns (i.e., moderate versus heavy), may have beneficial effects on cognitive dysfunction observed in people with BD, and that THC-specific products may mediate this effect. Ongoing studies in our lab are being conducted to provide directionality of these effects by 1) Determining whether there are differential effects of acute THC and CBD on attention and inhibition in people with BD, and 2) whether chronic THC or CBD improves attention/inhibitory control in our mouse model of BD.

Keywords: Bipolar Disorder, Cannabis, Attention, Inhibitory Control

Disclosure: Nothing to disclose.

P271. Whole-Brain Networks Support Activation of the Ventral Tegmental Area During Motivational Thinking With Real-Time fMRI Neurofeedback

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Background: People often attempt to motivate themselves using specific thoughts and imagery, with mixed effectiveness. Failures to successfully self-induce motivational states may be in part related to failing to effectively engage the dopaminergic brain regions that underlie motivated behavior. Real-time fMRI neurofeedback training can be a powerful tool to train individuals to link specific mental processes with brain activity. We have previously demonstrated that individuals can learn to upregulate and sustain BOLD activation in the ventral tegmental area (VTA) during neurofeedback by using self-relevant motivational thoughts and imagery.1 Further, this original study found that although individuals could not upregulate VTA BOLD activation at baseline (without neurofeedback), they could upregulate this signal without neurofeedback after completing neurofeedback training, demonstrating a transfer effect. The present study aimed to replicate these findings in a larger sample and extend these findings by examining whole-brain activity during neurofeedback (compared to partial-volume data in the original study).

Reference:

1. MacInnes, J. J., Dickerson, K. C., Chen, N. K., and Adcock, R. A. (2016). Cognitive neurostimulation: learning to volitionally sustain ventral tegmental area activation. Neuron, 89(6), 1331-1342.

Methods: In our current study (n = 29, 17 Females, Mean age = 29), participants completed a single study session during which they performed three runs of fMRI neurofeedback training and two test runs (without neurofeedback) before and after training. During the neurofeedback training task, participants were instructed to motivate themselves while increasing a thermometer display of real-time VTA fMRI signal (activate trials) or to count backwards by four from a three-digit number displayed on the screen (count trials). To examine transferability, before and after training participants completed test trials of the same conditions, but without neurofeedback during activate trials.

Results: fMRI data was preprocessed using fMRIprep and univariate whole-brain analyses were conducted in FSL. Whole-brain univariate analysis during neurofeedback training contrasting activate and count trials (activate > count) revealed significant activation in the VTA, thalamus extending into posterior cingulate, superior and medial frontal gyrus, bilateral insula, and visual cortex (cluster corrected at $Z > 2.3$, $p < 0.05$). Comparing Pre and Post-training Test runs revealed a shift from dorsal medial prefrontal cortex and posterior cingulate during Pre-Test (key regions of the default mode network) to dorsolateral prefrontal cortex, paracingulate and anterior cingulate, supramarginal gyrus, superior parietal lobule, and frontal pole during Post-Test (key regions in the dorsal frontoparietal network) (cluster corrected at $Z > 2.3$, $p < 0.05$).

Conclusions: Individuals can successfully learn to upregulate VTA activation with internally-generated motivational thoughts during neurofeedback, replicating original study findings. Upregulation invokes activation in widespread brain regions involved in reward and sensory processing, motivation, and learning. Neurofeedback training was associated with a shift from recruitment of default mode network notes to frontoparietal network nodes during attempts to regulate without feedback. Future analyses will examine how activation during neurofeedback training relates to whole-brain engagement at Pre- and Post-Test. Collectively, these findings indicate that neurofeedback training can successfully increase VTA activity and reorganize prefrontal engagement during self-motivation.

Keywords: Motivation, Real-Time fMRI Neurofeedback, Learning, Emotional Regulation

Disclosure: Nothing to disclose.

P272. Invasive and Noninvasive Causal Evidence of Amygdala Engagement to DLPFC Stimulation

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Background: While invasive modulation of amygdala activity has shown promise in treating certain refractory psychiatric cases, its widespread use among millions of treatment-resistant patients is impractical and entails inherent neurosurgery-related risks. Our recent study indicates transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex (DLPFC) provides a potential noninvasive alternative. However, given the amygdala's deep location in the medial temporal lobe, there is a critical need for definitive causal evidence to determine whether and how DLPFC stimulation engages the amygdala.

Methods: Aiming at this goal, we performed 4 studies utilizing an unparalleled combination of invasive and noninvasive stimulation and recording methods in humans. We began with Study 1 in which we delivered single-pulse intracranial electrical stimulation (iES) to the left DLPFC while concurrently recording responses in the amygdala (n = 11 electrodes) with intracranial EEG (iEEG) used in epilepsy patients being evaluated for surgery. The effect of iES to a control region, i.e., the left ventrolateral prefrontal cortex (VLPFC), in the amygdala was also assessed. To move towards

clinical translatability, we performed another two noninvasive stimulation studies by delivering TMS to the left DLPFC while recording responses in the amygdala with iEEG in epilepsy patients (n = 30 electrodes, Study 2) and with functional MRI (fMRI) in healthy individuals (N = 78 subjects, Study 3). The effects of TMS to control regions, e.g., parietal cortex, in the amygdala were also assessed. Finally, we evaluated the potential role of DLPFC-amygdala connectivity assessed with resting state functional connectivity MRI in predicting amygdala responses induced by DLPFC stimulation in same participants from Study 2 and 3 (Study 4).

Results: In Study 1, we found single-pulse iES to the DLPFC evokes significant potentials in the amygdala in early time window (100~200ms) as compared to baseline (Cohen's d = 0.67~1.54, Power = 0.51~0.99). In contrast, single-pulse iES to the VLPFC did not evoke similar amygdala response. In Study 2, we observed that single-pulse TMS to the DLPFC also evokes significant early amygdala potentials (0~100ms) as assessed with concurrent iEEG in epilepsy patients (Cohen's d = 0.52~0.81, Power = 0.79~0.99). In contrast, TMS to the parietal cortex did not evoke similar amygdala response. In Study 3, DLPFC TMS evokes strongest BOLD responses in the amygdala as assessed with concurrent functional MRI (fMRI) in healthy individuals among TMS to 11 TMS sites (Cohen's d = 0.39, Power = 0.92). Finally, in Study 4, we identified significant correlations between DLPFC-amygdala functional connectivity and early TMS-evoked potential component (30~100ms, r = 0.44, p = 0.042) and TMS-evoked BOLD responses (r = 0.28, p = 0.023) in the amygdala.

Conclusions: Together, these results provide compelling and conclusive causal evidence of amygdala engagement to DLPFC stimulation through a functional connectivity mechanism, highlighting the potential of personalized, circuit-guided noninvasive neuromodulatory therapies aimed at modulating the amygdala in treatment of psychiatric disorders.

Keywords: TMS, DLPFC, Amygdala, Intracranial EEG, Interleaved TMS/fMRI

Disclosure: Nothing to disclose.

P273. GABA/Glutamate Co-Release Allows Sub-Cellular Temporal Difference Calculations and is Abundant in the Rodent and Primate Lateral Habenula

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Background: The lateral habenula (LHb) responds bidirectionally to aversive and rewarding stimuli, and its hyperactivity is hypothesized to contribute to depression. Studies in rodents showed that inputs from the basal ganglia and ventral tegmental area to the lateral habenula co-release GABA with glutamate; the balance of GABA and glutamate at these synapses may regulate LHb activity and plasticity in downstream circuits. In the present study, we investigated whether the magnitude of co-release of GABA and glutamate in the LHb is conserved in primates and how simulated GABA/glutamate co-release affects output in neural networks.

Methods: We immunolabeled for GAD and Vglut2 in mouse (N = 14 slices, 7 mice), rat (N = 30 slices, 8 rats), and monkey (N = 23 slices, 5 monkeys) brain sections containing the habenula. To quantify overlap of GAD and Vglut2 in synaptic terminals, we developed and used a machine learning classifier that was trained with confocal images scored by a human observer. We performed neural simulations in NEURON using custom Python code.

Results: Our data indicate that the majority of GAD-expressing synaptic terminals in the mouse, rat, and monkey LHb also express Vglut2, consistent with abundant and conserved co-release of GABA and glutamate from individual terminals onto LHb neurons. In addition, there was overall more GABA/glutamate co-releasing terminals in monkeys compared to rats ($P < .05$, ANOVA), and in rats compared to mice ($P < .05$, ANOVA). Simulations showed that, in addition to reducing neuronal output, co-release of GABA with glutamate also stabilizes neuronal output over a wide range of tonic input activity levels – an effect which appears to depend on the spatial, but surprisingly, not the temporal, overlap of GABA/glutamate co-release from individual terminals. Phasic (500 ms) increases or decreases in input activity were capable of driving corresponding changes in neuronal output. Increased levels of GABA co-release transformed the phasic input into an output signal that resembled the temporal derivative of the input.

Conclusions: These data suggest that GABA co-release in excitatory inputs stabilizes the basal activity of mammalian LHb neurons, thus preventing maladaptive plasticity in downstream circuits, while also allowing phasic changes in activity to propagate and induce adaptive plasticity.

Keywords: Habenula, Mood Disorders, Reward, Glutamate GABA Co-Release

Disclosures: Biogen: Employee (Spouse/Partner), Roche: Other Financial or Material Support (Spouse/Partner)

P274. Examining Pattern of Associations Among Depression, Inflammation, and Reward Processing in Mother-Child Dyads

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Background: Depression is a leading cause of mental health burden; prevalence is increasing in both children and adults. While potential mechanisms of the transmission of depression have been extensively studied, the etiology of major depressive disorder (MDD) risk and onset remains unclear. Given increasing rates of childhood depression and its significant health burden, it is imperative to identify familial risk markers of depression early to develop targeted prevention and intervention efforts at the earliest possible point for these high risk (HR) offspring. A system of risk factors implicated in the transmission of depression involves maternal history, perceived and actual physical health, and aberrant reward circuitry. This study aimed to examine potential psychophysiological mechanisms of the transmission of depression, especially during early childhood in the context of maternal MDD.

The current study aims to clarify inflammatory marker and depression transmissibility links among depressed mothers and their offspring in early childhood. This study is preliminary, and we expect to analyze the full sample of 120 mother-child dyads by December 2023.

Methods: Sample: Participants included a community sample of 38 mothers and their biological children; though we expect our N to increase (81.6% white). Children are ages 5-6 years old (47.4% male, 52.6% female), and no more than one child per mother participated.

Measures: Depressive Symptoms: Mothers completed the Preschool Feelings Checklist (PFC), a parent-report questionnaire assessing children's depressive symptoms. Mothers also completed the Beck Depression Inventory (BDI), a 21-item self-report measure of adult depression, and the Hamilton Depression Rating Scale (HAM-D), a clinician administered measure of adult depressive symptoms, to assess continuous measures of symptomatology. Finally, mothers were categorized into MDD and HC groups based on diagnostic criteria from the SCID-5.

Body Mass Index: BMI in children has been shown to correlate with adverse health outcomes, and are related to parental BMI. We included this as a covariate in analyses using inflammatory markers.

Saliva Collection and Assay: Saliva samples (500ul) were be collected from dyads with passive drool procedures, stored in a freezer set at -20°C, and shipped to the Stressmarker Assay Service Laboratory and assayed for CRP and IL-6. IL-6 and CRP levels were log-transformed prior to analyses.

EEG Data: EEG data was recorded during the Doors Reward Task, a well-validated reward paradigm used to assess neural responses to monetary win and losses. The RewP was calculated using the difference score of response to wins minus response to loss of the pool of FCz, Fz, and Cz electrodes.

Results: Within this sample, mother depression symptoms significantly predicted child depression symptoms (BDI: $\beta(36) = 0.101$, $SE = 0.026$, $p < .005$; HAM-D: $\beta(36) = 0.204$, $SE = 0.067$, $p < .005$). In addition, mother IL6 levels predicted child IL6 ($\beta(36) = 0.548$, $SE = 0.180$, $p = .005$); these results held even when controlling for mom and child BMI. Dyadic CRP results and RewP results were not significant, and were therefore not followed up with further dyad analyses.

We then conducted stepwise mediation to assess the relations within dyads between depression, inflammation, and reward reactivity (RewP). Covariates included: child gender, mom age, child BMI, mom BMI, and MDD history. Child age was not included as a covariate as all children were 5 or 6 years old. In the model where Mom Depression Symptoms was the independent variable, Child Depression Symptoms was the dependent variable, and Mom IL-6 and Child IL-6 were mediators, there was only a direct effect of Mom Depression (BDI) on Child Depression ($\beta(38 = 0.076$, $SE = 0.036$, $p = .044$, CI = (0.002-0.150); the model with HAM-D was not significant. In the model where Mom IL-6 was the independent variable, Child IL-6 was the dependent variable, and Mom Depression was a mediator, there was only a direct effect of Mom IL-6 on Child IL-6 (β ($38 = 0.507$, $SE = 0.181$, $p = .009$, CI = (0.138- 0.877).

Of note, mother IL-6 predicted mother depression symptoms when moderated by MDD history (BDI: $\beta(38) = -6.27$, $SE = 2.758$, $p = 0.029$; HAM-D: $\beta(38) = -2.841$, $SE = 1.025$, $p = 0.009$). Similarly, mother IL-6 predicted mother RewP when controlling for MDD history ($\beta(38) = -2.49$, $SE = 1.234$, $p = 0.052$).

Conclusions: As expected, the current study found a significant relationship between mother and child depressive symptoms and mother/child IL-6. However, contrary to the current literature, we found no association between mother/child CRP. In addition, we did not find a relationship between depression symptoms and inflammatory markers, or RewP and inflammatory markers, with one notable exception: Mother inflammation predicted RewP. This is in line with previous research demonstrating inflammation is related to anhedonic depression profiles. Further analysis is warranted to improve the power of these findings.

Keywords: Depression, EEG/ERP Electrophysiology, Inflammatory Markers

Disclosure: Nothing to disclose.

P275. Sex Differences in the Neurobiology of Stress Reactivity and Emotion Dysregulation in Major Depression

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Background: Major depressive disorder (MDD) is the third leading cause of disease burden and shows prominent sex differences in risk of onset, with women having approximately two times the risk than men. Thus, understanding the differential risk will provide insights into the disorder itself and potential strategies for development of sex-dependent treatment. Some of the key brain regions implicated in MDD regulate the stress response, suggesting a loss of inhibitory control of arousal due to negative stress exposure. However, sex differences in the connectivity of the neural circuitry that is dysregulated in MDD are not completely understood. In the present study, we used two complementary functional magnetic resonance imaging (fMRI) tasks, a stress reactivity task and an emotion regulation task to identify sex differences in negative stress reactivity in MDD followed by directly challenging the circuitry to regulate their negative emotional responses. Given the importance of loss of inhibitory control in MDD, understanding sex-dependent pathophysiology of MDD has widespread implications for attenuation and prevention of disease burden, particularly in women.

Methods: 110 adults (20 healthy control (HC) women, 38 MDD women, age: 57.9 ± 2.1 years; 26 HC men, 26 MDD men, age: 57.9 ± 2.5 years) recruited from the New England Family Study underwent two fMRI tasks. In the Affect-Stress Reactivity task, participants passively viewed negative and neutral stimuli the International Affective Picture System (IAPS) in a block design. To assess active downregulation of negative reactivity, we developed an Emotion Regulation task using IAPS images matched to negative valence and high arousal from the reactivity task. Participants viewed negative and neutral images with instructions to either "Maintain" attention to image without altering emotional reaction or (for negative images only) "Decrease", i.e., reappraise, their emotional response by imagining the scene is not real or had a different outcome than depicted. This event-related paradigm was designed to recruit stress/arousal regions (during "Maintain") and inhibitory regions (during "Decrease") within the same task. fMRI data were analyzed using independent-sample t-tests in SPM12, stratified by sex and case status. (Tests for interactions with sex will be conducted when the full sample is complete.) Using a ROI-based approach, the following hypothesized brain regions/masks were included: hippocampus (HIPP), anterior cingulate cortex (ACC), hypothalamus (HYPO), amygdala (AMYG), dorsolateral and ventromedial prefrontal cortices (DLPFC, VMPFC). In parallel, analyses conducted in CONNv19b examined seed-to-voxel connectivity in stress response circuitry.

Results: During the Affect-Stress Reactivity task, we observed hyper-reactivity to negative (vs. neutral) emotion stimuli (at corrected trend levels) in inhibitory arousal regions: HIPP [$T = 3.27$, $p(FWE\text{-}corr) = 0.07$] and ACC [$T = 4.02$, $p(FWE\text{-}corr) = 0.06$] in MDD vs. HC men. However, in MDD vs. HC women, there was significant hypo-reactivity to negative emotion stimuli: HYPO [$T = 2.96$, $p(FWE\text{-}corr) = 0.04$], AMYG [$T = 3.91$, $p(FWE\text{-}corr) = 0.01$], HIPP [$T = 3.96$, $p(FWE\text{-}corr) = 0.04$], and DLPFC [$T = 3.78$, $p(FWE\text{-}corr) = 0.04$], which held when restricted to recurrent MDD women. During the Emotion Regulation task, we observed greater recruitment during Decrease vs. Maintain in inhibitory control regions in HC vs. MDD women [DLPFC: $T = 2.83$, $p(uncorr) < 0.001$] and HC vs. MDD men [dorsal ACC: $T = 2.77$, $p(uncorr) < 0.001$]. Within sex, we also observed greater AMYG-middle temporal gyrus [MTG; $T = 5.41$, $p(FWE\text{-}corr) < 0.001$], HYPO-MTG [$T = 4.22$, $p(FWE\text{-}corr) < 0.001$], and HYPO-inferior temporal gyrus (ITG; $T = 5.06$, $p(FWE\text{-}corr) < 0.001$] connectivity among MDD vs. HC women during negative emotion downregulation. Analyses contrasting MDD men vs. women yielded greater HYPO-HIPP [$T = 3.66$, $p(FWE\text{-}corr) < 0.05$] and ACC-DLPFC [$T = 3.49$, $p(FWE\text{-}corr) < 0.05$] connectivity in MDD women vs. MDD men.

Conclusions: Using complementary tasks that test both the neural circuit reactivity to negative stimuli as well as the active downregulation of negative reactivity, our findings suggest that men and women with MDD show differential dysregulation in the neural response to negative stress and inhibitory control of

arousal, with greater abnormal connectivity in MDD women vs. MDD men. In the Affect-Stress Reactivity task, MDD men showed hyper-reactivity to negative emotion stimuli in inhibitory arousal regions compared to HC men, suggesting a compensatory effort to inhibit arousal. In contrast, MDD women showed hypo-reactivity to negative emotion stimuli in this circuitry. When assessing potential loss of inhibitory control using the Emotion Regulation task, HC women showed greater recruitment of inhibitory control regions compared to MDD women, but MDD women showed hyper-connectivity of arousal regions with middle and inferior temporal gyri. Findings suggest that an inability to recruit the DLPFC during regulation may be compensated for by hyper-connectivity with other control regions.

Keywords: Sex Differences, Functional Neuroimaging, Depression, Emotional Dysregulation

Disclosure: Nothing to disclose.

P276. Shortened Cognitive Behavioral Therapy (CBT) With Computer Augmentation Increases Prefrontal Cortex Functional Connectivity in Major Depression

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Background: We have previously shown that following a treatment course in major depression (MDD) of traditional 12-16 sessions of CBT there were longitudinal changes in fronto-parietal network (FPN) connectivity resulting in increased resting state fMRI connectivity with the amygdala. The current study used a shorter (5 CBT sessions, conducted primarily remotely) protocol that was augmented by computer practice sessions at home. The goal was to determine if the same brain plasticity effects accompanied the beneficial treatment outcomes.

Methods: Following consent and psychiatric assessment, functional MRI data were collected in 60 MDD (mean ag 29.7, SD 8.9, 70% female) and 40 healthy control (HC) subjects (mean age 34.3, SD 8.1; 64% female). fMRI scans were repeated for patients following a 10 week CBT treatment course consisting of therapist administered CBT and computer training exercises. Patients received 5 sessions of manualized CBT, conducted by a skilled Beck Institute trained therapist: two sessions in-person and the other sessions remotely as well as a debriefing session. In addition, at home they completed a minimum of once/week x 10 weeks computer training program (Good Days Ahead) designed to teach and reinforce CBT principles. Additional training was available on demand.

Results: Baseline MADRS scores differed between controls (mean 0.9 +/- 1.4) and MDD (mean 25.8 +/- 5.2. MADRS scores decreased significantly (mean 14.3 +/- 8.6, $p < 0.001$) following treatment. At baseline the groups differed in connectivity with MDD showing greater connectivity of the default mode network (DMN) with left middle frontal gyrus (MFG) ($p = 0.019$). In addition, connectivity analyses conducted following treatment showed significant treatment related changes: MDD had significant decreases in connectivity of L MFG with DMN ($p = 0.01$) and significant increases in connectivity of left BA9/46 with R anterior insula ($p = 0.015$). The frontoparietal network (FPN) exhibited significant increases in connectivity with multiple limbic regions, including subgenual cingulate ($p = 0.014$), R nucleus accumbens ($p = 0.007$), L amygdala ($p = 0.029$), R amygdala ($p = 0.015$), L hippocampus ($p = 0.003$) and R hippocampus ($p = 0.04$). There were no significant correlations between change in MADRS and change in rsfMRI.

Conclusions: We found evidence that, similar to results with traditional CBT, this new shorter CBT protocol was associated with changes in connectivity between amygdala and FPN. Further, in addition to amygdala, other limbic structures also exhibited greater rsfMRI connectivity with FPN following treatment. CBT may work by strengthening connections with multiple brain regions that are involved in cognitive control, through enhanced top-down control of affective processes that are dysregulated in MDD. Thus it appears likely that a smaller number of CBT sessions representing a large decrease in resources is sufficient to achieve the brain plasticity changes required for effective top-down control of affective processes.

Keywords: Depression, CBT, Resting-State fMRI

Disclosure: Nothing to disclose.

P277. Neural Activation During Response Inhibition Task Following Acute Aerobic Exercise is Associated With Suicide Risk in Youth With Bipolar Disorder

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Background: Youth with bipolar disorder (BD) are at high risk for suicide and have high rates of suicide attempts and non-suicidal self-injury. In longitudinal cohort studies, in youth and adults, suicide attempts and non-suicidal self-injury confer equal risk for future suicide attempts. Taken together with other clinical similarities, suicide attempts and non-suicidal self-injury have been grouped within the broader construct of self-harm. Executive dysfunction has been associated with suicide risk and there have been many task-based neuroimaging studies examining self-harm in recent years. Meta-analyses of exercise trials indicate potential reductions in self-harm vs. comparison groups, although the mechanisms of this intervention remain unknown. Our group has previously reported on neurophysiologic effects of acute aerobic exercise among youth with BD in general. Here we integrate acute aerobic exercise with neuroimaging to concurrently glean insights regarding the neurophysiology of suicide risk and the putative mechanisms through which exercise mitigates risk of self-harm.

Methods: Participants were 95 youth, aged 13-20 (16.8 ± 1.8) years, 53% female, including 24 with BD and history of self-harm (BDSH+), 22 with BD and no history of self-harm (BDSH-), and 49 healthy controls (HC). HC youth had no personal or familial history of BD or psychotic disorders. All youth and their parent completed the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children- Present and Lifetime Version (K-SADS-PL) semi-structured interview to ascertain psychiatric diagnoses. Self-harm was defined as having a history of any self-injurious behavior with or without lethal intent (i.e., including suicide attempt and/or NSSI). Self-harm behaviors were assessed via interview using the Longitudinal Interval Follow-up Evaluation Self-Injurious/Suicidal Behavior Scale interview. All youth completed a Go/No-Go task during two fMRI sessions. Participants completed a 30 minute aerobic exercise session, including 20 minutes at 70% of aerobic maximum (i.e., moderate aerobic intensity), between imaging sessions on a recumbent stationary bicycle. Imaging and exercise occurred on the same day. 3T fMRI data were processed using FSL and exercise effects on BOLD fMRI activation was modeled as pre-exercise minus post-exercise activation. Whole brain analysis examined for between-group differences (BDSH+ vs. BDSH- vs. HC) in the changes between pre and post-exercise BOLD activation during the Go/No-Go trials. Age and sex were included as covariates in all analyses.

Results: Whole brain analyses of the Go trials revealed two significant clusters with peak cluster regions in the anterior cingulate gyrus ($F(2,90) = 5.05$, $p = 0.007$, $\eta p2 = 0.10$), and the caudate ($F(2,90) = 4.05$, $p = 0.011$, $\eta p2 = 0.08$). These clusters extended to regions encompassing the prefrontal cortex and subcortical structures including the putamen. In both clusters, there was a linear association characterized by significant post-exercise increase in BOLD activation within the HC group, significant post-exercise decrease in BOLD activation in the BDSH+ group, with BDSH- intermediate and not significantly different from either of the other groups. There were no significant exercise effects on findings between groups in BOLD activation on the No-Go trials.

Conclusions: This study found preliminary evidence of differential changes in neural response during a response inhibition task following acute aerobic exercise between youth with BD at risk for suicide vs HC youth. Findings were significant for Go trials but not No-Go trials. Significant clusters encompass brain regions involved in reward-processing, inhibitory control, and suicidality. Prior studies with a single neuroimaging session have shown lower neural activation associated with self-harm relative to higher neural activation in control participants. Although the BD and HC groups were matched for exercise intensity, youth with BD have lower levels of cardiovascular fitness and therefore may have higher levels of exertion during acute aerobic exercise. There is evidence that high-intensity exercise acutely worsens cognitive performance, and perhaps this sedentary group may acutely have decreased neural activation during the Go trials. In contrast, repeated sessions of exercise appear to benefit individuals at risk for suicide. These differences may be due to the timing of the neuroimaging session, the single-session of acute aerobic exercise or the unique pathophysiology of suicide risk within youth with BD. Future studies with repeated sessions of exercise are needed to parse the long-term implications on the neurophysiology of suicide risk.

Keywords: Suicide, Bipolar Disorder, BOLD fMRI Signal

Disclosure: Nothing to disclose.

P278. The mPFC Glutamate Stress Response in Humans and Non-Human Primates

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Background: Chronic psychosocial stress is associated with increased risk of psychopathology in primates. Magnetic Resonance Spectroscopy (MRS) in humans has found glutamate levels in medial prefrontal cortex (mPFC) following acute stress exposure adapt to recent chronic stress levels, which is absent in depressed individuals (Cooper et al., Nature Communications, 2021). Here, we sought to replicate and extend this in two ways: first, we tested a new sample of healthy humans with novel, whole-brain MRS sequence to determine spatial extent of glutamate response to an acute stressor. Second, we sought to reverse translate the glutamate stress response adaptation to the translational psychosocial stress model of social subordination in female rhesus macaques. Specifically, we tested the hypothesis that the change in mPFC glutamate after an acute stressor would be moderated by behavioral factors associated with social rank in monkeys.

Methods: A sample of healthy humans ($n = 19$, 20-62 yrs.) with a range of self-reported chronic stress completed two 3D-echoplanar spectroscopic imaging (EPSI) scans before and an after acute stress challenge using the Maastricht Acute Stress Task (MAST). Adult female rhesus monkeys (Macaca mulatta, $n = 17$, 13-23 yrs.) housed in small social groups, five monkeys each, were observed over ten weeks. Behavioral observations were collected using a standard monkey ethogram over five weeks to capture rates of aggression, submission, affiliation, and anxiety-like behavior. Plasma samples were collected prior to each of two mPFC MRS scans that were analyzed for cortisol concentrations. The first scan occurred after acute stress manipulation involving relocation and social isolation. The second scan occurred without stress (baseline condition). We examined changes in mPFC glutamate to total creatine (creatine and phosphocreatine) ratios (Glu/tCr) and their associations with social rank, a psychosocial factor that has previously been associated with chronic stress phenotypes seen in humans.

Results: For the human sample we observed a trend-level replication of prior work in the same area of mPFC ($r = -0.345$, $p = 0.074$) such that higher levels of chronic stress were associated with a reduced glutamate response to acute stress. Importantly, this association was not observed for other prefrontal areas (all $p's > 0.05$). For the monkey sample, cortisol was significantly elevated prior to a stress scan relative to a baseline scan ($p = 0.01$). Higher rates of submission-received, a behavioral proxy for high social rank, were significantly associated with a greater change in Glu/tCr as a result of the acute stressor ($r = 0.753$, $p < 0.001$). The association between behavioral measures of rank and change in Glu/tCr were confirmed using partial least squares regression and leave-one-subject out cross validation. A permutation test with 10,000 iterations was used for inference, and found that behavioral variables related to aggression and submission were significant predictors of change in Glu/tCr ($p < 0.001$).

Conclusions: Here we replicated and extended our prior work, showing the specificity of the glutamate stress response to mPFC in humans, and demonstrating this response in socially-housed, non-human primates. Specifically, we found mPFC glutamate levels increased following acute stress in higher-ranking monkeys, while lower-ranking monkeys exhibited a blunted glutamate response to stress in the mPFC. Implications of successful back-translation for understanding stress biology will be discussed.

Keywords: Acute and Chronic Stress, Glutamate, Spectroscopy, Non-Human Primates

Disclosure: Boehringer Ingelheim: Consultant (Self)

P279. Changes in Functional Connectivity Within Emotion Regulation Neurocircuitry Following Accelerated Intermittent Theta Burst Stimulation of the Inferior Parietal Lobule in Suicidal Depressed Patients

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Background: Difficulties regulating negative emotions have been linked to an increased risk of suicide (Rajappa et al., 2011). Suicidal ideation and behaviors have been suggested as maladaptive attempts to escape negative emotions when individuals lack emotion regulation strategies to cope with emotional distress. We are currently conducting a study to examine whether stimulation of a key region within the neurocircuitry supporting emotion regulation (ER) using an accelerated transcranial magnetic stimulation protocol (accelerated intermittent theta burst stimulation or iTBS) can rapidly reduce suicidal ideation (SI) in depressed patients with suicidality. Specifically, we are examining whether stimulation of the inferior parietal lobule (IPL), a key region

implicated in the earliest stages of emotion regulation through the reorienting of attention, can reduce SI and improve suicidality. The current study is a preliminary examination of the effects of IPL stimulation on the broader neurocircuitry supporting emotion regulation. Further, we examined whether changes in connectivity within ER networks was associated with improvement in SI and depressive symptoms.

Methods: Data presented here are from the first eight patients of our trial (data collection is ongoing). Depressed patients with active SI completed a pre-treatment resting state fMRI scan followed by individualized MRI network-guided accelerated iTBS to the right IPL (10 sessions in 1 day, 1800 pulses/session, 120% rMT). Patients completed a second resting state fMRI scan within 24-48 hours post treatment. Clinician-rated depression (HAM-D) and suicidality (Columbia Suicide Severity Rating Scale; CSSR) was assessed at baseline and post treatment. Functional connectivity (correlated time series) between the IPL target and key regions within ER circuitry [dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), anterior insula (dAI), dorsal anterior cingulate (dACC), superior temporal gyrus (STG)] was calculated following standard preprocessing using fMRIPrep and in house scripts. Correlations between significant changes in IPL target–ER circuit ROI functional connectivity (z-transformed values) and endorsement of depression (HAM-D) and suicidality (CSSR) were conducted in R.

Results: Accelerated iTBS to the right IPL resulted in significant increased functional connectivity between the IPL target and the broader ER circuitry including the right dAI ($t = 2.37$; $p = .02$, Cohen's $d = 0.57$); right VLPFC ($t = 2.21$; $p = .03$, Cohen's $d = 0.32$); left IPL ($t = 2.04$; $p = .04$, Cohen's $d = 0.30$); and right STG ($t = 2.03$; $p = .04$, Cohen's $d = 0.67$). Medium to large effect size correlations were found between changes in depression symptoms and SI and changes in IPL target functional connectivity with the right VLPFC (HAM-D: $r = .31$; CSSR-SI: $r = .42$) and right STG (HAM-D: $r = -.47$; CSSR-SI: $r = -.30$). A large effect size correlation was found between changes in IPL-STG functional connectivity and suicide severity (CSSR-SS: $r = -.55$).

Conclusions: Preliminary results from this study suggest accelerated stimulation of the right IPL with iTBS may result in the strengthening of functional connectivity along the broader ER related neurocircuitry, associated with reductions in depression symptoms and SI. Data collection for this study is ongoing, and final presented results will include data from the most updated sample.

Keywords: Suicide Prevention, Emotion Regulation, Theta Burst Transcranial Magnetic Stimulation, Rapid Depression Treatment

Disclosure: Nothing to disclose.

P280. Rumination Induction MRI Task Reliability and Change With Treatment in Adolescents

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Background: Rumination, or repetitive negative thinking, is often problematic in major depressive disorder (MDD). It also confers risk for future depressive episodes, indicating that rumination may be a key intervention target in treating MDD and preventing depression recurrence. Rumination Focused Cognitive Behavioral Therapy (RF-CBT) explicitly targets the ruminative habit, has shown promise in both adults and adolescents with MDD, and has demonstrated neurobiological changes during resting state. While adolescents with high levels of rumination show differential neural activation during the rumination blocks of a rumination induction fMRI task, we have yet to examine changes in brain activation during this task following RF-CBT. The present study 1) examined changes in brain activation during a rumination induction task in adolescents with remitted MDD following RF-CBT and 2) evaluated the reliability of the rumination task in adolescents with remitted MDD who did not receive RF-CBT.

Methods: Fifty-five adolescents ages 14-17 completed a rumination induction fMRI task and were then randomized to either RF-CBT ($n = 30$) or assessment only (AO; $n = 25$). Participants completed the task a second time either following 10-14 sessions of RF-CBT or the equivalent amount of time for the AO group. Based on a recent meta-analysis of rumination studies, we focused on five regions of interest, all of which in the left hemisphere: 1) paracingulate and anterior cingulate cortex (ACC), angular gyrus, inferior frontal gyrus (IFG), precuneus, and superior temporal gyrus (STG). We created spherical ROIs for these regions and extracted the activation values for the rumination instruction, rumination prompt, and distraction blocks of the rumination task at both time points. We assessed changes in activation in the RF-CBT group using paired-samples t-tests and assessed reliability of the task by calculating the intraclass correlation coefficients (ICCs) of the five ROIs during each of the three blocks for the AO and RF-CBT group separately.

Results: The RF-CBT group demonstrated a significant increase in activation of the left angular gyrus ($p = .02$), precuneus ($p < .01$), and STG ($p = .03$) during the rumination instruction, and in the left angular gyrus ($p < .0001$), precuneus ($p = .02$), and STG ($p = .007$) during the rumination prompt following RF-CBT. Regarding task reliability, the AO group demonstrated excellent reliability for the angular gyrus ($ICC(C,1) = .86$), good reliability for the precuneus ($ICC(C,1) = .69$) and fair reliability for the ACC and paracingulate ($ICC(C,1) = .52$), IFG ($ICC(C,1) = .51$, and STG ($ICC(C,1) = .40$) during the rumination instruction blocks. In contrast, the RFCBT group demonstrated largely poor ICCs across the five ROIs and three task blocks, which we anticipated.

Conclusions: Targeting rumination leads to significant changes at the neurobiological level, particularly involving the angular gyrus, precuneus, and STG. Importantly, we demonstrated that the rumination induction task has fair to excellent reliability among individuals who do not receive an intervention that explicitly targets the ruminative habit, whereas reliability of this task is largely poor in the context of RF-CBT. This has meaningful implications in longitudinal work, particularly treatment studies, as it allows for greater confidence in attributing whether neurobiological changes are due to treatment versus noise.

Keywords: Rumination, Test-Retest Reliability, Functional Neuroimaging, Adolescence

Disclosure: Nothing to disclose.

P281. Multidimensional Assessment of Fatigue in Depressed Adults: Associations With Childhood Trauma and Potential Sex Differences

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Background: Fatigue is a common symptom of major depressive disorder that is associated with impairments across multiple domains of life. The multidimensional fatigue inventory (MFI) was developed to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. However, recent studies have raised concerns about the five-dimensional factor structure of this scale. Early life adversities, including childhood traumatic experiences, have been linked to diagnoses of depression as well as chronic fatigue syndrome.

However, the association between childhood traumatic experiences and symptoms of fatigue in adults with depression is not well understood. Therefore, in a trans-diagnostic sample of adults with depression, we evaluated the psychometric properties of MFI, and evaluated its association with childhood trauma and potential sex differences.

Methods: Adults with depression in the ongoing Texas Resilience Against Depression (T-RAD) study with MFI data at baseline visit were included (n = 666). Fatigue was measured with MFI and childhood traumatic experiences were assessed with Childhood Trauma Questionnaire (CTQ). Confirmatory factor analyses (CFA) were used to validate the 5-factor structure of MFI. Exploratory factor analyses (EFA) were used as the model fit on CFA were suboptimal. Association of the factors from EFA with CTQ were evaluated for the full sample as well as stratified by biological sex. Linear regression analyses with CTQ domain-by-sex interactions were used to evaluate statistically significant differences in association after controlling for age, race and ethnicity.

Results: Participants had an average age of 42.9 [standard deviation (SD) = 15.8] years and was predominantly female (n = 556, 83.7%). The model fit statistics for the 5-domain structure of MFI was suboptimal (Goodness of Fit Index = 0.81, RMSEA = 0.10, Comparative Fit Index = 0.81). Three factors were identified on EFA that corresponded to general/physical fatigue, mental fatigue, and reduced motivation/activity. All three domains were significantly correlated with symptoms of depression and anxiety with highest coefficients noted for the mental fatigue domain. Domains of CTQ were correlated with general/physical fatigue domain ($r = 0.14$-0.21, all $p < 0.005$) but not with mental fatigue and reduced motivation/activity domains (all $r < 0.10$). In exploratory linear regression analyses, there was a significant CTQ domain-by-sex interaction in predicting general/physical fatigue ($p < 0.05$) with two-fold stronger association between CTQ domains and general/physical fatigue among males as compared to females.

Conclusions: The MFI had a three-factor structure in T-RAD, with these factors providing estimates of distinct aspects of fatigue-related impairments. Childhood trauma experiences were associated with general/physical fatigue only, with two-fold stronger associations among males as compared to females.

Keywords: Fatigue, Depression, Childhood Trauma, Psychometric Properties

Disclosures: Neurocrine, Navitor/Supernus, Janssen Research and Depression: Contracted Research (Self). Eleusis, Janssen Global Services, Janssen Scientific Affairs, Boehringer Ingelheim, Guidepoint Global, IQVIA, Worldwide Clinical Trial, Vicore Pharma: Consultant (Self). NACCME, Global Medical Education, Clinical Care Options, Medscape/WebMD, H C Wainwright and Co: Honoraria (Self).

P282. Disease Progression Modeling of Cortical Macrostructure in Treatment-Resistant Depression

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Background: Approximately 30% of patients with major depressive disorder (MDD) fail to respond to standard antidepressant treatment (i.e., treatment-resistant depression [TRD]). Although repetitive transcranial magnetic stimulation (rTMS) is effective for TRD, large individual differences exist in its therapeutic response, accruing from the heterogeneous pathophysiology behind TRD. Some studies have noted the recurrence of depressive episodes is associated with cortical macrostructural changes (Zaremba et al., 2018, Lemke et al., 2022). Given that TRD is associated with the recurrence of episodes (Murphy et al., 2017), there is the possibility that TRD may be associated with more disease progression. The Subtype and Stage Inference (SuStaIn) algorithm, an unsupervised machine learning methodology, is able to reveal distinct disease subtypes with separate progression trajectories (Young et al., 2018). Here, we applied the SuStaIn algorithm to perform biotyping of TRD and explored the associations between each biotype and clinical characteristics including rTMS treatment response.

Methods: This study was approved by the Keio Certified Review Board and registered in the Japan Registry of Clinical Trials. All participants provided written informed consent. In this study, we included 116 patients with TRD (44.9 ± 12.8 years old, 50 females [43%]) and 54 healthy controls (HC) (37.1 ± 15.1 years old, 26 females [48%]). They underwent T1-weighted magnetic resonance imaging (MRI) scans using a Siemens Prisma 3T MRI scanner. Based on a recent systematic review on structural MRI studies on TRD (Miola et al, 2023), we computed the cortical thickness and volume of 8 cortical regions on both sides using FreeSurfer 6.0. These metrics, controlled for age and sex, were then transformed into Z-scores using HC data. Subsequently, we applied the SuStaIn algorithm to estimate and cross-validate the stages and subtypes of all subjects. We selected the optimal number of subtypes by cross-validation information criterion and similarity between subtypes. Among the included patients, 99 (85%) patients with TRD underwent rTMS treatment targeting the bilateral dorsolateral prefrontal cortex. Response was defined as an improvement of 50% or more compared to the baseline score in the Montgomery-Åsberg Depression Rating Scale (MADRS) and remission as a MADRS score ≤ 10 at the time of final treatment. MADRS items were converted into 4 factors: Sadness, Neurovegetative, Detachment, and Negative thoughts. For statistical analyses, we examined group differences in clinico-demographics including rTMS treatment response by t-tests for continuous variables and Chi-squared tests for categorical variables. We also explored correlations between the stages and other variables within each subtype employing the Spearman's rank correlation tests. As stages represent estimated disease progression, the HC cohort (n = 23) with stages more than one and TRD cohort (n = 31) with stage zero were excluded from the statistical analyses.

Results: The SuStaIn algorithm discerned the two distinct subtypes. In the estimated progression, subtype1 (cortical thickness [CT] type) (n = 48, 41 completed rTMS sessions) displayed a mild cortical thinning in frontal areas at first, followed by thinning in temporal, and, markedly, insular areas. CT type also showed cortical volume reduction in the right insula. In contrast, subtype2 (cortical volume [CV] type) (n = 32, 27 completed rTMS sessions) manifested a marked decrease in cortical volume, followed by relatively slight reduction in cortical thickness in the estimated progression.

Patients with subtype1 (CT type) experienced a later illness onset than those with CV type ($p = 0.02$) with no significant group difference in age ($p = 0.12$). All patients (n = 5) aged over 60 at onset were assigned to CT type, and notably, had comorbid cardiometabolic syndrome. There was no significant difference in baseline total MADRS scores between CT and CV types ($p = 0.81$). However, among the four factors of MADRS, the baseline score of the negative thoughts factor was higher in CT type than CV type ($p = 0.003$). The baseline total MADRS score did not show significant correlation with stage for each subtype.

No significant relationships were found between the subtypes and rTMS treatment response. The changes in total score of MADRS following rTMS treatment did not correlate with stage in each subtype nor were they significantly different between the subtypes ($p = 0.06$). Changes in the four factors did not show significant group differences.

Conclusions: This study detected the two subtypes within TRD: one was classified as cortical thinning type (CT type) and the other as reduced cortical volume type (CV type). The difference in the negative thoughts factor between the subtypes suggests the role of cortical thickness of the insula on the negative thoughts. This result is in line with previous findings that showed that the insular cortex is involved in emotional and cognitive functions and depressive rumination. Furthermore, the CT subtype was associated with a later onset of depression than the CV type, which may be attributable to the different nature of the disorder related to the timing of the onset of depression. On the other hand, no significant relationships between rTMS response and the SuStaIn outputs suggest that biotyping with only the cortical macrostructures may not account for treatment response to rTMS, warranting future research with multimodal biometrics.

Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS), Structural MRI, Treatment-Resistant Depression, Machine Learning Clustering

Disclosure: Nothing to disclose.

P283. Oxidative Stress and Aging With Bipolar Disorder

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Background: Oxidative stress is a proposed mechanism in bipolar disorder (BD) evidenced by preclinical, postmortem, and peripheral studies. However, evidence of oxidative stress in the brain in vivo in individuals living with BD has been inconsistent. We aimed to test whether midlife adults living with BD have increased markers of oxidative stress in cortico-limbic network brain regions as compared to healthy individuals, and to examine the impact of age on these relationships.

Methods: We recruited 53 adult participants ages 35-65 (mean = 49), including 23 individuals living with BD and 30 healthy control participants (HC). A fasted 7 Tesla MRI scan with magnetic resonance spectroscopy was collected to assess a marker of oxidative stress (glutathione) in the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (VMPFC), and left dorsolateral prefrontal cortex (DLPFC). Measures of demographic and clinical features were collected, including age and duration of illness, and peripheral glutathione levels were measured from a fasted blood draw.

Results: Age was negatively correlated with glutathione level in the ACC ($r = -0.29$, $p = 0.034$), consistent with greater oxidative stress in older adults. Independent of age, glutathione levels in the ACC were lower in the group with BD as compared to the HC group ($\beta = -0.41$, $p = 0.027$), consistent with greater oxidative stress in BD. Post hoc within group analyses showed a significant correlation between age and ACC GSH in BD ($r = -0.58$, $p = 0.004$) but not in HC ($r = -0.23$, $p = 0.226$). Within the BD group, duration of illness was negatively associated with glutathione level in the DLPFC only. Peripheral glutathione levels did not correlate with glutathione levels in any of the brain regions tested.

Conclusions: Our findings demonstrate that brain glutathione levels are decreased in BD and with age, locally in the ACC, and that assessment of brain glutathione levels provides unique information not captured by peripheral measurement. These results are consistent with increased oxidative stress as a mechanism in BD in midlife, with potential implications for age-informed targeted treatment strategies.

Keywords: Bipolar Disorder, 7T MRS, Glutathione, Aging

Disclosure: Nothing to disclose.

P284. Resolution of the Explore-Exploit Dilemma, Attempted Suicide, and Suicidal Thinking in Daily Life

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Background: Decision-making involves a form of mental exploration of one's internal states and choice options. During search for solutions in a suicidal crisis, people choose an action to pursue (exploit) after evaluating (exploring) the options under current consideration. From the formal framework of reinforcement learning (RL), this process represents the exploration-exploitation dilemma. Suicide attempts have been linked to trait-like neurobehavioral impairments in value-based decision-making, but the unique impacts of a crisis state on decision-making are understudied. Clinical theory describes this state as myopic and inflexible and commonly refers to it as cognitive constriction, but offers little insight into the neurobehavioral mechanisms that underlie it. In contrast, RL makes strong normative theory-based predictions about decision-making under uncertainty and is well-suited to study alterations that may bias choices toward suicide over plausible alternatives. Here, we combined computational modeling and ecological momentary assessment (EMA) to examine how demographically and diagnostically diverse adults across two high-risk samples resolve the exploration-exploitation dilemma. We also exampled how this behavior relates to their suicide attempt history and suicidal ideation in daily life. We hypothesized that (1) suicide attempters would exhibit altered short-term reinforcement-based adjustment and (2) greater alterations in the explore-exploit transition, with these deficits scaling based on the severity of prior suicidal behavior. We further expected that (3) these indices of task behavior would be linked with prospective suicidal ideation in daily life.

Methods: Sample 1: 171 adults between the ages of 18 and 62 (mean age: 30.55, 79% female). Of these 171 participants, 54 were healthy controls and 117 were diagnosed with borderline personality disorder (BPD). Individuals with BPD comprised three groups: (1) no lifetime history of suicide attempts; (2) a history of at least one low-lethality attempt; (3) a history of at least one high-lethality attempt. In addition to the experimental paradigm described below, a subset of these participants also completed a 21-day EMA protocol assessing daily instances of suicidal ideation.

Sample 2: 143 adults between the ages of 49 and 80 (mean age: 62.03, 57% female). Of these 143 participants, 43 were healthy controls and 100 were diagnosed with a unipolar, non-psychotic major depressive disorder (MDD). Individuals with MDD comprised four groups: (1) no lifetime history of self-injurious behavior, suicidal ideation, or suicide attempts; (2) suicidal ideation with a specific plan, but no lifetime history of suicide attempts; (3) a history of at least one high-lethality suicide attempt; (4) a history of at least one low-lethality suicide attempt.

Experimental paradigm and computational model: All participants completed a well-validated 1-dimensional continuous explore-exploit task referred to as the Clock task. They were instructed to extensively explore on each trial to uncover the most rewarding options. Clock task behavior was fitted with the SCEPTIC computational model (developed and validated in our lab across multiple samples) that employs learning elements implemented as Gaussian temporal basis functions to represent a time-varying instrumental contingency. SCEPTIC applies updates and makes choices at the trial level while selectively maintaining action values by allowing for forgetting of the values not chosen on the current trial. Model parameters were fit to participant data

using an empirical Bayesian procedure implemented within the Variational Bayesian Analysis toolbox. Shannon's entropy, or the information content reflective of the number of likely action values in one's environment, was estimated to examine the emergence of the global value maximum that facilitates the transition from exploration to exploitation. Due to a clustered structure of behavioral observations with the trials nested within subjects, we fit multilevel regression models to trial-level data using restricted maximum likelihood.

Results: Across both samples, a history of high-lethality suicide attempts was associated with impaired levels of short-term reinforcement-based behavioral adaptation (i.e., their behavior was not properly informed by recent feedback), especially after reward omissions (ps < .01). Further, altered (reduced) exploration, but not exploitation, was linked with higher suicidal ideation in daily life ($p = .001$). The findings were robust to sensitivity checks accounting for plausible confounds.

Conclusions: While considering solutions in a crisis, biased learning from one's actions may lead to attempting suicide over the more valuable in the long-run alternatives. The association between reduced exploration (particularly following an adverse outcome) and increased suicidal ideation may imply that in a crisis, suicide could be deemed a solution when a limited range of alternatives are under consideration. If the extent of exploration turns out to be a consistent behavioral characteristic in daily life, our findings point to the potential benefit of a compensatory strategy that could strengthen the capacity of individuals at risk to refrain from engaging in suicidal behavior during a crisis, specifically when the ability to generate or evaluate new solutions is compromised.

Keywords: Suicide, Explore-Exploit Dilemma, Computational Modeling, Value-Based Decision Making, EMA

Disclosure: Nothing to disclose.

P285. A Network Control Theory Approach to Relapse Prediction in Major Depressive Disorder: A Report From the CAN-BIND-1 Trial and Wellness Monitoring Study

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Background: Major Depressive Disorder (MDD) is a complex mental health condition characterized by heterogeneous symptom profiles and a high risk of relapse. Understanding the dynamic interplay of symptoms within MDD and their association with relapse may enable personalized relapse prevention. We investigated the degree to which instability of depressive symptom networks relates to depressive episode relapse in MDD.

Methods: We analyzed serially-collected mood rating data from 43 patients who achieved remission in an open-label trial of escitalopram with or without aripiprazole augmentation (the Canadian Biomarker Integration Network for Depression 1 trial; CAN-BIND-1; NCT01655706), and subsequently underwent longitudinal follow-up in the CAN-BIND Wellness Monitoring study. Clinicians assessed ten depressive symptoms every two weeks during CAN-BIND-1 and every eight weeks during CAN-BIND-Wellness with the Montgomery-Åsberg Depression Rating Scale (MADRS). For each patient, we computed an index called minimum control energy (MCE), which quantifies the degree to which a depressive symptom network is resistant to perturbations. We tested the association between MCE and relapse risk in Cox proportional hazards models.

Results: Higher MCE was associated with a lower risk of relapse during the follow-up period (hazard ratio 0.56; $p = 0.0123$; $c = 0.66$ [SE 0.062]). Patients with high MCE exhibited symptom networks characterized by dense, yet indirect, connections between symptoms. Conversely, low MCE was associated with either limited connectivity or higher direct connectivity between symptoms.

Conclusions: Network control theory may inform relapse prediction in MDD and should be considered a potential target measure for future longitudinal monitoring studies in depression. Specifically, depressive symptom networks with higher control energy may be associated with greater stability and lower relapse risk. That this was related to higher degrees of indirect connectivity between symptoms also implies the potential for the development of personalized interventions to maintain euthymia or restore it early, before full relapses occur.

Keywords: Network Control Theory, Major Depressive Disorder (MDD), Relapse Biomarkers

Disclosure: Nothing to disclose.

P286. Drift-Diffusion Modeling of Attention Shifting During Frustration: Associations With State and Trait Irritability

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Background: Irritability, an increased proneness to anger relative to peers, is a transdiagnostic symptom commonly occurring in many mood and anxiety disorders. Irritability is conceptualized as aberrant behavioral and emotional responses to frustrative nonreward, defined as the emotional state induced by the failure to receive an expected reward. Past research on irritability have used a cued-attention task with rigged feedback, called the Affective Posner (AP) Task, to induce frustrative nonreward and assess attention shifting during frustration (Deveney et al., 2013, Deveney, 2019, Tseng et al., 2017; 2018). However, previous studies have not been successful in uncovering links between individual differences in irritability and traditional reaction time (RT) metric in the AP task (e.g., Tseng et al., 2018). This is potentially because past research has not considered the speed-accuracy trade-off during this task, especially unpacking it using a theory-driven computational approach. Computational modeling, by allowing for the estimation of more nuanced parameters reflecting latent cognitive processes, has the potential to improve our mechanistic understanding of the cognitive mechanisms of irritability. A detailed understanding of the cognitive processes associated with irritability, particularly under emotional contexts, may reveal potential targets for mechanism-based interventions. Therefore, the aim of this study was to apply a drift-diffusion model (DDM) to the AP task to determine if DDM parameters are useful in discovering the cognitive mechanisms underlying individual differences in irritability.

Methods: A sample of 87 young adults ages 18-25 years (Age: $M \pm SD = 21.29 \pm 2.27$; 62.22% females; 20% Asian, 8.89% African American, 63.33% White/Caucasian, 7.78% Multi-race) completed the AP Task (Deveney, 2019). Participants rated their state irritability using a 9-point Likert scale during the task, and their trait irritability over the last 2 weeks using the Brief Irritability Test (BITe), and over the last 6 months using the Affective Reactivity Index (ARI). We used hierarchical DDM (Wiecki et al., 2013) to estimate drift-diffusion parameters (i.e., threshold separation, drift rate, non-decision time, and starting bias) via the Bayesian modeling of participants' RT during the task. Different models were tested in which DDM parameter(s) were allowed to vary as a function of trial type, i.e., valid (in which the cue and target were in the same location and attention

shifting was not required) vs. invalid (in which the cue and target were in opposite locations and attention shifting was required) and run type, i.e., non-frustrating (without rigged feedback) vs. frustrating (with rigged feedback) runs. Then, we determined the best model fit through the comparison of deviance information criterion (DIC), posterior mean deviance (d), and the effective number of parameters (pD). Linear regression models were used to test the hypothesis that DDM parameters better predict state and trait irritability than traditional RT metrics. Models accounted for age and gender.

Results: The model in which drift rate was allowed to vary by trial type (valid vs. invalid) and the non-decision time was allowed to vary by run type (non-frustrating vs. frustrating) best fitted the data. State irritability was predicted by (1) faster non-decision time during frustrating runs ($\beta = -21.08$, $p < 0.01$), reflecting faster visual and perceptual encoding of the stimuli and motor execution and (2) lower drift rate during invalid trials ($\beta = -0.92$, $p < 0.05$), reflecting lower processing efficiency during attention shifting, above-and-beyond traditional RT metrics ($R2 = 0.44$; Adj. $R2 = 0.36$; $F(8, 51) = 5.09$, $p < 0.01$). Regression models using measures of trait irritability as the outcomes were not significant, although BITe and ARI scores were negatively correlated with non-decision time during frustrating runs ($rs = -0.25$ and -0.22 respectively, $p < 0.05$).

Conclusions: DDM parameters, reflecting latent cognitive processes, were linked to individual differences in state irritability. More specifically, higher state irritability (i.e., self-rated frustration) during the task was related to faster non-decision time during the frustration condition, indicating that either encoding and/or response execution times were reduced when participants were frustrated. Furthermore, higher state irritability was associated with worse efficiency in processing invalid trials, which may reflect impairments in attention shifting under an affective context. The ability to flexibly deploy cognitive resources in response to changing environmental demands contribute to emotional regulation, and this mechanism may be impaired in individuals with high irritability, which may increase inappropriate responses to frustration and temper outbursts. These findings have potential clinical implications, suggesting that cognitive flexibility or attention shifting in a frustrating context may be intervention targets for individuals with high irritability. The utility of DDM awaits validation from in populations with clinical levels of irritability. Future experimental work or clinical trials are necessary to clarify the causal associations between DDM parameters and state and trait irritability.

Keywords: Irritability, Attention Shifting, Frustration, Drift Diffusion Model

Disclosure: Nothing to disclose.

P287. Predicting Treatment Outcomes From Questionnaire Data: A Feasibility Study

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Background: In recent years, predictive modeling has gained significant traction in various healthcare fields. However, in the realm of psychiatry, predictive scoring has not been as widely adopted, experiencing most of its growth in the past five years. The potential of prediction models in psychiatry lies in their ability to enhance clinical decision-making with structured tools and foster personalized treatment approaches. Questionnaires, as a low-cost intervention, offer a more structured approach than data from electronic health records, making them a promising target for the initial development of predictive models in psychiatric care. In this study, we explore the feasibility of utilizing questionnaire data and machine learning algorithms to predict treatment outcomes for multiple patients, aiming to pave the way for more informed and tailored psychiatric care.

Methods: Psychometric questionnaires were collected from $N = 1497$ inpatients at admission and discharge at McLean Hospital. The questionnaire data included demographic information, the 24-item Behavior and Symptom Identification Scale (BASIS-24), the Quick Inventory of Depression Severity (QIDS), Snaith-Hamilton Anhedonia Pleasure Scale (SHAPS), McLean Screening Instrument for Borderline Personality Disorder (MSI) and the PTSD Checklist for DSM-V (PCL-5). 144 features from these questionnaires were to train a machine learning model predicting depression severity measured by QIDS at discharge. A machine learning pipeline consisting of a mean imputation, a standard scaler and an automatic relevance determination regression was used to predict QIDS scores at discharge. The model was evaluated using nested 10x10 K-Fold cross-validation and optimized using a Bayesian optimization strategy. A permutation test was performed to assess whether model predictions performed above chance. Feature importance was analyzed using permutation importance and Bayesian regression models.

Results: Our model was able to predict QIDS at discharge from the psychometric admission data with a mean absolute error of 1.96 and Pearson correlation of 0.79 between predicted and true values for QIDS score at discharge. The permutation test revealed a highly significant correlation between predicted and true values ($p < 0.001$). Among highly predictive items were age and items related to concentration, general functioning, suicidality and sleep. Further analysis of the different predictors revealed strong relationships between QIDS at discharge and suicidality (CI: 0.25 - 2.27), sleep (CI: 0.31 - 2.37), general functioning (0.25 - 2.03), but not concentration (CI: -1.27 - 1.52).

*CI: Bayesian Credibility Interval

Conclusions: The findings of our study demonstrate the feasibility of predicting scores at discharge based on scores at admission, revealing promising potential for predictive modelling in the psychiatric context. However, further investigations are warranted to thoroughly examine the validity and reliability of our predictive model, particularly in diverse subgroups. In order to establish the robustness and generalizability of our model, replication in an external sample is essential. Additionally, to enhance the predictive power and accuracy of the model, the incorporation of other relevant data types may be necessary, expanding the scope of information and enriching the predictive capabilities of our approach. Through continued research and refinement, predictive models have the potential to significantly impact psychiatric care, facilitating better patient outcomes and personalized treatment strategies.

Keywords: Clinical Prediction, Psychometric Tests, Computational Psychiatry

Disclosure: Nothing to disclose.

P288. Predicting the Effect of ECT and Ketamine/Esketamine on Suicidal Ideation Using the Personalized Advantage Index

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Background: Depression is a leading cause of disability across the world. Suicidal ideation, a frequent symptom of a major depressive episode, is also one of the most important predictors of completed suicide. Both electroconvulsive therapy (ECT) and ketamine have been reported to have anti-suicide effects. We retrospectively applied a machine learning approach to a cohort of patients treated with ECT or ketamine/esketamine to determine

whether treatment could be optimized on the basis of pre-treatment patient characteristics. The model used demographics, prior treatment history, the pretreatment Quick Inventory of Depressive Symptomatology (QIDS) total score and the QIDS SI item to predict treatment response to each modality. These predicted responses were used to calculate a Personalized Advantage Index, PAI, and determine the optimal treatment for each patient. We hypothesized that subjects who received optimal treatment based on the PAI would have a significantly greater reduction in suicidal ideation after treatment than those who received the sub-optimal treatment.

Methods: Depressed subjects were retrospectively chosen from the patient cohort at McLean Hospital that underwent treatment with ECT (n = 2458) or ketamine/esketamine (n = 222) between 2012 and 2022. Baseline demographics, treatment history and symptom severity data, including pre and post-treatment QIDS scores were extracted from the hospital's Epic database. 222 subjects from each treatment group were propensity score matched based on baseline QIDS score. A series of random forest regressors (RFR) were trained to predict end-QIDS SI score using a leave-one-out cross validation to estimate a personalized advantage index (PAI) of suicidal ideation symptom reduction. The SI item in the post-treatment-QIDS for subjects that received treatment identified as optimal by the RFR predictions were compared to those who received the predicted non-optimal treatment by means of a two-sample, two-tailed t-test.

Results: After matching, the baseline QIDS scores (p = 0.95) and post-treatment-QIDS scores (p = 0.33) did not differ between the ECT and ketamine groups. ECT was predicted to be optimal for 238/444 patients of which 126 received ECT. Ketamine/esketamine was predicted to be optimal for 206/444 of which 110 received ketamine/esketamine. Subjects who received optimal treatment based on their PAI had a significantly lower post-treatment QIDS SI score than subjects who received non-optimal treatment as determined by their PAI for SI (mean difference = 0.23, t = 3.00, p = 0.003, Cohen's D = 0.29). There was no difference in the change in overall QIDS score between the two groups after treatment (p = 0.15).

Conclusions: This retrospective study applied a machine learning analysis of pretreatment patient characteristics to predict whether ECT or ketamine/esketamine was the optimal treatment for an individual subject's SI as measured by the QIDS. When the subjects who received their predicted optimal treatment were compared to those who received the non-optimal treatment, the post-treatment QIDS SI score was significantly lower for the group of subjects who received optimal treatment. Notably, there was no difference in the change in overall QIDS score between the two groups after treatment.

These results also confirm the literature that reports anti-suicide effects for both treatments. They also suggest that a machine learning approach based on pretreatment patient profiles may have utility in guiding treatment selection. Additional prospective studies are indicated to confirm these results and explore whether the model can be refined to improve its predictive value.

Keywords: Suicidal Ideation, Machine Learning, Electroconvulsive Therapy, Ketamine/Esketamine

Disclosure: Roche: Employee (Spouse/Partner).

P289. Unsupervised Neurobiologically-Driven Stratification of Clinical Heterogeneity in Treatment-Resistant Depression

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Background: Major depressive disorder (MDD) is a heterogeneous psychiatric condition embracing various and coexisting symptoms, with 30% of patients not adequately responding to treatments [1]. Despite increasing efforts in discovering MDD biomarkers, their prognostic value is still puzzling due to the weak consistency between clinical outcomes and the underlying neurobiology [2]. Stratifying patients based on neurobiological data could help in unveiling disease subtypes and tailoring personalised treatments. Using an unsupervised machine learning approach, we aim to define biologically-driven MDD clusters based on multimodal structural neuroimaging data. The identified clusters are then clinically profiled for treatment-resistant depression (TRD), depressive symptomatology, and childhood trauma.

Methods: T1-weighted and diffusion tensor images were acquired from 102 MDD patients. TRD was defined as a failure to respond to at least two antidepressant treatments [3]. In 64 patients, depressive symptomatology was rated on the Beck Depression Inventory–Short Form (BDI-SF), and composite scores for different domains (Negative Self-Esteem, Anergy, and Dysphoria) were derived [4]. Childhood trauma was evaluated with the Childhood Trauma Questionnaire (CTQ). Clustering analyses were performed using a stability-based relative clustering approach within a cross-validation framework [5]. Clustering analyses were performed with extracted tract-based fractional anisotropy (TBSS, FSL), cortical thickness, and regional measures of grey matter volumes (CAT12). Gaussian mixture model was implemented for clustering, and support vector machine was trained to learn and predict clusters' labels through a 10x2 repeated cross-validation. By iterating over a number of clusters from 2 to 5, the best clustering solution that minimised the stability (i.e., prediction error) was identified. Statistical significance was assessed by 10000 simulations from a single null Gaussian distribution. A parallel grid search was implemented for hyperparameter tuning. Confounding effects of age, sex and total intracranial volume were controlled in cross-validation. The clinical relevance of the discovered clusters was explored with a MANOVA, considering clusters' labels as fixed factors and BDI-SF and CTQ domains as dependent variables. Linear discriminant analysis (LDA) was performed to assess their discriminative power. The proportion of TRD patients between clusters was investigated with Chi-square test.

Results: The stability-based clustering approach identified 2 clusters with normalised stability = 0.316 (p < 10e-9), differentiable with 67% of accuracy: 1) one cluster (n = 59) was associated with a higher proportion of TRD compared to the other ($\chi2(1) = 7.00$, p = 0.008), and higher scores of energy-related depressive symptoms, minimization, emotional neglect and history of childhood abuse and emotional neglect (MANOVA: Wilks' lambda = 0.68, F(9,50) = 2.64, p = 0.014); this cluster showed a widespread reduction in cortical thickness and volumes, along with fractional anisotropy in the right superior fronto-occipital fasciculus, stria terminalis, and corpus callosum (pFDR < 0.05; 2) the second cluster (n = 43) was associated with cognitive and affective depressive symptoms and thicker cortices and wider volumes compared to the other.

Conclusions: With a stability-based clustering approach, we demonstrated that structural neuroimaging can uncover depression subtypes indicative of clinically meaningful insights. The high-TRD cluster is associated with energy-related depressive symptomatology and minimization of childhood trauma, whereas the low-TRD subtype is characterised by cognitive and affective depressive symptomatology. A multimodal stratification can help in understanding the pathophysiological mechanisms of MDD and improve personalised healthcare in a precision psychiatry perspective.

Keywords: Major Depressive Disorder (MDD), Machine Learning Clustering, Treatment-Resistant Depression, Structural MRI, Multimodal Neuroimaging

Disclosure: Nothing to disclose.

P290. Habenula and Paraventricular Thalamus Connectivity in Healthy, Depressed, and Anxious Adolescents

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Background: Adolescence is a vulnerable developmental period when symptoms of psychiatric illness and substance abuse often first emerge. Frequently, these symptoms entail hypersensitivity to threats, pain, and other negatively valenced stimuli. Extensive work in rodents and non-human primates has identified two midline subcortical structures, the habenula (Hb) and paraventricular thalamic nucleus (PVT), as highly responsive to aversive environmental stimuli, important for harm avoidance behaviors, and key pharmacological sites for many drugs. However, the relationship between these important structures remains poorly understood, and their small size has limited in vivo research, with no studies to date directly examining human PVT function. Extending our prior work to precisely map human Hb connectivity and its relationship to depression symptomatology, we jointly examined Hb and PVT function in two clinically diverse cohorts of adolescents.

Methods: Our study included 122 adolescents recruited locally and 300 adolescents from the public Adolescent Brain Cognitive Development (ABCD) study. Local subjects were ages 12-19 with mood and anxiety symptoms (99) or healthy controls (23). ABCD subjects were ages 11-13 (Year 2 timepoint) with symptoms of depression (100), anxiety (100), or healthy controls (100). All subjects completed diagnostic assessment and questionnaires to assess depression and anxiety severity. Resting-state fMRI was collected at 3T using similar protocols. Local data preprocessing followed Human Connectome Project (HCP) pipelines, including ICA- and aCompCor-based denoising, bandpass temporal filtering (0.1-0.01Hz), and multimodal surface matching (MSMAll) for robust cortical alignment to a group-derived template. ABCD data were preprocessed by the DCAN study site using pipelines similar to the HCP. Subject-level Hb connectivity seeds were optimized using our previously published methodology. A template PVT connectivity seed was obtained from the Morel Thalamus Atlas.

Subject-level resting-state functional connectivity was calculated as z-transformed correlation maps between mean timeseries from bilateral seed regions, extracted from unsmoothed resting-state fMRI data, and minimally smoothed (4mm FWHM) whole-brain fMRI data in 32k CIFTI space. Group-level FC maps were generated via FSL PALM using threshold-free cluster enhancement (TFCE) and non-parametric sign-flipping (one-sample tests) or permutation tests (two+ sample tests and correlations). Familywise error rate (FWE) correction was applied to all statistical tests. Due to acquisition, age, and design differences, the local ($N = 122$) and ABCD ($N = 300$) cohorts were treated separately throughout analyses. All results were adjusted for age and sex and considered statistically significant at pTFCE-FWE < 0.05, with exploratory findings also examined at relaxed puncorrected<0.005 and unthresholded levels.

Results: Adolescent Hb connectivity encompassed subcortical midbrain/brainstem monoamine nuclei and the ventral striatum as well as "task-positive" cortical areas, including primary sensory cortices and the salience network. These results are consistent with our previous Hb connectivity findings in healthy young adults from the HCP dataset. PVT connectivity with the subcortex strongly resembled Hb connectivity, including medial midbrain/brainstem and ventral striatum regions. However, PVT connectivity with the cortex was limited to areas within the "task-negative" default network, specifically portions of the medial parietal, posterior cingulate, ventral anterior cingulate, and parahippocamus. Relative to healthy controls, the clinical cohort had significantly stronger Hb connectivity with the posterior cingulate, with exploratory analyses revealing more extensive increases in Hb connectivity throughout the default network as well as increased PVT connectivity with the salience network. Maps of unthresholded correlations (Pearson r) with symptom scales in the combined healthy and clinical samples indicated that stronger Hb connectivity with the default network was specifically associated with anxiety severity, rather than overall depression severity.

Conclusions: To our knowledge, this was the first study to describe human PVT connectivity. Similar to the Hb, the PVT showed a pattern of strong positive connectivity with conserved subcortical targets known from animal studies, particularly dopaminergic regions of the midbrain and striatum critical to reward and motivation. By contrast, the Hb and PVT had very different relationships with the cortex: whereas the Hb was characterized by connectivity with the externally oriented salience network and sensory systems, the PVT was almost exclusively associated with the internally oriented default network. Together, these findings suggest that the Hb and PVT may play complimentary roles in aversion processing, enabling signals from distinct cognitive systems to ultimately converge on the same neural circuits underlying harm avoidance behaviors. Intriguingly, though, our group contrast results appeared to show a breakdown in this opposed pattern of cortical connectivity, with clinical subjects simultaneously exhibiting increased Hb connectivity with the default network and PVT connectivity with the salience network. Finally, preliminary symptom severity analyses suggested that stronger Hb-default network connectivity found in clinical subjects was driven by anxiety.

Keywords: Adolescent Depression, Adolescent Anxiety, Resting State Functional Connectivity, ABCD Study, Paraventricular Nucleus of the Thalamus

Disclosure: Nothing to disclose.

P291. Left-Lateralized Ventrolateral Prefrontal Cortex and Amygdala Hyperactivation in Response to Emotional Images Distinguishes Psychostimulant-Free ADHD Youth With and Without a Family History of Bipolar I Disorder

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Background: The initial onset of bipolar I disorder (BD) is commonly preceded by attention deficit/hyperactivity disorder (ADHD), and ADHD significantly increases risk for developing BD. Having a first-degree relative with BD also increases the risk of developing BD, and youth with a first-degree BD relative exhibit higher rates of ADHD and more severe symptom profiles compared with ADHD alone. While extant evidence suggests that familial risk for BD in conjunction with ADHD may represent a different and more severe illness that confers greater risk for developing BD, associated neurofunctional risk biomarkers remain poorly understood. The onset of BD most frequently occurs during late childhood and adolescence, a maturational period associated with progressive functional changes in frontolimbic circuits that regulate emotional reactivity. Youth who developed BD exhibit amygdala (AMY) hyperactivation in response to emotional stimuli, which is regulated in part by the ventrolateral prefrontal cortex (VLPFC), whereas ADHD youth exhibit reduced or no difference in AMY activation compared with healthy youth. However, prior studies did not control for BD familial risk in ADHD youth, ADHD comorbidity in BD, and/or psychostimulant exposure. In this cross-

sectional fMRI study, we investigated AMY and VLPFC activation in psychostimulant-free ADHD youth with and without a first-degree relative with BD and a typically developing control group while they performed the continuous performance task with emotional and neutral distractors (CPT-END). Prior evidence in healthy subjects indicates that the VLPFC and AMY are activated in response to unpleasant emotional images but not attentional targets. Our a prior hypothesis was that ADHD youth with a BD family history would exhibit greater emotion-generated AMY and VLPFC activation compared with ADHD youth without a BD family history and healthy youth. Exploratory analyses evaluated correlations among VLPFC and AMY responses and relevant symptom measures.

Methods: We enrolled ADHD youth (ages 10-18 years) with at least one biological parent or sibling with BD ('high-risk', HR) or had no first- or second-degree relative with a mood or psychotic disorder ('low-risk', LR), as well as healthy controls (HC) with no personal or family history of a DSM-5 Axis I psychiatric disorder. All ADHD youth met DSM-5 criteria for ADHD (any type), were stimulant-naïve or had no exposure to psychostimulants for at least 3 months prior to enrollment, and had no current DSM-5 mood, conduct, eating, or psychotic disorders. fMRI scans were acquired on a Philips 3.0 T MR while subjects performed the CPT-END. Preprocessing was performed using SPM-12, and the boundaries of ROI regions were determined using the structural Jülich Brain Atlas. Clinician ratings of ADHD (ADHD-rating scale), mania (Young Mania Rating Scale, YMRS), and depression (Children's Depression Rating Scale-Revised) were obtained, and parents completed the Child Behavior Checklist (CBCL).

Results: A total of 144 youth (mean age 14.3 ± 2.5 years; HC, $n = 46$; low-risk, $n = 50$; high-risk, $n = 48$) were included in the analysis. No significant group differences were observed for age, sex, race, pubertal status, hand dominance, or prior psychostimulant exposure in the ADHD groups. Compared with LR, HR had higher ADHD-RS hyperactivity/impulsivity subscale scores ($P = 0.007$), CDRS-R total scores ($P = 0.019$), YMRS total scores ($P < 0.001$), CBCL total scores ($P < 0.001$), internalization ($P = 0.003$), externalization ($P < 0.001$), and dysregulation subscores ($P = 0.012$). For unpleasant emotional images, left VLPFC ($P = 0.011$), but not right VLPFC ($P = 0.27$), responses differed significantly among groups. Post-hoc tests revealed that the HR group exhibited greater left VLPFC activation compared to HC (+41%, $P = 0.004$) and LR (+30%, $P = 0.03$), and LR did not differ from HC ($P = 0.34$). Left AMY ($P = 0.03$), but not right AMY ($P = 0.15$), responses differed significantly among groups. Post-hoc tests revealed that the HR group exhibited greater left AMY activation compared to HC (+27%, $P = 0.03$) and LR (+27%, $P = 0.02$), and LR did not differ from HC ($P = 0.98$). Left VLPFC and left AMY were more robustly correlated in the HR ($r = 0.52$, $P = 0.0002$) and LR ($r = 0.42$, $P = 0.002$) groups compared with HC ($r = 0.32$, $P = 0.03$). For the attentional component, there were no significant group differences for either left AMY ($P = 0.48$) or left VLPFC ($P = 0.49$). Among all subjects, left AMY responses to emotional stimuli were positively correlated with YMRS scores ($r = 0.18$, $p = 0.03$), CBCL total scores ($r = 0.21$, $P = 0.01$), and externalization ($r = 0.22$, $P = 0.01$) and dysregulation ($r = 0.18$, $P = 0.04$) subscale scores.

Conclusions: Greater left VLPFC and AMY activation in response to emotional images distinguishes ADHD youth with and without a BD family history, and is associated with a more severe clinical profile including greater manic and dysregulation symptoms. Prospective investigation is warranted to evaluate VLPFC and AMY hyperactivation as potential risk biomarkers for developing BD in this high-risk population.

Keywords: Bipolar Disorder, ADHD, Amygdala, Ventrolateral Prefrontal Cortex, Emotion Perception

Disclosure: Nothing to disclose.

P292. Postnatal Refinement of Synaptic Afferents to Dorsal Raphe 5-HT Neurons: Implications for Psychiatric Disorders

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Background: Serotonin (5-hydroxytryptamine, 5-HT) neurons are implicated in the etiology and therapeutics of anxiety and depression. Critical periods of vulnerability during brain development enable maladaptive mechanisms to produce detrimental consequences on adult mood. 5-HT plays a pivotal role in these mechanisms, however, little is known about how synaptic inputs shaping the activity of 5-HT networks mature during postnatal development. We investigated in mice the postnatal trajectory of glutamate and GABA synaptic inputs to dorsal raphe nucleus (DRN) 5-HT neurons, a main source of forebrain 5-HT.

Methods: In C57BL/6 and Swiss mice (both sexes) we applied a multidisciplinary approach combining high-resolution morphological analyses (array tomography) together with ex-vivo patch-clamp recordings and pharmacology. Data were analyzed by multifactorial ANOVA followed by Tukey's comparisons.

Results: Our results showed that cortical glutamate synapses undergo a profound refinement process between the third and fourth postnatal weeks ($p < 0,05$), while subcortical glutamate inputs do not. Next, we asked whether this neurodevelopmental process could be altered in a mouse model of early-life emotional vulnerability. In this model, a brief exposure to fluoxetine (p.o.10mg/kg/day) during the first two postnatal weeks results in long-lasting depressive-like and anxiety behaviors. We found that fluoxetine-treated mice (both sexes) had a selective increase in cortical synaptic inputs to 5-HT neurons as early as the following day after the treatment cessation ($p < 0,05$ vs. sucrose-treated mice).

Conclusions: This suggests that postnatal fluoxetine exposure could enhance the synaptogenic potential of cortical inputs influencing the early activity of 5-HT neurons. Our study contributes to the understanding of neurodevelopmental vulnerability to psychiatric disorders.

Keywords: Serotonin, Synapses, Anxiety and Depression, Circuit Development, Prefrontal Cortex

Disclosure: Nothing to disclose.

P293. Reduced Emotion-Generated Frontolimbic Functional Connectivity in Psychostimulant-Free ADHD Youth With and Without Familial Risk for Bipolar I Disorder: A Cross-Sectional Event-Related fMRI Study

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Background: Attention deficit/hyperactivity disorder (ADHD) commonly precedes the onset of bipolar I disorder (BD), and prospective studies have found that antecedent ADHD significantly increases the risk of developing BD. Additionally, having a first-degree relative with BD robustly increases the risk of developing BD, and youth with a first-degree BD relative exhibit higher rates of ADHD and more severe ADHD symptoms. While these findings suggest that ADHD in conjunction with familial risk

for BD may represent a different and more severe illness that confers greater risk for developing BD, associated neurofunctional mechanisms remain poorly understood. The ventrolateral prefrontal cortex (VLPFC) - amygdala (AMY) circuit plays a central role in emotional regulation, and greater emotion-generated VLPFC-AMY functional connectivity (FC) has consistently been implicated in the pathophysiology of BD. In contrast, youth with ADHD exhibit lower VLPFC-AMY FC in response to emotional stimuli relative to both healthy youth and youth with BD. However, prior studies did not control for BD familial risk in ADHD youth, ADHD comorbidity in youth with BD, and/or psychostimulant exposure, and no studies have directly compared VLPFC-AMY FC in unaffected psychostimulant-free ADHD youth with and without a first-degree BD relative. In the present cross-sectional event-related fMRI study, we investigated VLPFC-AMY FC in psychostimulant-free ADHD youth with and without a first-degree relative with BD and a typically developing healthy control (HC) group. Exploratory analyses evaluated relationships among VLPFC-AMY FC and relevant symptom measures.

Methods: We enrolled ADHD youth (ages 10-18 years) with at least one biological parent or sibling with BD ('high-risk', HR) or had no first- or second-degree relative with a mood or psychotic disorder ('low-risk', LR), and healthy controls (HC) with no personal or family history of a DSM-5 Axis I psychiatric disorder. All ADHD youth met DSM-5 criteria for ADHD (any type), were stimulant-naïve or had no exposure to psychostimulants for at least 3 months prior to enrollment, and had no current DSM-5 mood, conduct, eating, or psychotic disorders. fMRI scans were acquired on a Philips 3.0 T MR while subjects performed a continuous performance task with emotional and neutral distractors (CPT-END). Studies of healthy subjects with the CPT-END task reported that the VLPFC and AMY are activated in response to unpleasant emotional images but not to attentional targets. Generalized psychophysiological interaction (gPPI) analysis assessed region of interest (ROI)-to-ROI FC between bilateral VLPFC and AMY. Clinician ratings of ADHD (ADHD-rating scale), mania (Young Mania Rating Scale, YMRS), depression (Children's Depression Rating Scale-Revised, CDRS-R), global functioning (Children's Global Assessment Scale), and global symptom severity (Clinical Global Impression-Severity Scale) were performed, and parents completed the Child Behavior Checklist (CBCL).

Results: A total of 144 youth (mean age 14.3 ± 2.5 years; HC, $n = 46$; low-risk, $n = 50$; high-risk, $n = 48$) were included in the analysis. No significant group differences were observed for age, sex, race, pubertal status, hand dominance, or prior psychostimulant exposure in the ADHD groups. Both HR and LR ADHD groups differed from HC on all ratings ($P \leq 0.001$). Compared with LR, HR had higher hyperactivity/impulsivity subscale scores ($P = 0.007$), CDRS-R total scores ($P = 0.019$), YMRS total scores ($P < 0.001$), CBCL total ($P < 0.001$), internalization ($P = 0.003$), externalization ($P < 0.001$), and dysregulation scores ($P = 0.012$). For unpleasant emotional images, right VLPFC to left AMY FC differed significantly among groups ($P = 0.001$). Post-hoc tests revealed that both LR ($P = 0.04$) and HR groups ($P < 0.001$) exhibited lower right VLPFC-left AMY FC compared to HC, and the HR group had lower right VLPFC-left AMY FC compared with the LR group ($P = 0.04$). For attentional targets, there were no differences in right VLPFC-left AMY FC among the three groups ($P = 0.462$). For unpleasant emotional images, right VLPFC-left AMY FC was positively correlated with YMRS total scores in the HR group ($r = 0.33$, $P = 0.02$) but not in the LR group ($r = 0.1$, $P = 0.48$).

Conclusions: Psychostimulant-free ADHD youth with familial risk for BD exhibit blunted right VLPFC-left AMY FC in response to unpleasant emotional stimuli compared with ADHD youth without familial risk for BD and healthy youth. Positive associations between right VLPFC-left AMY FC and manic symptom severity within the HR group suggests potential clinical relevance and may represent a BD resilience biomarker warranting additional investigation in prospective longitudinal studies.

Keywords: Bipolar Disorder, ADHD, fMRI Functional Connectivity, Amygdala, Ventrolateral Prefrontal Cortex

Disclosure: Nothing to disclose.

P294. Long-Term Trajectories of Depressive Symptoms in Deployed Military Personnel: A 10-Year Prospective Study

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Background: Military missions have been associated with an increased risk of depression. Understanding the long-term development of depressive symptoms after deployment is important to improve decision-making regarding deployment and mental health policies in the military. Therefore, this study aims to investigate trajectories of depressive symptoms from pre- to post-deployment and assess the role of specific factors, such as posttraumatic stress disorder (PTSD) and deployment stressors, in the Dutch army.

Methods: The study cohort comprises a cohort of 1032 military men and women deployed to Afghanistan between 2005 and 2008. From pre- to 10 years post-deployment, depressive and PTSD symptoms were assessed at 6 different time points. Demographics and deployment experiences were collected at baseline and after deployment, respectively. For the analysis a Latent Class Growth analysis was performed to investigate the growth and shape of the development of depressive symptoms over time.

Results: The study identified four trajectories for depressive symptoms: resilient (65%), intermediate-stable (20%), symptomatic-chronic (9%), and late-onset-increasing (6%). The late-onset-increasing group had the highest proportion of individuals younger than 21 years, and the resilient group was less likely to experience deployment stressors compared to the other groups. In addition, for individuals classified in trajectories with higher levels of depressive symptoms, PTSD symptoms were higher at all time points.

Conclusions: Multiple trajectories for depressive symptoms were identified in a military population up to 10 years after deployment. These trajectories were associated with age, deployment stressors and PTSD symptoms. The majority of the sample fell within the resilient trajectory, supporting the notion that deployed military personnel possess a high level of resilience. Overall, these findings provide valuable insights and a foundation for further research in this area.

Keywords: Depression, Veterans, Trajectories

Disclosure: Nothing to disclose.

P295. Correlates of Cannabis Use Disorder and Cannabis Use Among Adolescents With Bipolar Disorder and Major Depressive Disorder in the National Comorbidity Survey-Adolescent Supplement (NCS-A)

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Background: Despite evidence regarding prevalence and correlates of cannabis use disorder (CUD) and cannabis use (CU) in

adult bipolar disorder (BD) and major depressive disorder (MDD), little is known about this topic among adolescents.

Methods: The 2001-2004 National Comorbidity Survey—Adolescent Supplement, an in-person epidemiologic survey of mental disorders, implemented a modified version of the Composite International Diagnostic Interview. Participants included adolescents, ages 13-18 years, with BD-I or BD-II (n = 295), MDD (n = 1112), or controls without mood disorders (n = 8716). Analyses examined prevalence and correlates of CUD and CU within the BD and MDD groups.

Results: CUD was most prevalent in BD followed by MDD then controls. CU was most prevalent in MDD followed by BD then controls. In a step-wise trend BD adolescents with CUD versus CU versus no cannabis use were more likely to be female, have longer depressive episodes, lifetime history of suicide attempts, lifetime history of alcohol use disorder (AUD), and increasing rates of seeing a professional for depression. Similarly, MDD adolescents with CUD versus CU versus no cannabis use had higher lifetime rates of lifetime suicidal ideation, lifetime conduct disorder, AUD, and seeing a professional for depression, as well as lower rates of past year stimulant use.

Conclusions: CUD and CU are both associated with multiple adverse clinical characteristics in community adolescents with BD and MDD. Evidence that risks of cannabis extends across the spectrum of use is particularly important for adolescents with BD and MDD, in whom cannabis-related consequences have the potential to be more severe.

Keywords: Adolescents, Cannabis Use, Bipolar Disorder, Major Depressive Disorder

Disclosure: Nothing to disclose.

P296. Racial Differences in Association Between Higher Levels of Adverse Childhood Experiences and History of Self-Reported Depression Among Cancer Survivors

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Background: Depression is experienced by 25% of cancer survivors in the United States, and there are racial differences in how Adverse Childhood Experiences (ACEs) affect depression. While previous studies have examined association between ACEs and depression in general population, studies focusing on cancer survivors are lacking. The purpose of this study was to assess the association between ACEs and history of self-reported depression among cancer survivors in different race groups.

Methods: This study was a cross-sectional analysis of the 2020 Behavioral Risk Factor Surveillance System among 19,241 cancer survivors. The ACE category (zero, one, two-three, ≥four) included questions assessing exposure to eight types of adverse childhood experiences: three types of abuse (physical, emotional, and sexual) and five types of household challenges (household member substance misuse, incarceration, mental illness, parental divorce, or witnessing intimate partner violence) before age 18 years. The outcome is self-reported history of depression (yes/no). Three weighted multivariable logistic regression models were used to examine the association between ACE and depression for each race group: Non-Hispanic White (NHW), Non-Hispanic Black (NHB) and Hispanics, adjusting for age, sex, smoking status, income, education, marital status, body mass index, health status.

Results: In this sample of cancer survivors, 41%, 22%, 21% and 16% reported having experienced zero, one, two-three, and > = 4 ACEs respectively. Majority of survivors were NHW (82.5%) while 6.2%, 6.4% and 4.9% were NHB, Hispanics, and Others respectively. Personal history of depression was reported by 21% of survey respondents. Among survivors experiencing > = 4 ACEs, depression was reported by 46.9 % of NHW, 55.2% of NHB and 50.6% of Hispanics. In the adjusted models, among NHW survivors with 1 ACE (aOR: 1.7, 95% CI. 1.3– 2.2), 2-3 ACEs (aOR: 1.9, 95% CI. 1.5– 2.4), or > = 4 ACES (aOR: 4.2, 95% CI. 3.3– 5.5) had higher odds of depression compared with those with zero ACEs. Among NHB, survivors with > = 4 ACEs had higher odds of depression (aOR: 2.5, 95% CI. 1.2– 5.0) compared with those with zero ACEs; no significant difference was observed for survivors with 1 or 2-3 ACEs. Similarly, among Hispanics, survivors with > = 4 ACEs had higher odds of depression (aOR: 11.3, 95% CI. 5.4– 23.8) compared with those with zero ACEs whiles no significant difference was observed for survivors with 1 or 2-3 ACEs.

Conclusions: Persons with ACEs may represent an important targeted prevention group to reduce risk of depression among cancer survivors. While there is a relationship between all categories of ACE and depression among NHW cancer survivors, only those with > = 4 ACEs had association with depression among NHB and Hispanics. Potential variation by race warrants additional studies regarding potential for selective prevention and identification of resilient, cultural, and healthcare access factors.

Keywords: Depression, Cancer, Adverse Childhood Events, Racial Minorities, Sexual Trauma

Disclosure: Nothing to disclose.

P297. Maternal Stress and Child Genetic Susceptibility Jointly Predict Hippocampal Structure to Impact Risk for Depression – a Study Across Species and Cohorts

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Background: Rodent and human studies suggest the hippocampal dentate gyrus (DG) region is crucial for resilience to stress and depression. We showed that maternal stress is associated with offspring DG structural changes in a mouse model of maternal stress and in human offspring. DG microstructure is also associated with susceptibility versus resilience to depression across species. However not all human offspring exposed to maternal stress have decreased DG microstructure and increased depressive symptoms. Using cross-species (functional) genomics, we now investigate whether gene x environment interactions might explain which children exposed to maternal distress will be susceptible and who will be resilient. Specifically, we translate brain region specific gene expression data from mouse models to novel, biologically informed and region specific expression based polygenic scores (PGS) in human cohorts to assess whether differences in predicted gene expression can explain DG structural difference and depression development in children at risk for depression.

Methods: We use two human cohorts, 1) a three generation family study (N = 306; TGS) and 2) the population-based Adolescent Brain and Cognitive Development Study (N = 6285; ABCD) to ensure robustness and replicability of findings. Gene networks associated with maternal stress exposure were extracted from mouse DG RNA sequencing data using weighted gene correlation network analysis. Using GTEx we translated the mouse gene network to a human expression based PGS that predicts over/underexpression of the gene network in the human

hippocampus (DG ePGS). In addition, broad depression PGS was calculated from the Howard et al. 2018 summary statistics at different GWAS p-value thresholds (p < 10-5-p < 1). We performed enrichment analysis using Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA_GWAS) on all polygenic scores.

For MRI, we extracted DG mean diffusivity with FreeSurfer and MRtrix pipeline. Clinical data on the mother and offspring was assessed. Regressions in a generalized estimating equation framework, accounted for family structure with adjustments for sex, age, population stratification and scanner head motion.

Results: In ABCD, higher DG ePGS was significantly associated with higher rates of depression and DG ePGS interacted with maternal stress, such that only children with high DG ePGS who were exposed to maternal stress have disrupted DG microstructure and higher rates of depression development (all ps < 0.05). In TGS the same patterns were present, although not significantly, likely due to smaller sample size. We also show that GWAS-based Depression PGS predicts DG microstructure and depressive symptoms. Enrichment analysis showed that the genes associated with the polygenic score that best predicted DG structure were most differentially expressed in the hippocampus and are involved in pathways associated with neurogenesis and neurodevelopment, which is interesting since the DG is one of few regions with neurogenesis into adulthood.

Conclusions: Converging results across mice and two independent human samples suggest that the dentate gyrus is an important predictor of resilience to stress and depression, and it is moderated by both genetic and environmental risk factors. Gene networks associated with the effects of maternal stress are conserved across species and associated with depression.

Expression based polygenic scores provide an avenue of using gene expression data from mouse models or deceased patients to predict outcomes in live populations.

Keywords: Hippocampus, Gene Co-Expression Networks, Polygenic Scores, Depression, Maternal Stress

Disclosure: Nothing to disclose.

P298. Polygenic Risk Score Analysis of Antidepressant Treatment Response: Results From the CAN-BIND-1 Cohort

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Background: The genetic architecture of antidepressant response is poorly understood. Here, we used polygenic risk scores to investigate the genetic overlap between psychiatric and non-psychiatric traits and response to antidepressant treatment in the CAN-BIND-1 cohort.

Methods: The Canadian Biomarker Integration Network for Depression (CAN-BIND-1) sample of 211 major depressive disorder (MDD) patients was used as our target dataset. The CAN-BIND-1 included patients that were treated with escitalopram for 16 weeks. Response and remission status were assessed on Weeks 8 and 16. Those who were non-responders at Week 8 were also given augmentation therapy with aripiprazole (antipsychotic). First, polygenic risk scores (PRSs) were constructed on the target dataset using summary statistics from the most recent and well-powered genome-wide association studies (GWAS) obtained through the Psychiatric Genomics Consortium (PGC) including depression(7), bipolar disorder(8), schizophrenia(9), attention-deficit hyperactivity disorder (ADHD)(10), anxiety(11), post-traumatic stress syndrome (PTSD)(12), neuroticism(13), opioid dependence(14) and antidepressant response(15). PRS were calculated using the clumping and thresholding method (with PRSice v2). The constructed scores were then evaluated with remission status and percentage symptom improvement at the end of Phase I (Week 8) and Phase II (Week 16) using logistic and linear regressions. Remission status as a dichotomous measure, (remitter vs. non-remitter) was used as our primary outcome measure. The percentage of symptom improvement, defined as the percentage change in MADRS from baseline on Weeks 8 and 16, was used as our secondary continuous outcome of interest. Regression models were adjusted for covariates including age, sex, baseline MADRS (for remission outcome only), treatment arm (for Week 16 only) and the first three principal components to account for population stratification. Bonferroni correction for multiple testing and 10000 permutation tests were also applied to mitigate overfitting.

Results: PRS for PTSD negatively correlated with antidepressant symptom improvement (Beta = -29.7 (9.71), p-value = 0.015, PThreshold = 0.05, Nsnp = 17950) and remission at Week 8 (OR = 0.08 [0.013-0.42], p-value = 0.017, PThreshold = 0.05, Nsnp = 17950). PRS for MDD was negatively correlated with antidepressant remission at Week 8 (OR = 0.38 [0.18-0.78], p-value = 0.043, PThreshold = 0.05, Nsnp = 20793). However, PRS for MDD showed positive correlation with antidepressant symptom improvement (Beta = 5.56 (2.22), p-value = 0.04, PThreshold = 0.0001, Nsnp = 206) and remission at Week 16 (OR = 1.86 [1.18-2.90], p-value = 0.025, PThreshold = 0.0001, Nsnp = 206). None of the PRS associations survived the Bonferroni threshold (0.001).

Conclusions: Our results show that higher polygenic loading for PTSD and MDD is associated with worse antidepressant treatment response and remission, confirming previous findings. Interestingly, in the group of patients where aripiprazole was added, a higher PRS for MDD was associated with better response and remission.

Keywords: Pharmacogenomics, Antidepressant, Antipsychotic, CNS Clinical Trials

Disclosure: Nothing to disclose.

P299. MicroRNA Expression Profiles From Peripheral Blood May Serve as Biomarkers for Depression Risk in Children and Adolescents

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Background: Identifying reliable molecular indicators for psychiatric risk can significantly contribute to early intervention and prevention strategies. Given the emerging significance of microRNAs in neurodevelopment and mental health disorders, it is crucial to explore accessible and non-invasive approaches for obtaining microRNAs early in development. This study aimed to analyze microRNA profiles in peripheral blood samples from children and adolescents, comparing those with and without clinical depression, using a high-throughput approach.

Methods: A total of 60 dried blood spots samples from the Teen Inflammation Glutamate Emotion Research (TIGER) cohort and 170 blood plasma samples from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO), collected from both sexes, were sequenced using small RNA protocol. Trimmed reads were processed following the exceRpt small RNA-Seq pipeline and

differential expression was analyzed using DESeq2 package. Categorical groups were assigned based on clinical diagnosis and developmentally validated self-report measures of depression.

Results: We identified several differentially expressed (DE) microRNAs (padj < 0.05), upregulated in individuals diagnosed with clinical depression compared to controls, and mainly downregulated in children with lower versus higher self-report levels of depression. A common microRNA miR-1-3p was upregulated in both cohorts ($p < 0.05$). Gene ontology based on predicted DE microRNA targets confirmed association with depression, as well with cardiomuscular biological processes.

Conclusions: Using peripheral blood samples collected from children and adolescents, this investigation sheds light on microRNAs linked to early vulnerability to depression. This novel approach will allow us to probe into ongoing developmental processes that may be shaping lifelong psychiatric risk.

Keywords: MicroRNA, Adolescence, Major Depression Disorder, Biomarker Analysis

Disclosure: Nothing to disclose.

P300. Expression Polygenic Risk Scores in Hippocampus Identify Lipid Pathways in a Multigenerational Study of Depression

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Background: Major Depressive Disorder (MDD) is a common disorder with a complex etiology and a lifetime prevalence of nearly 20%. Depression is a highly familial illness that is more prevalent in the biological offspring of depressed individuals (2–5-fold) than in the general population. While the epidemiology and clinical course are well understood, biological mechanisms of transmission remain unclear. One promising emerging field for understanding neuronal function and dysfunction in the context of MDD is lipidomics, and the role of lipid metabolites and lipid signaling pathways, particularly in the underlying pathway characterized by overactivation of phospholipase A (PLA2), and a concurrent deficit in acyl chain remodeling, Lands Cycle. Specifically, the loss of phospholipids, including phosphatidylcholine (PC) and phosphatidylethanolamine (PE), and an increase in lyso-PC and lyso-PE implicates the overactivation of PLA2 and a concurrent deficit in acyl chain remodeling. In this study, we evaluated whether co-expression polygenic risk score (ePRS) related to lipid pathways, namely acyl chain remodeling, phosphoinositol metabolism, and cholesterol metabolism, can predict the risk for depression in a multigenerational study of depression.

Methods: The multigeneration study for depression began in 1982 with probands (G1) in two groups: patients with moderate-to-severe MDD recruited from an outpatient medication clinic, and controls without lifetime psychiatric disorders, as determined by several clinical interviews. Children (G2) and grandchildren (G3) of the G1 probands were included as they aged in at age six, without other selection criteria. At baseline and follow-up (approx. year 2, 10, 20, 25, 30, and 38), direct interviews were conducted. Expression polygenic risk scores (ePRS) in hippocampus identify lipid pathways study includes $N = 306$ G2 and G3 for who ePRS and depression data are available (G2 mean age: 47 yrs., 52.6% female, 70.7% high risk for depression; G3 mean age: 19 yrs., 49.7% female, 61.8% high risk for depression). DNA was extracted from the buccal cells of the participants, and genome-wide genotyping was performed using a microarray. The genetic score for the lipid pathway gene network was created using Genotype-Tissue Expression (GTEx). The list of common SNPs was subjected to linkage disequilibrium clumping ($r2 < 0.25$), resulting in a few hundred SNPs of interest. For ePRS calculation, alleles for each SNP were weighted by the estimated effect of the genotype on gene expression obtained from GTEx (hippocampal). To generate a gene-focused, expression-based score, we selected lipid pathways genes of interest based on previous studies and mapped all the SNPs in each of these genes. The New York State Psychiatric Institute IRB approved all procedures, and informed consent was obtained.

Results: Generalized Estimating Equations (GEE), adjusted for family structure, sex, and the first five principal components from population stratification (PC1-5), demonstrated that the hypothesized acyl chain remodeling pathway ePRS predicted age of onset of MDD ($p = 0.027$), but not high risk for depression ($p = 0.6453$) or lifetime history of impairing MDD ($p = 0.5776$). Furthermore, phosphoinositol ePRS and cholesterol ePRS were not associated with any depression outcomes analyzed in the multigenerational study of depression. In addition, we found that a genetic score for pathway associated genes as a predictor and risk status as the outcome, adjusting for family structure, sex, and PC1-5. This analysis identified associations between MBOAT2 ($p = 0.0152$), PLCB3 ($p = 0.0077$), and PCSK9 ($p = 0.0024$) gene expression and high risk for depression in the G2 and G3.

Conclusions: These findings offer insights into the nuanced relationships between expression polygenic risk score, and specific gene expression involved in these pathways, and depression. Previously reported changes in the lipid profile in MDD, including reduced PC, PE, PI, and increased LPC, LPE, TAG, and DAG levels, and our current findings support the hypothesis that the Lands Cycle for acyl chain remodeling is dysregulated in association with MDD. Ultimately, it is highly likely that tractable cellular targets will emerge from these studies by uncovering the convergence of lipidomics and expression of lipid metabolic enzymes as biomarkers for predisposition to MDD as well as potential targets for therapeutic development for MDD.

Keywords: Depression, Expression Polygenic Risk Score, Lipid Metabolism, Acyl Chain Remodeling

Disclosure: Nothing to disclose.

P301. Preliminary Assessment of Longitudinal Blood Transcriptomic and Methylomic Changes in Hospitalized Individuals With Mood Disorders and Suicidal Ideation

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Background: Suicide is a complex multifactorial event resulting from an interaction between biological and psychosocial factors. Identifying the molecular basis of suicidal ideation (SI) may provide targets for the development of novel treatment strategies and help better identify individuals at risk of suicide. We aimed to longitudinally characterize the transcriptomic and methylomic dynamics of peripheral blood mononuclear cells (PBMCs) from hospitalized individuals with mood disorders admitted due to acute SI. We hypothesize that improvement of SI is associated with significant changes in blood gene expression, DNA methylation, and cell composition.

Methods: We recruited forty-two individuals with mood disorders, ages 18 or older, hospitalized with SI as a significant aspect of their presentations (Beck Scale for Suicidal Ideation (BSS) > 4). All subjects provided blood samples upon admission (T1) and immediately before discharge (T2). Bulk and single-cell RNA-sequencing was performed at the two time points in a subset of N = 15 and N = 3 individuals with significant improvement of SI (> 50% of reduction in BSS scores between T1 and T2), respectively, using Illumina 2x150bp sequencing and 10X Genomics ChromiumTM 3′ gene expression system. DNA methylation was also assessed at the two time points in N = 16 individuals with the Infinium EPICMethylation BeadChip (Illumina). Paired analysis compared gene expression and differentially methylated positions (DMPs) between T1 and T2 with correction for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR) procedure. Weighted gene coregulation network analysis (WGCNA) was also carried out with the bulk RNA-sequencing data using a soft power threshold of 7, grouping filtered genes from all 30 samples into coordinated expression modules. Expression in these modules was related to time point using linear models adjusted for between-patient differences and corrected for multiple comparisons using the FDR correction ($q < 0.05$). Gene sets from the FDR-significant modules were assessed for functional enrichment (KEGG and GO) on WebGestalt. Finally, the levels of different blood cell types were estimated with transcriptomic data by cell-type deconvolution analysis and also compared between the two time points.

Results: Twenty-six individuals showed significant improvement of SI during hospitalization (mean (SD) BSS scores were 17.8 (8.31) at T1 and 1.0 (4.75) at T2). 'Non-improvers' had a mean (SD) BSS score of 21.3 (6.36) at T1 and 16 (7.75) at T2. No demographic or clinical variables at baseline were different between the two groups of patients. Three genes were differentially expressed between T1 and T2 (FDR = 0.10) in patients that showed SI improvement, including ZNF704 (logFC = 1.70), STMN1 (logFC = 0.49), and DDIT4 (logFC = 0.67). Changes in BSS significantly correlated with changes in ZNF704 expression ($r = 0.597$, $p = 0.019$). WGCNA analysis revealed 17 coregulation modules ranging from 74 to 3,729 genes. Expression in three of these modules (orange [102 genes], magenta [625 genes], and black [2,433 genes]) was different between time points after FDR correction. Implicated KEGG pathways from the module genes include ECM-receptor interaction and amino sugar and nucleotide sugar metabolism (orange), graft-versus-host disease and natural killer (NK) cell-mediated cytotoxicity (magenta), and systemic lupus erythematosus and alcoholism (black). While DNA methylation analyses did not identify significant DMPs at FDR $q < 0.05$, 1,303 CpG sites showed nominal differences ($p < 0.01$) between time points in improvers. The top-ranked probe (cg23671665, log2FC = -0.69, p = 4.69E-05) was annotated to the LUC7L2 gene, an RNA-binding protein that negatively regulates innate antiviral responses. Finally, the levels of B-cells and monocytes were significantly down-regulated at T2 compared to T1, while the levels of NK and T-cells were up-regulated ($p < 0.05$ for all). Specifically, the levels of the classical CD14+ monocytes were downregulated while the levels of the non-classical CD16+ monocytes were upregulated ($p < 0.05$) alongside SI improvement.

Conclusions: SI symptom improvement could not be predicted by demographic and clinical variables at baseline, but was associated with significant blood transcriptomic and methylomic changes. In addition, SI symptom improvement was associated with major blood cell changes and specific changes in monocyte subtypes. Future studies are needed to explore alterations in individuals who did not show symptom improvement during hospitalization, increase sample size of current analyses, and replicate findings in independent cohorts.

Keywords: Suicide, Transcriptomics, DNA Methylation, Immune Biomarkers, Single-Cell RNA Sequencing

Disclosure: Nothing to disclose.

P302. Brain Structure Signatures of Molecular Genetic and Familial Risks for Suicidal Behavior in Children

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Background: Suicidal behaviour aggregates within families. Though, less is known regarding the underlying biological mechanisms. Recent genome-wide association studies (GWASs) identified genomic loci associated with suicide death in adults of European ancestry admixtures and suicidal behaviour (suicide attempt and death) in adults of multiple ancestry admixtures. People with a greater number of blood relatives with documented suicidal behaviour may be enriched for genetic and environmental risks. In addition, associations of risk markers of suicidal behavior with brain structure remain poorly understood. The eventuation of risk for suicidal behaviour may arise from developmental cascades of molecular genetic and familial liability on brain structure. In this study, we leverage a large, epidemiologically-informed cohort of U.S. children (ages 9-10 years) to examine associations between molecular genetic risks and familial risks for suicidal behavior and brain structure.

Methods: Children (N = 11,899, mean age = 9.91 years, 48% female) are from the Adolescent Brain Cognitive Development (ABCD) Study baseline assessment version 4.0 release. The ABCD Study is an epidemiologically-informed U.S. cohort being followed with multi-modal measures across adolescence, including provision of salivary DNA and neuroimaging (T1 weighted structural magnetic resonance imaging, diffusion tensor imaging) at baseline. A European ancestry admixture subset of the ABCD sample (ABCD-EUR), restricted to children with European genomic admixture ancestry proportions > 0.80, is used for some analyses (N = 6,504, mean age = 9.93 years, 47% female).

Polygenic risk scores (PRS) were calculated in all children across ancestry admixtures from genotyped salivary DNA at p-value threshold of 1.0 using PRSice-2. In ABCD-EUR, a PRS for suicide death (PRS-SD-EUR) was calculated based on a discovery GWAS in European ancestry admixtures adults. In ABCD-EUR, a PRS for suicidal behaviours (i.e., suicide attempt and death) was calculated based on a discovery GWAS in European ancestry admixtures adults (PRS-SB-EUR). In the full ABCD sample, a PRS for suicidal behaviours was calculated based on a discovery GWAS in multi-ancestry adults (PRS-SB-ALL).

In the full ABCD sample, a family risk score for suicidal behaviour (FRS-SB-ALL) was taken as the total number of blood relatives with a caregiver-reported history of suicide attempt or death. This measure was completely derived from caregiver reports on a family history questionnaire, not molecular genetic data.

Analyses involving PRS-SD-EUR and PRS-SB-EUR were conducted in the ABCD-EUR subset, while analyses involving PRS-SB-ALL and FRS-SB-ALL were conducted in the full ABCD sample. Linear mixed effects models related PRS-SD-EUR, PRS-SB-EUR, PRS-SB-ALL, and FRS-SB-ALL to volumes, surface areas, and thicknesses of 68 bilateral cortical regions; volumes of 26 bilateral subcortical regions; and fractional anisotropies (FA), mean diffusivities (MD), and volumes of 35 white matter tracts. Fixed effects were age, sex, first 20 genomic principal components (not for FRS-SB-ALL models), and a global score for each brain modality (e.g., total cortical volume/area, mean cortical thickness, total subcortical volume, average FA for all DTI fibers, MD for all DTI fibers, total

volume for all DTI fibers). Random effect was family nested within MRI scanner serial number. False discovery rate (FDR) multiple comparisons correction (significance threshold pFDR < 0.05) was applied within each imaging metric (26-68 comparisons), within each genetic/familial predictor.

Results: In the molecular genetic analyses, PRS-SD-EUR was significantly related to reduced volumes of left cerebellum cortex (B = -4.88 × 10-11, pFDR = 0.024) and right cerebellum cortex (B = -5.49 × 10-11, pFDR = 0.0089). PRS-SB-EUR was not significantly related to any brain structural outcomes after multiple comparisons adjustment. Across all ancestry admixtures, PRS-SB-ALL was significantly related to reduced volumes of left cerebellum cortex (B = -9.07 × 10-11, pFDR = 0.021), right cerebellum cortex (B = -9.48 × 10-11, pFDR = 0.021), and right accumbens area (B = -4.71 × 10-9, pFDR = 0.021), and reduced cortical thickness of the right precentral gyrus (B = -3.62 × 10-6, pFDR = 0.036).

In the family history analysis, FRS-SB-ALL was significantly related to reduced fiber tract volumes in left fornix (B = -3.62 × 10-5, pFDR = 0.017) and right fornix (B = -3.62× 10-5, pFDR = 0.011), reduced volumes of left cerebellum cortex (B = -2.87 × 10-6, pFDR = 0.017), right cerebellum cortex (B = -2.77 × 10-6, pFDR = 0.017), left putamen (B = -3.14 × 10-5, pFDR = 0.017), and right putamen (B = -3.31 × 10-5, pFDR = 0.017), and increased volumes of left lateral ventricle (B = 3.86 × 10-6, pFDR = 0.017), right lateral ventricle (B = 4.75 × 10-6, pFDR = 0.0086), and 3rd ventricle (B = 8.16 × 10-5, pFDR = 0.00024).

Conclusions: The impacts of molecular genetic and familial risks for suicidal behaviour on development may be captured at the level of neurobiological structure in childhood. Multiple lines of evidence point to involvement of specific brain regions in risk embedding, especially subcortical regions and white matter tracts. Notably, some brain regions (i.e., left and right cerebellum cortex) are implicated in both molecular genetic and familial risks analyses, with consistent volume change directions suggesting a convergence across the sources of information.

Keywords: Suicide, Polygenic Risk Score, Adolescent Brain Cognitive Development Study, Imaging Genetics, Brain Structure

Disclosure: Nothing to disclose.

P303. Longitudinal Stability of Reward-Related Resting-State Networks in Youth With Bipolar-I/II Disorder

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Background: Bipolar disorder (BD) is characterized by temporal instability of mood and energy, but the neural correlates of this instability are poorly understood. We leverage new developments in precision imaging, which show high within-person stability of functional connectivity (FC) networks in healthy adults when sufficient data are collected (e.g., >20 minutes), to test whether this stability is reduced in BD. Based on previous cross-sectional studies, mania has been correlated with increased FC of regions key to reward processing, while depression has been associated with decreased FC of these regions. Here, we assess whether BD is associated with more longitudinal instability within a reward-related network, and whether this instability is associated with mood symptoms, medications, and/or sleep disturbances.

Methods: Eleven participants (16-25 years old) with BD-I/II (>1 hypo/manic and depressive episode in past year) were scanned 3-6 times over 9 months, preferentially in different mood states. To achieve this, participants completed weekly mood questionnaires and were assessed for a potential scan visit when they reported a significant change in mood. Six age-matched healthy controls (HC) were also scanned 4 times over 9 months. All scans were conducted using a Prisma 3T scanner. Following preprocessing of 20-minute resting-state scans using fmriprep LTS 20.0.2 and xcp_d, we assessed between-scan correlation of functional connectivity (FC), focusing on reward circuitry previously implicated in mood state (i.e., ventral striatum, ventral tegmental area, amygdala, ventromedial prefrontal cortex, and thalamus), as defined in neurosynth; all subsequent analyses were conducted in R. We assessed the relationship between diagnostic group (BD vs. HC) and within-person, between-scan correlation. Analyses were conducted on the level of scan-pair and subject. Because frequentist scan-pair models did not converge when nesting within scan and subject, we used Bayesian models to assess relationships between diagnostic group and FC instability, adjusting for motion (mean framewise displacement; FD), time of day, and inter-scan interval; 95% prediction intervals are reported. For the subject-level analyses, we assessed the relationship between mean within-subject scan-pair correlation and diagnostic group. Due to the small sample size, we did not adjust for confounds in subject-level analyses and report a non-parametric Mann-Whitney U. Area under the curve (AUC) for distinguishing BD vs. HC was also calculated. Within BD, we assessed the relationship between network instability and mood symptoms, medication changes, and sleep/arousal (as measured via arousal items on the ABCD questionnaire and PROMIS sleep questionnaires).

Results: We excluded one HC for high motion (>20% of volumes censored at a filtered threshold of FD = 0.1 mm) and a single BD scan due to poor coverage, leaving a sample of 16 youth (11 BD, 5 HC) with a total of 70 scans (50 BD, 20 HC). Whole-brain FC showed higher within- than between-person correlation (within-person = .71 vs. between-person = .50; $p < .0001$), as did FC within the reward circuitry of interest (within-person = .70 vs. between-person = .54; $p < .0001$). Whole-brain within-person correlation did not significantly differ between BD (r = .70) and HC (r = .73) (β = -.02; 95% prediction interval -0.07, 0.03). In contrast, reward FC showed an average of 11% less stability over time in BD (r = .66) vs. HC (r = .77) (β = -.11; 95% prediction interval -0.18, -0.03); adjustment for motion, inter-scan interval, and difference in time of day did not change results (β = -.11; 95% prediction interval -0.18, -0.04). On the subject level, reward FC stability distinguished youth with BD from HC (Mann-Whitney U p = .002; AUC = .95) with a large effect size (Cohen's d = 2.41). Reward FC instability was marginally more pronounced with manic symptoms (β = -.006; 95% prediction interval -.013, .001), but was still present even when predominantly hypomanic mood states were removed; there were no effects of depressive symptoms on stability of reward circuitry. Medication changes were not associated with decreased reward FC stability and did not confound observed associations. Similarly, adjusting for specific medication classes (i.e. lithium, atypical antipsychotics, stimulants, antidepressants, and lamotrigine) did not impact results. There were also no significant effects of sleep or arousal, as measured, on reward FC.

Conclusions: While FC (given sufficient data) is stable within-person, we find that BD is characterized by less within-person stability of a reward-related network, a possible biomarker of the disorder. Within this pilot sample, longitudinal instability of this network almost perfectly separated BD from HC and was also correlated with manic symptoms. While preliminary, these results highlight a possible role for precision imaging approaches as a diagnostic marker for BD. Future work will assess this potential biomarker in a larger sample, further testing the effect of medication changes and sleep disturbances, as well as whether these differences are specific to BD or also found in other mood disorders.

Keywords: Precision Imaging, Bipolar Disorder, Young Adults

Disclosure: Nothing to disclose.

P304. Fatty Acid Amide Hydrolase in Major Depressive Disorder: An [11C]CURB Positron Emission Tomography Study

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Background: Less than 50% of cases with major depressive disorder (MDD) respond to first line treatments. There is growing interest in the endocannabinoid system (ECS) as an alternative signaling pathway to treat symptoms of MDD. Fatty acid amide hydrolase (FAAH) is an enzyme that degrades the ECS ligand, anandamide, which modulates stress. Preclinical evidence suggests that FAAH levels are elevated within fronto-limbic brain regions in depressive models. A FAAH gene variant (rs324420) also contributes to differential levels of FAAH expression. The ECS, however, has never been characterized in humans with MDD using in vivo imaging techniques. We hypothesized that brain [11C]CURB λk3, an index of FAAH density, would be elevated in the prefrontal cortex (PFC), hippocampus, and anterior cingulate cortex (ACC) in humans with MDD compared to healthy controls using [11C]CURB positron emission tomography (PET) imaging.

Methods: [11C]CURB λk3 was measured using PET in 15 unmedicated MDD cases and 15 age- and sex-matched healthy controls, aged 18 to 65 years. There were 11 females in each group. All MDD participants met DSM-5 criteria for a current major depressive episode. Control participants were excluded if they had any lifetime history of a psychiatric disorder. All participants had negative drug urinalysis testing on all scanning and assessment days. Participants also underwent genotyping to determine the FAAH gene polymorphism. A linear mixed effects model was employed to determine the differences in FAAH binding between the two groups, with genotype as a fixed factor. The Beck Depression Inventory (BDI) and Marin Apathy Evaluation Scale (MAES) were administered for exploratory correlational analyses.

Results: No significant differences in [11C]CURB λk3 were observed between MDD patients and controls (linear mixed effects model; PFC, $F1,34 = 0.010$, $p = 0.992$; ACC, $F1,34 = 0.461$, $p = 0.502$; hippocampus, $F1,34 = 1.017$, $p = 0.320$). However, exploratory analyses revealed a significant positive correlation between MAES scores and FAAH binding in the medial prefrontal cortex ($r = 0.673$, $p = 0.012$), ventrolateral prefrontal cortex ($r = 0.586$, $p = 0.035$), and amygdala ($r = 0.660$, $p = 0.014$) amongst MDD patients. There were no significant correlations for the BDI.

Conclusions: Our study is the first to investigate FAAH in MDD using [11C]CURB PET. Our exploratory analyses suggest that fronto-limbic FAAH might be related to apathetic behavior in MDD, which is relevant because a diminution of motivation and goal-directed behavior is a core feature of the disorder. Further investigation of FAAH inhibitor therapeutics for MDD with high levels of apathy may be considered.

Keywords: Fatty Acid Amide Hydrolase, Major Depressive Disorder (MDD), Positron Emission Tomography Imaging

Disclosure: Nothing to disclose.

P305. Diverse Geometric Patterns of Frontostriatal Brain Wiring in Early Psychosis Affective Subjects and in Healthy Controls Assessed Using MRI Diffusion Imaging Tractography

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Background: Alterations in brain connectivity may underlie neuropsychiatric disorders such as affective and non-affective psychoses. We assessed frontostriatal wiring organization using diffusion MRI tractography from the Human Connectome Project in 56 healthy controls, and 46 Early Psychosis Affective patients; Mean age: 23.9 years; sex: 44 females; 58 males; 25 EP-AFF females and 21 EP-AFF males; 19 HC females and 37 HC males. We employed our novel method of fiber cluster analysis of whole brain diffusion Magnetic Resonance Imaging (dMRI) tractography which allows us to quantify the degree of deviation from a topographic, parallel, arrangement in brain wiring connectivity between the frontal cortex (FCtx) and the caudate (Cd), a component of the associative striatum.

Methods: The data used in this study come from the shared data set from the Human Connectome Project for Early Psychosis (HCP-EP) study (MPI: Shenton, Breier). Diffusion MRI Data from 3 HCP sites (University of Indiana, Massachusetts General Hospital and McLean Hospital) were harmonized (Cetin-Karayumak S et al, 2019). From this harmonized data set we generated whole brain tractography using our unscented Kalman filter (UKF) 2-tensor tractography methodology (Malcolm JG et al, 2010). We used a data-driven fiber clustering atlas that allows for a whole brain tractography parcellation into 2000 white matter fiber clusters according WM fiber geometric trajectory (Zhang et al., 2018). Then, fiber clusters of interest (i.e., from FCtx to Cd) based on FreeSurfer parcellation from the whole brain WM were identified for each subject in each subject group. We identified 17 WM fiber clusters that connect FCtx and Cd in both left and right hemispheres in each subject group. To determine the pattern of frontostriatal connectivity in both groups, first, we generated scatter plots for each hemisphere (not shown) based on the 17 fiber clusters (with 136 pairs of fiber clusters, yielding 136 data points), showing the relationship between the cortical distances and the corresponding caudate distances of the fiber cluster pairs that connect the prefrontal cortex and the caudate. Second, in both groups, we generated scatter plots (not shown) for each of the 17 clusters. For each cluster in each group, we performed paired t-tests of the distance between that cluster to the other clusters in the hemisphere, comparing the mean inter-cluster streamline endpoint distances at the level of the frontal cortex and at the level of the caudate, per hemisphere, using a Bonferroni adjustment. In addition, we assessed the between-group difference for each cluster pair in each cluster in the degree of convergence, reflected by a convergence quotient (CQ). Our CQ was calculated as: (Cortex Distance - Caudate Distance)/ (Cortex Distance + Caudate Distance). For each cluster, we employed a mixed model regression analysis of the degree of cluster pair convergence, i.e., the cluster pair CQs, in both left and right hemispheres separately. We used mixed-model regression, with subject as a random effect to test for a significant group by pair interaction (i.e., to test whether the difference in means of 16 cluster pairs differed significantly between groups).

Results: First, based on the plots of distances in the FCtx and Cd for all 136 fiber clusters (not shown) for both groups (HC and EP-Non-affective subjects) in both hemispheres, we showed the relationship between cortical and corresponding caudate distances of the 136 fiber cluster pairs per hemisphere was non-linear, i.e., non-topographic, in both sexes, driven by the results from the same 10 cluster pairs. Second, based on the paired t-tests comparing mean inter-cluster endpoint distances in FCtx and Cd between each cluster with the other 16 clusters, for both groups, we found that 3 specific clusters, bilaterally, from orbitofrontal and inferior frontal prefrontal cortex significantly converged (i.e., Cd endpoint distance < FCtx endpoint distance; Bonferroni adjusted (x34) p value < 0.05). Third, using a mixed model regression analysis of the degree of cluster pair convergence, for both left and right hemisphere separately, we showed a significant group by fiber cluster pair interaction for 3 RH fiber clusters (4, 8 and 13)

and 1 LH fiber cluster (7) which were significant with Bonferroni adjustment ($p < 0.05$).

Conclusions: Using a novel dMRI fiber cluster topography analysis we showed 1) globally, FCtx-Cd brain wiring in both groups deviated from a strictly topographic organization, which was true for males and females analyzed separately driven by the same 10 cluster pairs. We note that these results are similar to that which we found in our prior study of healthy subjects (Levitt, 2021); (2) regionally, for both groups, the same FCtx-Cd clusters showed significantly convergent patterns of connectivity, again similar to our what we found in our prior study of healthy subjects (Levitt, 2021); and (3) we showed a significant group by fiber cluster pair interaction for 3 right hemisphere fiber clusters projecting from rostral middle frontal gyrus/superior frontal gyrus (cluster 4), inferior frontal gyrus, pars triangularis (cluster 8) and rostral frontal gyrus (cluster 13) and for 1 left hemisphere fiber cluster projecting from frontal pole (cluster 7). We believe the importance of our long-tract brain wiring measures is that they reflect trait biomarkers which can identify subjects with early affective psychosis, early in their development, who would benefit from early, more specific, treatment intervention.

Keywords: Diffusion Tractography, Frontostriatal, Early Psychosis, Affective Disorders

Disclosure: Nothing to disclose.

P306. Differentiation Between Bipolar Disorder and Major Depressive Disorder Based on AMPA Receptor Distribution Using Novel Pet Tracer [11C]K-2 and Machine Learning

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Background: Bipolar disorder (BD) and major depressive disorder (MDD) have been operationally diagnosed based on expressed symptoms, which makes it tough to accurately diagnose since they manifest similar symptoms during depressive episodes. Notably, since most bipolar disorders initiate with depressive symptoms, approximately 40-60% of patients with bipolar disorder are initially misdiagnosed with depression. It has been reported that it takes 4-10 years to diagnose bipolar disorder from the onset of symptoms. Moreover, prolonged periods of misdiagnosis lead to various problems including an increased risk of rapid cycling, decreased quality of life, suicide-related issues, increased hospitalizations, and higher medical costs. Thus, there is a critical need for a method that can diagnose bipolar disorder early, utilizing biological indicators.

The excitatory glutamate AMPA receptor is a fundamental component of neurotransmission. Changes in the amount of AMPA receptors on the postsynaptic membrane surface play a role in synaptic plasticity, and it could influence mental functions such as memory and learning directly. Our recently developed PET tracer for the AMPA receptor, [11C]K-2, enables the visualization of AMPA receptor distribution quantitatively [Nature Med, Miyazaki, 2020] and it is considered useful for characterizing regional synaptic phenotypes in psychiatric diseases. The purpose of this study is to develop a method to differentiate these two disorders based on AMPA receptor density using machine learning.

Methods: This study was approved by Yokohama City University Human Investigation Committee and Yokohama City University Certified Institutional Review Board in accordance with the Ethical guidelines for medical and health research involving human participants by the Japan Ministry of Health, Labour and Welfare and the Clinical Trials Act in Japan (trial ID: UMIN000025132, jRCTs031190150). We recruited patients with BD and patients with MDD from Yokohama City University Hospital, Keio University Hospital, Kyushu University Hospital, and University of Fukui Hospital between August 2016 and April 2022. Since there is no need to differentiate between manic patients with BD and patients with MDD, our target patient group consisted of patients with BD or MDD in a depressive state. The criteria for depressive state were Montgomery–Asberg Depression Rating Scale $\geqq 8$ and Young Mania Rating Scale $\leqq 7$. The participants underwent a 60-minute PET scan with [11C]K-2 and an MRI scan. PET images and T1-weighted images were spatially normalized into Montreal Neurological Institute standard space using PMOD. Time activity curves were generated for 75 VOIs in the Hammers atlas. A summed image at 30 to 50 minutes after injection of [11C]K-2 was obtained for all PET images of each patient. Standardized uptake value ratio (SUVR) images in 30-50 minutes were obtained by dividing values by a reference region of the whole brain. We examined group differences in AMPA SUVR between MDD and BD using voxel-wise analysis with SPM ($P < 0.05$, False Discovery Rate corrected). We divided regions with significant group differences based on the Hammers atlas and extracted the ROIs with a volume larger than 100 voxels. The SUVR values of 37 ROIs were employed as input data for machine learning. A support vector machine model with a Gaussian kernel was trained to make diagnostic predictions based on AMPA SUVR. Model performance was assessed with 5-fold cross-validation techniques.

Results: We included 34 patients with MDD and 37 patients with BD. We detected significant group differences in AMPA SUVR in the parietal lobe, the cerebellum, and the frontal lobe, including the DLPFC. Under the validation test set, the support vector machine model achieved an average accuracy rate of 85.6%. The average probability of accurately diagnosing the bipolar disorder patients was 83%, and the average probability of accurately diagnosing the depression group was 89.5%.

Conclusions: Our study demonstrates that AMPA SUVR provides modest discrimination between BD and MDD cases, suggesting that AMPA receptor density measured with [11C]K-2 could have utility in subjects for whom clinical symptoms are poorly measured or yet to manifest.

Keywords: Bipolar Disorder, Major Depressive Disorder (MDD), AMPA Receptors, Machine Learning

Disclosure: Nothing to disclose.

P307. Distinct Homotopic Functional Connectivity Patterns of the Amygdalar Sub-Regions in Major Depressive Disorder

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Background: Major depressive disorder (MDD) affects multiple functional neural networks, which was demonstrated in many studies on resting-state functional connectivity (FC) in MDD. Numerous neuroimaging studies have focused on the amygdala, though these generally did not assess the connectivity changes of the amygdala's different nuclei. We hypothesized that each amygdalar sub-regions will display different HoFC patterns in patients with MDD compared with healthy controls and that these abnormal HoFC patterns will correlate with depressive symptoms severity and with performance in an emotional recognition task. Finally, we hypothesize that baseline HoFC will differ between patients who will respond to conventional medication therapy

compared with those who will not respond, enabling this measure to be used as a predictor of treatment response.

Methods: A total of 67 treatment-seeking patients with MDD and 64 matched healthy controls were recruited. An atlas seed-based approach was used to identify the lateral and medial sub-regions of the amygdala. Homotopic resting state functional connectivity (HoFC) of these sub-regions was compared between groups and correlated with severity of depression, and emotional processing performance. Finally, patients were treated with Serotonin selective reuptake inhibitor (SSRI) and were followed for clinical improvement after 2 months. Baseline HoFC levels were used to predict treatment response.

Results: Significant differences in HoFC between MDD and HC were found in the medial amygdala ($F3,120 = 4.11$, $p = 0.008$, $\eta2 = 0.096$), but not lateral ($F3,119 = 0.29$, $p = 0.82$, $\eta2 = 0.008$) amygdala. Group comparisons revealed that compared to HC, MDD patients exhibited significantly decreased ($F1,120 = 7.74$, $p = 0.006$, $\eta2 = 0.063$) HoFC in the medial amygdala.

Significant negative correlations were observed between medial amygdala HoFC and both HDRS ($r = -0.33$, $p < 0.001$) and DASS ($r = -0.2$, $p < 0.05$) scores. A significant positive correlation was observed between medial amygdala HoFC and ERT scores ($r = 0.38$, $p < 0.001$). No significant correlations were observed between lateral amygdala HoFC and HDRS, DASS, or ERT scores ($p > 0.05$).

Significant differences in medial amygdala HoFC were also observed when comparing responders, non-responders and HC ($F4,107 = 4.61$, $p = 0.002$, $\eta p2 = 0.153$), by which non-responders showed decreased HoFC compared with HC (post hoc $F2,102 = 7.65$, $p < 0.001$, $\eta p2 = 0.13$, controlled for age and gender, see figure 2). The logistic regression model for predicting treatment response was significant $\chi2(1) = 6.27$, $p = 0.013$, and explained 15% (Nagelkerke R2) of the variance in medial amygdala HoFC and correctly classified 65.4% of cases. No significant differences were found between groups for age ($t51 = 0.23$, $p = 0.81$), gender ($\chi2(1) = 1.161$, $p = 0.281$) and years of education ($t48 = 0.34$, $p = 0.73$).

Conclusions: Our results help clarify inconsistency regarding the inter-hemispheric FC of the amygdala, as several studies have reported increased and other decreased HoFC. Looking at homotopic FC of the amygdala divided into 2 distinct areas, allowed us to elucidate different inter-hemispheric FC patterns in MDD patients compared to healthy controls. Accordingly, the medial amygdala, which is known to be involved in executing emotional responses and social interest, demonstrated decreased connectivity, emphasizing the role of interhemispheric communication in depression.

Keywords: MRI, Major Depressive Disorder (MDD), Amygdala

Disclosure: Nothing to disclose.

P308. Suicide Prediction in Major Depressive Disorder Using Connectome Based Modeling

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Background: The rate of suicide continues to rise despite major advancement in medicine. There are currently significant knowledge gaps that hinder our ability to provide effective suicide prevention and anti-suicide care, leaving great opportunity and immense need for empirical research to be conducted to help fill in these gaps. The major roadblocks in this area include poor understanding of the biological mechanisms of suicidal behavior and the scarcity of suicide-specific pharmacotherapies. Neuroimaging studies have begun to unravel the brain regions and circuits implicated in the pathophysiology of suicide.

Methods: We apply a Connectome Predictive Modeling (CPM) machine learning approach to identify a reproducible network associated with suicidal ideation in the hopes of demonstrating possible targets for novel anti-suicidal therapeutics. Patients recruited from an inpatient facility at The Menninger Clinic, in Houston, Texas ($N = 261$) with current major depressive episode (MDE) and recurrent MDD underwent resting-state functional magnetic resonance imaging. CPM combines network restricted strength methods and connectome-based predictive modeling by conducting full assessment of the brain connectome and providing network informed results.

Results: Using this approach, we found a robust and reproducible biomarker of suicidality showing that increased suicidality was associated with greater internal connectivity and reduced internetwork external connectivity. Specifically, reduced external connectivity in the central executive, default mode, and dorsal salience networks. We also found evidence for higher external connectivity between ventral salience and sensorimotor/visual networks as being associated with increased suicidality.

Conclusions: Overall, these observed differences may reflect reduced network integration and higher seclusion of connectivity in individuals with increased suicide risk. Our findings provide avenues for future work to test novel drugs targeting these identified neural alterations, for instance drugs that increase network integration. Our findings may help identifying novel drugs that target the observed network alterations.

Keywords: Suicide Prediction, Clinical Neuroimaging Research, Depression, Inpatient, Suicide Mechanisms

Disclosure: Nothing to disclose.

P309. Psilocybin's Acute and Persisting Effects on Brain Networks: A Precision Functional Mapping Data Resource

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Background: Psilocybin is a promising psychedelic and experimental drug for mood disorders and addiction. It is a serotonin-2A receptor agonist with unknown acute and persisting effects on human brain networks. Precision functional mapping (PFM) combines dense repeated resting state functional MRI (rsfMRI) sampling and individual-specific network mapping to improve signal-to-noise ratios and effect size. Here, we present data from a randomized cross-over study in which PFM was used to characterize psilocybin's acute and persisting effect on the brain networks.

Methods: Healthy volunteers underwent 1) baseline imaging, 2) MRIs 60-90 minutes after psilocybin or active control (methylphenidate) ingestion, and 3) longitudinal imaging for up to three weeks after drug exposure. Four individuals also participated in an open-label psilocybin replication protocol >6 months later. Extensive rsfMRI, task fMRI, structural, and diffusion basis spectral imaging, as well as assessments of subjective experience, physiological data, and personality were collected.

Results: Seven adults (mean age 34.1 years, $SD = 9.8$; $n = 3$ females, $n = 6$ Caucasians) completed the study. Six individuals had < 0.2mm average framewise head motion on psilocybin, with a mean of 4.3 ($SD = 2.8$) 15-minute rsfMRI scans per individual on

psilocybin. On psilocybin, a decrease in cortical infraslow power was significant in a linear-effects model controlling for participant and head motion, and an acute decrease of modularity was no longer significant via linear-mixed effects model after controlling for participant and head motion.

Conclusions: We are releasing this high quality dataset as a resource for neuroscientists to study the effects of psilocybin on neural networks at an individual level.

Keywords: Precision Psychiatry, Psychedelics, Neuroimaging

Disclosure: Nothing to disclose.

P310. Clinical and Polygenic Associations of Coronary Microvascular Reactivity in Youth With Bipolar Disorder

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Background: Cardiovascular disease (CVD) is excessively prevalent and premature in bipolar disorder (BD). Importantly, the excessive rates and premature onset of CVD exceeds what can be explained by traditional cardiovascular risk factors. The question arises as to what other factors may be driving the excess and prematurity of CVD beyond traditional cardiovascular risk factors. In a prior study, using oxygen-sensitive cardiac magnetic resonance imaging (CMR) with an established breathing paradigm, we found that youth with BD have impaired coronary microvascular reactivity (CMVR) despite normal gross cardiac structure and function. Here we build upon those prior findings by examining polygenic and clinical factors in relation to CMR metrics.

Methods: Participants were 86 youth, ages 13-20 years (n = 39 BD, n = 47 controls). All youth completed the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) semi-structured interview to ascertain psychiatric diagnosis, clinical characteristics, and medication usage. Coronary microvascular reactivity (CMVR) was assessed using quantitative T2 magnetic resonance imaging during a validated breathing-paradigm. Quantitative T2 maps were acquired at baseline, following 60-seconds of hyperventilation, and every 10-seconds thereafter during a 40-second breath-hold. Left ventricular structure and function were evaluated based on 12-15 short- and long-axis cardiac-gated cine images. Finally, genetic samples were also acquired from participants. BD, coronary artery disease, and myocardial infarct (MI) polygenic risk scores (PRS) were then calculated using PRS-CS-auto based on independent adult genome-wide summary statistics. Linear mixed-effects model that controlled for age, sex, and body mass index assessed for the effect BD-PRS, MI-PRS, and CAD-PRS scores had on CMVR in the overall sample; and for the effect that clinical characteristics (e.g., medication) had on CMVR in the BD sample. Additionally, general linear models examined the association between clinical characteristics and gross cardiac structure and function.

Results: Higher MI-PRS was significantly associated with lower CMVR ($\beta = -0.12$, $p = 0.006$) in the overall sample. Within the BD group, current treatment with second-generation antipsychotics ($\beta = 0.11$, $p = 0.02$) and stimulants ($\beta = 0.11$, $p = 0.02$), and greater severity of current manic ($\beta = 0.14$, $p = 0.004$) and depressive ($\beta = 0.10$, $p = 0.03$) symptom severity were associated with higher CMVR. Additionally, within the BD group current treatment with lithium was associated with lower indexed left ventricular mass ($\beta = -0.42$, $p = 0.03$), and current selective serotonin reuptake inhibitors treatment was associated with higher indexed end diastolic ($\beta = 0.30$, $p = 0.047$) and systolic ($\beta = 0.34$, $p = 0.03$) volume.

Conclusions: The present study builds upon our prior finding of impaired coronary microvascular function in youth with BD by demonstrating that a higher polygenic risk for MI is associated with lower CMVR in youth. Furthermore, the study found that current medications, and symptom severity are associated with both novel and clinical measures of cardiac structure and function in a sample of youth with BD early in their course of illness. Future studies integrating larger samples, prospective follow-up, and blood-based biomarkers are warranted.

Keywords: Bipolar Disorder, Youth, Cardiac Reactivity, Polygenic Scores, Psychotropic Medications

Disclosure: Nothing to disclose.

P311. Allopregnanolone, Cortisol, and Inflammation in Response to Sertraline in Premenstrual Dysphoric Disorder

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Background: Premenstrual Dysphoric Disorder (PMDD) is characterized by neurobiological sensitivity to normal hormonal fluctuations of the menstrual cycle (MC), resulting in affective and behavioral symptoms during the luteal phase of the MC. PMDD pathophysiology is unknown, but candidate mechanisms include dysregulation in 1) interactions between ovarian and stress hormones, 2) immune function, 3) serotonergic neurotransmission. Progesterone metabolizes into allopregnanolone (ALLO), a neuroactive steroid that has been shown to attenuate the cortisol response (reducing cortisol and ACTH). In PMDD patients, this feedback loop appears disrupted, leading to increased cortisol response in laboratory experiments and a failure of ALLO to lower the stress response (compared to controls). Meanwhile, inflammatory markers may increase in the luteal phase of the MC, and increased peripheral inflammation (e.g., TNFα, IL-6, IL-8) has been associated with mood symptoms in other samples. Despite independent links between the MC and mood with inflammation, few studies examine inflammation in PMDD. Finally, PMDD can be treated with selective serotonin reuptake inhibitors (SSRIs), with response rates under 24 hours, suggesting a unique mechanism of SSRI efficacy in PMDD. We aim to identify 1) if relationships between the MC to stress or inflammatory markers differs between PMDD and controls; 2) if ALLO affects cortisol differently in PMDD versus controls; and 3) how luteal phase SSRI (sertraline) treatment impacts stress and inflammatory markers.

Methods: Female participants with natural menstrual cycles (24-39 days; confirmed ovulation) who were not using psychotropic or hormonal medications were recruited. Participants completed a structured clinical interview (SCID) and two months of prospective ratings (Daily Rating of Severity of Problems; DRSP) prior to laboratory testing to confirm PMDD symptoms (PMDD group) or absence of symptoms (control group). Three blood draws were timed in the follicular (5-11 days post-menses onset; N = 1 visit) and luteal phases (8-12 days post ovulation; N = 2 visits). During the second luteal phase, PMDD participants were treated with open-label sertraline (50mg/d) from ovulation to menses. The PMDD group was divided into Treatment Responders (PMDD-TR) and Treatment Non-Responders (PMDD-N) based on sertraline response, defined as >= 30% improvement in luteal phase DRSP score (vs. untreated luteal phase). Serum ALLO was measured by gas chromatography/mass spectroscopy, serum cortisol was measured via ELISA, and serum inflammatory markers were measured via multiplex kits (plates read by MSD Sector Imager 2400 measuring electrochemiluminescence). Multilevel linear models predicted log-

transformed stress markers (cortisol, ACTH) from MC phase (follicular, untreated-luteal, treated-luteal), log-transformed ALLO, group (PMDD-TR, PMDD-N, Control), and the MC phase * group interaction. A second set of multilevel linear models predicted log-transformed inflammatory markers (TNFα, IL6, and IL-8) from MC phase and group (PMDD vs. control). Finally, multilevel linear models predicted DRSP score from inflammatory markers and MC phase.

Results: The sample included N = 42 participants (20 controls, 22 PMDD). There were no main effects of MC phase, group, or ALLO on cortisol (all p's>0.05). There was a significant interaction between phase*group*ALLO predicting cortisol in the sertraline treatment phase, showing that luteal phase ALLO predicts lower cortisol in controls and PMDD-TR, but not in PMDD-N (Est = 0.74, CI = 0.05-1.43, p = 0.036). There were no main effects of group (PMDD or control) or untreated MC phases (luteal, follicular) on IL-6, IL-8, or TNFα (all p's>0.05). IL-8 was significantly higher in the sertraline-treated luteal phase compared to the untreated luteal phase in PMDD (Est = 0.52, CI = 0.15-0.90, p = 0.011). There was no relationship between TNFα, IL-6, or IL-8 and DRSP score (all p's>0.05).

Conclusions: The present study analyzed peripheral markers of stress and inflammation to probe possible mechanisms underlying PMDD and/or response to SSRI treatment. Our findings support the hypothesis that ALLO attenuates cortisol to exert homeostatic control over the stress response, and this relationship is dysregulated in patients with PMDD. As expected, ALLO predicted lower cortisol in the luteal phase of controls. This relationship held true in PMDD-TR but not PMDD-N. Thus, we propose that the ALLO-cortisol relationship may be a marker of SSRI efficacy, as this relationship appeared dysregulated in PMDD patients who did not respond clinically to SSRI, but normalized to match controls in patients who did. Surprisingly, we did not find relationships between MC phase and inflammatory markers in PMDD patients or controls. This suggests that despite well-established anti-inflammatory effects of progesterone and ALLO in preclinical models, these relationships may not translate to peripheral TNFα, IL-6, or IL-8. Finally, we found increased luteal phase IL-8 under sertraline treatment. Evidence is mixed regarding SSRI effects on inflammatory markers, but some prior work has shown that IL-8 may be upregulated after SSRI use in patients with depression. Future work is warranted to further examine the relationship between IL-8 and SSRIs in larger samples of patients with PMDD. Broadly, our work suggests roles of cortisol and IL-8 in mechanisms underlying PMDD treatment response.

Keywords: Allopregnanolone, Premenstrual Dysphoric Disorder, Cortisol, Inflammatory Markers

Disclosure: Nothing to disclose.

P312. Impact of Adverse Life Experiences on Postpartum Behavioral Changes via Glucocorticoid Signaling and Cortico-Cortical Pathway

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Background: Pregnancy and delivery are significant life events in a woman's life, resulting in substantial physical and psychological changes. It is common for mothers to experience mood disturbances and cognitive impairments during the postpartum period, which can lead to serious mental health problems. Adverse life experiences during the developmental period (ALEs) have been associated with changes in mood and social cognition during the postpartum period. However, the underlying mechanisms and the role of glucocorticoid signaling in this relationship are not well understood. In the present study, we aimed to investigate the longitudinal influences of ALEs on hypothalamic-pituitary-adrenal (HPA) axis function and postpartum behaviors in both humans and a mouse model.

Methods: We examined the relationship between ALEs (history of mental illness, abnormal home environment, abnormal childhood behavior, and traumatic events), plasma cortisol levels, and the development of postpartum depression (PPD) in 116 women. In an animal model, we assessed the plasma corticosterone levels in dams exposed to adolescent social isolation from 5 to 8 weeks of age (N = 9-30). We also investigated the effects of one-week post-delivery treatment with fluoxetine [selective serotonin reuptake inhibitor (SSRI)], ganaxolone [γ-aminobutyric acid type A receptor (GABAAR) modulator], and CORT113176 [glucocorticoid receptor (GR) antagonist] on postpartum behavioral changes in stressed dams (N = 12). Additionally, we explored the role of the anterior insula (AI)-prelimbic cortex (PrL) pathway in social novelty behavior using in vivo microendoscopic calcium imaging and optogenetics (N = 8). To examine the role of GR in the AI-PrL pathway in postpartum social behavior, we used the Cre recombinase dependent on GFP (CRE-DOG) method in GRfl/fl mice to generate pathway-specific GR knock-out mice (N = 6). We used only female mice in the present mouse study because we considered the effects of pregnancy and delivery as well as adolescent psychosocial stress on postpartum behaviors. Statistical tests, such as Fisher exact test, linear regression, t-tests, ANOVA, Mann-Whitney test, Chi-squared test, and correlations, were used to analyze the data. A significance level of $p < 0.05$ was considered.

Results: In humans, a history of mental illness as an ALE was associated with an increased risk of developing PPD. Women with PPD and a previous mental illness diagnosis exhibited elevated and sustained levels of plasma cortisol until at least six weeks postpartum, indicating dysregulation of the HPA axis ($p < 0.01$). In the animal study, stressed dams showed prolonged elevation of corticosterone levels, suggesting a potential alteration in HPA axis control ($p < 0.05$). Treatment with a GR antagonist normalized the behavioral changes in stressed dams ($p < 0.01$), while treatment with an SSRI or a GABAAR modulator did not. Additionally, stressed dams showed decreased activity in the AI-PrL pathway and reduced preference for social novelty ($p < 0.01$). Manipulation of the AI-PrL pathway through optogenetics revealed that the hypofunction of this pathway was responsible for the stress-induced changes in social novelty recognition during the postpartum period ($p < 0.05$). Calcium imaging further demonstrated altered activity patterns of PrL neurons in response to AI-PrL pathway manipulation, with distinct changes observed in unstressed and stressed dams ($p < 0.01$). Furthermore, the deletion of GR in the AI-PrL pathway normalized the behavioral changes in social novelty recognition in stressed dams and restored c-Fos immune reactivity in AI and PrL ($p < 0.01$). These findings suggest that enhanced corticosterone signaling in the AI-PrL pathway may contribute to the behavioral changes observed in stressed dams during the postpartum period.

Conclusions: This study sheds light on the complex interplay between ALEs, sustained glucocorticoid signaling, and disturbed mental health during the postpartum period. Dysregulation of the HPA axis and the AI-PrL pathway may be involved in postpartum behavioral changes. Additionally, our mouse model shows promise as a valuable tool for investigating the pathological mechanisms underlying postpartum behavioral changes in mood and social cognition. Further research focused on understanding how GR signaling specifically regulates the function of the AI-PrL pathway and its role in recognizing social cues would greatly enhance our mechanistic understanding of the pathological trajectory associated with ALEs leading to abnormal postpartum behaviors.

Keywords: Postpartum Depression, Adverse life Experiences, Glucocorticoid Signaling, HPA Axis Dysregulation, Anterior Insula-Prelimbic Pathway

Disclosure: Nothing to disclose.

P313. Utilizing Growth Mixture Modeling to Identify Unique Trajectories of Depressed Mood Across the Ovarian Hormone Cycle in a Transdiagnostic Sample With Past-Month Suicidality

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Background: Menstrual-cycle-related affective symptoms arise due to abnormal neurobiological sensitivity to normal ovarian steroid flux. The prevalence of prospectively- confirmed premenstrual dysphoric disorder (PMDD) is around 5.5%, but this excludes individuals with similar cyclical symptoms that fail to show sufficient clearance of symptoms in the follicular phase, usually due to the comorbidity of a more stable psychiatric disorder. This phenomenon, described as premenstrual exacerbation (PME), may be broadly prevalent in female patients with emotional disorders, with rates as high as 60% in major depressive disorder. Previous literature reveals the presence of distinct temporal subtypes of depressed mood in PMDD, with some patients showing a severe premenstrual week with menstrual offset, some showing a severe premenstrual week with late offset, and some showing a moderate premenstrual week with menstrual offset. Understanding this heterogeneity in symptom timing may have important implications for targeted pathophysiology and treatment. While there is evidence supporting temporal subtypes in PMDD, there is no work to date investigating unique patterns of cyclical symptoms in transdiagnostic psychiatric populations with varying PME. This study uses exploratory growth mixture modeling to determine if there are differing trajectories of depressed mood across the cycle in a transdiagnostic population of psychiatric patients recruited for recent suicidal ideation.

Methods: 129 psychiatric outpatients recruited for past-month suicidal ideation completed daily ratings of depressed mood (scored from 1 = " Not at All" to 5 = " Extremely") across 2-3 menstrual cycles. Following an iterative process, we fit a series of baseline models using the R package OpenMx: linear growth, quadratic growth, and spline models with a knot placed on menses (e.g., linear-linear splines, latent basis splines, and linear-quadratic splines). The best-fitting baseline model was determined through likelihood ratio tests and comparing fit statistics (e.g., AIC, BIC, and CFI). We then specified 1-group, 2-group, and 3-group growth mixture models (GMM) with varying latent means and latent variances/covariances, considering both between and within-person differences in depressed mood across the cycle. Fit statistics between GMMs were compared to determine the best-fitting model. For the best fitting GMM, group trajectories and probability of group membership were examined.

Results: The best fitting GMM for depressed mood across the cycle was a 2-group solution, in which the luteal phase was modeled linearly, and the follicular phase was modeled quadratically. Throughout the cycle, the groups differ in their mean intercept (average depressed mood at menses), mean linear slopes (average rate of change across the luteal phase and follicular phase), and mean quadratic slope (characterizing the mean curvature of depressed mood trajectory across the follicular phase). They also differ in their variances and covariances, indicating varying individual differences in intercept and slopes between groups. Group 1 includes 81% of the sample (N = 104) and group 2 includes 19% of the sample (N = 25). In group 1, the trajectory of depressed mood increases through the luteal phase (gamma = 0.273, SE = 0.091), peaks 4 days after menses onset, and then descends in a concave pattern throughout the mid-follicular phase (gamma (linear) = 0.197, SE = 0.300; gamma (quadratic) = -0.460, SE = 0.283). In group 2, the trajectory of depressed mood increases less rapidly through the luteal phase (gamma = 0.168, SE = 0.071), peaks at menses, and then descends quickly in a convex pattern through the follicular phase (gamma (linear) = -0.911, SE = 0.317; gamma (quadratic) = 0.589, SE = 0.361). The average symptom score at menses for group 1 is 2.84 (SE = 0.107) and the average symptom score at menses for group 2 is 3.08 (SE = 0.171). Compared to group 2, group 1 has a more rapid increase of symptoms across the luteal phase, a lower peak of symptoms, and a slower offset of symptoms in the follicular phase.

Conclusions: This study extends current literature by showing that even in samples with underlying psychiatric disorders, there are variations and subtypes of mood sensitivity across the cycle. Unique mechanisms like sensitivity P4 flux or E2 withdrawal may underlie these different trajectories. Replicating these groups in larger samples and probing the pathophysiology of these differences could lead to precision medicine approaches with the ultimate goal of reducing sex disparities in depression.

Keywords: Ovarian Steroids, Depression, Growth Mixture Modeling

Disclosure: Nothing to disclose.

P314. Change in Nucleus Accumbens Volume Predicts Perimenopausal Depression Trajectories With Estradiol Treatment

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Background: Despite decades of clinical research, biomarkers of depression susceptibility, course, and treatment response remain elusive, due in part to diverse etiologies. Research is needed on homogeneous depressive subtypes to characterize etiology and mechanisms of treatment efficacy. Perimenopausal-onset major depression episodes (PO-MDE) represent a depression subtype with a neuroendocrine trigger. Estradiol alleviates PO-MDE, which may be linked to its action on the dopaminergic mesolimbic reward circuit. We present data on changes in depressive symptoms and nucleus accumbens (NAcc) volume, a node in the mesolimbic reward circuit, with short-term E2 treatment in PO-MDE as well as associations between depressive symptom trajectories and NAcc volume changes.

Methods: Women with a current perimenopause-onset major depressive episode (MDE; n = 16) and euthymic perimenopausal women ("controls"; n = 19) were treated with transdermal E2 (100 μg/day) for 3 weeks. Depressive symptoms were assessed using the Inventory of Depression and Anxiety (IDAS) General Depression Scale. MRI sessions at baseline and post-treatment included structural T1 image acquisition using a Siemens Magnetom Prisma 3T scanner. Data were preprocessed using the Freesurfer version 7.1.0 longitudinal pipeline, and subcortical volume measurements were extracted for the left and right nucleus accumbens (NAcc).

Results: There was a significant Group ($F(1, 51.9) = 23.39$, $p < .0001$) and Group-by-Time effect ($F(1, 55.9) = 9.51$, $p = .003$) for IDAS General Depression Scale scores, such that the PO-MDE group showed more substantial reductions in depressive symptoms than the control group (as expected). There was no main effect of Time, Group, or Group-by-Time interactions for right or

left NAcc volumes. With respect to IDAS trajectories, longitudinal mixed models in PO-MDE showed a significant NAccΔ effect, but no significant Time-by-NAccΔ interaction, for right hemisphere NAccΔ ($F(1,28.8) = 15.14$, $p = .001$). Specifically, IDAS intercepts are predicted to be higher (more depressed at baseline) for PO-MDE participants with more positive NAccΔ (increase with treatment). In contrast, IDAS intercepts are predicted to be lower (less depressed at baseline) for PO-MDE participants with more negative NAccΔ (decrease with treatment). Left NAccΔ was not a significant predictor of IDAS intercepts or slopes for PO-MDE. Furthermore, neither right nor left NAccΔ were significant predictors of IDAS intercepts or slopes in the euthymic control group.

Conclusions: As expected, short-term E2 administration reduced depressive symptoms in both the PO-MDE group and the euthymic control group, with more dramatic reductions in the PO-MDE group. At the group-level, women with PO-MDE vs. euthymic controls showed no changes in MRI measurement of left or right NAcc volumes with short-term E2 treatment. However, MRI measurements of right NAcc volume change with E2 significantly predicted depressive symptom intercepts in MDE but not in euthymic controls. PO-MDE participants whose NAcc volumes increased with treatment were predicted to be more depressed at baseline, while participants whose NAcc volumes decreased were predicted to be less depressed at baseline. Speculatively, this may suggest quadratic or nonlinear trajectories of NAcc change with perimenopausal depression, with estradiol treatment contributing to volume normalization. The unilateral nature of this finding is consistent with evidence of hemispheric lateralization of estradiol effects, but characterizing mechanisms driving lateralization is warranted. Together, this study highlights the need for characterizations of brain changes across perimenopause and with estradiol treatment measuring across multiple timepoints and with a longer follow-up duration.

Keywords: 17-β-Estradiol, Nucelus Accumbens, Mesolimbic Reward Circuitry, Perimenopausal Depression, Perimenopause

Disclosure: Nothing to disclose.

P315. Evidence of a Novel Role for the Microbiome-Gut-Brain Axis in Psilocybin's Mechanism of Action

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Background: Growing evidence supports the therapeutic potential of psilocybin for several psychiatric disorders. However, molecular mechanisms are understudied. The microbiome-gut-brain axis, a known mediator of host function and medication effects, is a plausible but unexplored target of psilocybin.

Methods: Adult male and female C57BL/6J mice were exposed to a single oral dose of saline, psilocybin, the 5HT2A/5HT2C receptor antagonist ketanserin, or psilocybin co-administered with ketanserin. The head twitch response, a measure of central 5HT2A receptor agonism, was assessed 30 minutes after treatment. Elevated plus maze behavior was assessed 4 days after treatment and intestinal contents were collected for microbiome analysis. In a second study, mice were exposed to a single oral dose of saline or psilocybin followed by behavioral testing. Four days after treatment, intestinal contents were collected for sequencing and plasma samples were collected for metabolomics. Gut contents from saline-treated and psilocybin-treated mice were also transplanted to naïve mice. Three days after microbiota transplantation, behavioral, microbiome, and metabolomic analyses were conducted.

Results: Psilocybin induced a head twitch response ($F = 36.6$, $P < 0.001$) and increased exploratory behavior in the plus maze ($F = 18.0$, $P < 0.001$). Ketanserin blocked the head twitch (psilocybin*ketanserin interaction $F = 28.7$, $P < 0.001$) without altering psilocybin's effects on plus maze behavior. Psilocybin produced microbiome changes (Bray-Curtis dissimilarity saline v. psilocybin $p < 0.001$) that were not blocked by ketanserin. Effects of psilocybin on the microbiome were replicated in a second cohort, which also demonstrated effects of psilocybin on several metabolites (6 metabolites with $P < 0.05$). Transplantation of intestinal contents from psilocybin-treated mice to naïve mice resulted in behavioral and metabolic changes consistent with the effects of psilocybin itself (5 metabolites with $P < 0.05$ and overlap with results from the treatment study).

Conclusions: In a mouse model, a single dose of psilocybin results in increased openness to exploration of a novel environment, alters the gut microbiome, and alters levels of several metabolites. Transplantation of gut contents from psilocybin-treated mice to naïve mice reproduces psilocybin's effects on behavior and metabolism. The effects of psilocybin on behavior and the microbiome appear partially independent of 5HT2A and 5HT2C receptors. These data suggest that psilocybin may act through a previously unknown mechanism involving the microbiome-gut-brain axis.

Keywords: Gut Microbiome, Psychedelics, Metabolomics, Preclinical Models and Endpoints

Disclosure: Nothing to disclose.

P316. Major Depressive Disorder is Associated With Altered Metabolic Capacity of the Gut Microbiome

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Background: The gut-microbiota-brain axis (GMB) has emerged as a novel pathway implicated in the pathogenesis of Major Depressive Disorder (MDD), but a mechanistic understanding of this pathway remains elusive. The gut microbiota is capable of producing an array of metabolites that can serve as signals mediating GMB axis communication, and perturbations in the gut microbiota ("dysbiosis"), which have been linked to MDD, may alter these gut microbial derived signals to contribute to psychiatric disease. To date, few studies have examined alterations in microbial encoded functions. We examined changes in both microbial composition and function in depressed patients (before and after 8 weeks of antidepressant treatment) compared to matched healthy controls.

Methods: Stool samples were obtained from physically healthy unmedicated depressed patients with moderate to severe depression (MDD; $n = 34$) and matched healthy controls (HC; $n = 50$). A subset of the depressed patients were treated with selective serotonin reuptake inhibitors (SSRIs) for 8 weeks and stool samples were collected. To analyze the composition and functional potential of the gut microbiome, shotgun metagenome sequencing was performed. Group differences in microbiome composition and function at baseline were assessed via Wilcoxon rank-sum test. Differences between pre- and post-treatment samples were assessed via linear mixed effects model with repeated measures. Weighted correlation network analysis (WGCNA) was applied to identify clusters of microbial encoded

functions related to MDD and antidepressant treatment. Results were corrected for multiple comparisons using FDR procedure.

Results: Significant differences in beta diversity were observed between MDDs and HCs at baseline as well as between pre- and post-treatment samples ($p < .001$). Specifically, we observed MDD to be associated with an enrichment of Bacteroidetes spp. (including Alistipes spp., Phocaeicola spp., and Acidaminococcus spp). In addition, MDD was also observed to be associated with a depletion of Bifidobacterium spp., Actinomyces spp., and Rothia spp. Antidepressant treatment was associated with reductions in Romboutsia spp., Peptostreptococcaceae and Pediococcus acidlactici ($p < .05$). We applied WGCNA on shotgun metagenomics data to identify functional categories of microbial genes present in the gut microbiome. Microbial genes were grouped into 22 unique co-abundance clusters. Two modules were altered in unmedicated MDD compared to healthy controls ($p < .05$). These modules were enriched for genes associated with glutathione metabolism, purine metabolism and several classes of amino acid metabolism including arginine/proline metabolism, histidine metabolism, aromatic amino acid biosynthesis, and lipopolysaccharide biosynthesis. One module was observed to be altered in MDD and appeared to normalize with antidepressant treatment ($p < .05$). This module was enriched for genes involved in polyamine metabolism, porphyrin metabolism, flagella biosynthesis/assembly, and sporulation.

Conclusions: In addition to identifying alterations in microbial composition, our shotgun metagenomics approach highlights functional changes in the gut microbiome associated with MDD and antidepressant treatment. These results suggest that MDD is associated with altered capacity of the gut microbiome to produce bioactive metabolites of amino acids, and in particular, affecting bacterial pathways involved in histidine, arginine, and proline metabolism which may relate to altered glutamate/GABA metabolism. Interestingly, our focus on bacterial encoded functions also revealed a potential link between MDD and both spore-forming bacteria and flagellated bacteria. While future study is required to better understand this potential link, these changes may relate to altered serotonin metabolism (as indigenous spore forming bacteria have been shown to regulate serotonin metabolism in the gut) or to gut barrier dysfunction/immune activation (as enrichment of flagellar genes has been linked to inflammation and disease). Future studies will aim to identify the organisms linked to these functional changes as well as integrating metabolomics and assessments of immune function. Additionally, we will examine associations between organisms and co-associated functions with depression severity and treatment response. This approach will offer a deeper understanding of the microbial mechanisms involved in gut-brain axis signaling and their role in psychiatric illnesses.

Keywords: Gut Microbiome, Depression, Microbiota-Gut-Brain Axis

Disclosure: Nothing to disclose.

P317. Single Nucleotide Polymorphisms in the Expression of Interleukin 6 (IL 6) May Contribute to Treatment Resistance and Outcome in Bipolar Depression

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Background: Immune system activation and inflammatory response have been increasingly linked to the pathophysiology of psychiatric disorders. Innate immune system activation and pro-inflammatory cytokine elevations have been reported for both phases of bipolar disorder, but results have been mixed. Elevated expression of the pro-inflammatory cytokine IL-6 has been associated with depressive and anxiety symptoms in several studies and may be associated with symptom severity and poor response. Furthermore, single nucleotide polymorphisms (SNPs) have been shown to influence IL-6 expression and serve as a risk factor for depression. In this secondary study, we analyzed IL-6 SNPs associated with treatment resistant bipolar depression (TRBDD) and modulation of the inflammatory response to better understand what role IL-6 and associated SNPs may play in the pathophysiology and treatment of BDD.

Methods: This was a 10-week, double-blind, randomized, placebo-controlled trial; 43 patients diagnosed with TRBDD and meeting criteria for bipolar I or II received escitalopram (ESC) with placebo (PBO) or ESC with celecoxib (CBX). Blood samples were measured at baseline and week 8. Details of the design and clinical findings were published previously (Halaris et al., 2020). Plasma IL-6 levels were determined by ELISA. Genome-wide genotyping was performed using the Infinium Multi-Ethnic Global-8 v1.0 Kit. After searching the literature and running the SNPs associated with bipolar disorder through a GWAS database of the study's patients, two SNPs were identified: rs1800795 and rs1800796, located on the promoter of the IL 6 gene on chromosome 7 and thus influencing its expression. IL6 rs1800795 consists of the three following genotypes with the C and G alleles: CC, CG, and GG. The allele frequencies of C versus G vary in different ethnic populations. IL6 rs1800796 is most associated with the following genotypes: CC, CG, and GG, with the polymorphism of interest being G > C. Data were analyzed by way of multiple regression and analysis of covariance.

Results: Due to the small size of our study, we did not subgroup the subject population by demographics or BMI, but primarily sought to detect patterns which may/not have reached statistical significance. At baseline, mean IL-6 values were significantly elevated in the TRBDD group ($p = 0.007$) compared to Healthy Controls, as we reported previously. For rs1800795, the mean IL-6 baseline blood levels (ng/ml) were 1.21, 1.99, and 1.48 for CC, GC, and GG respectively, with GC having the highest SE of 0.55 and SE's of 0.14 and 0.18 for CC and GG, respectively. For rs1800796, the mean IL-6 baseline blood levels were 1.58 and 1.08 for CC and GC, respectively, with standard errors of 0.23 and 0.21. Statistical analyses of our subject group demonstrated that, for rs1800795, the C allele had the highest frequency (CC of 21, GC of 14, GG of 7). The pre-treatment HAMD levels for rs1800795 by genotypes were all approximately 22. When analyzing the ESC plus CBX treatment arm versus ESC plus PBO for the GG genotype, which has been associated with highest production of IL-6 in Caucasians, as published in the literature, the ESC plus PBO group had a mean HAMD score of 14.99, and the ESC plus CBX group had a mean score of 7.2. Those with the GC genotype had a score of 10.71 in the PBO group versus 6.71 in the CBX group; the CC genotype by contrast, had the least striking difference of 13.21 for PBO and 9.45 for the CBX group. Despite the low numbers of patients with the rs1800795 G allele, it appeared that this allele was associated with the greatest mean improvement in HAMD score when treated with CBX add-on. The rs1800796 SNP had a disproportionate number of subjects with the CC of 36 and GC of 6. There were no subjects with the GG genotype, despite a previous study stating the minor allele was C within subjects of European ancestry. The pretreatment mean was 22.11 for CC and 21.83 for GC. In the CBX arm, 16 patients were identified with the CC allele and had a HAMD mean score of 7.56, while in the PBO arm it was 12.88. Three patients with the GC allele had a HAMD score of 11.81 in the CBX arm, and a score of 10.33 in the PBO arm. At end of treatment the group that received the CBX add-on had a better outcome in terms of responders and remitters as compared to the PBO add-on (Halaris et al., 2020).

Conclusions: At baseline, IL-6 levels did not significantly correlate with either of the two SNPs. While not statistically significant, there was a noteworthy pattern with the allele studied and depression severity as reflected in the HAMD score. This was especially notable in the treatment group with CBX add-on. The HAMD scores were significantly lower in those with the G allele in rs1800795. It is difficult to determine rs1800796 risk allele, but given the much higher IL-6 baseline blood level for the homozygous C, as well as the lower HAMD mean score in the CBX group versus the PBO group, it appears that patients with the homozygous C allele had a greater response to the anti-inflammatory agent. For these types of analyses a much larger N would have been necessary, but these preliminary findings should stimulate further studies with a larger patient population and ethnic diversity.

Keywords: Psychoneuroimmunology, Treatment-Resistant Depression, Bipolar Disorder, SNP

Disclosure: Nothing to disclose.

P318. Early-Life Adversity Alters Microglial Function in the Central Nucleus of the Amygdala

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Background: Early-life adversity is a risk factor for developing neuropsychiatric disorders like depression. The central nucleus of the amygdala (CeA) is a stress-sensitive region of the brain that mediates appetitive and aversive responses. We recently showed that ELA-induced anhedonia-like behaviors, including reduced social play, are mediated by corticotropin-releasing hormone (CRH) overexpression in the CeA. In another stress-sensitive brain region, we find that deficits in microglial engulfment of excitatory synapses onto CRH+ neurons in the paraventricular nucleus of the hypothalamus (PVN) is one mechanism that contributes to the altered stress responsivity of male mice exposed to ELA. Here we test the hypotheses that 1) microglial synaptic pruning is impaired in the CeA by ELA and 2) ELA alters operant social reward, which is mediated by the CeA.

Methods: To test these hypotheses, we induced ELA using limited bedding and nesting from postnatal days (P)2-10. We used male and female CX3CR1-GFP; CRH-tdTomato mice to assess microglial synaptic pruning and excitatory synapse counts via confocal microscopy and microglial dynamics via 2-Photon imaging. To assess operant social reward, we trained mice to lever press to receive access to social interaction with a conspecific. We then assessed involvement of the CeA in these behaviors using c-fos immunostaining.

Results: We find that ELA enduringly increases the number of excitatory synapses onto CeA-CRH+ neurons at P24/25, weeks after ELA has ended. Additionally, microglial engulfment of excitatory synapses is decreased after ELA in the amygdala at P8. Interestingly, we find that there are few to no CRH-tdTomato+ neurons located in the CeA prior to ~P12. Furthermore, our preliminary data indicates that ELA modifies microglial dynamics in stress-sensitive brain regions. We are currently optimizing the operant social reward protocol, and the analysis of behavioral changes in ELA vs. CTL mice is ongoing.

Conclusions: ELA diminishes microglial engulfment of excitatory synapses and augments excitatory synapses onto CeA-CRH+ neurons during development, an effect that may be due to altered microglial dynamics. Additionally, ELA alters reward-related behaviors in adulthood, and future work will investigate if ELA impairs operant social reward, and if these impairments can be prevented by modulating microglial dynamics during development.

Keywords: Microglia, Central Nucleus of the Amygdala, Early-Life Adversity

Disclosure: Nothing to disclose.

P319. Microglia Integrates Multiple Stress Signals Via Distinct Molecular Pathways for Behavioral Dysfunctions

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Background: Clinical studies have reported the association between depression and inflammation. Rodent studies have demonstrated that chronic stress activates microglia, leading to neuronal dysfunctions and depression-related behaviors via proinflammatory molecules. However, since previous studies have relied on a limited number of microglial activation markers, the entire view of stress-induced microglial response remains elusive. Thus, essential questions, such as how differently microglia respond to acute and chronic stress, how differently microglia respond to stress among individuals, and what determines these properties of microglial responses, are also unanswered.

Methods: We subjected male C57BL/6N mice to acute or chronic social defeat stress. We categorized the mice after chronic social defeat stress into susceptible and resilient mice according to the level of social avoidance, a typical depression-related behavior. Then, we isolated microglia from multiple brain areas of these mice, including the medial prefrontal cortex (mPFC), primary sensory and motor cortices, hippocampus, nucleus accumbens (NAc), and hypothalamus, and subjected these cells to single-cell RNA-seq. In addition, we more deeply analyzed the transcriptome of microglia from the mPFC and NAc, two representative brain areas with distinct responses to social defeat stress, with bulk RNA seq. We then predicted transcription factors responsible for stress-induced changes in the microglial transcriptome and examined their functional significance using genetic and surgical manipulations.

Results: Single-cell RNA-seq revealed that acute stress altered microglial transcriptome in all the examined brain regions. The microglial transcriptome was further changed with chronic stress in susceptible mice but returned to the original state in resilient mice. Microglial transcriptome also varied among brain regions and even more after stress. Thus, microglial transcriptome manifested chronic stress selectivity, stress susceptibility selectivity, and brain region selectivity. Clustering analysis revealed that gene expressions selective to chronic stress and those selective to stress susceptibility were mostly segregated and that brain region selectivity emerged within the former gene expressions. Nonetheless, these selectivities coincided in the same microglial clusters. Bulk RNA-seq analysis of mPFC and NAc microglia reproduced the segregation of chronic stress and stress susceptibility selectivities. Epigenomic analyses with H3K27ac ChIP-seq and ATAC-seq predicted distinct transcription factors for the respective gene expressions. Surgical and genetic manipulations suggested that gene expressions selective to chronic stress and stress susceptibility are mediated by different molecular pathways and involved in distinct behavioral domains.

Conclusions: These findings demonstrate that microglia integrate chronic stress, stress susceptibility, and brain region selectivity in gene expression through distinct molecular pathways, causing multiple neural dysfunctions and aggravating stress-related mental illness.

Keywords: Chronic Social Stress, Microglia, Multi-Omics

Disclosure: Nothing to disclose.

P320. Similar and Unique Immune Proteomic Profiles of Major Depressive Disorder and Primary Dermatological Disorders: A Potential for Novel Treatments

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Background: Immune dysregulation has been linked to major depressive disorder (MDD) and may contribute to treatment resistance in a subgroup of depressed patients. Depressive symptoms are common in patients with inflammatory conditions such as atopic dermatitis and psoriasis. Treatments targeting specific inflammatory markers in these disorders are commonly associated with improvement of depression, suggesting a shared underlying inflammatory process that is yet to be identified.

Methods: Blood samples collected from 108 participants (18-70 years old; 44% female) were analyzed using the proteomic Olink assay of 363 proteins consisting of four panels of general, cardiovascular, and neural inflammatory markers. The study sample included 25 individuals with MDD and no history of inflammatory conditions, 30 patients with atopic dermatitis, 21 patients with psoriasis, and 32 healthy controls (HCs). Differentially expressed proteins in blood between any comparison were defined by fold-change > 1.5 and false discovery rate < 0.05. Gene set variation analyses (GSVA) were performed on previously curated datasets of immune markers.

Results: Compared with the other 3 groups, MDD patients showed higher expression of markers related to vascular inflammation and atherosclerotic cardiovascular disease signaling (e.g., PECAM1, SELP/P-selectin, VWF, SIRT2, STAMBP) as well as pro-apoptotic pathways (e.g., CD274, CASP3, CASP8) (all ps < 0.001). Compared with HCs, MDD and atopic dermatitis patients had higher T-helper 2 (Th2) immunomodulators such as CCL13 ($p < 0.001$), whereas MDD and psoriasis patients had higher Th17 markers such as CXCL1 and KYNU ($p < 0.001$, $p < 0.01$, respectively). GSVA pathway analyses also showed protein enrichment of T-cell signaling pathways (e.g. Th2).

Conclusions: Although MDD is associated with an immune dysregulation profile that is distinct from atopic dermatitis and psoriasis, there is a striking similarity in their adaptive immune system proteomics (i.e., Th2 and Th17 markers). Effective treatments targeting Th2 and Th17 markers could be promising in patients with MDD who demonstrate dysregulation of these immune pathways.

Keywords: Depression, Immune, Biomarkers, Proteomics

Disclosure: Nothing to disclose.

P321. HIV Modifies the Impact of Childhood Trauma on the Peripheral Innate Immune Response and Attenuates the Effects of Estradiol

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Background: Childhood trauma is a significant risk factor for the development of adverse behavioral and physical health outcomes. The long-term effects of childhood trauma on the immune system are of particular interest within neuropsychiatry due to our growing understanding of the influence of immune function and inflammation on the brain and behavior. Childhood trauma increases circulating pro-inflammatory cytokines as well as augments the ex vivo response of peripheral blood mononuclear cells (PBMCs) to an immunogenic stimulus. Women living with HIV (WLWH) experience high rates of childhood trauma exposure, and neuropsychiatric disorders including depression and post-traumatic stress disorder occur more frequently among WLWH than in the general population. The previous work regarding the impact of childhood trauma on immune function and inflammation has not considered the impact of a primary immune disorder on the residual effects of childhood trauma. Therefore, the overall goal of the current study was to characterize the extent to which HIV interacts with childhood trauma exposure to influence the innate immune response to an ex vivo immune stimulus.

Methods: All participants ($n = 54$, 18 without HIV, 36 WLWH) were women >30 years of age who were recruited from the Women's Interagency HIV Study (WIHS) in Atlanta, GA and provided informed consent. Inclusion criteria included being a women age ≥ 30 years who was either at risk for HIV or living with HIV, had an entry HIV-1 RNA of < 50 copies/mL, were currently on ART with ≥ 2 years of ART, and had creatinine clearance (CrCl) ≥50 mL/min estimated by the Cockcroft-Gault equation. All subjects participated in a clinical interview conducted by a trained clinician on trauma assessment instruments and a completed a blood draw where PBMCs were extracted and stored in liquid nitrogen. Childhood trauma history was assessed via the Childhood Trauma Questionnaire (CTQ). CTQ was summed and a group variable was created for reported rates of none-to-low ("low") and moderate-to-severe ("high") emotional, physical, and sexual abuse. PBMCs were cultured and supernatant was assessed from four conditions: basal, lipopolysaccharide (LPS), estradiol (E2), and LPS + E2. MesoScale Discovery multiplex assays were conducted to determine concentrations of IL-1b, IL-6, IL-8 and TNF-alpha for all culture conditions. ANOVAs were used to assess the effects of HIV status, childhood trauma exposure (low vs. high levels), LPS, E2, and their interactions.

Results: Rates of childhood trauma exposure were greater in those without HIV compared to WLWH ($p = .04$). Sociodemographic variables were not different based on HIV status, including age, race, education and income (p's > .05). LPS administration increased all four cytokines (p's = < .002). IL-1b concentrations were impacted by a LPS by HIV status interaction ($p = .047$), such that the increase in IL-1b due to LPS administration was lower in WLWH ($p = .036$). IL-6 concentrations were impacted by a LPS by HIV status by childhood trauma interaction ($p = .017$). Individuals without HIV and low childhood trauma showed greater LPS induction of IL-6 compared to WLWH and low childhood trauma, and all women with high childhood trauma exposure (all p's < = .005). IL-8 concentrations were impacted by an interaction of E2, HIV status, and childhood trauma ($p = .029$). In women with low childhood trauma, E2 increased baseline IL-8 concentrations in women without HIV ($p = .015$) but decreased baseline IL-8 concentrations in WLWH ($p = 0.014$). E2 had no effects on baseline IL-8 concentrations in women with high childhood trauma exposure (p's > .05). E2 increased the LPS induction of IL-8 concentrations only in WLWH with high childhood trauma history ($p = .041$). TNF concentrations were impacted by LPS, E2, HIV status, and childhood trauma interaction ($p = .048$). While E2, HIV status, and childhood trauma did not influence baseline TNF concentrations, these factors influenced TNF concentrations upon LPS administration. The LPS induction of TNF was greater upon E2 treatment only in women without HIV with low childhood trauma exposure ($p = .01$). Additionally, the LPS induction of TNF was lower in WLWH compared to women without HIV with low childhood trauma exposure ($p = .021$).

Conclusions: Taken together, these data suggest that the impact of childhood trauma on innate immune function is

modified by the presence of HIV. The interaction between HIV and childhood trauma was most evident in the presence of low childhood trauma such that PBMCs from WLWH demonstrated a blunted cytokine response to ex vivo LPS challenge as compared to women without HIV. Interestingly, high childhood trauma blunted the response to LPS stimulation regardless of the presence of HIV suggesting that the immune implications for women with a high childhood trauma history are substantial even in the absence of a primary immune disorder. Furthermore, the effects of estradiol which are generally considered as anti-inflammatory, led to an augmented IL-8 response to LPS in WLWH and high childhood trauma. Given the relationship between IL-8 and cancer metastasis, this could be of particular importance in the context of HIV-associated cancers. Although beyond the scope of this study, these findings may also have implications for the manifestation and treatment of neuropsychiatric and neurocognitive disorders with a known psychoneuroimmunology connection.

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Keywords: Childhood Trauma, Women's Health, HIV and Inflammation, Psychoneuroimmunology, Immune

Disclosure: Nothing to disclose.

P322. Frequency-Dependent Effects of Transcutaneous Auricular Vagus Nerve Stimulation on the Regulation of Mood and Inflammation in Recurrent Major Depression

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Background: Transcutaneous auricular vagus nerve stimulation (taVNS) has been recently proposed as a safe, non-invasive alternative to implanted vagus nerve stimulation (iVNS). This novel neuromodulation technique involves the electrical stimulation of the auricular branch of the vagus nerve (ABVN), which innervates the skin of the auricular concha and the auditory meatus. Previous studies have demonstrated that ABVN stimulation with taVNS activates brain circuitry involved in stress response and has beneficial effects in reducing depressive symptoms and upregulating cardiovagal activity in patients with major depression. It has also been suggested that taVNS administration could have significant effects on the activation of the cholinergic anti-inflammatory pathway resulting in the inhibition of pro-inflammatory cytokines release. Despite these promising results, current stimulation parameters are based on historical VNS data, and optimal stimulation parameters for taVNS in major depression patients have not been established. Stimulation frequency has been described as a major parameter impacting the effects of taVNS, and our group has recently identified a greater effect of high-frequency stimulation (100 Hz) compared to standard stimulation VNS frequencies (30 Hz) on the modulation of medullary vagal nuclei activity. Therefore, taVNS actions on regulating mood and physiological alterations in patients with major depression could also be frequency dependent. Addressing this knowledge gap could provide valuable information to develop optimized stimulation protocols with improved clinical efficacy for major depression. The objective of this pilot study was to evaluate the potential frequency-dependent effects of taVNS on the regulation of depressed mood and anxiety symptoms, cardiovagal activity, and pro-inflammatory cytokines levels in patients with recurrent major depression.

Methods: Fifteen women (30.5 ± 6.0 years) with recurrent major depressive disorder in an active depressive episode from a community-based sample were included in the study. Subjects attended five stimulation sessions, during which they were randomized to receive 30 min of taVNS at frequencies of 2, 8, 30, and 100 Hz or sham stimulation. All other stimulation parameters were kept constant across sessions (300 us pulse width, 1.5s duration) with current intensity set to achieve moderate (but not painful) sensation. Surface electrodes were placed over vagal-innervated regions (cymba concha) in the left ear. Before and after the stimulation period, subjects underwent a mild visual stress challenge task. Each task consisted of a presentation of blocks of negative valence/high arousal, neutral valence/low arousal, and fixation images adapted from the International Affective Picture System (IAPS). Subjects completed a Beck's Depression Inventory (BDI) and a State-Trait Anxiety Inventory (STAI) at the beginning and end of each stimulation session. Continuous ECG was collected throughout the experimental sessions, and the high-frequency component of heart rate variability (HF-HRV) was estimated. A blood sample was collected at the beginning and 60 minutes after the stimulation period of each experimental session. Serum levels of cytokines were examined using multiplexed, bead-based immunoassays (including IL-6, TNF-α, IL-1β, and IL-10) on a Luminex 3D detection platform. Generalized estimating equations (GEE) models adjusted for baseline values were used to evaluate the effects of each of the taVNS frequencies (2, 8, 30, and 100 Hz) versus sham on behavioral (BDI, STAI scores) cardiovascular (heart rate, HF-HRV) and inflammatory (IL-6, TNF-α, IL-1β, and IL-10) outcomes.

Results: Administration of taVNS at a 100 Hz frequency was associated with a significant reduction in depressive symptoms (BDI score reduction) ($\beta = -3.43$, $p = 0.01$) and anxiety symptoms (STAI score reduction) ($\beta = -5.69$, $p = 0.001$) compared to sham stimulation. In addition, taVNS at frequencies of 8 Hz ($\beta = -1.90$, $p = 0.003$), 30 Hz ($\beta = -1.59$, $p = 0.01$), and 100 Hz ($\beta = -1.64$, $p = 0.02$) was associated with significant reduction of TNF-α serum levels post-stimulation. No significant effects were identified for other stimulation frequencies or for modulation of heart rate or cardiovagal activity (HF-HRV).

Conclusions: Our results demonstrate frequency-dependent effects of taVNS administration on the modulation of mood and anxiety symptoms in patients with recurrent major depression. This study also provides evidence of potential taVNS frequency-dependent effects on the modulation of the cholinergic anti-inflammatory pathway in depressive subjects. Our findings highlight the importance of developing optimized stimulation protocols for taVNS to achieve a greater therapeutic impact on the modulation of physiological and clinical outcomes in this population.

Keywords: Depression, Transcutaneous Auricular Vagus Nerve Stimulation (taVNS), Inflammation, Frequency Optimization

Disclosure: Nothing to disclose.

P323. Dosing Transcranial Magnetic Stimulation in Major Depressive Disorder: Relations Between Number of Treatment Sessions and Effectiveness in a Large Patient Registry

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Background: In recent naturalistic studies, the effectiveness of TMS in major depressive disorder (MDD) has improved substantially from that documented in earlier randomized controlled trials (RCTs). One major difference is that RCT outcomes were based on TMS courses usually involving 10-20 sessions. In routine community care, the

number of sessions in an acute course is considerably greater, with 36 sessions being most common. There is little documentation of the relations between number of TMS sessions and MDD clinical outcomes, and few studies have characterized trajectories of improvement and the point at which maximal symptom reduction is typically achieved. In a registry sample exceeding 7,000 patients with serial PHQ-9 assessment, this knowledge gap was addressed with novel information about three questions: (1) What are the "real-world" relations between the number of sessions in the acute TMS course and endpoint clinical outcomes? (2) What is the trajectory of improvement in depressive symptoms during the TMS course, both overall and in the subgroups differing in number of sessions? (3) Does extending the TMS course beyond the standard 36 sessions result in additional meaningful improvement and is there evidence that the effectiveness of TMS diminishes or plateaus despite additional treatment?

Methods: This naturalistic, open-label study was conducted with data from the NeuroStar® Clinical Outcomes Registry, involving 110 US private practice sites. From the HIPPA compliant registry with a total of 13,732 unique participants, de-identified data were extracted for 7,215 patients of both sexes treated for MDD with PHQ-9 assessments before and after their TMS course, among other inclusion criteria. Six groups were defined by number of treatment sessions: 1-19 (N = 658), 20-29 (N = 616), 30-35 (N = 1,375), 36 (N = 3,591), 37-41 (N = 626), or > 41 (N = 349) and compared in PHQ-9 clinical outcomes at endpoint (percentage change, response, remission) and at fixed intervals (after 10, 20, 30, and 36 sessions). For continuous measures, omnibus one-way analyses of variance were conducted. Significant effects of group were followed by Tukey-Kramer post hoc comparisons, with a similar strategy applied to the categorical outcomes. Repeated measures mixed models tested group differences in the trajectory of symptom change. All effects reported below were significant with $P < 0.05$.

Results: The six groups differing in number of sessions had markedly different clinical outcomes: e.g., for percentage change in PHQ-9 at endpoint, $F(5, 7209) = 105.27$, P 41 sessions) had intermediate endpoint outcomes and differed from all other groups by manifesting less antidepressant response early in the course and had a slower but steady rate of improvement over time. Extending treatment beyond 36 sessions was associated with a substantial increase in response and remission rates. There was no evidence of a plateau in antidepressant effects in any group. In all groups that received up to 36 sessions, the average rate of improvement in PHQ-9 scores corresponded to a 3% reduction in symptom severity per session over the first 10 sessions followed by a 1.0-1.3% reduction per session at all intervals thereafter.

Conclusions: In real-world practice, there are strong relations between number of TMS sessions and the magnitude of symptom reduction. Courses with less than 30 sessions are associated with diminished benefit. Patients with longer than standard courses typically show less initial improvement and a more gradual trajectory, but meaningful benefit accrues with treatment extended beyond 36 sessions. The average trajectory of improvement with TMS involves rapid symptom reduction over the first 10 sessions (3% per session) followed by a slower but steady rate of improvement (1-1.3% per session). The findings derive from a naturalistic, observational study and causality of number of sessions impacting on effectiveness was not tested. This study described dose-response relations in a large naturalistic sample where multiple factors determined treatment duration, including effectiveness of the intervention. The findings regarding the trajectories of symptom change are not subject to this limitation and preventing the large drop in the rate of improvement after 10 sessions could accelerate clinical change, substantially enhancing treatment efficiency.

Keywords: Transcranial Magnetic Stimulation, Major Depressive Disorder, Dose-Response Relations, Treatment Duration, Trajectory of Symptom Improvement

Disclosure: Neuronetics Inc: Advisory Board (Self).

P324. A Preliminary Investigation of NMDA and GABA Roles in iTBS and 10-Hz rTMS

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Background: Little is known about the comparative neuronal mechanisms of intermittent theta-burst stimulation (iTBS) and 10-Hz repetitive transcranial magnetic stimulation (rTMS). Motor-evoked potentials (MEPs) have been widely used to test the cortical excitability and plasticity of each of these protocols separately. Based on these studies, we hypothesized that iTBS works primarily through NMDA receptor-dependent mechanisms (i.e., long-term potentiation (LTP)), while 10-Hz rTMS may work through a combination of LTP and GABA receptor reduction.

Methods: We conducted a double-blind, placebo-controlled, crossover study with six healthy adult subjects who completed two separate randomized four-arm studies (by drug condition) in sequence (iTBS, then 10Hz), for a total of 8-arms and 48 subject visits. For each TMS protocol, we employed clinically relevant parameters save that we targeted the left motor cortex and delivered stimulation at 80% of resting motor threshold to reduce seizure risk. Each drug condition consisted of a single dose of identical capsules containing placebo, NMDA receptor agonist, d-cycloserine (DCS, 100mg), NMDA receptor antagonist dextromethorphan + 100mg d-cycloserine (DMO 150mg+DCS 100mg, combined to "knock down" the NMDA receptor activity and demonstrate specificity of DCS agonism effects), or GABAA agonist, lorazepam (LZP, 2.5mg). MEPs were recorded before repetitive (r)TMS and 0 min and 30 min after rTMS, all in the presence of drug. Averaged values from both time points were normalized to baseline and differences across all groups were analyzed with Kruskal-Wallis. Wilcoxon tests analyzed within-subject differences between each active drug and placebo. Power analysis for Wilcoxon analyses is indicated for sample size < 50 with power at 80%. Plasticity was defined as change in MEP amplitude from pre-TMS to post-TMS.

Results: In this preliminary pilot study, we observed statistical differences across 10Hz stimulation ($H(3) = 11.605$, $p = .009$, eta-squared = 0.196) but not iTBS ($H(3) = 2.167$, $p = .539$, eta squared = -.019). In comparing between iTBS and 10Hz protocols, we normalized each active drug condition to placebo because iTBS always preceded 10Hz, introducing confounding order effects, with no statistical differences noted (DCS/PBO: $p = .206$, $r = .402$, $n = 42$; DMO+DCS/PBO: $p = .413$, $r = .268$, $n = 92$; LZP/PBO: $p = .966$, $r = .027$). In our comparison of each individual drug vs. placebo for both iTBS and 10Hz, only lorazepam with 10Hz differed from placebo, though other trends were present (10Hz LZP: $p = .016$, $r = 0.679$, $n = 16$; 10Hz DCS: $p = .151$, $r = .430$, $n = 37$; 10Hz DMO+DCS: $p = .204$, $r = .385$, $n = 46$; iTBS LZP: $p = .193$, $r = .445$, $n = 35$; iTBS DCS: $p = .638$, $r = .161$; iTBS DMO +DCS: $p = .070$, $r = .134$).

Conclusions: This pilot study of corticomotor plasticity was the first to compare the synaptic-level mechanisms of the two predominant TMS clinical protocols; and the first to directly compare NMDA and GABA receptor function with any modulatory TMS protocol. Further, it demonstrates the feasibility of an 8-arm study and provides effect sizes for future power analysis. Our conclusions are limited by the small sample size inherent to such a study, and while drug order was randomized within each protocol, order of protocol was not, necessitating normalization to placebo rather than direct comparison of each drug condition between protocols. Translation to clinical TMS is limited by the unknown

relationship between healthy motor cortex and depressed prefrontal cortex plasticity induced by TMS. With caution, we interpret these results to indicate that iTBS tends to produce a more robust plasticity; both protocols appear to employ LTP-like processes; and neither appear to increase excitation predominantly through GABAA reduction. A mechanistic understanding of how TMS changes neuronal connections will likely prove to be essential to optimize TMS clinical effectiveness.

Keywords: TMS, Synaptic Plasticity, Neurophysiology, NMDA Receptor, GABA-A Receptors

Disclosure: Nothing to disclose.

P325. Electroconvulsive Therapy-Induced Volumetric Brain Changes Converge on a Common Causal Circuit in Depression

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Background: Electroconvulsive therapy (ECT) is a well-established treatment for various psychiatric disorders, but its underlying mechanism of action remains unclear. Previous studies have identified a common neural network associated with treatment response in other neurostimulation modalities such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS), however similar neural network has not been identified for ECT. We know that ECT-induced electric field (EF) stimulation has spatially selective effects on the brain. However, the direct impact of these structural changes on clinical outcomes is not well understood.

Methods: In this study, we analyzed data from 386 ECT-treated individuals from the Global ECT-MRI Research Collaboration (GEMRIC) consortium. Longitudinal 3T T1-weighted MRI images were processed using FreeSurfer, and volume changes were calculated for 85 brain regions. EF modeling was performed using the Roast 3.0 software. Principal component analysis (PCA) was applied to both the volume change and EF data to investigate multivariate relationships.

Results: Multivariate PCA analysis of the volume changes showed that the first two principal components captured most of the variance and the second principal component (PC) were associated with clinical outcomes. Multiple regression analysis (ΔMADRS ~ PC1ΔVOL + PC2ΔVOL + age + nECT) indicated that PC2, had a significant correlation with clinical response ($F_{4,381} = 15.95$, $p = 5x10\text{-}12$; $tPC1 = -0.51$, $p = 0.61$; $tPC2 = -2.35$, $p = 0.019$; $tage = -5.83$, $p < 0.0001$; $tnECT = 2.96$, $p = 0.003$).Moreover, the spatial patterns of this second PC component were remarkably similar to the causal circuit identified in TMS and DBS efficacy studies. Notably this same neural network was found in three independent samples with different electrode placements (RUL: $r = 0.65$, $p = 2x10\text{-}11$; BT: $r = 0.58$, $p = 6x10\text{-}9$, MIX: $r = 0.40$, $p = 0.0002$; $df = 83$).

Conclusions: The neural network implicated in TMS and DBS were found based on functional connectivity studies, ours was found on robust volume change patterns. The similarity between these networks supports the hypothesis that the structural and functional effects of neuromodulation might converge on a similar underlying biological architecture that is also associated with its clinical efficacy.

Keywords: Depression, Electroconvulsive Therapy, Electric Field Modeling, Human Neuroimaging, Multivariate Pattern Analysis

Disclosure: Nothing to disclose.

P326. Pilot Intervention Using Text Messages to Deliver Culturally Adapted Infographics About Antidepressant Use

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Background: Despite consistent evidence of the effectiveness of antidepressants for management of depression symptoms, early discontinuation is common even for those with a long-term antidepressant prescription. Limited English proficiency and Latinx ethnicity are associated with low adherence rates to antidepressants. Improved access to language and culturally concordant information about depression and antidepressants could improve adherence to antidepressant therapy. Text messages and infographics are effective tools to increase access to health information. We conducted a pilot intervention study to assess the acceptability, appropriateness, and feasibility of text messaging to deliver language and culturally concordant infographics about depression and antidepressant use (the intervention) to Latinx adults previously diagnosed with depression.

Methods: We recruited Latinx adults with depression from two primary care clinics. Participants completed phone interviews in Spanish or English to assess the acceptability (agreeable and satisfactory); appropriateness (relevant and compatible); and feasibility (successful use) of the proposed intervention. The content and images included in the infographics were developed from previous findings of a qualitative study of the intersection of Latinx ethnicity, having depression, and antidepressant use. During the phone interview, participants received five culturally tailored, language concordant (English or Spanish) infographics by text message. Each infographic corresponded to a theme as follows: 1. patient portal access, 2. depression is a medical condition, 3. adherence to antidepressants, 4. purpose and duration of antidepressants, and 5. misconceptions of antidepressants.

We asked closed- and open-ended questions to assess demographic characteristics and the acceptability, appropriateness, and feasibility of the proposed intervention. Responses were assessed using descriptive statistics, and content and thematic analysis. Infographics were revised based on participant and steering committee suggestions. The revised infographics were delivered with the next round of phone interviews; the previous iteration of the infographic was retired. We completed three rounds of phone interviews.

Participants provided verbal consent before beginning the phone interview and received a $50 incentive after completion of the interview. This study was exempt from review status by the University of Michigan Institutional Review Board (IRBMED; HUM 00115676).

Results: In this pilot intervention study, Latinx adult participants with depression ($N = 27$) were mostly female (23, 85%) and on average 50 ± 14 years old. Most participants were of Mexican descent (13, 48%) and requested the interview be in Spanish (24, 89%). All participants had been previously enrolled in different observational study conducted by our study team. Most participants (26, 96%) reported that delivery of infographics by text message was acceptable, appropriate, and feasible. All participants reported that they were able to access and view all infographics sent to their smartphones as a text message. Most participants (22, 81%) reported that the content and design of the five infographics were acceptable, appropriate, and feasible with additional modifications.

Conclusions: Delivery of language and culturally concordant infographics by text message to Latinx adults could improve access to information about depression and antidepressants. Participants recommended various modifications to the infographics, and

the intervention requires further study to assess effectiveness outcomes.

Keywords: Hispanic/Latinos, Depression, Antidepressants, SMS Text Messaging, Language

Disclosure: Nothing to disclose.

P327. The Effects of Vagus Nerve Stimulation on Peripheral Organ System (REVEAL): Experimental Design and Data Collection

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Background: The activation or blockade of the vagus nerve produces central and peripheral multi-organ physiological responses. Implantable cervical vagus nerve stimulation (VNS) is clinically approved for treating epilepsy, depression and post-stroke recovery. Yet despite over 100,000 VNS patients and numerous studies in various animal models, its physiological effects on peripheral organs in humans remains poorly understood. The NIH Common Fund's Stimulating Peripheral Activity to Relieve Conditions (SPARC) program aims to accelerates development of "bioelectronic medicine". In Phase 2, SPARC will focus on the anatomy and functional connectivity of the human vagus nerve (SPARC-V), build a new ecosystem of open-specification neuromodulation device components (SPARC-O), challenge the innovator community to prove new capabilities (SPARC-X), and will continue to share data and digital resources through the SPARC Portal. Research Evaluating Vagal Excitation and Anatomical Linkages (REVEAL) 7-site clinical trial aims to research the effect of vagal nerve stimulation (VNS) on four key systems: the autonomic nervous system, the cardiovascular system, the immune system, and the metabolic system.

Methods: We will conduct assessments on 144 mainly newly implanted VNS patients (new = 96, previously implanted = 48) with either a standard LivaNova clinical device. We will examine the effects of acute and chronic VNS on the physiology of the organ systems described above. Subjects will be split evenly between epilepsy and depression patients. We have incorporated Ancillary Project 1 to identify, via in vivo human vagal nerve recording, a minimum current level to achieve effective vagal nerve activation without requiring identification of levels for clinical efficacy that can take months to years. We will then test all participants on multi-organ measured physiological outcomes twice: immediately after an accelerated titration period (Early Effects - Visit 1) and 12 weeks after (Late Effects - Visit 2). Three different stimulation settings per patient will be evaluated within and between each of these 2 visits. Outcome measures include arterial pressure, cardiac sympatho-vagal tone, muscle sympathetic nerve activity (MSNA), autonomic reflex function, cardiac mechanics, glucose and lipid metabolism, and immune function.

Results: Enrollment is expected to begin September 31st, 2023 and last for 2 years. Data will be normalized and transformed as needed, and merged into a structured database, Vagabase made public by the NIH.

Conclusions: This research will produce a first-in-the-world dataset on downstream VNS effects that will be foundational for the development and refinement of VNS-based therapies for peripheral organs as well as refine treatment optimization for depression and epilepsy. Add to it, the results from the vagus anatomical studies and the open source neuromodulation devices, SPARC will facilitate the development of new best-in-class bioelectronic medicine therapies.

Keywords: Vagus Nerve Stimulation, Depression, Inflammation, Chronic Diseases, Peripheral Neuromodulation

Disclosure: Nothing to disclose.

P328. Psilocybin Therapy for Treatment Resistant Depression: Prediction of Clinical Outcome by Natural Language Processing

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Background: Therapeutic administration of psychedelic drugs has shown significant potential in historical accounts and in recent clinical trials in the treatment of depression and other mood disorders. A recent randomized double-blind phase-IIb study demonstrated the safety and efficacy of COMP360, COMPASS Pathways' proprietary synthetic formulation of psilocybin, in participants with treatment resistant depression. While promising, the treatment works for a portion of the population and early prediction of outcome is a key objective.

Methods: Transcripts were made from audio recordings of the psychological support session between participant and therapist one day post COMP360 administration. A zero-shot machine learning classifier based on the BART large language model was used to compute two-dimensional sentiment (valence and arousal) for the participant and therapist from the transcript. These scores, combined with the Emotional Breakthrough Index (EBI) and treatment arm were used to predict treatment outcome as measured by MADRS scores. Code and data are available at https://github.com/compasspathways/Sentiment2D.

Results: Two multinomial logistic regression models were fit to predict responder status at week 3 and through week 12. Cross-validation of these models resulted in 85% and 88% accuracy and AUC values of 88% and 85%.

Conclusions: A machine learning algorithm using NLP and EBI accurately predicts long term patient response, allowing rapid prognostication of personalized response to psilocybin treatment and insight into therapeutic model optimization. Further research is required to understand if language data from earlier stages in the therapeutic process hold similar predictive power.

Keywords: Machine Learning, Depression, Natural Language Processing (NLP), Psychedelic Medicine

Disclosure: Compass Pathways: Employee (Self).

P329. The Feasibility and Clinical Utility of Digital Phenotyping to Identify Clinically-Significant Sleep Disturbance in Adolescents

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Background: People with bipolar disorder (BD) often experience significant sleep dysregulation, the nature of which can vary widely depending on their current mood state. Changes in sleep can predate significant mood changes, offering an "early alert" of an impending episode. Related, improving sleep stability can indicate a positive treatment response and possible remission of the mood episode. There are different methods used for assessing

sleep clinically; sleep diaries and other forms of self-reported sleep data are relatively easy and inexpensive to collect, but are often unreliable and difficult for patients to sustain over time. Methods that are more accurate, like sleep lab assessments, are expensive and not practical for ongoing monitoring. Digital phenotyping, which measures behavior and mental status using data collected from smartphones, may be a practical way by which to conduct long-term sleep monitoring. This approach may be especially useful in youth; young people are digital natives and tend to use their smartphones on a near-constant basis, providing very rich data. Additionally, being able to differentiate clinical sleep disturbance from more typical adolescent sleep patterns – which are often irregular – would be particularly valuable clinically. The goal of the present study was to evaluate the feasibility and clinical utility of smartphone-based digital phenotyping to assess sleep in adolescents with BD and typically-developing (TD) peers.

Methods: Participants (aged 14-19) and their caregiver participated in a comprehensive diagnostic evaluation to determine group status (BD or TD). Following the baseline assessment, the adolescent and caregiver were interviewed monthly about the adolescent's mood and behavior. During this time, the adolescent used the Beiwe smartphone application, which collects surveys, location/mobility (GPS), and phone locked/unlocked status, among other data. Participants also completed self-report about their sleep quality the night before three times a week and reported monthly on their overall sleep quality. We assessed associations between phone-derived sleep duration/quality and both participant self-report about sleep and clinician-rated changes in mood from January 1, 2021 to January 1, 2022.

Results: Passive and survey data were obtained with minimal missingness among BD ($n = 22$) and TD ($n = 21$) participants; median number of days with phone data during the follow-up period was 223 (IQR: 116–322), the median number of sleep surveys was of 98 (range 53–148). Phone sensor-derived sleep duration data correspond with participant self-reported sleep and wake times. Inspection of behavioral features and screen lock/unlock data indicate unique sleep and circadian patterns between BD and TD participants; on average BD participants had less consistent sleep schedules and were more likely to have disturbed sleep. Additionally, on average BD participants spent 71 more minutes (95% CI: [27.6, 114.4]; $p = 0.002$) in state that is positively correlated with both sleep duration and prolonged phone usage. Finally, changes in sleep, as measured by digital phenotyping, are observed prior to clinician-rated mood changes.

Conclusions: Digital phenotyping is a feasible approach to collect objective sleep data from adolescents over a long period of time. This population, which is often reluctant to engage in mental health services and among whom smartphone use is ubiquitous, may be an ideal population for this low burden approach. Adolescence is the period during which mood disorders most often present and sleep disturbance can be an early symptom. Being able to detect clinically-significant sleep changes in high risk adolescents could support early detection and intervention to avoid long-term consequences associated with delayed diagnosis and treatment (e.g., worsening symptoms, hospitalization, suicide).

Keywords: Bipolar Disorder, Digital Phenotyping, Sleep

Disclosure: Nothing to disclose.

P330. Machine Learning of Hedonic Facial Reactions in Freely Moving Mice

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Background: Reward processing plays a fundamental role in survival across species and its disruption in humans contributes to a wide range of psychiatric disorders. As such, investigating the neurobiology underlying how reward processing goes awry in rodent models represents an opportunity to advance the mechanistic understanding of mental illness. Different subcomponents of reward processing, including anticipatory motivation (wanting) and hedonic evaluation (liking), depend on different neural circuits. However, while decades of research have revealed evolutionarily conserved facial expressions during studying hedonic evaluation of palatable stimuli, studying the dynamic neural circuit activity associated with anhedonia has been hampered by the challenge of recording these behaviors in freely moving mice in a variety of contexts. Here we have developed a method for recording and analyzing facial expressions in freely behaving mice during a classical conditioning cued reward task, allowing us to observe the evolution of hedonic reactions, including tongue protrusions, paw licking, and mandibular movements, on a trial-by-trial basis.

Methods: We trained 5 male and 4 female mice to associate a tone with water reward availability (CS+) and another tone with no water reward (CS-) to a criterion of 70 percent correct responses to the CS+ for two consecutive days. We surgically mounted a lightweight mirror and camera system that captured the mouse's face and used DeepLabCut pose estimation software to track various points of the face, paws, and tongue. We then developed algorithms to process these points in order to identify and quantify distinct hedonic behaviors across sessions. Using these behaviors as predictors, we trained supervised machine learning algorithms in MATLAB to classify trials with different hedonic valence. Statistical significance was evaluated using linear regression with mixed effects and 1-way ANOVAs.

Results: We found that the frequency of classical hedonic and novel facial behaviors depend on the reward volume ($N = 9$ mice; lick rates, $p < 0.00001$; mandible movement rate $p < 0.00001$; mandible amplitude $p < 0.00001$; tongue protrusion number $p < 0.00001$; paw lick number $p < 0.0001$, linear model with mixed effects. Classical measures such as tongue protrusions and paw licks also correlate with post-consumption lick rates within a reward bout (R for lick rates vs tongue protrusions $= 0.79$, $p < 0.0001$; R for lick rates vs paw licks - 0.8, $p < 0.0001$. Additionally, we were able to utilize these distinct behavioral events, as well as additional facial feature information, as predictors to train a machine learning algorithm that accurately classifies trials of varying reward sizes and identities ($N = 9$ mice for water trials and 4 mice for sucrose trials. Prob > FSize < 0.00001 and prob > FIdentity = < 0.00001, 1-way ANOVA of trials compared to shuffled data.)

Conclusions: Our method allows for granular understanding of behaviors underlying hedonic evaluation and allows for real-time quantification and manipulation of neural circuit activity underlying hedonic evaluation in freely moving mice.

Keywords: Reward Liking, Anhedonia, Machine Learning Classification, Computational Ethology

Disclosure: Genetika, Inc: Advisory Board (Self).

P331. Intrinsic Network Disruptions in Major Depressive Disorder Revealed by Whole-Brain Functional Connectivity Multi-Voxel Pattern Analysis

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Background: In this study, we used whole-brain functional connectivity multi-voxel pattern analysis (fc-MVPA) of functional magnetic resonance imaging data to investigate resting-state functional connectivity (rsFC) patterns distinguishing participants with major depressive disorder (MDD) from healthy controls (HC).

Methods: MDD and HC participants were recruited as part of the initial trial of the Canadian Biomarker Integration Network in Depression (CAN-BIND-1), and rsFC analysis was performed at baseline to contrast 147 MDD vs. 98 HC. Data-driven whole-brain fc-MVPA was applied on MDD vs. HC contrast to first identify regions of interest (ROIs), which were then used in seed-to-voxel post-hoc rsFC analyses.

Results: The fc-MVPA results converged to 6 clusters localized in the left cerebellar crus I/lobule VI, right precuneus, left superior lateral occipital cortex, left superior parietal lobule, right caudate, and dorsal anterior cingulate cortex, indicating whole-brain rsFC differences in MDD compared to HC. The largest cluster was localized at the border of the left crus I and lobule VI of the cerebellum, which corresponded to functional areas involved in attention. Post-hoc analyses revealed patterns of altered rsFC in the default mode, central executive, visual recognition, reward, salience, and sensorimotor networks in MDD participants.

Conclusions: Altered rsFC is a potential neurobiological signature of MDD that can be studied using data-driven methods. The unbiased nature of the analysis strategy can be useful in gaining a mechanistic understanding of the brain networks with altered rsFC in MDD.

Keywords: Novel Methods, Resting State Brain Imaging, Major Depressive Disorder (MDD)

Disclosures: Novartis, Eisai, Roche Canada: Grant (Self).

P332. Individual Prediction of Optimal Treatment Allocation Between Electroconvulsive Therapy or Ketamine Using the Personalized Advantage Index

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Background: Depression is a leading cause of disability and imparts a high social burden. Despite its global burden, clinicians are left with little guidance to assign patients to optimally effective treatments. Standard first-line antidepressants elicit remission in only one third of patients with diminishing efficacy for secondary and tertiary treatments. This has motivated an increasing interest in developing methods to prospectively allocate individual patients to treatments best suited to treat their symptoms. Here, using a large retrospective cohort of patients in a naturalistic treatment setting, we apply machine learning methods to generate individualized end-treatment symptom severity predictions for two treatments, electroconvulsive therapy (ECT) and ketamine, using pretreatment medical record and demographic measures. Evaluation of the predicted difference in end-treatment symptom severity between the two treatments yields a measure referred to as the Personalized Advantage Index (PAI), an indicator of the expected differential benefit of treatment selection. We then compare treatment outcomes between patients who were naturalistically assigned to their predicted optimal versus sub-optimal treatments. We hypothesized that patients who received a predicted optimal treatment would have significantly lower depressive symptoms compared to those who received a sub-optimal treatment.

Methods: Clinical and medical record data on 2671 patients who underwent ECT ($n = 2526$) or ketamine ($n = 235$) at McLean Hospital was aggregated. Depressive symptoms were measured using the nine-item Quick Inventory of Depressive Symptomatology (QIDS) before and after treatment. Propensity score matching was used to match patients between treatments on pretreatment QIDS scores using a 1:1 ratio yielding a final sample of 470 patients ($n = 235$ per treatment). Individual PAI scores were computed using leave-one-out cross validation in which a series of random forest regression (RFR) models with 1000 regression trees were trained to predict end-QIDS using N-1 patients. Model predictors were 119 demographic and medical record measures including a treatment (ketamine or ECT), the 24-item Behavior and Symptom Identification Scale (BASIS) subscales, Montreal Cognitive Assessment (MoCA) scale, medication history, and comorbid neurological, psychiatric, or general health diagnoses. Two end-QIDS predictions were made for each held-out patient: one using the patient's true treatment label and a counterfactual prediction in which the treatment label was switched to the treatment the patient did not receive. The prediction resulting in the lowest end-QIDS score was deemed the patient's predicted optimal treatment. We then compared distributions of end-QIDS scores between patients who received their predicted optimal treatments to those who did not using a two-sample, two-sided t-test. We then fit a RFR model with same outcome and predictors to the whole sample. This global model was evaluated using explainable artificial intelligence (AI) Shapley values to identify important predictors and predictor interactions with treatment type in the determination of end-QIDS predictions. Model performance was based on the coefficient of determination (R2) comparing predicted and actual end-QIDS scores. The significance of the model's performance was evaluated using permutation testing with $B = 1000$ resamples.

Results: Age, sex, pretreatment and end-QIDS score did not significantly differ between treatments after matching. ECT was predicted to be optimal for 111 patients who received it while ketamine was predicted to be optimal for 136 of patients who received it. Patients who received their optimal treatment ($n = 247$, 52%) had significantly lower end-QIDS scores compared to those who received a sub-optimal treatment (mean difference end-QIDS $= 1.68$, $t = 4.01$, $df = 464.45$, $p < 0.001$, Cohen's $D = 0.37$). The global model predicted end-QIDS significantly above chance ($R2 = 0.09$, $p < 0.001$). Shapley values revealed that higher pretreatment QIDS and BASIS self-harm scores predicted worse outcomes while older patients generally had more reduced end-QIDS. Important predictors had interactive effects with treatment: specifically, patients with elevated pretreatment QIDS, BASIS subscales (self-harm, relationships, and psychosis), older patients, and those with bipolar disorder, insomnia, or an elevated number of general-health diagnoses had improved outcomes with ECT versus ketamine. Meanwhile, patients with higher BASIS emotional lability scores, a primary diagnosis of MDD, and female patients had better outcomes with ketamine.

Conclusions: Treatment allocation is a central aim of psychiatric research and personalized medicine. We applied machine learning methods and the PAI approach to identify patients differentially suited to receive either ECT or ketamine based on easily acquired and inexpensive demographic and medical record data. As we hypothesized, patients who received their predicted optimal treatment had significantly better outcomes. Using novel, model agnostic explainable AI methods, we showed that certain patient characteristics differentially predicted treatment outcomes between ECT and ketamine which could be used to prospectively assign individual patients to each treatment arm. Our future work will extend this framework to predict treatment allocation across additional treatments.

Keywords: Major Depressive Disorder, Treatment Allocation, Machine Learning, Electroconvulsive Therapy, Ketamine

Disclosure: Nothing to disclose.

P333. Using Active and Passive Digital Phenotyping to Augment Efficacy Assessments in an Early-Stage Drug Development Program

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Background: Early stage drug development requires balancing cost and optimization of data collection. Aa a result, blinded trials may not be feasible because of the risk/benefit analysis. This involves assuming risks of potential placebo effects in order to not miss potentially beneficial elements of a novel compound. One strategy to reduce risk, by both increasing data collection and collecting data that is less susceptible to placebo effects is to use technology-based approaches which can actively and passively collect densely sampled digital phenotyping data. Clearly, passively collected data are less likely to manifest a participant-driven placebo effect. Some elements of actively sampled data are also not transparently related to efficacy measures, such as engagement in activities that are more frequent when participants are in a better emotional state, such as social and physical activities. This poster presents the results of an open-label treatment study with participants with Major Depressive Disorder study of a "ANC-501", a V1b receptor antagonist, wherein sampling with passive and active technology-based assessments occurred daily and clinical ratings were more widely dispersed.

Methods: In this study, 13 participants were treated with ANC-501 50mg adjunctive to ongoing AD medication in a non-blinded design for 8 weeks and examined with clinical ratings of depression (MADRS) anxiety (HAM-A) and that were collected at days 1, 8, 15, 29, 43, and 56. During the protocol, participants also answered ecological momentary assessment (EMA) surveys, 2 times per day, 7 days per week, as well as wearing an actigraph smartband which measured daily steps. EMA surveys examined depression (HAM-D 6) and Anxiety (GAD7) as well as a previously validated survey of daily activities which included location (Home vs away), social context (alone vs. with someone), productive and unproductive home-based activities and away from home activities. Data analyses included changes in symptoms based on in-person and EMA assessments of symptoms as well as EMA-based assessments of activities and daily steps. Concurrent and lagged analyses were used to determine if EMA and actigraphy-based assessments both converged with and predicted symptoms assessments.

Results: A total of 658 EMA surveys were collected over 8 weeks from the 13 participants. In person and EMA based ratings of depression identified clinical improvement, to day 56, all p .05) and both clinical and EMA depression ratings correlated with concurrent step counts (p.45). Productive activities significantly increased over time ($p = .02$) and increases in productive activities from baseline to days 8, 15, and 29 predicted clinical ratings of depression at the later assessments.

Conclusions: Even in a small, unblinded trial, passive and active digital phenotyping assessments converge with and predict clinical ratings. Most importantly, digital phenotyping content that is not an obvious element of an efficacy assessment (productive activities; step counts) correlates with concurrent clinical ratings and predicts later clinical changes. In this study, adherence was high and digital phenotyping data anticipated later clinical ratings, suggesting that these clinical ratings are truly sampling the stream of behavior that leads up to the dispersed ratings. These data suggest that low-cost, technology-based assessments can efficiently provide high volumes of information that could never be collected by an in-person assessment strategy.

Keywords: Major Depression, Ecological Momentary Assessment, Digital Phenotyping, Clinical Trial Rating Methods

Disclosures: Alkermes, Bioexcel, Boehringer-Ingelheim, Karuna Therapeutics, Minerva Neurosciences, Sunovion Pharmaceuticals, EMA Wellness: Consultant (Self). WCG Endpoint Solutions: Royalties (Self). iFunction, Inc: Founder (Self).

P334. An EEG-Based, Machine Learning Biomarker to Identify Responsive Vs. Non-Responsive Subjects in an MDD Clinical Trial: Initial Validation Data From the EMBARC Study Database

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Background: Failure on primary endpoints remains one of the most pressing issues in clinical trials of Central Nervous System (CNS) drugs. One issue may be the selection of appropriate patient (sub)populations, given that some patients respond well to a drug that others respond poorly to, or not at all. Neumarker's proprietary technologies offer a promising solution to reduce the failure rate of clinical trials and improve treatment effect sizes, by leveraging an EEG-based biomarker to identify the population of patients most likely to respond to a given therapeutic.

Methods: We conducted a post-hoc analysis of baseline resting state scalp EEG data from the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) study, a multi-site, double-blind, placebo-controlled clinical trial of sertraline in major depressive disorder (MDD). Brain functional connectivity was used as one set of features, and Neumarker's data analytic platform was employed with unsupervised machine learning and clustering algorithms to discover biomarkers based on brain functional connectivity. We successfully divided MDD patients into two subtypes (subtype 1 and subtype 2) and calculated the Cohen's d effect sizes and p-values for each subtype. Qualitative and quantitative cross-site consistency analyses were performed to validate our clustering algorithm. Further analyses based on demographic factors of age, gender, and race were performed to compare subtype 1 and subtype 2 patients.

Results: Subtype 1 patients, comprising approximately 46% of the total patient population, exhibited a significant treatment response to sertraline vs. placebo on change from baseline (CFB) on the primary outcome of the Hamilton Rating Scale for Depression 17-item version (HAMD-17) with a 12.5-point reduction in the sertraline group and a 6.8-point reduction in the placebo group; the Cohen's d effect size was 1.007 ($p < 0.0001$). These results showed a sizable improvement compared to the treatment results of the entire patient group (after outlier elimination), with a Cohen's d effect size of 0.319 ($p = 0.032$). Conversely, subtype 2 patients did not respond to sertraline treatment, with a 5.3-point reduction in the sertraline group and a 6.6-point reduction in the placebo group; the Cohen's d effect size was -0.073 ($p = 0.716$). Cross-site validation in this multi-site study was strong. Analysis of HAMD-17 individual items indicated significant treatment effect differences between subtype 1 and subtype 2 on depressed mood, somatic general, weight loss, and 3 other items. The treatment effect size differences were particularly pronounced for female patients, patients aged 40 or above, and both Caucasians and African Americans when age, gender, and race subgroups were analyzed.

Conclusions: Neumarker's data analytical technologies based on brain functional connectivity features extracted from baseline EEG data offer a novel approach to enrich patient selection for CNS clinical trials. This technology has the potential to identify populations with significantly enhanced treatment effect sizes in clinical trials, reducing the failure rate of clinical trials, and substantially decreasing the required sample size, thereby reducing the overall cost and shortening the enrollment time for successful clinical trials. Further validation of other MDD and other CNS disease datasets, are underway.

Keywords: EEG Biomarkers, Major Depressive Disorder (MDD), Clinical Trial Methodology

Disclosure Neumarker, Inc: Consultant (Self).

P335. Using a Longitudinal Model to Predict Outcomes to Ketamine Intravenous Therapy for Depression

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Background: Recent large-scale real world evidence studies have shown that ketamine intravenous therapy (KIT) can be a highly effective treatment for depression for roughly 50% of patients. The ability to predict which patients will respond to KIT is important as it is costly and additional treatment failures take a toll. However, there are two challenges for predicting which patients will respond to KIT. First, there is considerable variability in response to KIT treatment at the individual level – individuals may be considered "responders" at one time point, but a subsequent mood survey delivered on a bad day could be interpreted as relapse. Second, patients do not receive a uniform number of treatments, and the number of treatments is known to affect treatment response (McInnes et al. 2022, Hietames et al., 2023).

In this work, we present two innovations to overcome these challenges: i) we develop a model to predict longitudinal outcomes to KIT and ii) we predict long-term outcomes conditioned on the number of treatments a patient may receive, and combine this with the prediction of the number of treatments a patient will receive. This predictive algorithm can provide clinicians with important information, such as i) how many treatments a patient will need to achieve a particular response threshold, ii) how likely it is that a patient will adhere to a particular number of treatments, and iii) how likely a patient is to respond to KIT without a priori knowledge of how many treatments the patient will receive.

Methods: We used data from a large sample of patients who initiated KIT within Osmind's electronic health record-derived de-identified database. We identified a total N = 11,641 patients that had received at least one infusion prior to May 1, 2023. For analysis, a subset of these patients who met the following criteria were used: i) patients who completed a Patient Health Questionnaire (PHQ-9) depression survey within 60 days prior to their first infusion (baseline) and at least one PHQ-9 within 28-56 days after their first infusion (post-index), and ii) patients who had a baseline PHQ-9 score > 9. This resulted in a final N = 5,192. The complete sample was then split into a model development set (70%) and a model validation set (30%).

First, we developed a Bayesian non-linear mixed effects model (similar to Berlow et al., 2023) to model patient outcomes continuously over time. To predict which patients exhibit the best response to treatment, demographic and clinical variables, as well as the number of induction infusions a patient received, were used to train the model to predict the intercept (baseline score) and slope (change in score over time) for new patients. We then used demographic and clinical variables from new patients to predict a patient's personal response trajectory if they received from 1 to 7+ induction infusions. Next, we used a Bayesian Cox Proportional Hazards regression model to predict the probability that a patient would receive 1 to 7+ induction infusions given their demographic and clinical variables. The final predicted response of a new patient was the weighted average of the patient's response if they received 1 to 7+ induction infusions, weighted by the probability that the patient would receive 1 to 7+ induction infusions.

We used Bayesian leave-one-out cross-validation to test whether each model performed better than a null model (models that do not include patient demographic and clinical variables). As the integrated model predicted a continuous outcome – the response trajectory – we evaluated the correlation between observed PHQ-9 change scores and model predicted PHQ-9 change scores in 4 week (28 day) bins from the index date to 16 weeks post-index.

Results: Both the response and adherence models performed better than their respective null models. Integrated response predictions (the predicted response accounting for the predicted number of induction infusions a patient will receive) were significantly correlated with observed response as measured via PHQ-9 scores, from the induction period out to at least 16 weeks post induction. Pearson correlations between the observed change in PHQ-9 score from baseline to follow up and the predicted change score were 0.35 during the induction period, 0.40 from 4-8 weeks post-index, 0.39 from 8-12 weeks post-index, and 0.44 from 12-16 weeks post-index.

Conclusions: This novel integrated response-adherence prediction approach applied to KIT yields good predictive performance, with moderate correlations between observed and predicted outcomes for months following the initiation of treatment using only clinical and demographic variables available at baseline. Compared to response classification models, i) it predicts long-term average outcomes in the future at any time point, and ii) it can be easily extended to update throughout the course of treatment (e.g., if a patient takes a PHQ-9 survey 2 weeks after the first treatment, future predictions will become more accurate).

Keywords: (R,S)-Ketamine Infusion Therapy, Clinical Outcome Prediction, Machine Learning

Disclosure: Osmind: Employee (Self).

P336. Mood Instability as a Stratification Method for Bipolar Disorder

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Background: Bipolar disorders (BD) are highly heterogeneous necessitating stratification and phenotyping methods that can capture variability and trajectories of illness. Preliminary evidence points towards mood instability as a clear phenotype underlying BD. Yet, no studies to our knowledge have examined whether patients with BD can be stratified by an instability score calculated based on patient reported outcomes measures (PROMs) within measurement-based care. Stratification of patients based on instability in depression, mania, and anxiety could provide a usable metric for predicting risk as well as treatment response and outcomes. The goal of the present study was to identify ideal stratification methods based on instability of depression, mania, and anxiety scores and to test whether this stratification method accounts for significant variance in mental and physical health outcomes.

Methods: Participants were drawn from the Prechter Longitudinal Study of BD (PLS-BD), an observational cohort study with deep clinical and biological phenotyping over a median of 9 years. Participants complete the Patient Health Questionnaire (PHQ9), Altman Self-Rating Mania Scale (ASRM), Generalized Anxiety Questionnaire (GAD7), and SF-12 mental and physical health questionnaire, bimonthly throughout participation. We identified individuals with BD (n = 290) and healthy controls (HC; n = 129) who had been followed for at least 10 years and had at least 12 repeated PROMs. We calculated mood instability as the rolling within-person variance over a 1-year period. Low, moderate, and high instability thresholds were identified for each mood measure based on the 60th and 95th percentiles. Linear mixed effects models tested whether: (1) groups differed based on rolling variance scores and (2) whether instability thresholds predicted significant variance in physical and mental health outcomes after accounting for sex, race, age, mean levels of PHQ9, ASRM, and GAD7, and comorbidities.

Results: There were 4,724 variance observations across an average of 37.2 instances for HC and 9,167 variance observations across an average of 35.4 instances for those with BD. Individuals with PHQ9 variance scores ≥ 12 fell in the medium threshold (60th percentile) and ≥ 39 fell into the high threshold (95th percentile). On average, the BD group had significantly higher PHQ9 variance scores compared to HC (Cohen's D = .97, p < .001) and a greater proportion of individuals with BD fell into the medium (1.6% vs. 53.5%) and high thresholds (0% vs. 11%). Individuals with ASRM variance scores ≥ 4.5 fell in the medium threshold and ≥ 15 fell into the high threshold. On average, the BD group had significantly higher ASRM variance scores compared to HC (Cohen's D = .30, p < .001) and a greater proportion of individuals with BD fell into the medium (15.2% vs. 49%) and high thresholds (2.4% vs. 10%). Individuals with GAD7 variance scores ≥ 11 fell into the medium threshold and ≥ 31 fell into the high threshold. On average, the BD group had significantly higher GAD7 variance scores compared to HC (Cohen's D = 1.03, p < .001) and a greater proportion of individuals fell into the medium (2.5% vs. 51.3%) and high thresholds (0.8% vs. 8.9%).

Higher variance scores were associated with worse mental health outcomes for those with BD (PHQ9: slope = -.27, p < .001; ASRM: slope = .30, p < .001; GAD7: slope = -.07, p = .04) but not HC (PHQ9: slope = -.16, p = .05; ASRM: slope = .14, p = .51; GAD7: slope = .14, p = .38). A different pattern emerged for physical health outcomes. Instability in depression and anxiety was unassociated with physical health outcomes for both BD (PHQ9: slope = 0.03, p = .20; GAD7: slope = 0.05, p = .05) and HC (PHQ9: slope = -.13, p = .05; GAD7: slope = 0.00, p = .97). For mania, greater ASRM variance scores were associated with better physical functioning for those with BD (slope = .43, p < .001) but not for HC (slope = .23, p = .18).

Next, composite mood instability scores were calculated as the average of the rolling variance of PHQ9, ASRM, and GAD7 scores. This composite score was classified as "low", "moderate", and "high "mood instability at the same thresholds (60th and 95th percentiles). We re-ran our models predicting mental and physical health outcomes to see if the composite stratification methods accounted for significant variance in outcomes. Those in both the moderate mood instability group (Est. = -2.25, p < .001) and the high instability group (Est. = -5.42, p < .001) had worse mental health outcomes than those in the low instability group. In contrast, for physical health outcomes, those in the high instability group had better physical health outcomes (Est. = 1.23, p = .04).

Conclusions: Individuals with BD were able to be stratified by the within-person variance of their mood measures. A higher proportion of individuals with BD fell into the moderate and high instability groups and those with BD had greater rolling variance in depression, mania, and anxiety scores. Furthermore, the composite mood instability stratification method accounted for significant variance in mental health outcomes for those with BD but not HC indicating evidence of specificity of the phenotype. Future studies will test wither these stratification methods account for significant variance in treatment outcomes and response. Thresholds with high sensitivity and specificity will be established based on greater amounts of data (e.g., PROMs from electronic health records across medical systems).

Keywords: Bipolar Disorder, Precision Medicine for Mood Disorders, Patient Reported Outcomes

Disclosure: Nothing to disclose.

P337. Exponential Decay: A Generalized Nonlinear Model of Antidepressant Response

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Background: In clinical trials for depression, effective treatments are often associated with large reductions in depressive symptoms within the first few weeks, followed by smaller but continued improvements approaching a plateau. This nonlinear pattern of treatment response has been demonstrated to be well-modeled with an exponential decay function for several antidepressant medications as well as multiple transcranial magnetic stimulation (TMS) protocols (Scientific Reports 13.1 (2023): 7138). This study aimed to apply the exponential decay model to several novel and emerging treatments for depression and assess the generalizability of this approach to characterize treatment response across various agents and modalities.

Methods: Longitudinal group-level symptom rating data from eight randomized controlled trials (RCT) for depression were collected, representing a broad range of novel medications and modalities. Studies included a double-blind trial of psilocybin versus escitalopram (n = 59, N Engl J Med. 2021 Apr 15;384(15):1402-1411); an open-label RCT of repeated IV ketamine versus electroconvulsive therapy (ECT)(n = 403, N Engl J Med. 2023 Jun 22;388(25):2315-2325); a double-blind trial of transcranial direct current stimulation (tDCS) versus escitalopram and placebo (n = 245, N Engl J Med. 2017 Jun 29;376(26):2523-2533); a double-blind trial of an accelerated intermittent theta burst stimulation (iTBS) protocol (Stanford Neuromodulation Therapy (SNT))(n = 32, Am J Psychiatry. 2022 Feb;179(2):132-141); a double-blind trial of dextromethorphan plus bupropion versus bupropion (n = 80, Am J Psychiatry. 2022 Jul;179(7):490-499); a placebo-controlled trial of zuranolone (n = 534, Am J Psychiatry. 2023 May 3:appiajp20220459); a placebo-controlled RCT of adjunctive cariprazine (n = 751, Am J Psychiatry. 2023 Mar 1;180(3):241-251); and a placebo-controlled trial of adjunctive pimavanserin (n = 207, J Clin Psychiatry. 2019 Sep 24;80(6):19m12928). Outcome measures included the Hamilton Depression Rating Scale (HAMD), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Quick Inventory of Depressive Symptoms (QIDS). Longitudinal group-level mean symptom rating data were extracted from figures using www.graphreader.com and included tables.

Nonlinear mixed-effects (NLME) models were constructed for each study using the exponential decay function, D(t) = A*e^(-t/B) +C, in which symptom ratings (D) at time (t) are described using the magnitude of total response (A), decaying at a time constant (B), and approaching a minimum value (C). Model parameters A and C were treated as random effects at the treatment arm level. These NLME models were then compared to corresponding linear mixed-effects (LME) models in which the slope and intercept were treated as random effects by treatment arm using the Akaike

information criterion (AIC), Bayesian information criterion (BIC) and likelihood ratio test (LRT).

Results: The NLME models converged for seven of the eight studies investigated. The data from the SNT trial of accelerated iTBS did not contain enough longitudinal data during the treatment phase to estimate the time constant B. For the remaining seven studies, the NLME models yielded significant estimates for all model parameters ($p < 0.05$ for all parameters for all models, with 95% (20/21) of parameter estimates yielding $p < 0.005$). When compared to corresponding LME models, the seven NLME models yielded consistently lower AIC and BIC values and significant LRTs (LRT range 21.6-49.0, all $p < 0.001$), suggesting the nonlinear exponential decay models are better fits. The study-wise estimates of the time constant B ranged from 3.1-18.9 days. The zuranolone study ($B = 3.1$ days) and the psilocybin vs. escitalopram study ($B = 3.4$ days) had the shortest estimates of the time constant B, suggesting a rapid approach to a plateau. The ketamine vs. ECT study ($B = 6.5$ days) and tDCS vs. escitalopram and placebo ($B = 8.7$ days) had intermediate estimates of B. The dextromethorphan and bupropion study (13.3 days), the adjunctive pimavanserin (11.5 days) and cariprazine (18.9 days) studies had the longest estimates of B. It is important to note that these time constants are estimated using all treatment arms in the studies, meaning that the comparison arm (active or placebo) often demonstrated a similar time constant and pattern as the treatment modality of investigation.

Conclusions: These results demonstrate that improvements in depressive symptoms during clinical trials often follow a nonlinear pattern that is well-modeled with an exponential decay function. This pattern is seen across multiple treatment modalities, including novel and emerging approaches such as psychedelics, NMDA antagonists, neuromodulation, and new adjunctive treatment strategies. These findings suggest that the exponential model of antidepressant treatment response generalizes to most biological depression treatment modalities and may provide a useful framework to inform future treatment trials.

Keywords: Depression Model, Novel Antidepressant, Statistical Methods, Ketamine, Neurosteroids, Psychedelics, Neuromodulation

Disclosure: Nothing to disclose.

P338. Social Defeat Stress Induces a Depression-related Phenotype in Male Prairie Voles

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Background: Stress-induced illnesses, like major depression, are among the leading causes of disability across the world. Consequently, there is a dire need for the validation of translationally-suited animal models incorporating social stress to uncover the etiology of depression. Prairie voles (Microtus ochrogaster) are more translationally relevant than many other rodent models as they display monogamous social and parental behaviors and more primate-like neuroanatomy. Therefore, we evaluated whether the social defeat stress (SDS) model in male prairie voles induces depression-relevant behavioral outcomes.

Methods: Adult sexually-naïve male prairie voles experienced SDS bouts from a conspecific pair-bonded male aggressor, 10 min per day for 10 consecutive days. Non-stressed controls (same-sex siblings) were housed in similar conditions but never experienced physical stress. Twenty-four hr later, voles were evaluated in social interaction, sucrose preference, and Morris water maze tests – behavioral endpoints validated to assess social withdrawal, anhedonia-related behavior, and spatial memory performance, respectively.

Results: SDS-exposed voles displayed lower sociability and body weight, decreased preference for a sucrose solution, and impairment of spatial memory retrieval. Importantly, no differences in general locomotor activity were observed as a function of SDS exposure.

Conclusions: We found that repeated SDS exposure, in male prairie voles, results in a depression-relevant phenotype resembling an anhedonia-like outcome (per reductions in sucrose preference) along with social withdrawal and spatial memory impairment – highlighting that the prairie vole is a valuable model with potential to study the neurobiology of social stress-induced depression-related outcomes.

Keywords: Social Defeat Stress, Prairie Voles, Spatial Memory, Social and Behavioral Deficits

Disclosure: Nothing to disclose.

P339. Exploring Predictors of Bipolar Disorder Onset: An Analysis of Demographics, Proximal Risks, and Exposure to Medication

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Background: To test predictors of prospective development of bipolar disorder (BD) in a large outpatient sample, including demographic, diagnostic, and proximal risk factors, and prior exposure to antidepressants or stimulants.

Methods: Analysis of the $N = 585$ cases with data available through 72-month follow-up from the Longitudinal Assessment of Manic Symptoms (LAMS) project. Youth were 6-12 years old at baseline. The sample was enriched for elevated symptoms of mania (PGBI-10M score >11). Families completed semi-structured diagnostic interviews (KSADS-PL-W) with highly trained raters, returning for follow-up interviews in 6-month intervals. Interviews established date of onset of new mood episodes. Cox regression analyses examined time to onset of BD, using: (a) a "fully progressed" to DSM-5 defined BD I or II, and (b) an "any bipolar spectrum" definition, adding cyclothymia and Other Specified Bipolar and Related Disorder (OSBRD). A priori predictors were based on prior literature and included (1) distal demographic and risk factors (sex, race/ethnicity, Medicaid status, and parental history of mania), (2) other disorders that might be associated with risk (anxiety, ADHD, oppositional-defiant [ODD], and conduct [CD]), (3) proximal risk factors (baseline mood symptoms, parenting stress, stressful life events, early or delayed pubertal status), and (4) exposure to antidepressant or stimulant medication, each as a separate predictor.

Results: Missing data analyses found no significant differences between participants with missing or complete data on variables in models (the largest discrepancy was males were more likely to be missing data, $r = .07$, $p = .091$). By month 72, 113/595 (17%) had developed fully progressed BD, and 194/595 (28%) had developed any bipolar spectrum. Distal, diagnostic, and proximal variables significantly predicted both definitions of BD onset. Parental bipolar history, baseline PGBI-10M score, parenting stress, and prior conduct disorder all increased the hazard of both BD outcomes. Prior ADHD or oppositional defiant disorder decreased the hazard of the fully progressed definition, controlling for other variables. Advanced pubertal status at an early age was weakly associated (hazard = 1.63, $p < .10$) with later BD1/2, but not with broader "any BD" status. Stimulant and antidepressant exposure

showed no association with either BD outcome, either in isolation or after adjusting for other variables.

Conclusions: Results from these prospective analyses confirm the role of family bipolar history, family stress, and baseline symptoms of labile mood and energy as risk factors for later BD. Prior conduct disorder, but not ADHD, oppositional, or anxiety disorders, increased hazard of subsequent BD. Stimulant or antidepressant exposure did not significantly increase hazard of later BD, consistent with findings from longitudinal work with ADHD cohorts. Limitations include that the prospective follow-up did not extend through the entire age of risk for development of BD, and fewer than 50% of cases reached either definition of bipolar outcome within the observed follow-up period.

Keywords: Bipolar Disorder, Longitudinal, Pediatric Bipolar Disorder

Disclosures: Signant Health: Consultant (Self). American Psychological Association, Guilford Press: Royalties (Self).

P340. Associations of Polygenic Risk Score for Suicide Behavior With Frontal Gray Matter Morphology in Bipolar Disorder

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Background: Bipolar disorder (BD) has a high risk for suicide. However, the underlying mechanisms are not clear and methods to identify individuals with BD at especially high risk remain critically needed. In individuals with BD who have made suicide attempts, widely considered a major risk factor for death by suicide, neuroimaging studies have converged in showing differences in frontal cortex, especially in ventral prefrontal regions. In addition to the frontal differences having been shown in adolescents and adults with BD who made attempts in the past, frontal differences were also observed in adolescents and adults who made future attempts, suggesting that altered frontal neurodevelopment may contribute to risk for future suicide behavior. Frontal differences in BD have also shown relationships with suicide behavior risk-associated clinical and behavioral phenotypes, such as impulsiveness. A polygenic risk score (PRS) derived from genome-wide association studies (GWAS) of suicide attempts in the general population was identified and showed relationships with suicide risk factors (Mullins et al., 2022). We investigated the relationship between this suicide behavior PRS (SPRS) and frontal cortex morphology in individuals with BD, with and without previous suicide attempts.

Methods: SPRS scores were calculated using the threshold and clumping method deployed by PRSice-2 for 225 participants with BD (71 previous suicide attempters, SA;154 non attempters, nonSA) and 151 healthy comparison participants (HC). Participant ages ranged from 14 to 60 years, with mean age of 30 years and 56% female. European ancestry was assigned by clustering with 1000 Genomes Project reference samples of European, African, East Asian, and Latin American ancestry. Within BD, we assessed the association between SPRS and regional gray matter (GM) surface area and thickness for a ventral prefrontal region comprised by the inferior frontal gyrus (IFG) and orbitofrontal cortex (OFC) (defined using the Desikan-Klliany atlas), separately for the left and right hemisphere. We also explored the region subdomains (IFG: pars triangularis, pars orbitalis, pars opercularis; OFC: lateral and medial).

Results: SA group had the highest mean SPRS, then nonSAs, and HC group had the lowest mean SPRS, although group differences were not significant. Within the BD group, higher SPRS was significantly associated with lower right ventral prefrontal GM surface area (Pearson $r = -0.15$, $p = 0.028$). Within the ventral prefrontal cortex, this association was significant only for the right IFG (Pearson $r = -0.22$, $p = 0.0009$), including each of its three subdomain regions (right pars triangularis: $r = -0.22$, $p = 0.0008$; right pars orbitalis: $r = -0.16$, $p = 0.017$; right pars opercularis: $r = -0.14$, $p = 0.039$). The associations of SPRS with IFG surface area were significant for both the SA and nonSA subgroups. Mean right IFG GM surface area was the smallest in the SAs, then in the nonSAs, and largest in the HCs, although these differences were not significant. No significant associations were found with the left IFG, or right and left OFC GM surface area or GM thickness.

Conclusions: In individuals with BD, we observed an association between SPRS with GM surface area reductions in right IFG, a brain region previously associated with suicide behavior and other behaviors also previously associated with the SPRS. BD suicide attempters had the highest SPRS and the smallest right IFG surface area, however, replication in large-scale cohorts may be needed to show significant differences between SAs and nonSAs. These findings may help elucidate mechanisms underlying risk for suicide behavior in BD. They suggest that the SPRS may reflect genetic mechanisms that may contribute to brain differences underlying increased suicide risk in BD. The genetic-brain association observed in NSAs may provide an initial lead for the detection of especially high suicide risk in individuals with BD.

Keywords: Bipolar Disorder, Magnetic Resonance Imaging, Polygenic Risk Score, Genetics

Disclosure: Nothing to disclose.

P341. Sex Differences in the Relationship Between GABA and Aggression in Veterans With Suicide Behaviors: A Pilot Study

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Background: The Department of Veterans Affairs has identified suicide prevention and improving the health of female Veterans as two of its high-priority areas. Numerous individual and sociocultural factors, including gender differences in suicidal and aggressive behavior, have been associated with suicide (Holman and Williams, 2022; McCloskey and Ammerman, 2017). Human imaging studies applying magnetic resonance spectroscopy (MRS) have shown that brain metabolites such as gamma-amino butyric acid (GABA) are associated with aggression (Ende et al., 2017) and suicide (Pabba and Sibille, 2016). Pilot research has extended findings on GABA and suicide to female versus male Veterans with results showing decreased GABA/Creatine in female Veterans with suicide behaviors compared to female Veterans without suicide behaviors (Sheth et al., 2018). However, limited research has examined sex-specific risk factors in a model of brain metabolites with aggression and suicide behaviors. Therefore, the current pilot study focused on the association between GABA and aggression in female compared to male Veterans with a history of suicide ideation and attempts.

Methods: Twenty-seven Veterans (12 female, 15 male) between the ages of 18 and 55 completed a structured interview assessing history of suicidal behavior (Columbia Suicide Severity Rating Scales (CSSRS)). All Veterans included in the analyses reported a lifetime history of suicide ideation, aborted, interrupted, or actual

attempts. Participants also completed the self-report Buss Perry Aggression Questionnaire (BPAQ), which yields five subscale scores: Anger, Hostility, Physical, Verbal, and Total Aggression. The Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Inventory (HAM-A) were completed to assess symptoms of anxiety and depression. Participants completed MRS to investigate brain GABA levels in the anterior cingulate cortex (ACC). MRS acquisitions were conducted on a 3-Tesla Siemens Prisma MR scanner (Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. The ACC voxels were placed anterior to the genu of the corpus callosum and positioned on the midline on axial images. The edited spectrum was fitted using the Matlab-based Gannet ToolKit. Linear regression models were used to examine the relationships between GABA levels and aggression measures. Age was included in the regression model as a covariate.

Results: Females with a history of suicide behavior evidenced an association between GABA and aggression, including relationships between GABA and Total Aggression ($\beta = -0.49$, $P = 0.04$); Anger ($\beta = -0.58$, $P = 0.04$); and Physical Aggression ($\beta = -0.49$, $P = 0.04$). In contrast, male Veterans with suicide behaviors did not show any significant associations between GABA and aggression (all $P > 0.05$). Furthermore, Veteran groups did not differ on age, depression, or anxiety symptom scores (all $P > 0.05$), suggesting differences were not due to demographic and clinical variables.

Conclusions: In female Veterans, a decrease in GABA was associated with increases in total aggression, anger, and physical aggression. GABA is the major inhibitory neurotransmitter in the brain and as such is involved with a variety of behaviors, including inhibition of prepotent responses (Li et al., 2022). The current results are consistent with the hypothesis that GABA mediates aggressive behaviors in Veterans with suicide behavior and, in particular, female Veterans. Importantly, female and male Veterans did not differ in depressive or anxious symptoms, suggesting no marked influence of mood or anxiety on these sex-specific results. These results have significant implications, as GABA levels can be modified using medications which in turn may provide treatment options for aggressive behavior in female Veterans who report suicide behavior. Future research will benefit from study replication with a larger sample size.

Keywords: Sex-Specific Effects, Suicide, Aggression, GABA

Disclosure: Nothing to disclose.

P342. Early Improvement With Adjunctive Cariprazine as a Predictor of Response in Major Depressive Disorder: A Post Hoc Analysis of a Randomized Clinical Trial

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Background: Cariprazine is a dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist approved for the adjunctive treatment of major depressive disorder (MDD). Evidence suggests that early symptom improvement may be predictive of later response and remission in patients with MDD; therefore, early treatment response could inform therapeutic decision-making. The objective of this study was to assess whether early symptom improvement with cariprazine 1.5 mg/d or 3 mg/d as an adjunct to antidepressant therapy (ADT) predicts later depressive and anxiolytic response in patients with MDD.

Methods: In a post hoc analysis, data from a randomized phase 3 clinical trial (NCT03738215) were analyzed. Patients with MDD and a partial response (< 50%) to at least 1 antidepressant monotherapy in the current episode were randomized (1:1:1) to receive cariprazine 1.5 mg/d, 3 mg/d, or placebo + their current ADT for 6 weeks of double-blind treatment. Patients in the cariprazine 3 mg/d group initiated cariprazine 1.5 mg/d, which was subsequently increased to 3 mg/d on Day 15. Early improvement and subsequent response were assessed using change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HAM-A) total scores. Early improvement was defined as ≥ 25% reduction from baseline in MADRS (depressive) or HAM-A (anxiety) total scores at Week 2. Treatment response was defined as ≥ 50% reduction in MADRS or HAM-A total scores at Week 6. Sensitivity, specificity, positive predictive values, negative predictive values, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine whether early symptom improvement with adjunctive cariprazine predicts antidepressant and anxiolytic response.

Results: At Week 2, 53% of patients in the cariprazine 1.5 mg/d group ($n = 242$) and 49% in the cariprazine 3 mg/d group ($n = 245$) met criteria for early MADRS improvement. Of early MADRS improvers receiving cariprazine 1.5 mg/d, 61% had an antidepressant response (sensitivity = 74%, specificity = 64%; OR [95% CI] = 4.9 [2.84, 8.62]) and 52% had an anxiolytic response (sensitivity = 67%, specificity = 58%; OR = 2.8 [1.64, 4.80]) at Week 6. Of early MADRS improvers receiving cariprazine 3 mg/d, 60% had an antidepressant response (sensitivity = 77%, specificity = 68%; OR = 6.8 [3.79, 12.25]) and 58% had an anxiolytic response (sensitivity = 72%, specificity = 66%; OR = 4.9 [2.82, 8.62]) at Week 6. In patients without early MADRS improvement, uptitration to cariprazine 3 mg/d resulted in 18% and 22% of patients achieving antidepressant and anxiolytic response, respectively. At Week 2, 47% of patients in the cariprazine 1.5 mg/d group and 49% in the 3 mg/d group met criteria for early HAM-A improvement. Of early HAM-A improvers receiving cariprazine 1.5 mg/d, 57% achieved an antidepressant response (sensitivity = 60%, specificity = 64%; OR = 2.7 [1.60, 4.57]) and 56% achieved an anxiolytic response (sensitivity = 64%, specificity = 65%; OR = 3.4 [1.98, 5.79]) at Week 6. Of early HAM-A improvers receiving cariprazine 3 mg/d, 53% achieved an antidepressant response (sensitivity = 67%, specificity = 63%; OR = 3.4 [2.00, 5.93]) and 57% achieved an anxiolytic response (sensitivity = 70%, specificity = 66%; OR = 4.5 [2.57, 7.74]) at Week 6. In patients without early HAM-A improvement, uptitration to cariprazine 3 mg/d resulted in 25% and 23% of patients achieving antidepressant and anxiolytic response, respectively.

Conclusions: Among patients with MDD using cariprazine as an adjunct to ADT, those who displayed early symptom improvement had significantly greater odds of achieving MADRS and HAM-A response than those who did not. Approximately 18% to 25% of patients who did not display early improvement with cariprazine 1.5 mg/d subsequently achieved antidepressive and anxiolytic response following uptitration to 3 mg/d, supporting the need for dose options. Early symptom improvement with cariprazine as an adjunct to ADT may be a clinically useful predictor of response in patients with MDD.

Keywords: Cariprazine, Major Depressive Disorder, Early Improvement, Treatment Response, Post Hoc Analysis

Disclosure: AbbVie: Employee (Self).

P343. Long-Term Efficacy of Adjunctive Cariprazine in Patients With MDD: Results From an Open-Label 26-Week Safety Study

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Background: Cariprazine is a D3-preferring dopamine D3/D2 receptor partial agonist and 5-HT1A partial agonist. This phase 3, multicenter, open-label, long-term (26-week), flexible-dose (1.5–4.5 mg/day) study assessed the long-term safety and tolerability of cariprazine used adjunctively with antidepressant therapy in adult patients with major depressive disorder (MDD) who had either completed a lead-in study (n = 311) or had been newly recruited (n = 131). Patients from the lead-in study completed treatment with placebo or cariprazine plus antidepressant therapy (double-blind placebo, n = 109; double-blind cariprazine, n = 108; single-blind placebo, n = 94). This study also included outcome measures that allowed for the long-term efficacy to be evaluated in patients treated with adjunctive cariprazine treatment plus an on-going antidepressant.

Methods: The primary objective of this study was long-term safety and tolerability. Efficacy assessments were also collected, including change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score and Clinical Global Impressions-Severity (CGI-S) score. MADRS response (≥50% reduction from baseline in MADRS total score) and remission (MADRS total score ≤10) rates were evaluated. The baseline for efficacy assessments was the lead-in baseline for rollover patients and the last available efficacy assessment before the first dose of open-label cariprazine for new patients. Efficacy parameters were summarized using descriptive statistics for the intent-to-treat population (patients from the safety population who had at least one efficacy assessment after visit 2); no inferential statistical analyses were carried out for efficacy parameters.

Results: Of the 442 patients enrolled in the study, 345 fulfilled the inclusion criteria and received open-label study drug; 336 patients had a postbaseline MADRS assessment and were included in the intent-to-treat population. Baseline mean (SD) MADRS and CGI-S scores were 22.8 (9.0) and 3.8 (1.0), respectively. Using a last observation carried forward (LOCF) method, the mean (SD) changes from baseline to week 26 in the MADRS total score and the CGI-S score were −8.9 (10.5) and −1.1 (1.3), respectively. MADRS response rates from baseline to Weeks 4, 12, 18, and 26 were 34.8% (n = 117), 43.8% (n = 147), 44.0% (n = 148), 47.6% (n = 160), respectively. MADRS remission rates from baseline at Weeks 4, 12, 18, and 26 were 11% (n = 37), 34.8% (n = 117), 42.6% (n = 143), 46.4% (n = 156), 45.8% (n = 154), respectively.

Conclusions: Cariprazine 1.5–4.5 mg/day was generally safe and well tolerated when used as a long-term adjunctive therapy for MDD. MADRS and CGI-S scores continued to decrease during the 6-month treatment period, with an increasing proportion of patients achieving MADRS response and remission over study duration. These data suggest that long-term treatment with adjunctive cariprazine was associated with a durable antidepressant effect in patients with MDD.

Keywords: Cariprazine, Major Depressive Disorder, Depression, Adjunctive, Long-Term

Disclosure: AbbVie: Employee (Self).

P344. Metabolomic Signatures of RDoC Framework-Based Anhedonia Phenotypes and Change With Serotonergic Antidepressants in Major Depressive Disorder

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Background: Anhedonia is a debilitating symptom of major depressive disorder (MDD), associated with an increased risk of suicidality and poor functioning. The Research Domain Criteria (RDoC) framework provides a unique way to identify depressive phenotypes based on biological constructs. In a recent study we described three anhedonia phenotypes by applying RDoC framework to standardized depression scales: (i) Anhedonia (A); (ii) Core Depression – depressed mood and interest (CD); and (iii) Interest activity – concentration, interest, and energy (IA). These narrowly defined phenotypes may have important biological differences and may respond differently to monoaminergic antidepressants. Pharmacometabolomics provides an opportunity to define pathways implicated in mechanism of action and response to treatment with antidepressants. Metabolomic analyses provide an excellent opportunity to examine the role of plasma metabolites in MDD and study the variability in depression phenotypes and drug response.

In this study, using a metabolomic approach, first, we investigated the differences between anhedonia positive (A+, CD+, and IA+) and anhedonia negative (A-, CD-, and IA-) phenotypes at baseline. Second, we examined the effect of eight weeks of treatment with citalopram or escitalopram on anhedonia phenotypes using the plasma metabolomic profiles.

Methods: This is a secondary analysis of the Mayo Clinic Pharmacogenomics Research Network study where patients (n = 280) with MDD were treated with citalopram or escitalopram for eight weeks. Depression symptoms were measured utilizing the self-reported 16-Item Quick Inventory of Depressive Symptomatology (QIDS-SR) scale at baseline and eight weeks after treatment with citalopram or escitalopram. The QIDS-SR measures depression severity and contains 16 items corresponding to the nine Diagnostic and Statistical Manual of Mental Disorders–Fourth edition (DSM-IV) symptom criterion domains for MDD. Question 13 on the QIDS-SR measures symptoms of anhedonia. The CD (QIDS-SR questions 5 and 13) and IA (QIDS-SR questions 10, 13, and 14) phenotypes were identified based on the RDoC framework.

Plasma samples were collected at baseline and after eight weeks of treatment with citalopram or escitalopram. A targeted, liquid chromatography–electrochemical coulometric array metabolomics platform was used to assay metabolites in plasma samples. Linear mixed effects models were used to examine whether plasma metabolite concentrations differed between the anhedonia phenotypes at baseline, and whether temporal changes in metabolomic profiles differed among the groups.

Results: The study cohort included 66% females, mean age 40 ±13 years, mean BMI of 29 ± 6.8, 58% treated with escitalopram and 42% with citalopram. At baseline, A+ and CD+ phenotypes had higher acetylcarnitine (C2) concentration compared to A- and CD- phenotypes respectively. Arginine level were significantly higher in all the anhedonia positive (A+, CD+, and IA+) phenotypes as compared to anhedonia negative (A-, CD-, and IA-) phenotypes.

Plasma metabolite data were available for 152 patients at 8 weeks. Three metabolites (Spermidine, spermine and octadecanoylcarnitine [C18]) showed differential SSRI effect between + and – phenotypes after 8 weeks. Spermidine and spermine levels decreased only in the negative phenotypes and they were showing a statistically significant interaction effect. After 8 weeks of treatment with citalopram or escitalopram, there was a significant increase in arginine concentrations among the anhedonia negative (A-, CD-, and IA-) phenotypes while interaction effect of time and phenotype was not significant. There were significant decreases in serotonin, sarcosine, and ornithine concentrations among the anhedonia negative and positive phenotypes.

In anhedonia negative and positive phenotypes, there were significant decreases in the medium- and long-chain acylcarnitines (hydroxyvalerylcarnitine [C5-OH], octanoylcarnitine [C8], decanoylcarnitine [C10], dodecanoylcarnitine [C12], tetradecadienylcarnitine [C14:2], hexadecanoylcarnitine [C16], hexadecenoylcarnitine [C16:1], octadecenoylcarnitine [C18:1] and octadecadienylcarnitine [C18:2]), lysophosphatidylcholine (lysoPC a C20:4) while no significant differential effects were noted. Significant increases in multiple phosphatidylcholines (PC aa C30:0, PC aa C34:3, PC aa

C34:4, PC aa C36:2, PC aa C36:6, PC ae C30:0 and PC ae C36:5) were observed after 8 weeks of treatment with citalopram or escitalopram.

Conclusions: This study provides novel insights into the effect of serotonergic antidepressants and difference in mechanism among the anhedonia phenotypes. Medium and long-chain acylcarnitines are involved in the energy pathways, thus, highlighting a possible role for mitochondrial function and energy metabolism in citalopram or escitalopram's mechanism of action. These findings need to be replicated in independent cohorts. If replicated, these findings could provide potential biomarkers for anhedonia phenotypes and could help advance drug development for anhedonia. These differential biochemical signatures based on anhedonia phenotypes may help reduce the heterogeneity of depression and operationalize treatment outcomes based on biology.

Keywords: Anhedonia, RDoC, Antidepressant

Disclosure: Nothing to disclose.

P345. Attenuation of Ketamine-Induced Glutamatergic Activity and Antidepressant Effects by Naltrexone Pre-Treatment, Independent of Changes in Cerebral Blood Flow

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Background: The neural mechanisms underpinning ketamine's antidepressant actions are yet to be fully determined. In addition to N-methyl-D-aspartate (NMDA) glutamate receptor antagonism, ketamine also interacts with the opioid system. Previous clinical work has demonstrated attenuation of the acute antidepressant effects of ketamine by opioid receptor antagonism suggesting opioid system activation may contribute to ketamine's rapid-acting antidepressant effects. In this study, we examined the acute effects of ketamine on brain glutamatergic measures, cerebral blood flow, and depressive symptoms and investigated whether administering an opioid receptor antagonist, naltrexone, as a pre-treatment, impacted any neuroimaging or clinical measures changes.

Methods: A randomized, double-blind crossover study was conducted in twenty-six adults with major depressive disorder (13 female, 13 male), currently experiencing a major depressive episode. The study consisted of two arms: oral placebo or oral naltrexone 50 mg, followed by a ketamine infusion (0.5 mg/kg 40 minutes) during magnetic resonance imaging (MRI) on a GE MR750 3-Tesla scanner. Depressive symptoms were rated before each infusion and at post-infusion day 1 using the Montgomery–Åsberg Depression Rating Scale (MADRS). Using a pseudo-continuous arterial spin labelling (pcASL) sequence, whole brain cerebral blood flow (CBF) maps were obtained both at baseline and during the final 10 minutes of the ketamine infusion. CBF maps were co-registered and normalised, using the proton density image and T1-weighted images, and smoothed (6mm FWHM) within the Statistical Parametric Mapping (SPM) software package. Due to movement artefacts, one participant was excluded from the ASL analysis. Voxel-wise analysis was performed using a flexible factorial design, with an explicit grey matter mask and corrected for global CBF. Functional magnetic resonance spectroscopy (1H-fMRS) spectra were acquired continuously from an anterior cingulate cortex region of interest voxel (20 mm x 20 mm x 20 mm), for a 5-minute baseline period and during the initial 30 minutes of the ketamine infusion, using Point RESolved Spectroscopy (TE = 40 ms, TR = 2000 ms, NEX = 8). 1H-fMRS data were pre-processed using an automated FID-A toolbox pipeline, which includes coil combination, removal of motion corrupted scans and spectral registration. 1H-fMRS data were averaged per subject into seven blocks (a baseline block and six blocks during the ketamine infusion), that were processed with LCModel for spectral fitting. Two participants were excluded from the 1H-fMRS analysis due to poor quality spectra and missing data. Changes in Glx (glutamate+glutamine), referenced to total N-acetylaspartate (tNAA), for each of the six infusion blocks compared to the baseline were determined. A linear mixed effects model was used to determine effects of pre-treatment condition and infusion block on Glx/tNAA changes. An additional linear mixed effect model was used to determine effects of time (pre-infusion, day 1 post infusion) and pre-treatment condition on MADRS scores.

Results: There was a significant main effect of condition for Glx/tNAA change against the pre-infusion baseline ($p = 0.020$), with a higher mean increase in Glx/tNAA during the ketamine infusion for placebo compared to the naltrexone pre-treatment condition ($d = 0.25$). The whole-brain voxel-wise analysis revealed ketamine-induced increases in CBF in a large frontal cluster encompassing the subgenual, pregenual and dorsal anterior cingulate cortex, bilateral insula and inferior frontal gyri ($P < 0.05$ FWE-corrected), however there were no significant interactions between naltrexone and ketamine-induced changes in CBF. Finally, for the MADRS scores there was a significant main effect of time ($p < 0.001$), with reductions in mean MADRS scores at day 1 post-infusion (placebo + ketamine (mean = -14.65, SD = 7.77); naltrexone + ketamine condition (mean = -10.5, SD = 5.91)), and a significantly attenuated reduction for the naltrexone + ketamine condition (mean difference from placebo = 4.15, SD = 8.59, condition-by-time interaction, $p = 0.038$; $d = 0.6$).

Conclusions: This study provides clinical evidence that opioid system activation may contribute to the acute antidepressant effects of ketamine. Additionally, it provides preliminary mechanistic evidence for opioidergic and non-opioidergic neural mechanisms that may mediate ketamine's antidepressant effects. Future work should examine interactions between the glutamatergic and opioidergic systems to better understand the potential synergistic or independent contributions of these systems to ketamine response.

Keywords: Ketamine, Glutamate, Opioid, Depression, Naltrexone

Disclosure: Nothing to disclose.

P346. Clinical Profile Only Modestly Accounts for Emotional Breakthrough and Quality of Subjective Experience in Patients With Treatment Resistant Depression Undergoing COMP360 Psilocybin Treatment

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Background: Treatment-resistant depression (TRD) poses a significant mental health challenge, as first-line therapies fail to alleviate symptoms in a substantial number of patients. Psilocybin has demonstrated efficacy in clinical trials, including a recent phase IIb trial of COMP360 (COMPASS Pathways' proprietary synthetic psilocybin formulation) psilocybin treatment with significant improvements in depressive symptom severity following a single 25mg dose administered with psychological support. Evidence suggests that the acute subjective emotional breakthrough and psychedelic experience during COMP360 psilocybin administration are potentially important mechanistic elements of subsequent rapid and sustained antidepressant effect. Nevertheless, it remains unclear how patients' unique clinical

presentations influence the pharmacological effect of the drug to bring about these effects. Here, we investigate the relation between patient baseline cognitive-affective, somatic, and functional impairment profiles and emotional breakthrough and subjective psychedelic experience, measured with the Emotional Breakthrough Inventory (EBI) and Five-Dimensional Altered States of Consciousness (5D-ASC), respectively. We focus on participants from our phase 2b trial who received 25mg of COMP360 psilocybin, due to the demonstrated efficacy and psychedelic effect of this higher does.

Methods: 79 patients with TRD received a single dose of 25mg of COMP360 with psychological support in a phase IIb, multicenter, randomized, parallel group, double-blind trial. Cognitive-affective (HAMD-17 Anxiety Psychic and Psychomotor Retardation; GAD7; MADRS; PANAS; MSI-BPD), somatic (HAMD-17: Anxiety Somatic and General Somatic), and functional impairment (HAMD-17: Work and Activities; Sheehan Disability Scale) profiles were assessed at baseline, while 5D-ASC and EBI were completed at the end of the administration day and one day thereafter, respectively. Given that the complexity of TRD patient clinical presentation is influenced by numerous factors of potentially shared variance, we leveraged machine learning (ML) to test the predictability of cognitive-affective, somatic, and functional impairment variables on EBI and 5D-ASC domains. The ML pipeline combined the strengths of multiple base learners (i.e., support vector regression, random forest, and elastic net) to enhance predictive accuracy and generalizability. Performance of stack ensembles was assessed using a nested cross-validation (nCV) procedure with the inner loop building base and stacked models and the outer loop evaluating model performance, with 5-fold cross-validation in both inner and outer loops. Stacking also assessed for variable importance (VI), produced by averaging VI sets across folds.

Results: ML models with 12 features explained 17.3% of the variance in EBI, and for the 5D-ASC dimensions, 18.6% in Visionary Restructuralization (VR), 14.8% in Reduction of Vigilance (RV), 12.9% in Oceanic Boundlessness (OB), 8.3% in Anxious Ego Dissolution (AED), and 5.5% in Auditory Alterations (AA). VI analysis revealed negative affectivity, anxious apprehension, functional impairment, and emotion dysregulation as important features broadly contributing to performance in ML models. Examination of important features revealed that only baseline anxious apprehension positively related to AED [$r = .348$, $pcorr < .05$] following COMP360 administration, and baseline emotion dysregulation positively related to RV ($r = .350$, $pcorr < .05$) following COMP360 administration. EBI and the remaining 5D-ASC dimensions did not significantly relate to features after correcting for multiple comparisons ($pcorr > .05$).

Conclusions: This analysis revealed a relatively modest proportion of variance in patient emotional breakthrough and psychedelic experience following COMP360 administration explained by patient baseline affective and functional impairment profiles. Features that evidenced significant albeit small direct effects on tested outcomes suggest that patient anxious apprehension may play a role in increased dysphoric experience while emotional dysregulation may relate to greater reduction in alertness and attentiveness, in the non-ordinary state of consciousness during psilocybin experience. Although this analysis is limited by the number of tested features, the results suggest that the acute subjective emotional breakthrough and quality of psychedelic experience reported by patients in our study are largely due to the effect of psilocybin itself. Future studies are warranted to examine how these findings may be leveraged to enhance patient preparation for psilocybin treatment.

Keywords: Treatment-Resistant Depression, Psilocybin, Clinical Predictors

Disclosure: COMPASS Pathways: Employee (Self).

P347. Neural Complexity is Increased After Low Doses of LSD, But Not Moderate to High Doses of THC or Methamphetamine

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Background: Neural complexity, or entropy, is considered a neural correlate of consciousness. Relative to normal waking states, neural complexity is reduced during coma, anesthesia, and sleep, and increased during altered states of consciousness, including after the administration of the psychedelic drug lysergic acid diethylamide (LSD). In the present analysis, we examined whether low doses of LSD (13 and 26 μg) were sufficient to increase neural complexity in the absence of altered states of consciousness. In addition, neural complexity was assessed after doses of two other drugs that significantly altered consciousness and mood: delta-9-tetrahydrocannabinol (THC; 7.5 and 15 mg) and methamphetamine (MA; 10 and 20 mg).

Methods: Three separate groups of healthy volunteers ($N = 21$, LSD; $N = 24$, THC; $N = 29$, MA), aged 18-35, participated in within-subject, double-blind procedures in which they received placebo or drug (LSD, 13 and 26 μg; THC 7.5 and 15 mg; MA 10 and 20 mg) in 4-5 hour sessions separated at least four days. Electroencephalography (EEG) measures were obtained 1-2 hours after drug administration to align with anticipated peak drug effects. Limpel-Ziv complexity and spectral power were analyzed under 10-20 system electrodes during eyes-closed resting-state.

Results: LSD (13 and 26 μg) dose-dependently increased neural complexity across 10-20 electrodes compared to placebo, an effect not observed after either THC or MA. LSD-induced increases in neural complexity significantly correlated with face recognition accuracy in a task administered immediately after resting-state recordings. In addition, LSD (13 and 26 μg) reduced delta and theta power across 10-20 electrodes, effects not observed with THC or MA. LSD-induced reductions in spectral power were most robust over default-mode network regions and correlated with increases in anxiety and elation. LSD increases in complexity did not correlate with spectral power reductions, but correlated with increases in gamma power.

Conclusions: These data support the association between neural complexity and conscious processes, such as face recognition, while demonstrating that neural complexity is not necessary or sufficient for the induction of altered states of consciousness or mood states. The data also inform the relationship between neural complexity and spectral power. Together, the findings shed light on the nature of neural complexity as a measure of conscious processing.

Keywords: Neural Complexity, Consciousness, LSD Microdosing, THC, Methamphetamine

Disclosure: Nothing to disclose.

P348. Evaluation of GABA and Glutamate+Glutamine Levels in the Dorsal Anterior Cingulate Cortex of Patients With Bipolar Disorder: A Cross-Sectional 1H-MRS Study

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Background: Despite extensive research, the fundamental cause of bipolar disorder (BD) remains elusive. Previous studies using

peripheral blood plasma (Petty et al., 1990), cerebrospinal fluid (Gerner et al., 1984), postmortem brain samples (Benes and Berretta., 2001), and genetics (Konradi et al., 2011) have suggested the alteration of gamma-Aminobutyric acid (GABA) system in patients with BD. The ACC is involved in negative emotional processing, and its association with BD has also been studied (Phan KL et al., 2004) (Fountoulakis KN et al.). The dorsal anterior cingulate cortex (dACC) is a hub region of the salience network (Menon et al., 2010), which has been implicated in the detection and integration of emotional stimuli, and plays a crucial role in the pathophysiology of BD. Previous proton magnetic resonance spectroscopy (1H-MRS) studies on GABA levels in the dACC of BD patients have reported inconsistent results in the dACC of BD, including lower glutamate/GABA ratio in those with euthymia (Sotti-Muzzi et al., 2021), and no significant results in patients with euthymia (Prisciandaro et al., 2017). There is a limited number of studies on GABA levels in the brain of BD despite the potential implication of GABAergic dysfunction in BD. Therefore, this study sought to compare the levels of GABA and glutamate+glutamine (Glx), and Glx/GABA ratio in the dACC between patients with BD and healthy controls (HC) using 1H-MRS.

Methods: This study was approved by the Keio University School of Medicine Ethics Committee. All participants provided written informed consent. Patients with BD were recruited from Keio University Hospital (Tokyo, Japan) and online advertisements, and age- and sex- matched HCs from the general population. The study included 26 patients with BD (age: 50.5 ± 14.5 years, female: n = 11 [34.4%], type I: n = 10 [38%]; depression: n = 8 [31%], euthymia: n = 14 [54%], hypomanic: n = 4 [15%] intake of lithium: n = 17 [65%]), and 26 age- and sex-matched HC. We used a 3T magnetic resonance imaging (MRI) scanner (Siemens Prisma) and applied 1H-MRS (MEGAPRESS, 256 averages, TR = 1500ms, TE = 68ms) to measure the levels of GABA and Glx in the dACC (30 × 40 × 20 mm3). We collected patient information and clinical symptoms using the Montgomery Åsberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Japanese Adult Reading Test (JART), and Executive Interview 25 (EXIT25). Subsequently, we quantified the levels of GABA and Glx using GANNET 3.0. For statistics, we first conducted correlations analyses between clinicodemographics and neurometabolite levels. If any correlation existed between them, we controlled for the corresponding variable in the following analyses. GABA and Glx levels, as well as the Glx/GABA ratio, were then compared both between the BD and HC groups and within the subtype groups.

Results: GABA and Glx levels and Glx/GABA ratio did not show significant relationships with sex, age, age of onset, duration of illness, duration of treatment, or years of education. No significant differences were observed in GABA level ($p = 0.611$) or Glx level ($p = 0.245$) between the BD and HC groups. However, the BD group showed a higher Glx/GABA ratio compared to the HC group (BD: 2.92 ± 0.46 IU, HC: 2.69 ± 0.35 IU, $p = 0.048$). In addition, there were no significant differences in GABA level ($p = 0.273$), Glx level ($p = 0.280$), or Glx/GABA ratio ($p = 0.826$) between the BD type I and type II subgroups. There were no significant differences in GABA level ($p = 0.944$), Glx level ($p = 0.913$), or Glx/GABA ratio ($p = 0.886$) between patients with bipolar depression and patients with euthymia (n = 18).

Moreover, no significant correlations were observed between MADRS score and GABA level ($p = 0.162$), Glx level ($p = 0.383$), or Glx/GABA ratio ($p = 0.493$). A positive correlation was found between JART score and GABA level ($\rho 24 = 0.699$, $p < 0.001$), while a negative correlation was observed between the Executive Interview 25 (EXIT25) score and Glx level ($\rho 24 = -0.608$, $p = 0.002$).

In those administered with lithium, there was a positive correlation between lithium dosage and GABA level ($\rho 24 = 0.510$, $p = 0.009$) and a negative correlation between lithium dosage and Glx/GABA ($\rho 24 = -0.546$, $p = 0.005$). There were no significant group differences in GABA, Glx, and Glx/GABA ratio in terms of antiepileptic drug treatment (n = 16; $p = 0.152$, $p = 0.552$, $p = 0.224$, respectively).

Conclusions: Our study demonstrated a higher Glx/GABA ratio in the BD group compared to the HC group, but no significant group differences in GABA or Glx levels, suggesting an excitatory-inhibitory (E/I) imbalance in BD. Our result of higher Glx/GABA ratio in BD is partially consistent with a recent meta-analysis reporting elevated ACC Glx levels in BD, especially in bipolar depression (Ino et al., 2023). We also identified positive associations between premorbid total cognition and GABA levels, and between executive function and Glx levels, indicating that E/I imbalance in the dACC may contribute to cognitive impairment in BD. Conversely, we observed a positive correlation between lithium dosage and GABA level, along with a negative correlation between lithium dosage and Glx/GABA ratio. Given that basic neuroscience research noted that lithium increased GABA levels in the cerebrospinal fluid in mice (Vargas et al.,1998), lithium may improve BD symptoms by normalizing the E/I imbalance of dACC.

Keywords: H-MRS, E/I Imbalance, dACC, Cognitive Function, Pharmacology

Disclosure: Nothing to disclose.

P349. Long Term Toxicity of Lithium Treatment – A Longitudinal Population Based Study

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Background: Lithium is efficacious in the treatment of bipolar disorder; however, it has side effects that limit its use. This study analyzed a large population based dataset to examine the long-term side effects of lithium treatment.

Methods: Data were obtained from the Clalit Health Services (CHS) database, the largest provider of health insurance in Israel, n = 4.8 million, representing over 50% of the Israeli population. This study examined lithium use between the years 2000 and 2022, focusing on its impact on kidney and thyroid function. Kidney function was followed using the estimated glomerular filtration rate (eGFR), based on creatinine blood levels, age, and sex during the follow-up period, compared to baseline before the initiation of lithium treatment.

Results: We identified 9,736 patients treated with lithium who had baseline and at least one eGFR value at follow-up. There was a statistically significant mean decrease of eGFR of approximately 1mL/min/1.73m2 per year, similar to the physiological age associated decrease of eGFR (Table 1). We then compared all patients receiving lithium (n = 19,433) to all patients receiving valproic acid (n = 44,524). There was no different in the life-time rates of dialysis between patients treated with lithium and patients treated with valproic acid (1.03% vs 0.99%, $p = 0.683$). A lifetime diagnosis of hypothyroidism was more common in patients receiving lithium (21.84%) in comparison to patients treated with valproic acid (8.83%, $p = < 0.0001$).

Conclusions: In this large population study, treatment with lithium was not associated with decreased kidney function but was associated with a clinical diagnosis of hypothyroidism. These factors should be taken into account when considering treatment with lithium.

Keywords: Lithium, Renal, Thyroid, Kidneys, Valporic Acid

Disclosure: Nothing to disclose.

P350. Identifying Beneficial Receptors in Adjunctive Antipsychotic Treatment in Treatment-Resistant Depression: A Meta-Regression

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Background: Antipsychotics have been shown to be effective adjunctive agents when used for treatment-resistant depression. Although antipsychotics are engineered and marketed as D2 antagonists, each drug has a different profile of receptor binding affinity. Analysis of randomized controlled trials of individual antipsychotic drugs is not able to determine which of these receptors contributes to their therapeutic effects. However, given the existence of binding profiles for each drug, it is possible that meta-regression of antipsychotic drug studies is able to interrogate which of these receptors may have detectable therapeutic effects across drugs. In this study, we use a meta-regression technique to assess commonly hypothesized antagonist antidepressant mechanisms that may benefit treatment-resistant depressed patients.

Methods: Studies included in a recent meta-analysis of randomized controlled trials of adjunctive antipsychotics in treatment-resistant depressed patients were used to obtain response rates, which were subsequently regressed against receptor affinity values obtained from the Psychoactive Drug Screening Program. 34 effect sizes from 27 studies and 9 antipsychotics were included. Raw participant counts were obtained so that a Bayesian, one-stage meta-regression could be performed. Statistical dependencies present due to multiple effect sizes being drawn from the same antipsychotic, as well as multiple effect sizes from the same study, were taken into account in our model.

Results: In a multivariate analysis including the noradrenergic alpha-2A, alpha-2B, alpha-2C receptors; serotonin, norepinephrine, and dopamine reuptake transporters (SERT, NET, DAT); and serotonergic 5-HT2A, 5-HT6, 5-HT7 receptors, only affinity for 5-HT6 and NET were found to significantly improve response rate using 90% credible intervals. Affinity for SERT was found to significantly decrease response rate using a 90% credible interval. All other receptors were not found to be significant using 90% credible intervals.

Conclusions: We demonstrate that adjunctive 5-HT6 and NET affinity may increase response rates in treatment-resistant depressed patients and that adjunctive SERT affinity may decrease response rates in this population.

Keywords: Antipsychotic Medication, Major Depression Disorder, Meta-Analysis

Disclosure: Nothing to disclose.

P351. Characterization of Extrapyramidal Symptoms and Akathisia With Cariprazine Treatment in Patients With Mania or Depression Associated With Bipolar I Disorder

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Background: Extrapyramidal symptoms (EPS) and akathisia are common adverse events associated with dopamine-blocking medications that can negatively impact patient quality of life and medication adherence. Cariprazine is a dopamine D3-preferring D3/D2 and serotonin 5-HT1A receptor partial agonist approved to treat schizophrenia, manic, mixed, and depressive episodes associated with bipolar I disorder (BP-I), and as an adjunctive treatment for major depressive disorder. EPS and akathisia were reported in cariprazine BP-I trials and may be associated with higher doses and faster titrations. Nevertheless, a small proportion (< 3%) of patients discontinued treatment due to EPS or akathisia adverse events, suggesting events were manageable and/or transient. These post hoc analyses examined the time courses of EPS and akathisia events and their resolution with or without rescue medications to provide descriptive information about events that occurred during clinical trials of cariprazine treatment in adults with BP-I mania or BP-I depression.

Methods: All studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies of cariprazine in patients with BP-I who were currently experiencing an acute manic/mixed (NCT00488618, NCT01058096, and NCT01058668) or depressive (NCT02670538, NCT02670551, and NCT01396447) episode. Cariprazine doses were flexible (3–12 mg/day) in BP-I mania studies and fixed (1.5 mg/d or 3 mg/d) in BP-I depression trials. Patients with akathisia or EPS (excluding akathisia, restlessness, and tardive dyskinesia) events that occurred during treatment or within 30 days of the last dose were included in analyses. Post hoc outcomes included the incidence of EPS or akathisia, rescue medication use, the proportion of resolved events, and the median time to resolution (determined by Kaplan-Meier analysis). Events that occurred or resolved more than 30 days after the last dose were censored.

Results: A total of 1065 patients (placebo: $n = 442$; cariprazine 3–12 mg/d: $n = 623$) were included in the pooled bipolar mania analysis. The incidence of EPS was 13.1% with placebo and 29.2% with cariprazine. Rates of akathisia were 5.7% with placebo and 20.6% with cariprazine. The percentage of patients with EPS receiving rescue medication was 39.7% for placebo and 61.5% for cariprazine. The percentage of patients with akathisia receiving rescue medication was 72.0% and 71.9% in patients treated with placebo or cariprazine, respectively. EPS resolved in 82.8% of cases with placebo and 90.7% of cases with cariprazine; 88.0% and 92.2% of akathisia cases resolved with placebo or cariprazine, respectively. The median time to EPS resolution was 7.5 days with placebo and 8 days with cariprazine. For akathisia, the median time to resolution was 13 days with placebo and 10 days with cariprazine.

In the BP-I depression analyses, a total of 1407 patients (placebo: $n = 468$; cariprazine 1.5 mg/d: $n = 470$, 3 mg/d: $n = 469$) were included. The incidence of EPS was 2.1% with placebo, 3.4% with cariprazine 1.5 mg/d, and 5.1% with cariprazine 3 mg/d. For akathisia, rates were 2.1% with placebo, 5.5% with cariprazine 1.5 mg/d, and 9.6% with cariprazine 3 mg/d. The percentage of patients with EPS receiving rescue medication was 10% for placebo, 6.3% for cariprazine 1.5 mg/d, and 33.3% for cariprazine 3 mg/d. The percentage of patients with akathisia receiving rescue medication was 30% for placebo and 38.5% or 42.2% for cariprazine 1.5 mg/d and 3 mg/d, respectively. EPS resolved in 80.0% of cases with placebo, 87.5% with cariprazine 1.5 mg/d, and 91.7% of cases with cariprazine 3 mg/d. All akathisia cases resolved with placebo; 92.3% resolved with cariprazine 1.5 mg/d and 95.6% resolved with cariprazine 3 mg/d. The median time to EPS resolution was 23 days with placebo, 18.5 days with cariprazine 1.5 mg/d, and 18 days with cariprazine 3 mg/d. For akathisia, the median time to resolution was 24.5 days with placebo, 21.5 days with cariprazine 1.5 mg/d, and 21 days with cariprazine 3 mg/d. In both BP-I mania and BP-I depression analyses, time to resolution was generally comparable between cariprazine and placebo regardless of whether rescue medications were or were not used.

Conclusions: In both the BP-I mania and depression studies, cariprazine was associated with a greater incidence of EPS and akathisia than placebo. EPS and akathisia could be managed by

rescue medications and resolved in > 90% of cariprazine-treated patients, with the proportion of resolved events similar to or greater than those observed in placebo-treated patients. In addition, the duration of EPS and akathisia events was generally comparable between cariprazine and placebo groups.

Keywords: Cariprazine, Bipolar I Disorder, Post Hoc Analysis, Extrapyramidal Symptoms, Akathisia

Disclosure: AbbVie: Employee (Self).

P352. GM-1020: An Oral NMDA Receptor Antagonist for Depression Demonstrates Target Engagement at Doses That Do Not Cause Dissociation, Ataxia or Sedation in a Phase 1 Single Ascending Dose Study

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Background: The discovery of the rapid antidepressant efficacy of the NMDA receptor (NMDAR) antagonist ketamine sparked efforts to identify molecules that can achieve similar rapid and robust efficacy but improve on the limitations of ketamine. At the commonly administered antidepressant dose of racemic ketamine (0.5 mg/kg, iv infusion), patients experience dissociative side effects, sedation and ataxia, which restrict safe administration to a supervised, in-clinic setting and limits patient access to this treatment. In addition, ketamine has poor oral bioavailability that necessitates parenteral dosing. Esketamine (Spravato®) an intranasal formulation of the more potent S-isomer of ketamine, has been approved for patients with treatment-resistant depression, but still requires supervised administration due to its sedative and dissociative effects.

There remains an unmet need for a non-dissociative, non-sedative, orally bioavailable NMDAR antagonist with rapid and robust antidepressant efficacy. Preclinical data show that GM-1020 is an orally bioavailable NMDAR antagonist with robust, durable antidepressant-like effects in rodents at doses that do not affect motor activity. Here we describe the results of the Phase 1 single ascending dose trial of GM-1020 in healthy volunteers.

Methods: GM-1020 was evaluated in an adaptive, randomized, double-blind, placebo-controlled first in human study to evaluate the safety, pharmacokinetics, and pharmacodynamics of single ascending oral doses of GM-1020 in healthy adult volunteers. Study participants received single oral doses of GM-1020 (20, 60, 100, 140, 220, or 360 mg; n = 6/cohort) or placebo (n = 2/cohort). The effects of GM-1020/placebo on treatment-emergent adverse events (TEAEs), vital signs and 12-lead ECGs were recorded for each cohort.

Pharmacodynamic assessments included resting-state electroencephalogram (rsEEG) and the NeuroCart® test battery to assess sedative, cognitive and ataxic effects. Subjective effects were assessed using multiple questionnaires including the Mystical Experience Questionnaire-30 (MEQ-30) and the Five Dimensional Altered States Of Consciousness (5D-ASC) scale. The Clinician-Administered Dissociative States Scale (CADSS) was used to assess dissociative effects.

Results: GM-1020 was safe and well-tolerated at all doses tested. GM-1020 AUC0-24 and Cmax exposures increased in a dose-proportional manner over the 20 to 360 mg dose range. The exposures generally showed low variability (~15-25% CV) and were consistent with oral bioavailability of >60%. The mean t1/2 was 4.3 h and the median tmax value was generally 1.5 h across cohorts.

There were no SAEs or severe TEAEs. A dose-dependent increase in TEAEs occurred through the 220 mg dose; with most TEAEs categorized as mild. TEAEs occurring in more than 2 subjects in a cohort included anxiety, time perception altered, dissociation, disturbance in attention, euphoric mood, dizziness, paraesthesia, slow response to stimuli, headache, sensory processing disorder, feeling drunk, nausea and emesis. The 60, 140 and 220 mg cohorts increased systolic blood pressure (BP) by ~ 10 mmHg with minimal changes in diastolic BP. There were no consistent effects on respiratory rate at any dose.

GM-1020 produced dose- and plasma concentration-dependent effects on rsEEG consistent with NMDA receptor antagonism; clear target engagement was apparent in terms of reduction in alpha (8-13 Hz) EEG power at doses ≥60 mg, with increases in gamma (30-90 Hz) EEG power being observed at doses ≥100 mg.

Despite evidence of target engagement at doses ≥60 mg, the incidence of dissociation was very low at doses up to 140 mg where only 1 subject had a CADSS total score >4. Similarly, the NeuroCart® measures of sedation (saccadic peak velocity, SPV) and ataxia (body sway) were only modestly affected by GM-1020. Only the highest dose of GM-1020 (360 mg) produced a reduction in SPV (73 deg/s) similar to esketamine, and the 218 mm increase in body sway after 360 mg GM-1020 was less than those reported for esketamine (Kleinloog et al., 2015).

Conclusions: The oral bioavailability and the ability of GM-1020 to produce significant quantitative and subjective pharmacodynamic evidence of NMDA receptor antagonism without causing dissociation, sedation or ataxia at exposures expected to have antidepressant effects. This distinguishes this novel molecule from existing ketamine-based therapies. Consistent with the preclinical characterization of this molecule, GM-1020 produced significant changes in low and high frequency EEG power at doses below those associated with ataxia or sedation. In rodents exposures ~2-fold below those achieved at the 140 mg dose of GM-1020 in humans resulted in robust and durable efficacy in the chronic mild stress paradigm suggesting the potential for a greater therapeutic index than ketamine.

Together these data support the potential for GM-1020 to be a novel differentiated treatment for depression that could enable greater patient access than existing rapid acting antidepressants.

Keywords: NMDA Antagonists, EEG Electrophysiology, Phase 1 Study, Dissociation, Target Engagement

Disclosure: Nothing to disclose.

P353. N-Acetylcysteine Increases Brain Glutathione Levels in People With Bipolar Disorder: Results From a Randomized, Double-Blind, Placebo-Controlled, Crossover 1H-MRS Pilot Study

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Background: Though several FDA-approved medications are moderately effective in treating bipolar disorder (BD), they often leave patients with residual depressive symptoms and cognitive (e.g., memory) impairments that worsen over time. These residual impairments are believed to be caused, in part, by a progressive form of brain damage resulting from a chronic imbalance of so-called "free radicals" (which damage brain cells and DNA) and "antioxidants" (which neutralize free radicals). N-acetylcysteine (NAC), a safe and well-tolerated supplement, increases levels of the brain's primary antioxidant, glutathione (GSH), by providing cells with its metabolic precursor, cysteine, in exchange for

molecules of glutamate, the brain's primary excitatory neurotransmitter. Clinical trials of add-on NAC for BD have found it to be moderately effective in reducing depressive symptoms, and possibly effective in improving memory impairments, attributing these therapeutic effects to either increased brain GSH, or decreased brain glutamate, levels, though such mechanistic hypotheses have never been directly tested in individuals with BD. To address this gap in understanding, we conducted a pilot randomized, double-blind, placebo-controlled, crossover study of 3g/day of NAC vs. placebo on levels of GSH and glutamate in the dorsal anterior cingulate cortex (dACC), a frontal brain region critical to cortical control of goal-directed behavior.

Methods: Twelve healthy individuals with BD I or II, reporting a recent prolonged mood disturbance and daily use of ≥1 FDA-approved mood-stabilizing medications, were enrolled across a 12-month period. Exclusions included serious medical illness, history of head injury, meeting DSM-V criteria for any Substance Use Disorder (i.e., except Tobacco) within the preceding 6 months, and medication dose changes of ≥ 20%, ≤ 2 weeks before testing. Enrolled participants completed two, 14-day experimental conditions (3g/day NAC, placebo) in a randomized order, separated by a 14-day washout period. Each condition consisted of an in-person study visit for assessment of mood symptoms (via Young Mania [YMRS] and Montgomery-Asberg [MADRS] Rating Scales) and dispensing of medication (Day 1) and an MRI (Day 14). Each MRI included acquisition of T1-weighted images for proton MR spectroscopy (1H-MRS) voxel placement and tissue segmentation, followed by echo-time (TE) optimized resting-state acquisitions of GSH (via MEGA-PRESS with TE = 120ms) and glutamate (i.e., represented by "Glx" or glutamate+glutamine, via PRESS with TE = 40ms), respectively. MEGA-PRESS and PRESS data were processed using the Gannet MATLAB toolbox and LCModel 6.3, respectively, with metabolite values normalized to unsuppressed water, corrected for within-voxel CSF fraction, and expressed in arbitrary units. Linear mixed models; each containing the main effect of treatment, period, and sequence to ensure the crossover design and washout were successful; were estimated using IBM SPSS software to assess the effect of NAC vs placebo on dACC GSH and glutamate levels; though medication-related changes in mood symptoms were tested using the same modeling approach, no changes were anticipated given the brief duration of NAC dosing.

Results: Ten enrolled participants completed the study with analyzable data (8 female, mean [SD] age = 34 [13]); data from two additional participants were non-analyzable (n = 1, lost to follow-up; n = 1, excessive head motion). NAC was well-tolerated, with a single mild-moderate adverse event reported at the MRI visit of each condition, and adherence (i.e., estimated via returned-pill counts) was high and did not differ between conditions ($p = 0.26$). No evidence for carry-over effects was found across statistical models. NAC (relative to placebo) was associated with significantly higher levels of dACC GSH ($F = 8.44$, $p = 0.040$; Cohen's $D = 0.57$), without any corresponding association with levels of Glx ($F = 1.08$, $p = 0.325$; Cohen's $D = 0.24$). As anticipated, NAC (relative to placebo) was not associated with YMRS or MADRS scores (ps > 0.70).

Conclusions: In ten individuals with BD, NAC (3g/day for 14-days, relative to placebo) was associated with a statistically significant, moderate-large increase in brain GSH levels, without any corresponding significant change in glutamate levels. These findings may suggest that NAC exerts its therapeutic effects in individuals with BD via increasing brain GSH levels. Replication and extension of our findings in larger samples and across a longer, therapeutic dosing interval will be necessary to supporting this interpretation more definitively.

Keywords: Bipolar Disorder, N-acetylcysteine, Glutathione (GSH), Glutamate, Proton Magnetic Resonance Spectroscopy

Disclosure: Nothing to disclose.

P354. Ketamine Metabolite (2R,6R)-Hydroxynorketamine Induces Sustained Metaplastic Effects on Hippocampal Synaptic Plasticity in Mice

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Background: The pharmacologically active (R,S)-ketamine (KET) metabolite (2R,6R)-hydroxynorketamine (HNK) maintains the rapid and prolonged preclinical antidepressant-like effects of KET without adverse effects and has completed human phase I clinical trials. Metaplasticity is an alteration in plasticity induced by previous synaptic activity that influences synaptic function and may mediate sustained antidepressant action of KET and HNK.

Methods: To study in vitro KET/HNK metaplastic effects, we incubated slices collected from male and female mice with KET/HNK for 60 min followed by an artificial cerebrospinal fluid washout for 35 min or 3 h. To study the sustained effects of HNK ex vivo, mice were treated with HNK and sacrificed for electrophysiology experiments 24 h later. Primary outcomes assessed were input/output (I/O) excitatory postsynaptic potential slope, paired-pulse facilitation (PPF), and long-term potentiation (LTP) at the Schaffer collateral-CA1 synapse.

Results: Incubation with HNK enhanced presynaptic-mediated synaptic transmission 35 min after 2, 10, or 50 μM HNK washout (n = 15-28 slices/treatment level) in a concentration-dependent manner as indicated by enhanced basal I/O responses ($F(3,72) = 14.8$, $p < 0.0001$) and reduced PPF ($F(3,72) = 6.95$, $p = 0.00040$) while also impairing LTP magnitude ($F(3,72) = 8.58$, $p < 0.0001$) at 10 and 50 μM. No alterations in responses were observed 35 min after 1, 5, or 20 μM KET wash-out (I/O: $F(3,27) = 1.18$, $p = 0.33$; PPF: $F(3,27) = 0.32$, $p = 0.81$; LTP: $F(3,27) = 0.48$, $p = 0.70$; n = 6-10 slices/treatment level). The effects of HNK were blocked by preincubation with 10 μM adenylyl cyclase inhibitor SQ22536 (I/O: HNK main effect: $F(1,31) = 6.06$, $p = 0.020$, HNK*SQ22536 interaction: $F(1,31) = 9.42$, $p = 0.0044$; PPF: HNK main effect: $F(1,31) = 6.16$, $p = 0.019$, HNK*SQ22536 interaction: $F(1,31) = 4.35$, $p = 0.045$; LTP: HNK main effect: $F(1,37) = 4.18$, $p = 0.048$, HNK*SQ22536 interaction: $F(1,37) = 6.44$, $p = 0.016$; n = 8-11 slices/treatment level) or 10 μM cell permeable PKA inhibitor H89 (I/O: HNK main effect: $F(1,29) = 5.78$, $p = 0.023$, HNK*H89 interaction: $F(1,29) = 8.06$, $p = 0.0082$; PPF: HNK main effect: $F(1,29) = 4.19$, $p = 0.049$, HNK*H89 interaction: $F(1,29) = 5.91$, $p = 0.021$; LTP: HNK main effect: $F(1,29) = 14.7$, $p = 0.0006$, HNK*H89 interaction: $F(1,29) = 4.48$, $p = 0.043$; n = 7-10 slices/treatment level). Preincubation with the NMDAR antagonist D-APV (50 μM) neither blocked HNK's effects nor exerted metaplastic effects on its own (I/O: HNK main effect: $F(1,32) = 7.99$, $p = 0.008$, HNK*D-APV interaction: $F(1,32) = 0.08$, $p = 0.77$; PPF: HNK main effect: $F(1,32) = 21.0$, $p < 0.0001$, HNK*D-APV interaction: $F(1,32) = 0.93$, $p = 0.34$; LTP: HNK main effect: $F(1,32) = 27.8$, $p < 0.0001$, HNK*D-APV interaction: $F(1,32) = 0.25$, $p = 0.62$; n = 7-12 slices/treatment level). LTP magnitude was enhanced ($t(8) = 3.13$, $p = 0.01$) whereas basal transmission ($F(1,8) = 0.40$, $p = 0.54$) and PPF ($t(8) = 0.24$, $p = 0.82$) were unaffected 3 h after 10 μM HNK washout, suggesting HNK-induced metaplasticity (n = 4-6 slices/treatment level. No alterations in responses were observed 3 h after 1, 5, or 20 μM KET wash-out (I/O: $F(3,38) = 1.09$, $p = 0.37$; PPF: $F(3,38) = 0.17$, $p = 0.91$; LTP: $F(3,38) = 0.95$, $p = 0.43$; n = 10-11/treatment level). HNK-induced metaplasticity observed in vitro was recapitulated in ex vivo recordings in which 10 and 50 mg/kg, but not 2 mg/kg, HNK treatment (n = 10-11 mice/treatment level) led to a dose-dependent enhancement of LTP ($F(3,39) = 6.19$, $p = 0.0015$) without significant alterations in basal synaptic transmission ($F(3,39) = 1.33$, $p = 0.28$) or PPF ($F(3,39) = 0.15$, $p = 0.93$).

Conclusions: Our in vitro findings suggest that rapid HNK effects are induced by a presynaptic mechanism that enhances glutamatergic transmission whereas our ex vivo results suggest sustained HNK effects are maintained by a postsynaptic metaplastic mechanism. These findings provide insight into HNK's rapid and sustained mechanism of action that may facilitate novel antidepressant discovery.

Keywords: (2R,6R)-Hydroxynorketamine, (R,S)-Ketamine, Neural Plasticity, Antidepressants, Slice Electrophysiology

Disclosure: Nothing to disclose.

P355. The Enantiomer (R)-Tianeptine, but not (S)-Tianeptine, is an Agonist on the μ-Opioid Receptor and Decreases Immobility in the Murine Forced Swim Test

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Background: Tianeptine, an antidepressant marketed outside of the US, is a racemic drug composed of a 1:1 mixture of two enantiomers: (S)-tianeptine and (R)-tianeptine. We recently found that (S)-tianeptine but not (R)-tianeptine activates the peroxisome proliferator-activated receptor PPAR-β/δ and is responsible for tianeptine's positive effects on neuroplasticity in cell culture. Previous reports show that racemic tianeptine has weak μ-opioid receptor (MOR) activity and significantly reduces immobility in the forced swim test (FST), an animal model for behavioral "despair." It is not known if MOR activity and reduced immobility in the FST are properties specific to (S)- or (R)-tianeptine. Here we compare the activity of (S)- and (R)-tianeptine at the MOR using G-protein coupled receptor signaling via cAMP inhibition and β-arrestin recruitment and tested their effects on immobility in the FST.

Methods: MOR assays in vitro: MOR activation was assessed with fluorescent biosensors measuring cyclic adenosine 3,5-monophosphate (cAMP) inhibition and β-arrestin recruitment in HEK293T cells. Tianeptine test compounds included salts of racemic tianeptine, ≥99.9% pure (S)-tianeptine and ≥98.5% pure (R)-tianeptine (chiral purity). The positive control compound was [D-Ala2, NMe-Phe4, Gly-ol5]-enkephalin (DAMGO). Concentrations of the compounds ranged from 0.001 nM to 31620 nM. Concentration-response curves were generated and EC50 values were determined. FST in mice: Three experiments were conducted in male BalbC/J mice to test the effects of (S)-tianeptine sodium (>99% chiral purity), and (R)-tianeptine sodium (>98% chiral purity) on immobility in the FST. Racemic tianeptine and sertraline served as positive controls. In Exp 1, treatment groups ($n = 10$ per dose) were saline vehicle, (S)-tianeptine (3, 10, and 30 mg/kg), racemic tianeptine (30 mg/kg), and sertraline (20 mg/kg). In Exp 2, treatment groups ($n = 10$ per dose) were vehicle, (R)-tianeptine (3, 10, and 30 mg/kg), racemic tianeptine (30 mg/kg), and sertraline (20 mg/kg). Exp 3 was a replicate study of Exp 2. The three tianeptine compounds and saline vehicle were administered i.p. 60 min prior to the FST, and sertraline was administered i.p. 30 min prior to the FST. During the FST, animals were placed in a beaker of water and time immobile was recorded over one 6-min session. Immobility time (recorded in seconds) between groups were compared by analysis of variance (ANOVA) followed by Dunnett's post-hoc test. An effect was considered significant at $P < 0.05$.

Results: (R)-tianeptine exhibited agonism at the MOR via cAMP inhibition ($EC50 = 0.044$ μM) and β-arrestin recruitment ($EC50 = 1.873$ μM), whereas 99.9% pure (S)-tianeptine showed no evidence of activity in assays of MOR agonism up to the maximum concentration used. In the FST experiments, (R)-tianeptine showed a statistically significant reduction in immobility at 30 mg/kg compared to vehicle ($P < 0.0001$), and at both 10 and 30 mg/kg compared to vehicle in the replicate experiment ($P < 0.05$, $P < 0.0001$, respectively). (S)-tianeptine did not significantly reduce immobility at any dose tested. As expected, positive controls (racemic tianeptine 30 mg/kg and sertraline 20 mg/kg) significantly reduced immobility compared to vehicle ($P's < 0.001$).

Conclusions: (S)-tianeptine was devoid of MOR agonist activity, whereas (R)-tianeptine showed MOR agonism similar to that observed with racemic tianeptine. In the FST experiments, (S)-tianeptine did not reduce immobility at any dose tested, whereas (R)-tianeptine significantly reduced immobility at the higher doses (10 and 30 mg/kg). These findings suggest that (R)-tianeptine (or its main metabolite, an isomer of MC5), is responsible for the MOR-mediated effects of racemic tianeptine, including reduced immobility in the FST. Taken together with recent findings that (S)-tianeptine can improve working memory in the rat Novel Object Recognition test, and stimulates neuroplasticity in cultured neurons, these data suggest that (S)-tianeptine should be further explored for its potential effects to improve depression and to improve memory and cognition in conditions such as Alzheimer's disease, depression, and bipolar disorder without the potential μ-opioid abuse liability of (R)-tianeptine.

Keywords: Tianeptine, Mu Opioid Receptor, Major Depressive Disorder, Antidepressant, Forced Swim Test

Disclosure: Tonix Pharmaceuticals, Inc.: Employee (Self).

P356. ENX-104, a Novel and Potent D2/3 Receptor Antagonist, Increased Extracellular Levels of Dopamine and Serotonin in the Nucleus Accumbens and Prefrontal Cortex of Freely-Moving Rats

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Background: Anhedonia, defined by the loss of pleasure derived from previously rewarding activities, is a behavioral phenotype present in many neuropsychiatric conditions, including major depressive disorder. Alterations in dopaminergic (DA) corticostriatal circuitry and dysfunction of mesolimbic DA pathways underlie reward processing deficits. One potential way to enhance DA neurotransmission in reward pathways is to block presynaptic inhibitory D2/3 receptors with low doses of a D2/3 receptor antagonist. ENX-104 is a novel and potent antagonist for D2S, D2L, and D3 receptors ($Ki = 0.1$ nM, 0.01 nM, and 0.2 nM, respectively) that has demonstrated anti-anhedonic effects in translational models of reward responsiveness. We hypothesized that blockade of presynaptic inhibitory D2/3 receptors by ENX-104 would increase DA levels within the reward circuitry. To test this hypothesis, the effects of ENX 104, alone and in combination with d-amphetamine (AMPH), on extracellular levels of DA in the nucleus accumbens and prefrontal cortex were examined using dual probe microdialysis in freely-moving rats. Additionally, the effects of ENX-104 on extracellular levels of serotonin (5-HT) were evaluated.

Methods: For microdialysis experiments, rats were surgically implanted with dual probes in the prefrontal cortex (PFC) and the nucleus accumbens. Microdialysis experiments were performed one day after surgery. Microdialysate samples were collected from freely-moving rats at 30 mins intervals for a baseline period of 120 minutes prior to the administration of vehicle or drugs.

Samples were then collected for another 8 hours post drug treatment. Groups: (A) Vehicle (0.5% methylcellulose p.o.) + Saline (i.p.), (B) Vehicle + AMPH (0.3 mg/kg i.p.), (C) ENX-104 (2.5 mg/kg p.o.) + AMPH (0.3 mg/kg i.p.), (D) ENX-104 (1 mg/kg p.o.) + saline (i.p.) (E) ENX-104 (2.5 mg/kg p.o.) + saline. Detection and subsequent quantification of DA and 5-HT in the samples was based on reversed-phase, ion-pair HPLC coupled with electrochemical detection and used the ALEXYS™ monoamine analyser.

Microdialysis data were log transformed. Baseline was defined as the geometric mean of the four pre-treatment samples (i.e. those collected at -90 min, -60 min, -30 min and 0 min). Data were log transformed and analysis was by robust regression using M estimation. Each timepoint was analysed separately, together with the means during each of the eight hours after dosing, 0 2 and 0 4 hours and the overall 0-8 hours after dosing.

Statistical comparisons to vehicle were made using the Williams' test for ENX-104 and using multiple t-tests for AMPH and ENX-104+AMPH. Comparisons to AMPH alone and to ENX-104 alone for ENX-104+AMPH were done using multiple t-tests. A p-value of < 0.05 was considered statistically significant. Experiments were performed using 8 rats per experimental session.

Results: In the nucleus accumbens, ENX-104, at 1 and 2.5 mg/kg doses, covering a range of 40-70% D2/3 receptor occupancy, increased DA from 1-8 hours post-dose, i.e. over the entire duration of sampling (159% and 146% increase over vehicle, respectively, $p < 0.001$). Average DA levels were significantly higher during all the hourly intervals along with 0 2, 0 4 and 0 8 h bins post-drug. ENX 104 (2.5 mg/kg p.o.), in combination with AMPH, enhanced DA levels further with an immediate onset that lasted for 8 h post administration. A maximal increase was observed at 90 min post-dose (366% increase over vehicle, $p < 0.001$). Average levels were also significantly higher during all of the hourly bins and 0 8 h overall. The increases in the combination group were significantly greater than AMPH alone from 90 480 min (118% increase, $p < 0.001$ vs. AMPH alone).

In the PFC, only the highest dose of ENX-104, 2.5 mg/kg, resulted in significant increases in DA, 60 120 min post administration. A maximal increase was observed at 60 min post-dose (76.6% increase over vehicle, $p < 0.001$). Average levels were also significantly higher during the 0-2h interval. At 2.5 mg/kg, ENX-104 in combination with AMPH significantly increased DA levels. This effect was immediate in onset and lasted for 2.5 h post administration. A maximal increase was observed at 60 min post-dose (254% increase over vehicle, $p < 0.001$). Average levels were also significantly higher over the 0 4 h time interval bins. The increases in the combination group were significantly greater than AMPH alone at 60 120 min (~37% increase over AMPH alone, $p < 0.05$).

Interestingly, ENX-104 at both doses, 1 mg/kg and 2.5 mg/kg, transiently increased 5-HT levels. In the nucleus accumbens, both doses significantly increased 5-HT levels above vehicle at 60 minutes post-drug (at 1 mg/kg ~90% increase, $p < 0.05$; and at 2.5 mg/kg 136% increase, $p < 0.01$, vs. vehicle). In the PFC, ENX-104 caused significantly increased 5-HT levels above vehicle at 60 min post drug (at 1 mg/kg, 79.1% increase, $p < 0.05$; at 2.5 mg/kg 137% increase, $p < 0.05$).

Conclusions: These data demonstrate that at physiologically relevant doses, ENX-104 causes significant and lasting increases in extracellular DA and 5-HT within the reward circuit as well as the PFC. These data are consistent with the anti-anhedonic effects observed in translational behavioral models. Our data support further investigation of ENX-104, a potent and novel D2/3 antagonist for clinical use in treating psychiatric disorders in which anhedonia is prevalent.

Keywords: Anhedonia, Reward Circuitry, Dopamine (D2, D3) Receptors, D2 Dopamine and 5HT2A Serotonin Antagonists

Disclosures: Engrail Therapeutics: Employee (Self). Zoll Medical Devices: Employee (Spouse/Partner).

P357. Transcriptional Profiles of the Brain's Reward Circuitry in a Mouse Model 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. Fluoxetine (FLX) and like antidepressants have been widely used to treat MDD, nonetheless, ~50% of patients do not achieve full remission. Further, a subset of those afflicted are considered non-responsive to orally-available medications and are considered to have treatment-resistant depression (TRD). More recently, Ketamine (KET) has been shown to induce a rapid antidepressant response in ~50% of TRD patients, providing a novel therapeutic approach. However, the molecular mechanisms underlying TRD are poorly understood.

Methods: This study was aimed at characterizing the transcriptional profile of successful vs. unsuccessful response to KET in chronically-stressed mice that failed to respond to an initial course of FLX as a model of TRD. We exposed adult male mice to chronic social defeat stress (CSDS), a validated mouse model of depression that identifies a spectrum of resilient vs. susceptible outcomes based on a social interaction test (SIT). Mice classified as susceptible underwent antidepressant treatment with FLX in their drinking water for 28 days or 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 and assessed in the SIT 24 hr later. Transcriptome-wide changes in the prefrontal cortex (PFC) and nucleus accumbens (NAc) 48 hr 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%). We further identified a subset of treatment-resistant mice that 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 the identification of potential mechanisms underlying TRD. 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 a successful response to KET.

Keywords: Ketamine, Fluoxetine, Treatment Resistant Depression, Chronic Social Defeat Stress

Disclosure: Nothing to disclose.

P358. Discovery and Characterization of ITI-1549, a Novel Non-Hallucinogenic Psychedelic for the Treatment of Neuropsychiatric Disorders

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Background: Serotonergic hallucinogens (psychedelics) are powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes. These hallucinogens exert their psychoactive effects, at least in part, through agonist activity at brain serotonin 5-hydroxytryptamine 2a (5-HT2a) receptors and, potentially indirectly, through the ability to increase synaptic density in cortical regions of the brain. However, adverse effects of psychedelic hallucinogens have raised safety issues (i.e., abuse liability and persistence of perceptual disorders related to 5-HT2a agonism, and cardiac pathology related to 5-HT2b receptor agonism) that ultimately may limit their broad use, if proven effective.

Therefore, it is important to develop new drugs with improved pharmaceutical and safety characteristics to allow an exploration of the full therapeutic potential of this drug class. To this end, using structure- and ligand-based drug design, we have synthesized and characterized novel classes of compounds that are chemically unrelated to plant-derived and other synthetic psychedelics. We report here on the characterization of a promising candidate from this effort, ITI-1549: a novel non-hallucinogenic psychedelic with potential for acute and chronic treatment of mood, anxiety and other neuropsychiatric disorders.

Methods: The pharmacology of ITI-1549 was characterized in receptor binding assays and cell-based functional assays. Functional effects were measured within 5-HT2a receptor linked beta-arrestin and G-protein signaling pathways. Hallucinogen-like behavior in mice was measured by quantification of head twitch responses which has been shown to be a predictor of hallucinogenic activity in humans. Antidepressant, anti-anxiety, and social behaviors were also examined using established in vivo animal models in rodents.

Results: ITI-1549 exhibited high affinity binding to 5-HT2a receptors (Ki = 10.2 nM). Psychedelic hallucinogens act as full agonists at both the beta-arrestin and Gq signaling pathways linked to the 5-HT2a receptor. ITI-1549 displays an intrinsic efficacy of 72% relative to the positive control alpha-methylserotonin within the beta-arrestin pathway. In contrast to psychedelic hallucinogens, however, ITI-1549 does not activate 5-HT2a coupled Gq signaling pathways. Activation of the 5-HT2a receptor coupled Gq signaling pathway has been linked to hallucinogenic properties of psychedelic compounds.

As predicted based on this in vitro profile, ITI-1549 does not elicit head twitch behaviors in mice and therefore can be classified as a non-hallucinogenic agent. In other animal models ITI-1549 decreases anxiety in mice in an open field test and has prosocial activity, improving social interaction of rats (minimally effective dose of < 1.0 mg/kg in both tests). Effects in these two tests are like those induced by psychedelics in similar animal models. Further work is ongoing to determine the ability of ITI-1549 to alleviate stress-induced depressive behaviors and alter signaling pathways in the prefrontal cortex that are associated with synaptogenesis and that are disrupted in certain neuropsychiatric diseases.

ITI-1549 also binds with high affinity to 5-HT2b receptors (Ki = 4.8 nM), but ITI-1549 is functionally an antagonist at this receptor (IC50 = 13.8 nm) and not a 5-HT2b agonist. Lack of 5-HT2b agonism is a desirable characteristic as 5-HT2b receptor agonists have been associated with heart valve pathologies. Thus, based on this profile ITI-1549 could be safely administered acutely or chronically, if desired.

Conclusions: These data show that ITI-1549 is a biased (towards beta-arrestin signaling) non-hallucinogenic 5-HT2a receptor partial agonist without 5-HT2b agonistic activity. This profile predicts that ITI-1549 may be a safe, non-hallucinogenic psychedelic lacking the potential to induce hallucinations and cardiac pathologies but retaining the potential as an acute or chronic treatment of mood, anxiety and other neuropsychiatric disorders.

Keywords: Psychedelics, Hallucinogen, Mood and Anxiety Disorders, Serotonin 5-HT2A Receptor, New Drug Development

Disclosure: Intra-Cellular Therapies, Inc.: Employee (Self).

P359. PDE4B Inhibitor CV-1238 Demonstrates Both Anti-Depressant and Anti-Psychotic Properties in Preclinical Models

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Background: Psychiatric indications such as depression, schizophrenia and bipolar disorder represent a significant societal burden. Despite the presence of multiple treatment options for each, unmet needs remain to sufficiently control disease symptoms. One common feature these diseases share is the elevated pro-inflammatory marker expression in the periphery and/or the central nervous system [1].

Inhibitors of phosphodiesterase 4 (PDE4) have demonstrated strong anti-inflammatory properties [2] in the clinical setting and can also independently regulate neuronal excitability. Indeed, the PDE4 inhibitor rolipram has shown promise in clinical trials for depression [3], while roflumilast has been shown to improve EEG biomarkers of cognitive impairment in schizophrenia patients [4]. The utility of PDE4 inhibitors has often been limited by gastrointestinal side effects, which are thought to be at least partially driven by inhibition of the PDE4D isoform of the enzyme [5]. We have developed CV-1238, a novel, potent, and brain-penetrant PDE4D-sparing PDE4B inhibitor that was tested in a battery of behavioral models and pharmaco-EEG to evaluate anti-depressive and anti-psychotic efficacy.

Methods: Different cohorts of animals were used for the following experimental models. First, depression-like behavior was induced in male rats by chronic treatment with 170,000 IU/kg interferon-a (IFNa) three times a week for four weeks6; rats were then acutely treated with CV-1238 (0.01, 0.03 or 0.1 mg/kg SC), fluoxetine (10 mg/kg PO) or ketamine (5 mg/kg SC) before measuring immobility in the forced swim test. Second, 2.5 mg/kg amphetamine was injected IP to male mice, immediately followed by 0.02, 0.06, or 0.2 mg/kg CV-1238 SC or 0.1 mg/kg haloperidol SC, and locomotor activity was measured in an open field by the number of beam breaks. Third, male rats were trained in a conditioned avoidance paradigm for 14 days to learn to avoid an electric shock, then injected with 0.01, 0.03, or 0.1 mg/kg CV-1238 SC or 0.3 mg/kg risperidone IP and avoidance responses were measured. Finally, male rats implanted with DSI telemetry transmitters and subdural EEG electrodes were injected with 0.01, 0.03 or 0.1mg/kg CV-1238 SC, 0.3 mg/kg rolipram SC, or 10 mg/kg ketamine IP in a Latin-square design, and EEG were recorded for six hours. Recordings were analyzed to identify sleep/wake states, as well as to calculate power spectral density. To determine anti-inflammatory efficacy, CV-1238 was also tested in LPS-induced TNFa release in both human whole blood and peripheral blood mononuclear cells.

Results: Chronic IFNa treatment induced a depressive-like behavior in rats as indicated by increased immobility in the forced swim test. Ketamine and low doses of CV-1238, but not fluoxetine, significantly reduced the immobility time. In the amphetamine-stimulated locomotion assay, CV-1238 dose-dependently decreased locomotor activity. Similarly, in the conditioned avoidance response, CV-1238 dose-dependently decreased avoidance responses without increasing escape failure at low doses. Fourth, CV-1238, rolipram, and ketamine all increased time to sleep onset and reduced REM duration, consistent with known properties of ketamine and other anti-depressants. All compounds also increased gamma power, a response thought to mediate the long-lasting anti-depressant response of ketamine. Finally, CV-

1238 dose-dependently reduced LPS-induced TNFa secretion in human whole blood and PBMCs ex vivo.

Conclusions: CV-1238 showed anti-depressant-like properties in the IFNα model and on EEG signatures, and demonstrated effects consistent with anti-psychotic activity in the amphetamine-induced locomotion and conditioned avoidance response models. CV-1238 also showed potent anti-inflammatory activity ex vivo. These results suggest that CV-1238 may be beneficial in psychiatric indications featuring depressive or psychotic episodes or increased inflammation.

Keywords: Phosphodiesterase-4 (PDE4), Schizophrenia, Bipolar Disorder, Depression, Preclinical

Disclosure: Cerevel Therapeutics: Employee (Self).

P360. Role of 5-HT2AR in the Anti-Anhedonic and Neuroplasticity-Inducing Effects of DOI and TCB-2

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Background: Psychedelics have gained renewed interest both in clinical and preclinical fields because of the robust antidepressant responses after single- or two-dose administration. As a result, understanding the mechanisms of action for this class of compounds has been an area of great interest in the basic science. Recent studies emphasize the importance of 5-HT2A receptor (5-HT2AR) agonism in the antidepressant and neuroplasticity-inducing effects of psychedelics, yet the necessity for 5-HT2AR activation still remain to be addressed. In this study, using pharmacological approach, we investigated whether 5-HT2AR stimulation is responsible for anti-anhedonic effects and structural neuroplasticity-inducing effects of a psychedelic drug DOI, a 5-HT2A/2C receptor agonist, and a potent 5-HT2AR agonist TCB-2 in mice and rat cortical primary neurons, respectively.

Methods: We treated male C57BL/6J mice with corticosterone to induce anhedonia, observed as reduced sucrose preference ($n = 7$-8/group). To evaluate anti-anhedonic effects of DOI and TCB-2, we injected mice intraperitoneally with them 24 hours before the test. A 5-HT2AR antagonist volinanserin was subcutaneously administrated 10 min before the 5-HT2AR agonist injection. Primary cortical neurons from embryos of female SD rats were cultured and used for assessing effects of 5-HT2AR agonists on neurite length. The necessity for 5-HT2AR stimulation in the structural plasticity was examined using volinanserin and ketanserin which are selective 5-HT2AR antagonists. Comparisons between two-group were analyzed by unpaired t-test. Multiple group comparisons were assessed by one-way ANOVA followed by Dunnett's post hoc test. Significance was determined for $p < 0.05$.

Results: Although some experiments are underway, so far, we found that TCB-2 and DOI improved the chronic corticosterone-induced reduction in sucrose preference in dose-dependent manner. The anti-anhedonic effect of TCB-2 was antagonized by pretreatment with volinanserin. Treatment with DOI and TCB-2 over 2 days increased neurite length in concentration-dependent manner. Both ketanserin and volinanserin blocked the structural plasticity.

Conclusions: We demonstrated that DOI and TCB-2 exerted the antidepressant-like effects after a single injection in a behavioral model of anhedonia and both compounds increased neurite length of rat cortical neurons. The behavioral and structural plasticity effects were dependent on 5-HT2A receptor activation, as indicated by blocking 5-HT2AR using selective 5-HT2AR antagonists. Thus, our findings suggest that 5-HT2AR activation is necessary for the antidepressant and neuroplasticity-inducing effects of psychedelics. Given that traditional antidepressants are effective in the animal model with chronic corticosterone treatment, our findings indicate that the effects of DOI and TCB-2 are rapid onset. Furthermore, since the behavioral effects of DOI and TCB-2 were observed 24 hours after treatment and both compounds promoted structural neuroplasticity in vitro primary culture of cortical neurons, it is likely that such plasticity potentially mediates their antidepressant-like effects. This conclusion is further supported by our findings that 5-HT2A receptor activation is necessary for both behavioral and neuroplasticity effects. Future work that leads to a precise delineation of downstream signaling pathway of 5-HT2AR activation by psychedelics and neural circuits responsible for the antidepressant effects is needed to elucidate the mechanisms of action of psychedelics and develop an agent with more beneficial therapeutic effects.

Keywords: 5-HT2A Receptor, Psychedelics, DOI, TCB-2

Disclosure: Otsuka Pharmaceutical Co., Ltd.: Employee (Self).

P361. Preclinical Pharmacology of DLX-001, a Novel Non-Hallucinogenic Neuroplastogen With the Potential for Treating Neuropsychiatric Diseases

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Background: Cortical synaptic atrophy is a notable component of many neuropsychiatric disorders and treatments that can promote structural neuroplasticity display efficacy in treating them. Recently, psychedelic drugs, including the dissociative anesthetic ketamine, have been reported to show efficacy in humans for treating multiple neuropsychiatric disorders. The clinical effects of these compounds are hypothesized to be due to their ability to promote rapid and enduring effects on structural neuroplasticity, and as such, these compounds have been classified as "psychoplastogens" or "neuroplastogens." Unfortunately, the dissociative experiences, hallucinations, and/or cardiotoxic properties of these compounds will limit their widespread clinical use. Bringing these transformative therapies to a greater patient population would require an orally-bioavailable, non-hallucinogenic neuroplastogen. To that end, we discovered a novel isotryptamine, DLX-001, that is a potent neuroplastogen without hallucinogenic or cardiotoxic activity that can be administered orally. As we developed DLX-001, we deeply characterized its neuroplastic and behavioral effects through multiple preclinical assays to better define its potential clinical efficacy.

Methods: The effects of DLX-001 were examined in a series of in vitro, ex vivo, and in vivo assays relevant to neuroplasticity and the treatment of major depressive disorder. All experimental protocols in animal studies were approved by the appropriate 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: DLX-001 showed significant effects on structural neuroplasticity in in vitro and in vivo assays. In a phenotypic screen of neurite outgrowth in primary rat cortical neuronal cell cultures, DLX-001 produced significant increases in both neurite length and branching. Additionally, in an ex vivo assay of layer V PFC pyramidal neuron structure, Golgi staining revealed a significant effect of DLX-001 on spine count, spine density, and dendritic branching 24 hours after a single IP administration.

DLX-001 also exhibited antidepressant-like activity in rodents. Similar to ketamine, DLX-001 exhibited antidepressant-like effects in the rat forced swim test 24 hours after a single administration with a decrease in immobility and an increase in swimming. These antidepressant-like effects of DLX-001 and ketamine in the FST were maintained up to at least 7 days after a single administration. Similar to psilocybin and ketamine, DLX-001 improved social preference in the mouse chronic social defeat model 24 hours after a single administration. In the mouse head-twitch assay, DLX-001 did not significantly elevate head twitches of male C57BL/6J mice compared to vehicle while DOI did. In a study of cynomolgus monkeys, DLX-001 altered the powerband frequencies in the qEEG and, similar to ketamine, significantly increased the higher frequency gamma power band.

In studies relevant to cardiotoxicity, no signal was identified for DLX-001 in cardiovascular safety pharmacology studies at relevant concentrations/doses and DLX-001 was shown to be an antagonist at 5-HT2B receptors. In pharmacokinetic studies, DLX-001 was shown to be orally bioavailable and brain penetrant. Results will be presented for the affinity and functional activity of DLX-001 at a broad range of receptors and enzymes.

Conclusions: DLX-001 is an orally active, brain penetrant, small molecule that promotes structural neuroplasticity in the PFC without the hallucinogenic or cardiotoxic properties of the psychedelics. The preclinical data suggests that it will have rapid and enduring anti-depressant effects in humans without producing hallucinations.

Keywords: Structural Neuroplasticity, Psychoplastogens, Anti-Depressant Like Action, Non-Hallucinogenic

Disclosures: Delix Therapeutics: Employee (Self). Freedom Biosciences: Advisory Board (Self). Curie.Bio: Consultant (Self).

P362. Discovery of Novel 5-HT2A Receptor Agonists With Psychedelic Drug-Like in Vitro and in Vivo Pharmacological Activity and Therapeutic Potential for Treatment-Resistant Depression

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Background: Mood disorders, particularly treatment-resistant depression, remain a significant unmet medical need. DMT (N, N-Dimethyltryptamine) and psilocin (4-hydroxy-DMT), the active metabolite of psilocybin, are naturally-occurring psychedelic tryptamines that induce subjective experiences mediated via serotonin 5-HT2A receptor agonism. Clinical research with psilocybin, DMT and ayahuasca, a hallucinogenic botanical mixture containing DMT, suggests the potential to produce rapid and lasting antidepressant activity after a single dose. Preclinical studies also support antidepressant therapeutic potential, based largely on neuroplasticity-promoting and behavioral effects. The goal of the current research was to discover novel 5-HT2A receptor agonists with optimal drug-like properties that show in vitro and in vivo pharmacological profiles similar to hallucinogenic tryptamines. Antidepressant drug-like activity was characterized using the forced swim test (FST) behavioral screen and translational electroencephalography (EEG)-based measures of rapid eye movement (REM) sleep, an increase of which is a hallmark of depression in humans that is suppressed by several pharmacological classes of antidepressant drugs. Wistar Kyoto (WKY) rats exhibit behavioral, neurobiological and endocrine phenotypes consistent with symptoms observed in clinical depression. In particular, this strain shows increased REM sleep that is suppressed by acute psilocybin and ketamine but resistant to acute tricyclic or selective 5-HT reuptake inhibitor antidepressants, making it a potentially useful genetic model of treatment-resistant depression. As many known psychedelic molecules exhibit poor selectivity across serotonin receptors, novel agonists with improved 5-HT2A over 5-HT2B selectivity, in particular, were a focus of this work to potentially limit any associated physiological effects that have been attributed to prolonged 5-HT2B stimulation such as valvular heart disease in humans.

Methods: Artificial intelligence/machine learning-driven de novo drug design followed by medicinal chemistry structure-activity relationship development was used to identify novel small molecules with selective agonist activity at 5-HT2A over 5-HT2B receptors. In vitro testing of novel compounds included functional assessment of agonist potency and efficacy on recombinant human and rodent 5-HT receptor subtypes and screening across a broad panel of 87 receptors and enzymes. Adult male C57BL/6 mice were used to perform head twitch response (HTR, $n = 5$-8/group) studies, young adult male Sprague-Dawley rats were used to conduct FST ($n = 10$-15/group) studies and translational antidepressant drug- and psilocybin-like activity was evaluated using EEG-based measures in adult male WKY rats ($n = 7$).

Results: Novel compounds exhibited CNS drug-like physicochemical properties, nanomolar potencies for in vitro activation of human and rodent 5-HT2A receptor signaling pathways, and agonist selectivity for human and rat 5-HT2A over 5-HT2B receptors. Broad panel screening profiles of novel compounds were more consistent with DMT than psilocin. Novel compounds significantly induced HTR in mice in a dose-dependent manner, demonstrating potencies similar to DMT and lower than psilocin. Compound-induced HTR were attenuated by the selective 5-HT2A receptor antagonist, M100907, confirming in vivo 5-HT2A receptor activation-mediated hallucinogenic potential. Novel compounds exhibited antidepressant-like activity in the rat FST. In translational WKY rat EEG studies, novel compounds dose-dependently increased REM sleep latency and decreased REM sleep amount, consistent with psilocybin and indicative of antidepressant drug-like effects. Also similar to psilocybin, compounds significantly decreased low-frequency spectral power during non-REM sleep. Novel compound profiles differentiated from psilocybin on non-REM sleep latency and amount as well as alpha power during wake, while compounds differentiated from each other with respect to exhibiting psilocybin-like reductions in high-frequency gamma power during wake and body temperature.

Conclusions: Novel, potent 5-HT2A receptor agonists with CNS drug-like properties were discovered. In vitro pharmacological profiles and in vivo HTR activity showed greater overall similarity to DMT compared to psilocin. However, compounds exhibited increased agonist selectivity for 5-HT2A over 5-HT2B receptors, suggestive of the potential for improved cardiac safety profiles. Antidepressant drug-like activity was established using the FST and translational EEG-based measures in a rat model of treatment-resistant depression. Novel compounds exhibited significant, dose-related suppression of REM sleep, consistent with an antidepressant drug-like response. Psilocybin-like effects of compounds included REM sleep suppression and decreased non-REM low-frequency spectral power, which have been reported in healthy human volunteers following psilocybin administration, supporting translational validity of these measures. Together, the results suggest that these novel 5-HT2A agonists may have the potential to provide antidepressant benefits while minimizing unwanted pharmacological activities associated with many known psychedelic molecules.

Keywords: Psychedelics, REM Sleep, Mood Disorder, Major Depression Disorder, Serotonin 2A

Disclosure: Nothing to disclose.

P363. A Combined Microfluidic and Fluorescent Imaging Platform for Probing Neuropharmacological Mechanisms In Vivo

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Background: Neuroscience tools for circuit and genetic cell type dissection have rapidly developed over the past 10 years, though pharmacological tools have comparatively lagged behind. Understanding the precise mechanisms of action of pharmacological compounds is critical to the development of newer, more efficacious treatments for a variety of neurological and neuropsychiatric diseases. To date, it has been challenging to incorporate modern tools for assessing neural activity on a large scale with spatially specific intracranial drug delivery. Here we present a microfluidic platform that allows for simultaneous intracranial drug delivery with local neural activity monitoring allowing for precise mechanistic insight into the action of a pharmacological compound on neural activity in vivo.

Methods: We designed a wireless and battery free, miniaturized multi-channel optofluidic device combined with an optical fiber or gradient refractive index (GRIN) lens for monitoring fluorescence deep within the rodent brain. This combined device allows for spatially and temporally specific drug delivery into a brain region while recording activity-dependent fluorescence with numerous biosensors, including genetically encoded calcium indicators (GECIs) such as GCaMP. Optimizations to improve device robustness and repeatability in vivo, including multiple microfluidic outlets, thicker gold coating on the electrodes, and an oil-based plug at the tip of the fluidic have been made relative to prior device versions. We use benchtop as well as in vivo assessments to demonstrate that fiber- and GRIN-fluidic devices produce robust delivery of compounds from two independent drug reservoirs (1.5μL each) across the entire field of view (FOV). Subsequent experiments utilized mice with viral expression of various GECIs, including GCaMP6s and neurotransmitter and neuropeptide sensors (GRABDA and Opto-MASS) injected into several brain regions combined with local drug delivery. All in vivo experiments used both male and female mice.

Results: We find that in benchtop tests, fiber-fluidic devices produce robust and repeatable activation for upwards of 10 infusions (2 drug reservoirs operated 5x each). Using dye infusions in an agarose brain phantom, we find that fluorescent dye infusions rapidly (30s for complete infusion) cover the entire FOV ($n = 3$ devices). Next, we find that infusion of a fluorescent cholera toxin subunit B (Ctb) into secondary motor cortex (M2) of a mouse produces rapid and robust increases in fluorescence immediately at the onset of pump activation ($t(4) = 35.1, p < 0.0001$, $n = 5$). Further, we used a GRIN-fluidic device to demonstrate that fluorescent Ctb infusion produced a rapid (<10s) increase in fluorescence across the entire field of view of the 600um diameter GRIN lens ($n = 1$). Having observed successful infusions and detection of optical fluorescence changes, we next sought to assess whether we could detect changes in neural activity with acute intracranial drug delivery through our microfluidic platform. We first expressed GCaMP6s in M2 and then implanted our fiber-fluidic device. We then loaded drug reservoirs with either the AMPA receptor agonist AMPA (2.5mM), muscimol (0.75ng/0.5uL), or vehicle (ACSF). We find that infusion of AMPA into M2 robustly increased rotational behavior ($t(2) = 4.35$, $p < 0.05$, $n = 3$), indicative of activation of motor cortex. This rotational behavior was correlated with a simultaneous strong increase in GCaMP6s fluorescence ($t(3) = 3.53$, $p < 0.05$, $n = 4$). In a subset of mice, we infused the GABAA receptor agonist muscimol after AMPA (2.5mM) infusion, which rapidly reduced both the neural activity increase observed following AMPA infusion ($t(1) = 7.3, p = 0.08$) as well as the increase in rotation behavior. We next conducted experiments expressing calcium sensors detecting release of the neurotransmitter dopamine (GRABDA) and the neuropeptide enkephalin (Opto-MASS), finding that infusion of the ligands for these receptors produces robust response in a concentration-dependent manner. Finally, ongoing experiments using GRIN-fluidic devices seek to deliver pharmacological compounds while monitoring the activity of single neurons.

Conclusions: Here we present a platform for simultaneous intracranial drug delivery combined with fluorescence detection that allows for both temporally and spatially specific determination of pharmacological effects in a cell type specific manner. This preclinical pharmacology technique can be used to assess the direct effects of pharmacological compounds on neural activity via intracranial delivery, bypassing challenges associated with drug pharmacokinetics, blood-brain-barrier penetrance, and metabolism.

Keywords: Preclinical Pharmacology, In Vivo Fiber Photometry, Pharmacology, Drug Discovery - New Approaches, Two-Photon Calcium Imaging

Disclosure: Nothing to disclose.

P364. Systemic Trace Amine-Associated Receptor 1 (TAAR1) Activation Reduced Mania-Relevant Hyperexploration and Risky Decision-Making in Dopamine Transporter Knockdown Mice

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Background: Elevated risky decision-making is a cardinal feature of bipolar disorder (BD) that is observed across manic, depressed, and euthymic states. Laboratory measures of risk preference are associated with suicidal behaviors in this population, and are also predictive of future drug use. No pharmacotherapies have yet been approved that target this trait-related behavioral deficit, constituting a great unmet need. The Iowa Gambling Task (IGT) is a cross-species translatable test of risk preference that presents humans and rodents with four options providing probabilistic reward/punishment contingencies—two "risky" (large rewards and large punishments) and two "safe" (small rewards and small punishments). The IGT consistently identifies decision-making deficits (increased risk preference) in people with BD, which we have reproduced in mice by inducing a chronic hyperdopaminergic tone via genetic knockdown (KD) of the dopamine transporter (DAT). DAT KD mice exhibit the DAT hypoexpression observed in BD and a characteristic behavioral profile in the cross-species Behavioral Pattern Monitor (BPM) that is consistent with people with BD mania (i.e., hyperlocomotion, elevated specific exploration, straight-line path trajectories). BD treatments partially attenuated DAT KD behavior in both the BPM and IGT, validating this model. The trace amine-associated receptor 1 (TAAR1), a G protein-coupled receptor that presynaptically modulates dopamine transmission, may thus be a potential therapeutic target to normalize BD-relevant behaviors. We leveraged the clinical translatability of the BPM and IGT and the predictive validity of the DAT KD mouse to assess the therapeutic potential of TAAR1 activation in the context of BD-relevant risky decision-making.

Methods: The impact of the TAAR1 agonist R05256390 (0, 0.3, and 1.0 mg/kg, i.p.; within-subjects) was first determined on the exploratory behavior of male and female DAT KD ($n = 20$) and wildtype (WT; $n = 23$) mice in the BPM (45 min). The BPM quantified overall locomotion (distance traveled, transitions across regions), diversive exploration (rearing), and path trajectories (spatial d). The

BPM also quantified specific exploration (exploratory holepokes). The impact of 1.0 mg/kg R05256390 on risky decision-making (vs. vehicle), was then assessed in the same mice 7 weeks later via 60-min sessions of the rodent IGT (within-subjects). IGT stimuli were presented via a horizontal array of 4 illuminable apertures, with selections made via nosepoke. Rewards were 25 µL strawberry milkshake for safe and 50 µL for risky choices. Punishments were 6–12 s for safe and 66–132 s timeout periods for risky choices. Punishment/reward ratios were 1/4 and 1/2 across safe and risky options. Primary outcome measures were analyzed via repeated measures ANOVA, with significant interactions explored via pairwise comparisons (Fisher's LSD). Mice were bred, raised, and maintained in an animal facility approved by the American Association for Accreditation of Laboratory Animal Care (AAALAC). All procedures were approved by the UC San Diego Animal Care and Use Committee and adhered to the NIH Guide for the Care and Use of Laboratory Animals.

Results: DAT KD mice demonstrated hyperlocomotion, elevated specific exploration, and more linear movement in the BPM relative to WTs, as detected by main effects of genotype on distance traveled, transitions, holepokes, and spatial d [$F's(1,38) > 12.0$, $p's < .01$]. Main effects of R05256390 were observed on distance, transitions, holepokes, and rears [$F's(2,76) > 3.8$, $p's < .05$]. Drug × sex × genotype interactions indicated that 0.3 mg/kg selectively reduced transitions and distance traveled in DAT KD males [interactions: $F's(2,76) > 3.1$, $p's < .05$; post hocs: $p's < .05$], while 1 mg/kg reduced both measures in WT females ($p's < .05$). 0.3 mg/kg and 1 mg/kg R05256390 respectively reduced specific-(holepokes) and diversive exploration (rearing) regardless of genotype ($p's < .01$). In the IGT, a main effect of drug was detected on the primary outcome variable difference score (# safe choices − # risky choices) [$F(1,36) = 6.6$, $p < .05$]—with a drug × genotype interaction [$F(1,36) = 5.9$, $p < .05$] indicating that TAAR1 activation selectively reduced risky choice in DAT KD mice ($p < .01$). Critically, vehicle-treated DAT KD mice demonstrated near-significant elevations in this measure relative to WTs ($p = .056$), consistent with people with BD and prior findings.

Conclusions: The DAT KD mouse model of mania demonstrated an array of BD-consistent behaviors in the BPM (hyperlocomotion, hyperexploration, straight-line trajectories) and IGT (reduced difference score). Acute TAAR1 agonist administration (R05256390) reduced locomotion in DAT KD males and WT females, and also reduced exploratory holepoking and rearing across genotypes. TAAR1 activation also normalized risky choice behavior of DAT KD mice to WT levels, but did not affect WT decision-making. These findings support the potential for TAAR1 agonists as novel treatments for hyperexploratory behavior and elevated risk preference in BD. Future studies utilizing fiber photometry will be critical in determining the underlying mechanisms of TAAR1-mediated attenuation of DAT KD risky decision-making and hyperlocomotion, which likely involve normalization of hyperdopaminergia in regions like the striatum and/or medial prefrontal cortex.

Keywords: Bipolar Disorder, Risk-Based Decision-Making, Translational Animal Models, Sex Differences

Disclosure: Nothing to disclose.

P365. Pharmacokinetics-Pharmacodynamics Dissociation Indicative of Ketamine-Induced Plasticity as Revealed by Ultrasonic Ketamine Uncaging in Rat Medial Prefrontal Cortex

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Background: Ketamine, a dissociative anesthetic and recreational drug, is also used as a therapy for varied neuropsychiatric diseases, especially following the FDA approval of one of its isomers as a rapid onset treatment for refractory major depression. While ketamine has been identified as a 'psychoplastogen' related to its ability to induce synaptogenesis in key limbic brain regions, how ketamine selectively induces such plasticity-related changes is incompletely understood. To elucidate how ketamine may affect plasticity in different brain regions, and how physiologic biomarkers may relate to that plasticity, we turned to ultrasonic drug uncaging, in which ultrasound-sensitive drug-loaded nanoparticles, when paired with transcranial focused ultrasound, permits noninvasive localized drug administration to target brain regions thereby enabling noninvasive, spatiotemporally localized precision neuropsychopharmacology. We then used electrophysiologic and analytical chemical assays in rats to identify the pharmacokinetics-pharmacodynamics relationship for ketamine delivered either in a usual form or via ultrasonic ketamine uncaging.

Methods: Animals: Adult, male, Long Evans rats (300-350 gm body weight; Charles Rivers Laboratories) were used in all experiments, which were completed in accord with our institutional APLAC/IACUC.

Focused Ultrasound (FUS): A single element 250 kHz ultrasound transducer was used with a protocol of 50 ms burst length, 5 Hz burst frequency targeting an in situ pressure of 0.9 MPa, derated 10% to account for the rat skull, with mechanical index of 1.8, notably below the FDA guidelines for diagnostic ultrasound.

Pharmacokinetic analysis: Solid-phase microextraction (SPME) was used to sample from the brain at the sonication target versus a contralateral control region immediately following ketamine-HCl or ketamine-loaded nanoparticle infusion with our without sonication. SPME samples were analyzed downstream by LC-MS/MS to quantify the amounts of ketamine, norketamine, and hydroxynorketamine extracted by the SPME probes. Concurrently taken venous blood samples were processed with liquid-liquid extraction and analyzed by LC-MS/MS for ketamine, norketamine, and hydroxynorketamine levels.

Electrocorticography (ECoG): Jeweler screw electrodes were implanted near the medial prefrontal cortex (mPFC) sonication target with reference and ground electrodes placed caudal to the lambdoid suture, and the screws were secured by dental cement. At least one week recovery from electrode implantation to recording was maintained. Electrical potentials from the electrodes were recorded while the animal was awake and restrained. Recording was started and maintained for 1 hr and halted if the animals showed intolerance to the restraint apparatus. Recordings were maintained through and after the animal received an infusion of either saline, ketamine-HCl, or ketamine-loaded nanoparticles with sonication application during the latter half of the 5-min infusion. Potentials were analyzed off-line for the band powers in the gamma (30-60 Hz), delta (0.5-4 Hz), and theta (4-8 Hz) bands.

Results: Without FUS, there was minimal brain ketamine exposure following 1.5 mg/kg ketamine NP infused IV over 5 min; but with FUS (250 kHz; 0.9 MPa in situ peak neg. pressure; 50 ms/5 Hz PRF/2.5 min) brain ketamine increased significantly to match that of dose-matched ketamine-HCl ($N = 4$-5/group). Notably, there was no effect of FUS on the amount of ketamine in the brain seen after administration of ketamine-HCl. Ultrasonic ketamine uncaging yielded higher brain ketamine than the contralateral control site indicating that uncaging was spatially resolved to < 5 mm. The uncaged ketamine cleared with expected timing, equalizing to control at 15 min post FUS ($N = 10$/group).

We then applied ketamine uncaging to the rat medial prefrontal cortex (mPFC) while recording electrocorticography (ECoG) in rats during awake restraint stress. While saline infusion and FUS produced no specific ECoG change, a minimal but nonsignificant increase in gamma (30-60 Hz) band power was seen with 0.75 mg/kg NP infused IV over 5 min without FUS. A more prominent

increase in gamma band power was seen with 0.75 mg/kg ketamine-HCl infusion, which decreased proportionate to the clearance of ketamine from the brain. Surprisingly, a dose-matched NP infusion with FUS applied to the mPFC not only produced even higher gamma band power, but this power was sustained through > 20 min post FUS/infusion, surpassing the pharmacokinetics of ketamine in the brain.

Conclusions: These results indicate that the mPFC is particularly sensitive to the physiologic plasticity induced by ketamine in an acute stress model, and that gamma band EEG/ECoG may serve as a biomarker for these changes. The correlates of these results in other brain regions of interest and in relation to histologic markers of plasticity is being further investigated.

Keywords: (R,S)-Ketamine, Neuroplasticity, Focused Ultrasound, Pharmacokinetic and Pharmacodynamic, Gamma Oscillations

Disclosure: Nothing to disclose.

P366. Antidepressant-Like Effect of the Orally Administered 2-O-Salvinorin B Benzo[b]thiophene-2-Carboxylate (Heteroaromatic Derivative of Salvinorin A)

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Background: Preliminary screening of C(22)-fused-heteroaromatic derivative [2-O-salvinorin B benzo[b]thiophene-2-carboxylate (AK-1402)] from Salvinorin A in mice model of depression is aimed at assessing the antidepressant property of this neoclerodane diterpene with limited or no clinical applications in its new derivative.

Methods: Oral administration of vehicle 10 ml/kg, AK-1402 (1, 3, or 10 mg/kg), imipramine (IMI 10 mg/kg), diazepam (DZP 5 mg/kg) in male and female Swiss mice [6-week-old with weight = 30 ± 2 g; n = 8 (4 mice per sex) randomly distributed into the treatment groups and exposed to the forced swimming, tail suspension and open field tests (FST, TST, and OFT, respectively). Additionally, mice were pretreated intraperitoneally with p-chlorophenyl alanine 100 mg/kg (serotonin depletor), alpha-methyl-tyrosine 100 mg/kg (catecholamine depletor), WAY100635 0.3 mg/kg (selective 5-HT1A receptor antagonist) and prazosin 1 mg/kg (selective α1-receptor antagonist) or vehicle 10 ml/kg before (30 minutes interval) the oral administration of AK-1402 10 mg/kg, IMI 10 mg/kg or vehicle 10 ml/kg and behavioral evaluations after 60 minutes. All experimental procedures adhered 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). Data were subjected to ANOVA followed by Dunnett's s or Bonferroni's post hoc tests and expressed as mean ± SEM ($p < 0.05$ was considered statistically significant).

Results: The oral administration of AK-1402 and IMI at the dose of 10 mg/kg reduced the immobility and increased the swimming time [$F(5, 42) = 28.0$; and $F(5, 42) = 31.0$, respectively, $p < 0.05$] in FST, while a reduction in immobility time and an increase in movement time were recorded in TST [$F(5, 42) = 43.0$; and $F(5, 42) = 41.0$, respectively, $p < 0.05$]. Altogether, these data suggest an antidepressant-like effect of AK-1402. Unlike DZP, the immobility time, crossing and rearing activities were not changed significantly by AK-1402 and IMI ($p > 0.05$). The attenuation of the antidepressant-like effect of AK-1402 and IMI by p-chlorophenyl alanine and alpha-methyl-tyrosine suggests the involvement of a monoaminergic mechanism.

Conclusions: These preclinical findings support further pharmacological characterizations of AK-1402 to effectively establish an antidepressant-like effect devoid of Salvinorin A´s adverse properties.

Keywords: AK-1402, Depression Model, Monoamine, Derivative

Disclosure: Nothing to disclose.

P367. Poster Withdrawn

P368. Glyoxalase I Inhibitors Induce Fast-Acting Antidepressant-Like Effects Following Chronic Mild Stress

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Background: Depression is a complex mood disorder affecting millions of people of all ages worldwide. Current antidepressants require weeks of treatments for therapeutic effects to emerge, and one third of patients do not respond adequately. Ketamine is the only fast-acting antidepressant currently approved for clinical use, but lacks effectiveness in approximately thirty percent of patients, and can incur major side effects. Previously, we demonstrated that subchronic treatment (5 days) with glyoxalase I (GLO1) inhibitors, including methyl gerfelin (MeGFN), exerts antidepressant-like effects in several animal models of depression-like behavior. GLO1 is a key enzyme mediating the catabolism of methylglyoxal (MG), an endogenous GABAA partial agonist. Thus, GLO1 inhibitors increase endogenous MG concentrations. Here, we examined whether acute injection with MeGFN could also induce fast-acting antidepressant effects in mice using several behavioral paradigms assessing depression-like behavior.

Methods: We used adult male and female Balbc/J mice (n = 8/group) and exposed them to a 6-week long chronic mild stress (CMS) protocol, or standard facility housing. Next, mice received drug injections and were tested for frustrative non-reward following reward omission, coat state, open field behavior, social interaction, and the forced swim test (FST) within 1h-48 hours after drug injection. Thus, one hour before the first behavioral test (reward omission), mice received either MeGFN (12.5 mg/kg), ketamine (15 mg/kg, a fast-acting antidepressant control group), or their respective vehicles. All behavioral testing was completed within 48 hours of drug injection. Either one-way, two-way or three-way Anova statistical analysis has been performed. Significant interactions were resolved using post-hoc ANOVAs or Tukey's test.

Results: We found that a single systemic injection of MeGFN or ketamine induced fast-acting antidepressant-like effects by increasing reward-seeking following reward omission (1 hour after treatment), improving social interaction deficits (with no effects on social novelty), by reducing coat deterioration, and by reducing immobility time and increasing swimming time in the forced swim test (FST), all without affecting locomotor activity. In sum, our results show that within 1h-48h following acute treatment with either 12.5 mg/kg MeGFN or 15 mg/kg ketamine, mice exposed to CMS exhibit antidepressant-like effects on frustrative non-reward, coat state deterioration, social interaction deficits, and immobility in the FST.

Conclusions: Here, we demonstrate that the GLO1 inhibitor MeGFN induces fast-acting antidepressant-like effects following acute systemic administration in mice exposed to chronic mild stress in several behavioral paradigms assessing depression-like behavior. Overall, our study demonstrates that GLO1 inhibitors,

which enhance endogenous activity at GABAA receptors via increasing MG concentrations, may provide a novel target for the development of fast-acting antidepressant drugs.

Keywords: Depression, GABA-A Receptors, Glyoxalase 1, Behavioral Pharmacology, Neuropsychopharmacology (NPP)

Disclosure: Nothing to disclose.

P369. Prophylactic (R,S)-Ketamine and (2S,6S)-HNK Decrease Fear Expression by Differentially Modulating Fear Neural Ensembles

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Background: We previously reported that a single injection of (R,S)-ketamine and its metabolite (2S,6S)-hydroxynorketamine (HNK) prior to stress attenuate learned fear. However, whether these drugs are capable of attenuating learned fear through divergent or convergent effects on neural ensemble activity remains to be determined.

Methods: 129S6/SvEv male mice (8-week-old, $n = 10$ per group) were injected with saline, (R,S)-ketamine (30 mg/kg), or (2S,6S)-HNK (0.075 mg/kg) one week before a 3-shock contextual fear conditioning (CFC) paradigm. Five days later, mice were re-exposed to the aversive context, and euthanized one hour later to quantify active cells throughout several brain regions. Brains were processed for c-fos immunoreactivity and brain-wide neural networks were built following processing with a novel pipeline developed in our laboratory.

Results: (R,S)-ketamine and (2S,6S)-HNK administration attenuate learned fear compared to saline mice ($p < 0.01$ for both drugs). (R,S)-ketamine increases fear-related neural activity and connectivity in several brain regions (e.g., ventral CA3, restrosplenial cortex and prefrontal cortex ($p < 0.01$)), while (2S,6S)-HNK increases the connectivity specifically within and between prefrontal cortex and amygdalar regions ($p < 0.05$).

Conclusions: Our results indicate that (R,S)-ketamine and (2S,6S)-HNK attenuate learned fear by differentially altering network correlated activity. We found new nodes in the network that are altered by fear behavior so that we can target with pharmacological manipulations to alleviate fear. This work contributes to the understanding of prophylactic drugs as therapeutic aids for fear-related disorders.

Keywords: Depression, Emotional Stress, cFos, Fear Conditioning

Disclosure: Nothing to disclose.

P370. A Role of Splenic Heme Biosynthesis Pathway in the Persistent Prophylactic Actions of Arketamine in Lipopolysaccharide-Treated Mice

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Background: Relapse is common in remitted patients with major depressive disorder (MDD). Dissociative anesthetic ketamine has been reported to produce long-lasting prophylactic effects in rodents. Arketamine, a (R)-enantiomer of ketamine, has persistent prophylactic actions in an inflammatory model of depression (Ma L. et al. Transl. Psychiatry 2022). However, the precise mechanisms underlying these prophylactic actions remain unknown. Given the role of the brain–spleen axis in depression (Wei Y. et al. Mol. Psychiatry 2022; Brain Res. Bull. 2022), we sought to identify splenic molecular targets that play a role in the prophylactic actions of arketamine.

Methods: Male adult C57BL/6 mice (8 weeks old, body weight 20–25 g) were obtained from Japan SLC, Inc. (Hamamatsu, Shizuoka, Japan) and housed under controlled temperature and 12 h light/dark cycles (lights on between 07:00–19:00). The experimental protocols were approved by the Chiba University Institutional Animal Care and Use Committee. Lipopolysaccharide (LPS) (1.0 mg/kg) was administered for 6 days after a single injection of arketamine (10 mg/kg) or saline. The spleen was collected 24 hours after LPS injection. RNA-sequencing analysis of spleen samples was performed. The biological functions of RNA-sequencing data were analyzed using Ingenuity Pathway Analysis (IPA). Behavioral tests including locomotion and forced swimming test were performed. Pharmacological effects on LPS-induced depression-like behavior were examined. Plasma levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were determined using ELISA kits. Quantitative real-time PCR and Western blot analysis were also performed.

Results: RNA-sequencing analysis found altered expression in the heme biosynthesis II pathway. Quantitative RT-PCR revealed that pretreatment with arketamine blocked increased expression of genes involved in the heme biosynthesis II pathway in LPS-treated mice, namely, 5-aminolevulinase synthase 2 (Alas2), ferrochelatase (Fech), hydroxymethylbilane synthase (Hmbs). Interestingly, there were positive correlations between expression of these genes and spleen weight or plasma levels of pro-inflammatory cytokines (IL-6 and TNF-α). We also found higher expression of ALAS2 and FECH in postmortem spleen from MDD patients. Pretreatment with a key intermediate precursor of heme, 5-aminolaevulinic acid (300 mg/kg/day for 3 days), caused splenomegaly, higher plasma levels of pro-inflammatory cytokines, and depression-like behavior in low-dose LPS (0.1 mg/kg)-treated mice. Interestingly, pretreatment with a heme biosynthesis inhibitor, succinyl acetone (120 mg/kg/day for 3 days), had prophylactic effects in LPS (1.0 mg/kg)-treated mice.

Conclusions: These data suggest a novel role for the heme biosynthesis II pathway in the spleen for inflammation-related depression. Therefore, the heme biosynthesis pathway could be a new target for prevention of relapse in MDD patients.

Keywords: R-(-)-Ketamine, Ketamine, Inflammation, Prophylactic, RNA-Sequencing

Disclosures: Otsuka: Consultant (Self). Otsuka: Grant, (Self). Perception Neuroscience: Grant (Self).

P371. Proinflammatory Cytokines Plasma Levels are Increased in Youth With Familial Risk for Bipolar Disorder

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Background: Bipolar Disorder (BD) is a chronic and severe psychiatric illness, with a prevalence in the U.S. of more than 2 million cases in 2019, most affecting adolescents or young adults. Based on the Global Burden of Disease Study data, it is the 12th leading cause of disability for people aged 15-24, making it the third leading cause of disability overall. BD has a 60–80% heritability rate reported in twin studies, with a genetic risk that can manifest in clinical or subclinical neurodevelopmental,

emotional, or behavioral characteristics. High-risk prospective studies showed elevated rates of psychiatric disorders and bipolar spectrum disorders in offspring of adults with bipolar disorder. Based on longitudinal phenomenological, neurostructural, cognitive, neurochemical, and biochemical data, bipolar disorders undergo neurobiological progression. This leads to a significant and enduring impairment in social and occupational functioning that occurs in most patients. Several studies suggest that inflammatory disturbances are involved in BD pathogenesis. It has been reported that people with BD have altered both central and peripheral immune proteins. As a final consideration, children who have a parent with BD, particularly those who go on to develop a mood disorder, present an abnormal neuroimmune state. While increasing evidence indicates that inflammatory systems play a part in BD, the exact role is still unclear. Observational studies show that early intervention can improve disease progression and outcomes, whereas a delay in treating the disease is associated with poorer outcomes. There are currently no molecular markers that allow intervention in high-risk individuals, or early detection and specific treatment targets for early-onset patients. Therefore, it is crucial to identify warning signs earlier and improve intervention efforts. Based on this, we investigated inflammatory markers in plasma from children and adolescents who have BD or a familial risk for the disorder.

Methods: In this preliminary study, we investigated plasma samples from 100 children and adolescents aged 7 to 17, from UTHealth's Center of Excellence in Mood Disorders. Early-onset BD (BD Youth) consisted of individuals with diagnosis for BD type I, BD type II or BD not otherwise specified. Individuals with familial risk for BD (BD Offspring) were those without affective or non-affective diagnoses at the time of enrollment and had at least one parent who meets DSM-IV criteria for BD type I or BD type II. A third group of subjects was the non-psychiatric controls (Control), who had no history of psychiatric illness, abuse of illicit substances, presence of chronic medical conditions, or family history of psychiatric disorders in a first-degree relative. The total of samples per group was 29 for BD Youth, 25 for BD Offspring and 46 for control. Quantitative analysis of Tumor necrosis factor (TNFα), Interferon (IFNy), Interleukin (IL)1b, IL2, IL6, IL10, and IL18 plasma levels were performed using magnetic bead-based multiplex immunoassay commercial kit. One-way ANOVA was conducted to determine if each cytokine levels were different among groups. Statistical analyses were performed by One-Way ANOVA followed by Tukey's multiple comparisons test. Outliers were removed and age, sex, and ethnicity were used as biological variables. Data analyses were carried out using IBM SPSS Statistics 28 and GraphPad Prism 9. Significance levels were determined at a value of 0.05.

Results: TNFα and IL18 plasma levels was statistically significantly different between groups ($F(2, 87) = 4.617$, $p = 0.0124$, and $F(2, 89) = 7.069$, $p = 0.0014$, respectively). Tukey post hoc analysis revealed that both cytokines' levels increased in BD Offspring when compared to BD Youth and Control. Other cytokines levels where below the detection range.

Conclusions: Our results support the findings of the literature that individuals with familial risk have an aberrant immune state, which confirms that inflammation plays a major role in the physiopathology of BD. Although expected to have a similar proinflammatory profile, patients with early onset BD use medication that can influence cytokines levels, a confounder that was not investigated in this study. Future perspectives include examining the role of inflammation in BD risk further, and how it influences the symptoms of depression and manic episodes, as well as the functioning and cognitive scores of patients. This can help identify warning signs earlier and improve intervention efforts.

Keywords: Bipolar Disorder, Children and Adolescents, Familial Risk of Bipolar Disorder, Inflammation

Disclosure: Nothing to disclose.

P372. Stress Fingerprinting Depression: Association of Stress Measures and Stress Task-Based fMRI Activations Related to State and Trait Symptoms in Major Depressive Disorder

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Background: Stress across the lifetime plays a major role in increasing the incidence and severity of numerous psychiatric diseases, but exactly how stress translates into impact on brain circuitry remains an area of high interest. Brain areas responsible for processing of and response to stress have been implicated in depression, including limbic areas like the hippocampus, which itself is sensitive to damage by stress. We hypothesized that lifetime stress-induced perturbation of stress-sensitive cortico-limbic brain areas leads to altered functional activation in response to subsequent stressful situations during adulthood, underlying an altered stress responsivity in major depressive disorder (MDD) and contributing to symptoms.

Methods: We developed a highly translational stress induction paradigm that is human MRI compatible and ethical. The ankle shock threat task (AST) paradigm is analogous to the classic approach of inducing stress in animal studies using foot shock and unpredictability. For this pilot study, we recruited 26 patients with MDD (19/26 female) and 30 psychiatrically healthy adult community controls (HC, 17/30 female). Structured Clinical Interview for DSM-IV or -5 was completed to verify psychiatric diagnoses. Major early life stress was recorded using the Childhood Trauma Questionnaire, while recent stress (past 30 days) was measured with the Perceived Stress Scale. State, or recent, and trait, or longitudinal, depressive symptoms were measured with the Maryland State and Trait Depression scale. fMRI data was collected using a 3-T Siemens Prisma scanner and 64-channel coil, with an electrode attached to one ankle of each participant. A predetermined amperage was applied for 0.1s during the task (similar to a shock from touching a surface with static electricity, using the Transcutaneous Aversive Stimulator, Coulborne Instruments). There are 3 conditions in this paradigm: (1) a shock condition in which a few random shocks are delivered while a color sign on a visible screen indicating shocks are possible; (2) a threat condition in which the same color is present but no shock is given; and (3) a safe condition in which no shock is given and the displayed color indicates safety. All image preprocessing includes slice timing corrections and were volume co-registered. Images were linearly detrended, normalized into MNI standard space, and spatially smoothed (FWHM = 8mm) using SPM12. First level models were developed for each subject by entering all the volumes into a single analysis regressing the "shock", "threat" and "safe" conditions. The contrast of interest was the threat - safe condition to study brain processing of the threat of shock but without the interference of the actual shock. Regression analyses were completed in SPSS (IBM). All experimental protocols were approved by the University of Maryland Baltimore IRB.

Results: Nominally significant group differences were found in multiple regions from the threat - safe contrast ($p < 0.05$) in a previous larger sample analysis. Two regions with significant patient-control activation differences were selected from this list to examine in this pilot study in depression due to their roles in stress processing and symptomatology: right hippocampus and ventral anterior cingulate. In control participants, state and trait depression scores were highly correlated with each other ($r = +0.67$, $p < 0.001$), and both correlated with recent stress measured by PSS (state $r = 0.62$ $p < 0.001$; trait $r = 0.46$ $p = 0.015$). Developmental lifetime stress measured by CTQ correlated

significantly with R Hippocampal activation (r = +0.62, p = 0.006) in the threat task. CTQ also negatively predicted PSS score (r = -0.54, p = 0.026). In participants with MDD, State and trait depression scores were correlated (r = 0.55, p = 0.004), but PSS correlated with only the state depression score (r = 0.66, p < 0.001). PSS correlated negatively with R Hippocampal activation (r = -.45, p = 0.026), while CTQ was negatively associated with vACC activation (r = -0.64, p = 0.01) in patients. CTQ predicted trait depression (r = 0.59, p = 0.02), but not state depression (p = 0.5) in patients.

Conclusions: We have previously linked stress measures across the lifetime to highly stress- and disease-relevant functional brain activations using an anticipated threat task. Here, we observed relationships between current stress and depressive symptoms in both groups, but different association between lifetime developmental stress and stress task-related brain activations in patients and controls. These findings support a mechanism of altered stress vulnerability and stress processing in patients with MDD contributing to depressive symptoms.

Keywords: Depression, Stress, Neuroimaging

Disclosure: Nothing to disclose.

P373. Whole Blood Mitochondrial Copy Number and Mood Disorders: A Clinical Meta-Analysis and Preclinical Model

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Background: Major depressive disorder (MDD) and bipolar disorder (BD), are globally prevalent, contributing to significant disease burden and adverse health outcomes. These mood disorders are associated with changes in many aspects of brain reward pathways, yet cellular and molecular changes in the brain are not readily available in clinical populations. Therefore, the use of biomarkers as proxies for changes in the brain are necessary. The proliferation of mitochondria in blood has emerged as a potentially useful biomarker, yet a clear consensus on how these mood disorders impact blood mitochondrial DNA copy number (mtDNAcn) has not been reached. It is also unclear how preclinical stress models, such as chronic social defeat stress (CSDS), impact blood mtDNAcn. In this study we conducted a meta-analysis of available published studies examining whole blood/ cell-based blood mtDNAcn in patients with mood disorders to determine how these mood disorders impact mtDNAcn across multiple studies and patient populations. Further, we examined whether a preclinical mouse model of chronic stress induces a similar pattern in mtDNAcn as a clinical mood disorder. This will determine whether preclinical models can be used to further probe the utility of blood mtDNAcn in predicting mood-related physiological changes.

Methods: Following PRISMA guidelines for a systematic search, 22 papers met inclusion criteria for meta-analysis (10 MDD, 10 BD, 2 both MDD and BD). We extracted demographic, disorder, and methodological information with mtDNAcn. Using the metafor package for R, calculated effect sizes were used in random effects models for MDD and BD with subsequent subtype and meta-regression analyses. Preclinically, C57Bl/6 male mice underwent 10 days of CSDS or control housing (n = 10) and a social interaction test, after which trunk blood was used for whole blood mtDNAcn analysis.

Results: Our results show a trending increase in mtDNAcn in patients with MDD (n = 12 studies, effect size = 0.24, p = 0.105, I2 = 95.01), which reaches significance when one study with outlying demographic characteristics is excluded (n = 11 studies, effect size = 0.30, p = 0.038, I2 = 94.60). Overall, there was no effect of BD on mtDNAcn (p = 0.285), however, effects proved to be dependent on BD type in a subsequent subtype analysis (n = 18 studies, QM(df = 2) = 23.1045, p-val < .0001, I2 = 70.6). BDI was associated with a lower mtDNAcn (n = 8 studies, effect size = -0.374, p = 0.0014). Conversely, BDII studies showed significantly higher mtDNAcn (n = 2 studies, effect size = 1.254, p < 0.001). Subtype and meta-regression analysis for both MDD and BD showed no effect of age, percent women in the patient population, or geographic region/race on mtDNAcn. Preclinically, mice that underwent CSDS had significantly higher mtDNAcn than control mice (n = 10 CSDS, 10 Control; p = 0.045, Cohen's d = -1.007) and this measure negatively correlates with the time spent with the social target in the social interaction test (p = 0.045, r2 = 0.216).

Conclusions: This is the first comprehensive meta-analysis of whole blood mtDNAcn in MDD and while it is the second in BD, it is the first to differentiate by BD type, which we show significantly impacts the effect on mtDNAcn. This is the first demonstration of the significant increase of mtDNAcn with MDD across studies, and the decrease in BDI patients. This is also the first study of mtDNAcn in a preclinical CSDS model. Together our data suggest whole blood/cell-based mtDNAcn may be a useful biomarker for mood disorders, with MDD and BDII associated with higher mtDNAcn, and BDI associated with lower mtDNAcn. The CSDS mtDNAcn profile mimics the MDD/BDII phenotype of higher mtDNAcn. Further study of blood mtDNAcn could predict downstream health outcomes or treatment responsivity for individuals with mood disorders.

Keywords: Major Depressive Disorder (MDD), Bipolar I and II Disorder, Mitochondrial DNA Copy Numbers, Chronic Social Defeat, Peripheral Blood Marker

Disclosure: Nothing to disclose.

P374. Blood-Brain Barrier Modulation by Accelerated Intermittent Theta Burst Transcranial Magnetic Stimulation as a Mechanism in Depression Treatment

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Background: Treatment-resistant depression (TRD) is a leading cause of disability. Developing more effective treatments will depend on efforts to understand the pathophysiological mechanisms that drive TRD. The blood-brain barrier (BBB) is a neurovascular component tasked with maintaining neuronal microenvironments and cerebral homeostasis. Although its role in depression is not well defined, recent studies suggest that the BBB may be involved in treatment responses and depression pathophysiology in a subgroup of patients more vulnerable to vascular perturbations. Transcranial magnetic stimulation (TMS) has been reported to transiently open the BBB for targeted chemotherapy delivery using similar protocols to the FDA-approved parameters for TRD. However, this has never been studied for lasting, non-transient, effects, due to methodological limitations of clinical BBB assessments that require contrast injection or invasive cerebrospinal fluid testing. A novel MRI sequence called diffusion-prepared arterial spin label (DP-ASL) measures BBB function using a non-contrast, non-invasive, well-tolerated approach. Given that depression may harbor BBB dysfunction as part of its pathophysiology, and TMS may act by modulating the BBB, we aim to pair TMS with DP-ASL before and

after treatment to better understand this relationship. The goal of this project is to interrogate the effects of TMS on BBB in TRD, by testing the central hypotheses that: 1) BBB function is significantly improved in TRD participants responsive to a course of accelerated TMS; and 2) TRD symptom outcomes will be associated with BBB functional improvements in dorsolateral prefrontal cortex (i.e. the target site), frontostriatal, or limbic regions.

Methods: Participants received diffusion-prepared arterial spin label (DP-ASL) MRI to capture the active water exchange between the capillary space to the brain parenchyma as a proxy for BBB neurovascular dysfunctional activity (measured as "Kw"). Neuroimaging took place within one week prior to TMS treatment (NCT: 04982757) and within two-weeks following TMS treatment for participants with TRD as shown through the Mini International Neuropsychiatric Interview and a psychiatric evaluation. HDRS-17 will be administered within one-week prior to TMS treatment and will be assessed at one-week after TMS treatment as well. TMS will be administered using the MagVenture MagPro System with Brainsight neuronavigation device. Participants completed a 5-day course of 10x daily repetitive TMS delivered hourly at 5 Hz frequency. Each session delivered 1200 pulses of intermittent theta-burst stimulation. Protocol settings are as follows: Waveform: Biphasic burst; burst pulses: 3; interpulse interval 20msec; pulses per train: 10; number of trains: 60; inter-train interval: 8 sec; total time: 9′ 40″; dose: 100% resting motor threshold (RMT) of the ipsilateral (left) precentral gyrus "hand knob" location.

Results: We observed significant reductions in Kw in the TRD group compared to HC ($p < 0.05$), covaried for age and sex. The reduced value on DP-ASL signal implies a reduced function of the active water exchange transport process, a crucial driver of BBB function. Next, a structural parcellation map was applied to the DP-ASL signal to refine these findings with greater resolution across discrete brain regions of interest. Compared to HC, there was significantly reduced BBB function mostly contained to the left hemisphere and including frontal structures like the superior and middle frontal gyri, lingual and fusiform gyri, and superior, middle, and inferior orbital gyri ($p = 8{\cdot}10\text{-}4$ to $3{\cdot}10\text{-}6$). Right hemispheric dysfunction were only found in the pre- and post-central gyri ($p = 3{\cdot}10\text{-}6$ to $6{\cdot}10\text{-}6$). TMS was used to test the relationship between BBB functional improvements and symptom improvements. HDRS-17 scores anticorrelated at trend level significance with whole brain BBB (Kw) function ($r = -0.52$, $p = 0.07$). Brain regional analyses was performed to parse out regions of interest, revealing the middle frontal gyrus ($r = -0.65$, $p = 0.03$) as the most significantly associated region with depression scores. Of four subjects with complete data available, whole brain BBB function improved in three of them, as did their depression symptoms, while one subject whose BBB function did not improve, also demonstrated no improvements in depression symptoms. Moreover, of the three subjects with TRD whose BBB function improved, two of them remitted (≥50% reduction in HDRS-17), and one responded (25-50% reduction in HDRS-17).

Conclusions: These findings suggest that of the regions with BBB impairment in TRD, the MFG (which houses the DLPFC) may be most related to depressive features, which is also the region that TMS targets for TRD. Moreover, TMS may influence local BBB function underneath its stimulated target site, and that these improvements track concordantly with symptom improvement. Similarly, when MFG BBB function is not improved (or even negatively affected) by TMS, depressive symptoms are resistant to benefits of TMS. Mechanistically, TMS does appear to impart lasting effects on BBB function, that can be measured with non-invasive MRI approaches.

Keywords: Blood-Brain-Barrier, TMS, Depression, Neurovascular, Non-Invasive Brain Stimulation

Disclosure: Nothing to disclose.

P375. FGF21 and GDF15 Plasma Levels Are Increased in Patients With Treatment Resistant Depression and Bipolar Depression

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Background: Major depressive disorder (MDD) and bipolar disorder (BD) are common mental health conditions worldwide associated with significant morbidity and mortality. BD is a mental disorder characterized by extreme mood changes, ranging from manic to depressive and melancholic states. Like MDD, BD has a complex pathological course that often results in less favorable responses to treatment and adverse outcomes. The burden of these conditions affects various spheres of life, such as social, occupational and general quality of life. MDD treatments include psychotherapy, pharmacological treatments and neurostimulation. However, one in three adults with MDD does not show clinically significant improvement after the sequential use of several antidepressants, presenting with treatment-resistant depression (TRD). Although there is no universally accepted definition of TRD, the most commonly used criterion is failure to respond to two trials of pharmacologic therapy of adequate dose and duration during the current episode. The presence of TRD, in addition to contributing to high individual suffering, is associated with increased morbidity and mortality linked to MDD and raises health costs. Research advances in recent years have demonstrated the potential effect of novel biomarkers that affect mood. In this scenario, FGF21 (fibroblast growth factor-21) and GDF15 (growth differentiation factor-15) were considered two important endocrine-acting mitokines that are capable of initiating systemic adaptations that affect overall cellular energy metabolism and may be involved in depressive pathophysiology. GDF15 is a peptide hormone and a divergent member of the transforming growth factor beta (TGFβ) superfamily. In normal physiology, GDF15 is expressed in various tissues at low concentrations, however, in pathological conditions such as tissue injury and inflammation, it can be overexpressed. GDF15 has been shown to be a pleiotropic molecule and its biological effects likely depend on different biological contexts as well as chronological age. FGF21 is a newly discovered member of the FGF superfamily and an important endogenous regulator of glucose and lipid metabolism. These two mitokines play an active role in homeostasis, cell proliferation and survival, mediating adaptive responses to tissue injury and repair under stressful conditions. Hence, this work aimed to identify possible biomarkers in individuals who suffer from chronic systemic stress.

Methods: In this preliminary analysis of an ongoing pilot study, 24 non-psychiatric controls, 10 patients with MDD, 14 patients with TRD, and 15 patients with BD depression were analyzed. A comprehensive diagnostic clinical interview of each subject was conducted according to the DSM-IV. Their functional status and depressive symptoms were assessed using the Montgomery Asberg Depression Scale (MADRS). Using a multiplex assay commercial kits, plasma levels of FGF21 and GDF15 were measured quantitatively.

Results: One-Way ANCOVA showed that the mean FGF21 and GDF15 levels for TRD and BD depression participants were significantly higher compared to MDD patients and non-psychiatry controls, even after adjusting for age, sex, race, smoking status, and BMI ($F(3, 56) = 5.174$, $p = .003$, and $F(3, 58) = 5.942$, $p = .001$). We also found a significant correlation

between FGF21 and GDF15 levels and the severity of depressive symptoms and functional decline.

Conclusions: Our data, although preliminary, suggest that individuals experiencing chronic systemic stress conditions such as BD depression or chronic TRD may lose the beneficial acute stress response, resulting in higher levels of GDF15 and FGF21, which can lead to detrimental physiological effects, including inflammation, oxidative stress, and aging acceleration. However, in this preliminary study, we cannot rule out the possibility of a type I error since is a cross-sectional study with a small sample size. Moreover, the study did not control lifestyle factors like physical activity and alcohol use. Therefore, our results should be seen as exploratory and require replication and validation.

Keywords: GDF15, FGF21, Depression, Chronic Stress

Disclosure: Nothing to disclose.

P376. Impairment of Reward Processing Behaviours Relevant to Depression is Regulated by the Activity of Hypothalamic Corticotrophin-Releasing Hormone Neurons

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Background: Chronic stress is a risk factor for severe mental illnesses including depression. A key feature of depression is dysfunction of reward processing, which manifests as behavioural changes including reduced motivation and anhedonia. Much research on the link between stress and depression has focused on dysfunction in the stress hormone system, the hypothalamic pituitary adrenal (HPA) axis, which is initiated by hypothalamic corticotrophin-releasing hormone (CRH) neurons. In addition to their role in the HPA axis, activity of these CRH neurons rapidly modulates defensive behaviours on a timescale consistent with synaptic rather than endocrine mechanisms. In contrast to the heightened activity displayed by hypothalamic CRH neurons during defensive behaviours, recent studies show that this population is inhibited by reward consumption. Given the important role of stress and reward processing in the pathophysiology of depression, the current studies sought to examine the association between CRH neural activity and motivation and anhedonia.

Methods: Male and female CRH-cre, CRH:TdTomato and CRH:GCaMP6m transgenic mice were used for these experiments. In experiment 1, CRH-cre or CRH:TdTomato mice were infused with a virus expressing the excitatory opsin ChR2 or control fluorophore into the paraventricular nucleus of the hypothalamus (PVN), and fibre optic probe was implanted in the PVN ($n = 28$) or lateral hypothalamus (LH, $n = 12$). Mice were trained in operant chambers to acquire lever pressing, and were tested on a progressive ratio schedule to test motivation before and after 5 days of optogenetic stimulation (1 hour/day, 30 sec on/off). In experiment 2, CRH:GCaMP6 mice ($n = 9$) underwent surgery to implant an optic fibre targeting the PVN to measure neural activity using fiber photometry. Half were exposed to unpredictable chronic mild stress (UCMS), a protocol that induces a depressive-like phenotype. After 10 weeks of UCMS, the mice were given a palatable reward (peanut butter chip) in their home cage, and neural signal and behavioural responses were recorded.

Results: Repeated optogenetic stimulation of PVN CRH neurons reduced motivation in the progressive ratio task (main effect of virus $p < 0.001$). Similar effects were observed when PVN CRH terminals in LH were activated, albeit the effects were weaker than cell body stimulation (t-test, $p = 0.09$). Preliminary studies suggest that UCMS causes animals to engage in more bouts of shorter palatable food consumption compared to controls ($p < 0.05$ both measures), and this was associated with greater suppression of PVN CRH neural activity during palatable food consumption in UCMS exposed mice ($p < 0.01$).

Conclusions: These studies demonstrate that repeated optogenetic activation of PVN CRH neurons induces motivational deficits reminiscent of what is observed in depression following repeated stress. Furthermore, our preliminary results suggest that enhanced suppression on PVN CRH neurons by palatable food is associated with an anhedonia phenotype following chronic stress exposure. Together these findings point to a potential role of PVN CRH neurons in the development of reward processing disturbances associated with the symptoms of depression following chronic stress, and critically these effects appear to be at last partially independent of the role of these neurons in the control of the HPA axis. More work to elucidate the endocrine vs synaptic contributions of this population to stress-related neuropsychiatric disorders may help to guide the development of targeted treatments.

Keywords: Chronic Unpredictable Mild Stress, Reward Processing, Paraventricular Nucleus of the Hypothalamus, Corticotropin-Releasing Hormone, Depression

Disclosure: Nothing to disclose.

P377. Repeated Conditioned Stress Promotes a Shift in the Expression of Nucleus Accumbens Synaptic Plasticity

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Background: Behavioral stress is adaptive when acute while repeated stress is a risk factor for psychiatric illnesses including depression and substance use disorders. The Nucleus Accumbens (NAc) is a stress-sensitive brain region where stress alters plasticity and connectivity and promotes aversive behavioral output. Activity of one of the major NAc projection neurons, dopamine 2 receptor expressing (D2) SPNs, promotes aversion, anxiety, and blunts reward. This suggests D2-SPNs may be directly involved in promoting motivated responses to stress. In this study, we aimed to understand how stress-dependent plasticity on D2-SPNs is altered by acute and repeated stress.

Methods: Single day or multi-day sessions cued fear conditioning (2 cue/shock pairings per day) were used as conditioned stressors. Female and male A2a-Cre mice were used to selectively target NAc core D2-SPNs for assessment of calcium activity (GCaMP7f) using fiber photometry, for halorhodopsin optogenetic inhibition, or to record synaptic activity. Whole-cell patch clamp physiology was conducted on D2-SPNs from mice receiving cued foot shock for 1, 3, or 7 days and cells were filled with neurobiotin to assess spine density and morphology. Two-way ANOVA was used to compare outcomes from cue and cue/shock mice over multiple days.

Results: NAc core D2-SPNs displayed increased calcium activity in response to the foot shock, but not the cue, during conditioning. However, D2-SPN calcium activity transferred to the conditioned cue and displayed increased calcium activity to the cue during recall. Inhibition of D2-SPNs during recall reversibly inhibited freezing ($F(1, 13) = 33.63$, $p < 0.0001$), suggesting increased activity of D2-SPNs is required for recall of cues predicting stressful or aversive outcomes. In agreement with these findings, the amplitude of spontaneous excitatory post-

synaptic currents was increased on D2-SPNs 1 day after foot shock conditioning ($F(2,49) = 4.46$; post hoc cue vs. cue/shock $p < 0.05$) compared to groups subjected to the cue only and 1 day and 3 day conditions. This effect was not observed after 3 or 7 days. After 7 days of repeated foot shock conditioning, frequency of sEPSCs was observed on D2-SPNs from cued shock mice but not cue alone ($F(2,49) = 3.51$; post hoc cue vs. cue/shock $p < 0.01$), suggesting an alteration in the expression of long-term potentiation. D2-SPNs recorded at this 7 day timepoint displayed increased overall spine density ($F(1,11) = 7.48$; post hoc cue vs. cue/shock $p < 0.05$) and increased stubby spine density ($F(1,11) = 6.85$; post hoc cue vs. cue/shock $p < 0.05$) compared to cue only and the 3 day condition, suggesting post-synaptic potentiation was altered to be driven by spine density. No change in mushroom or thin spine density was observed. We are continuing to test additional timepoints including day 1 and day 5 to determine if mushroom spines and stubby spines change relative to electrophysiological readouts.

Conclusions: Our data provides evidence for a potential homeostatic change in long-term potentiation expression on NAc core D2-SPNs in response repeated conditioned stress. This data has further implications for how shifting plasticity on D2-SPNs promote altered NAc activity and behavioral response to acute and repeated conditioned stress. Overall, these findings could provide an underlying mechanism for how discrete stressful stimuli are processed over time and following repeated presentation which may have further implications for anxiety and depression-related disorders.

Keywords: Nucleus Accumbens Core, Glutamate, Synaptic Plasticity, In Vivo Calcium Imaging, Conditioned Fear Memory

Disclosure: Nothing to disclose.

P378. Long-Term Effects of Parity and Gestational Stress on Postpartum Brain Mitochondrial Respiration and Behavior

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Background: Chronic stress exposure during gestation is a significant risk factor for pathologies, including postpartum depression (PPD), an understudied psychiatric complication of childbirth that afflicts up to 20% of women. Yet the mechanisms by which gestational stress modulate postpartum behavior are relatively understudied. Mitochondria are dynamic organelles that are responsible for energy homeostasis as well as the synthesis and release of glucocorticoids from the adrenal glands in response to stress. Mitochondrial function in the brain is particularly important as neurons rely heavily on mitochondria for energy production and stress amplifies energy demands. Prior work shows gestational stress induced PPD-relevant behaviors associated with decreased mitochondrial respiration in the prefrontal cortex (PFC) in mid-postpartum female rats. However, the duration of stress effects on behavioral responses and metabolism in specific brain regions is unknown.

Methods: Adult female Wistar rats ($n = 6$-8/group) were separated into nulliparous controls, nulliparous stressed, primiparous controls, and primiparous stressed groups. Stress groups were exposed to 10 days of chronic mild unpredictable stress during gestational days 10-19. PPD-relevant behaviors including maternal care, sucrose preference, elevated plus maze, and forced swim test were performed across the postpartum period. Ex vivo mitochondrial respiration, and protein expression were measured in PFC and nucleus accumbens (NAc) of females at postpartum day (PD) 23 using high resolution respirometry and immunoblots. Data were analyzed by 2-way ANOVA, followed by post-hoc tests where appropriate. Associations between mitochondrial measures and behavior were tested with Pearson correlations.

Results: Gestational stress reduced early postpartum maternal care ($p = 0.043$) and induced a delayed onset of avoidance behavior at PD14 ($p = 0.049$) not evident at PD4 ($p = 0.70$). Parity alone reduced sucrose preference ($p = 0.003$). Gestational stress tended to decrease mitochondrial respiration in the PFC of females ($p = 0.05$) at a functional level, with no effects on protein expression of mitochondrial complex I or II. In the NAc, parity increased respiration ($p = 0.027$) at PD23 but not PD12 ($p = 0.93$). At the protein level, however, there were main effects of parity ($p = 0.015$) and stress ($p = 0.004$) to decrease complex I and II subunit expression. Interestingly, NAc complex I protein expression exhibited a positive correlation with avoidance behavior on the elevated plus maze ($R2 = 0.34$, $p = 0.02$).

Conclusions: Data reveal temporal and region-specific changes in mitochondrial function associated with altered postpartum behavior following stress exposure and parity. We show that the effects of gestational stress may incubate across the postpartum period, with both metabolic and behavioral consequences appearing several weeks after the last stress exposure. The specificity of these effects for primiparous animals highlights the postpartum period as a unique window for metabolic changes that may drive behavior.

Keywords: Mitochondria, Postpartum, Chronic Unpredictable Mild Stress, Medial Prefrontal Cortex, Nucleus Accumbens

Disclosure: Nothing to disclose.

P379. In Vivo Cellular-Resolution Calcium Imaging Reveals Functional Biomarkers of the Antidepressant Ketamine and Guides Preclinical Efficacy Testing

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Background: Despite decades of concerted effort and significant investment, there are few new treatment options for the ~970 million people living with Severe Mental Illness. The current paradigm for evaluating new treatments in psychiatry, primarily semi-anthropomorphic behavioral assessments, is severely underperforming as evidenced by the high rate of late-stage clinical trial failures due to lack of efficacy. A promising alternative approach for efficacy testing is to leverage our understanding of the neural circuitry that is compromised in psychiatric disease to develop preclinical assays that read out the instantaneous relationship between neural activity and behavior. A single, low dose of the NMDA receptor antagonist ketamine produces rapid and durable antidepressant effects in patients with Treatment Resistant Depression. Identifying replicable biomarkers, by way of in vivo cellular-resolution calcium imaging, of efficacious antidepressants such as ketamine in rodent models will allow for screening of novel putative antidepressants for preclinical drug development.

Methods: We used cellular-resolution calcium imaging in behaving mice to uncover functional biomarkers of stress induced depression, and of ketamine's effects at two temporal scales. The Mann-Whitney U test and repeated measures, two way ANOVA were used for statistical analysis. In Study 1, we looked at timescales coincident with ketamine's rapid antidepressant effect, during drug onboarding and the time of maximum brain exposure. In this study, mice ($n = 10$, male and female) were injected with AAV1-CaMK2-GCaMP6f and implanted with a

GRadient-INdex (GRIN) relay lens in the medial prefrontal cortex to enable cellular-resolution calcium imaging. After recovery, mice were habituated to the behavioral chamber and to wearing a miniature microscope (Inscopix nVista). In a given experimental day, mice were recorded (synchronized behavior and calcium imaging) for a 10 minute baseline, and then injected with R,S ketamine (0, 3, 10, and 30 mg/kg ip), and recorded for another 20 minutes. All subjects received all four treatments across four days of experiments spanning two weeks in a randomized and counterbalanced fashion. In Study 2, we looked for signatures of ketamine's durable antidepressant effects with a within-subject, longitudinal design. In this study, mice ($n = 20$, male and female) were prepared for in vivo imaging and habituated, as described above. All mice were imaged during a baseline session, and then chronically stressed by way of corticosterone treatment for 10 days. Mice were then imaged in a "post-stress" session. Subjects were then randomized into vehicle and ketamine (10 mg/kg, ip) groups. Mice were injected with vehicle or ketamine and then imaged three and 24 hours after treatment.

Raw neural imaging videos were processed through the Inscopix PCA/ICA algorithm and then automated cell filtering was performed by applying a logistic regression model on the output traces. Average event rate was obtained by taking the mean of the events over time and neurons and multiplying by the sampling rate. This yields a single scalar value. Neuronal traces were processed prior to computing pairwise correlations. The onset of a calcium transient was identified as occurring when dF/F exceeded two standard deviations above the baseline fluorescence. The baseline fluorescence was estimated from the high frequency content of the fourier spectra. For the purpose of calculating correlation, all other values in the time series (< 2 standard deviations) were set to 0.

Results: Results from Study 1 demonstrate that ketamine drives a dose-dependent suppression of calcium event rate in medial prefrontal cortex pyramidal neurons (vehicle vs 3 mg/kg $p < 0.05$, vehicle vs 10 mg/kg $p < 0.0001$, vehicle vs 30 mg/kg $p < 0.0001$). Assessing for changes in correlation structure after treatment, we observe that antidepressant doses (3, 10 mg/kg) of ketamine do not impact cell-cell correlation ($p > 0.05$), but that a dissociative dose of ketamine (30 mg/kg) drives a dramatic increase in correlation in mPFC ($p < 0.0001$). Results from Study 2 demonstrate that ketamine drives a long-lasting increase in cell-cell correlation ($p < 0.01$ 3 hours post-treatment, $p < 0.0001$ 24 hours after treatment. We conducted similar studies to assess the efficacy of the putative antidepressant scopolamine and the failed candidate rapastinel (GLYX-13), and found that their impact on neuronal function significantly diverges from ketamine.

Conclusions: In conflict with the "disinhibition hypothesis", we observe multiple functional ensembles with divergent responses to acute ketamine treatment, with suppression of neuronal event rate being the dominant effect. Furthermore, we observed enhanced cell-cell correlation of mPFC pyramidal neurons at dissociative, but not at antidepressant dosages suggesting that we are able to resolve correlative features of side effects with the model. We additionally observe signatures of ketamine's durable antidepressant effects, three and 24 hours after dosing, potentially providing a functional biomarker of sustained antidepressant effects.

These studies are the first of their kind imaging large populations of individual mPFC neurons during free behavior and provide novel signatures of ketamine's effects at antidepressant and dissociative doses. Furthermore the data suggests that functional brain imaging can serve as a comparative tool for efficacy testing of novel drugs in development.

Keywords: Ketamine, Antidepressants, In Vivo Imaging, Drug Discovery - New Approaches, Neuroimaging Biomarkers

Disclosure: Nothing to disclose.

P380. Astrocytic Cannabinoid Receptor 1 Promotes Resilience by Dampening Stress-Induced Blood-Brain Barrier Alterations

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Background: The endocannabinoid system (ECS) is a crucial regulator of stress responses and perturbations within the ECS have been observed in major depressive disorder. We recently reported that blood-brain barrier (BBB)-related changes underlie stress responses and resilience in mice and depression in human tissue. Alterations are sex-specific with loss of BBB integrity observed in the male nucleus accumbens (NAc) and female prefrontal cortex (PFC), two brain regions involved in emotion regulation. The ECS can regulate BBB permeability thus, here we set to elucidate if it could play a role in stress-induced vascular dysfunction and establishment of depressive symptoms vs maintenance of this barrier integrity and proper coping strategies.

Methods: The impact of chronic social defeat stress, a mouse model of depression, was evaluated for ECS-related gene expression using Taqman gene arrays and qPCR on male and female C57Bl/6 NAc and PFC (8-12 weeks). Cell-specific changes were confirmed with RNA scope, immunofluorescence, and confocal microscopy in mouse and human samples. In parallel, viral-mediated manipulations were performed to confirm a causal role of altered cannabinoid receptor (Cnr1) expression in astrocytes in the development of anxiety- and depression-like behaviors at baseline and after stress exposure.

Results: After social stress exposure, Cb1 gene expression (Cnr1) is increased in the NAc of resilient, but not stress-susceptible, males and correlated to social interactions ($n = 8$-14/group, one-way ANOVA social interaction (SI) test: $F = 38.79$, $^{****}p < 0.0001$; Cnr1 expression: $F = 6.851$, $^{**}p = 0.0032$; Pearson's correlation Cnr1/SI: $F = 18.94$, $^{***}p = 0.0002$). Enhanced Cnr1 expression is also observed in the PFC of resilient females in line with intact BBB integrity ($n = 8$-14/group, one-way ANOVA SI test: $F = 24.26$, $^{****}p < 0.0001$; Cnr1 expression: $F = 4.928$, $^{*}p = 0.0153$). Intriguingly, this adaptation is specific to astrocytes and not neurons which also express Cb1 ($n = 5$/group, one-way ANOVA SI test: $F = 28.51$, $^{****}p < 0.0001$; Cb1 immunofluorescence: $F = 10.36$, $^{**}p = 0.0024$; correlation Cb1/SI: $F = 24.19$, $^{*}p = 0.0012$). Loss of astrocytic CNR1 was confirmed in the brain of depressed individuals (RNA scope 3 individuals/group, one way ANOVA: $F = 6.489$, $^{*}p = 0.0107$). Viral-mediated overexpression of Cnr1 in the male NAc astrocytes has anxiolytic effects at baseline ($n = 12$/virus) as observed in the open field (t-test, $^{*}p = 0.0186$), elevated plus maze (t-test, $^{*}p = 0.0471$) and splash test (t-test, $^{*}p = 0.0500$). Despite exposure to 10-day chronic social stress, astrocytic Cnr1 overexpression promotes proper coping strategies ($n = 21$-23/virus/condition) with reduced anxiety (elevated plus maze: two-way ANOVA $F = 3.635$, $^{*}p = 0.0343$; splash test: two-way ANOVA $F = 6.421$, $^{*}p = 0.0145$) and immobility in the forced swim test (two-way ANOVA, $F = 30.48$, $^{****}p < 0.0001$).

Conclusions: Our results provide the first characterization and functional interrogation, in a sex-, region-, and cell-specific manner, of the role played by astrocytic endocannabinoids in stress responses, resilience and coping strategies.

Keywords: Chronic Social Stress, Astrocyte-Blood Vessel Interaction, Endocannabinoids, Depression

Disclosure: Nothing to disclose.

P381. Ventral Pallidal Cholinergic Input to the Basolateral Amygdala Mediates Valence Encoding of Olfactory Stimuli

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Background: The ventral pallidum (VP) is involved in encoding hedonic value of external stimuli and mediating motivated behaviors. The VP is comprised of a variety of cell types including a population of cholinergic neurons, whose function until recently was unclear. We have previously found two distinct subpopulations of VP cholinergic neurons that differentially encode valence: one subpopulation activated in response to a positive valence stimulus (appetitive odor, 2-phenylethanol), and a second, non-overlapping subpopulation activated in response to a negative valence stimulus (aversive odor, predator urine). The primary projection target of VP cholinergic neurons is the basolateral amygdala (BLA). The BLA is recognized as containing distinct neuronal subpopulations that encode valence. It is unknown if valence-encoding VP cholinergic neurons form functional connections with valence-encoding BLA neurons to mediate motivated behaviors. The goal of the present experiment is to examine the circuit between VP cholinergic neurons and the BLA and its role in innate motivation.

Methods: We first examined if valence-specific odors induced changes in the BLA. Mice were exposed to either the appetitive odor or aversive odor, and neuronal activation was examined in the BLA by assessing the immediate early gene cFos. A separate cohort of mice were injected with the acetylcholine sensor (GRAB-ACh) in the BLA, and in-vivo fiber photometry was used to measure acetylcholine release in the BLA following timed delivery of each odor. To determine the relationship between VP cholinergic neurons and the BLA in encoding valence of olfactory stimuli, we utilized optogenetic stimulation of VP cholinergic terminals in the BLA, combined with single-cell calcium imaging in the BLA. ChAT-cre mice were injected with a cre-dependent, red-shifted channelrhodopsin (AAV-FLEX-ChrimsonR) in the VP. Mice were simultaneously injected with a genetically encoded calcium indicator (AAV-CaMKII-GCaMP6F) and implanted with a GRIN lens in the BLA. We examined changes in the calcium activity of BLA neurons induced by each odor, with and without optogenetic stimulation of VP cholinergic terminals in the BLA. In the same mice, innate approach/avoidance behaviors in response to each odor was tested with concurrent optogenetic stimulation of VP cholinergic terminals in the BLA.

Results: We found that both the appetitive odor and aversive odor increased cFos and induced acetylcholine release in the BLA. Next, using in-vivo single-cell calcium imaging, we identified valence encoding neurons in the BLA that were exclusively activated by each odor. In comparison to negative valence BLA neurons that were only activated in response to the aversive odor, a greater percentage of BLA neurons were classified as positive valence neurons (i.e., neurons activated exclusively by the appetitive odor). Pairing odor delivery with optogenetic stimulation of VP cholinergic terminals in the BLA changed the ratio of identified positive vs. negative valence BLA neurons. With optogenetic stimulation, BLA neurons became increasingly more responsive to the aversive odor. Next, we assessed innate behavioral responses to each odor. Mice typically display approach to the appetitive odor, and avoidance of the aversive odor. Consistent with an increase in the number of negative valence BLA neurons, stimulation of VP cholinergic terminals in the BLA abolished approach to the appetitive odor, and mice displayed avoidance of an appetitive stimulus. Optogenetic stimulation did not alter avoidance to the aversive odor.

Conclusions: The results from these studies indicate: (1) valence-specific odors increase neuronal activation and acetylcholine release in the BLA; (2) distinct subpopulations of BLA neurons are activated by appetitive vs. aversive odors; (3) a greater proportion of valence-neurons in the BLA are responsive to an appetitive stimulus; (4) pairing optogenetic stimulation of VP cholinergic terminals in the BLA with odor delivery changes the ratio of identified positive vs. negative valence BLA neurons; (5) optogenetic stimulation of VP cholinergic terminals in the BLA alters approach behavior but does not affect avoidance behavior. Ongoing studies are examining the effects of optogenetic inhibition of VP cholinergic terminals in the BLA. Future studies will specifically target and manipulate negative vs. positive valence VP cholinergic neurons and map their functional connections with valence encoding BLA neurons.

Keywords: Acetylcholine, Ventral Pallidum, Basolateral Amygdala, Valence

Disclosure: Nothing to disclose.

P382. Effects of Electroconvulsive Shock on Hippocampal Dentate Gyrus Structure and Function

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Background: Therapeutic use of electroconvulsive shock (ECS) therapy is 70%-80% effective for the remission of treatment-resistant depression. Yet the question of how ECS produces these powerful effects remains unanswered. Structural MRI of patients with depression reveals an increase in dentate gyrus volume after ECS treatment, as compared to volume before treatment, and the increase in dentate gyrus volume correlated with symptom improvement. Like other more common forms of antidepressant treatment such as fluoxetine, ECS has been shown to increase neurogenesis in the hippocampal dentate gyrus of rodent models. Yet the question of how ECS-induced neurogenesis supports improvement of depressive symptoms remains unknown. Here we use a mouse model to examine the effects of ECS on dentate gyrus structure and function. First, we test the hypothesis that the presence of immature granule neurons is necessary for the therapeutic effects of ECS. We then use slice electrophysiology to ask how activity in immature granule neurons affects activity of mature granule neurons in ECS vs Sham subjects, we use slice electrophysiology. To assess axon terminal number in the granule cell layer using immunohistochemistry and electron microscopy. Finally, we test the hypothesis that metabotropic glutamate receptor 2 (mGluR2) expression in the dentate gyrus is required for ECS effects.

Methods: Mice were exposed to chronic corticosterone to induce a stressed phenotype. ECS was delivered every other day for 10 sessions in the experimental group, while Sham mice received isoflurane anesthesia and ear clip placement identical to the ECS group, yet no current was delivered to Sham mice. To ablate neurogenesis, X-irradiated mice received three sessions of x-ray exposure targeting the hippocampus bilaterally, while Sham mice received anesthesia only. For slice electrophysiology, we used a tamoxifen inducible nestin-creERT2 line crossed with a cre-dependent channelrhodopsin (ChR)-YFP to allow us to specifically activate immature granule neurons. We then measured electrophysiological responses in mature granule neurons. For RNA-sequencing experiments, we sorted for NeuN expressing cells in order to limit our exploration to neurons. For exploration of axonogenesis, we used a synaptophysin-YFP transgenic to identify terminals in the dentate gyrus. Alternatively, we used the nestin-creERT2-ChR-YFP transgenic to identify immature granule neurons and examine terminals in the granule cell layer. Finally, we used

cre-dependent mGluR2 shRNA delivered in a Dock10-cre transgenic mouse in order to specifically reduce expression of mGluR2 in mature granule neurons of the dentate gyrus. Antidepressant-like behavior was assessed by the novelty suppressed feeding test and the forced swim test.

Results: We found that that ECS-induced neurogenesis is necessary to improve depressive-like behavior of mice exposed to chronic corticosterone. Using slice electrophysiology, we found that optogenetic stimulation of immature granule neurons produces a hyperpolarization in mature granule neurons. We identified that this hyperpolarization requires the activation of mGluR2, as pharmacological blockage of mGLuR2 eliminates the effect. Consistent with this finding, we observed reduced expression of the early immediate gene cFos in ECS vs sham subjects. This result indicates that ECS amplifies the effect of a direct, inhibitory connection between immature and mature granule neurons. Evidence of this direct connection is present in our investigation of axon terminals in the dentate gyrus. We also found that ECS increases terminals present in the granule cell layer which co-label with a marker of mossy fiber terminals. By contrast, we found that ablation of neurogenesis reduces expression of terminals in the dentate gyrus. Finally, we found that conditional expression of mGluR2-shRNA virus to knockdown mGLuR2 expression specifically in mature granule neurons prevents antidepressant behavioral effects of ECS.

Conclusions: Together, our findings highlight the role of immature neurons as mediators of the therapeutic effects of ECS. We show that ECS increases the ability of immature cells to suppress activity of mature cells. Our findings also reveal the importance of mGLuR2 both in the suppression of mature granule neuron activity and in the therapeutic effects of ECS.

Keywords: Electroconvulsive Therapy, Adult Hippocampal Neurogenesis, Metabotropic Glutamate Receptor 2 (mGluR2)

Disclosure: Nothing to disclose.

P383. Spatial Transcriptomic Taxonomy of Human Hippocampus in Depression

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Background: Spatial transcriptomics are emerging technologies which bring unprecedented insights into cell types and underlying mechanisms of cell states in complex tissues. The human hippocampus has a complex anatomy, organized in several anatomical subfields where different types of neurons, processes, glia, and vascular cells are located. The fundamental tricellular circuit of the hippocampus, involving connections between dentate gyrus (DG), cornu ammonis (CA) 1 and CA3 neurons, is important for memory and emotional responses. Disruption of the hippocampus circuit occurs in several neuropsychiatric diseases, one of which is major depressive disorder (MDD). MDD is a common and complex disease accompanied by high risk of suicide and social/economic costs. The molecular and cellular basis of MDD pathogenesis remain largely unknown. Despite the latest breakthrough in spatial transcriptomics of mouse brain, limited access to high-quality postmortem human brain from both neurotypical and MDD subjects has limited the application of these technologies to depression research.

Methods: To capture the molecular complexity of human hippocampus cells in their anatomical context, we performed deterministic barcoding in tissue for spatial omics sequencing (DBiT-seq) on 10 human hippocampi at 50 um resolution (N = 10 male donors, age = 43 ± 13 yrs., RNA integrity number = 7.91 ± 0.88, 45,000 spots analyzed from 18 captured intact tissues). We included four age- and sex-matched untreated MDD and six neurotypical controls, who underwent psychological autopsy, toxicology exams, died by sudden death with short agonal state, and had no alcohol or substance use disorder. We used the RNA velocity algorithm (scVelo) to compute the rates of RNA synthesis, splicing, and degradation. Using a pre-annotated reference dataset of human hippocampus (GSE186538, n = 219,058 cells, 69 cell subtypes), we ran Cell2location algorithm to deconvolute the cellular composition in spatial spots. Spatial proteomics (30-plex) was performed using Akoya PhenoCycler to map phenotypes at a resolution of 200 nm. Differentially expressed genes between MDD and controls in each hippocampal subfield were identified by the "FindMarkers" function in Seurat (V4) using parameters: min.pct = 0.05, logfc.threshold = log(2). Top genes were selected with a pre-filtering step (p_val_adj < 1e-30, pct.1 > 0.1, pct.2 > 0.1, avg_logFC>0.5 or < -0.5) to remove low count and insignificant genes, then ranked by the absolute value of the log fold change.

Results: We provide the first spatial multi-omic taxonomy report of both neurotypical and MDD human hippocampus at a whole genome scale, with molecular atlas of spatial mRNA-seq and spatial ATAC-seq. Analysis of RNA velocity indicates that cell-type specific transcriptomic instability may be characteristic of MDD, with high inter-patient variability of RNA dynamics particularly in CA pyramidal neurons. These results suggest new treatment strategies for MDD by targeting RNA dynamics in a region-specific manner. Spatially resolved chromatin accessibility profiling further identified potential epigenetic underpinnings in MDD that contribute to MDD molecular neuropathology. We demonstrated the applicability and promise of spatial transcriptomics for the study of molecular neuropathology in human brains.

Conclusions: Our study provided a framework for studying neuropsychiatric diseases in human brain from an angle of spatial omics profiling. This represents a major leap in the field beyond the single cell genomic studies of hippocampus and lays out a corner stone for future hippocampal molecular profiling studies.

Keywords: Spatial Multi Omics, Spatial Transcriptomics, Major Depressive Disorder (MDD), Functional Genomics

Disclosure: Nothing to disclose.

P384. Feasibility of Precision Functional Mapping in Treatment-Resistant Depression

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Background: Treatment-resistant depression (TRD) is currently defined as major depressive disorder (MDD) failing to respond to two or more adequate dose-duration antidepressant trials. Although it has a relatively high rate of occurrence (15-20% of MDD), and claims disproportionate morbidity and mortality, we have very little understanding of the neurobiological basis of TRD. The lack of understanding of brain mechanisms underlying TRD, and depression more broadly, has motivated a decades-long search for meaningful biomarkers. Despite the promise of functional brain imaging as a non-invasive tool for whole-brain measurements, the identification of clinically useful biomarkers of depression has remained elusive. Major impediments to progress include substantial phenotypic heterogeneity in typical MDD cohorts and unreliable and imprecise imaging measures. In particular, previous functional neuroimaging studies have been

limited by including only small amounts of data for each subject (~5-10 min of resting state data). However, we have previously shown that subject-specific characterization of brain organization requires extended datasets (>30 minutes and more, depending on spatial scale and precision of the measure) to achieve reliable and accurate measures of resting state functional connectivity (RSFC) in healthy subjects. Thus, it is likely that accurate and effective fMRI-based biomarkers of depression will require similarly reliable imaging data. In this work, we report on the feasibility of collecting extended imaging datasets in the TRD population and the reliability of RSFC measures obtained in this cohort.

Methods: Five TRD patients were recruited from the TRD Clinic and other outpatient Psychiatry services at Washington University in St. Louis. Patients with unipolar MDD without psychosis who had >=4 failed adequate dose and duration antidepressant treatment trials were considered eligible. Exclusion criteria included lifetime diagnosis of schizophrenia, bipolar disorder, schizoaffective disorder, or obsessive-compulsive disorder; current primary diagnosis of personality disorder, eating disorder, or panic disorder; active substance use disorder in past 12 months; or major neurocognitive disorder. All participants were scanned on 5 separate sessions over 4-7 weeks. The MADRS, Q-LES-Q-SF and HAM-D symptom scales were obtained at each session. An additional ecological momentary assessment (EMA) depression scale was obtained daily. Neuroimaging data was acquired using a 3T Siemens Prisma with a 64-channel head coil. Each session included 5 x 10-minute eyes-open, resting state scans with passive fixation on a crosshair. A multi-band, multi-echo BOLD sequence was used to collect the resting state data: MB = 6, 5 echoes, 2.0 mm isotropic resolution, TR = 1.76 second. Framewise Integrated Real-time MRI Monitor (FIRMM) software was used to minimize data loss due to head motion. Data processing included strict frame-censoring implemented based on framewise displacement (FD) with threshold < 0.08 mm following suppression of high-frequency respiratory artifact. The data were further denoised using bandpass filtering, and component-based signal regression including CSF, white matter, extra-axial compartments, and the global signal. Processed data was sampled to each subject's individual surface and placed into CIFTI format. RSFC matrices were computed based on cortical area timeseries extracted using the Gordon, Laumann, et al., parcellation. RSFC reliability in each subject was estimated by correlation similarity between RSFC matrices computed from increasing amounts of data compared to split-half held out data from the same subject.

Results: All participants were able to tolerate the extended data collection and participated in all 5 sessions. Logistical constraints limited acquisition on one occasion. Thus, between 22 and 26 resting-state runs were obtained in each participant across all sessions (total resting-state scan time per participant: 220-260 minutes). Following very strict motion censoring criteria as above, 4 out of 5 TRD subjects retained on average >70% frames across all resting state runs (TRD1: 0.75 +- 0.13; TRD2: 0.74 +- 0.16; TRD3: 0.94 +- 0.05; TRD4: 0.46 +- 0.20; TRD5: 0.78 +- 0.24). RSFC correlation similarity demonstrated increased reliability with increasing scan time with an average across subjects of r = 0.86 at ~30 minutes and r = 0.93 at ~100 minutes.

Conclusions: We demonstrate the feasibility of acquiring extended fMRI data collection on TRD patients for precision functional mapping. RSFC reliability was found to depend on quantity of acquired data as we have previously demonstrated in extended datasets on healthy controls. Future work will include evaluation of the topology of brain organization at finer spatial scales as we move toward detailed brain mapping and functional localization in severe patient populations.

Keywords: Treatment-Resistant Depression, Resting State Functional Connectivity, Reliability, Functional MRI (fMRI), Brain Mapping

Disclosure: Turing Medical: Consultant (Self).

P385. Early Life Adversity Enhances Fear Generalization by Diminished Serotonergic Inhibition of the Ventral Dentate Gyrus

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Background: Early life adversity (ELA) increases the risk for psychiatric illness, including depression and anxiety, by changing the developmental trajectory of neural circuits important for fear and emotional processing. Fear generalization, during which a previous experience of a fearful context is transferred to a novel, non-fear associated context, is increased in both humans and mice who experience ELA and can lead to a heightened state of fear and chronic avoidance behavior in adulthood. Previously, we found that hyperactivity of the ventral dentate gyrus (vDG) region of the hippocampus mediates stress effects on avoidance behavior. Serotonin (5-HT) is an important neuromodulator of hippocampus function that has been widely implicated in the pathogenesis of psychiatric disorders and their treatment. Here, we investigated how ELA affects 5-HT regulation of vDG activity, and how these effects contribute to fear generalization across development. Understanding the neurobiological mechanisms underlying the contributions of ELA to fear-related behaviors may be relevant for the study of psychiatric disorders, such as depression, and anxiety.

Methods: To study the neurobiological mechanisms by which ELA affects fear generalization, we used the limited bedding and nesting (LBN) paradigm from postnatal day (P) 3-10, which causes fragmented and unpredictable maternal care. We then used ex vivo electrophysiology of the dorsal (DRN) and median raphe nuclei (MRN) to examine how ELA alters 5-HT neuron function at two developmental time points: adolescence (P35) and adulthood (P56). To test a role for the vDG in fear discrimination following ELA, we used in vivo fiber photometry during a contextual fear discrimination (CFD) task to record granule cell activity in the vDG using the calcium indicator, GCamp6f. During the CFD task, mice received a foot shock in context A on day 1 and were then re-exposed to context A on day 2 without a shock. Two hours later, mice were placed in a new context B in which shock was never delivered. Freezing behavior as an index for fear expression was recorded using FreezeFrame software (Actimetrics) and compared between the shock-assocaietd context A and the novel context B on day 2. To test if ELA effects can be rescued by increasing 5-HT signaling, we used a doxycycline-inducible transgenic mouse model with postnatal knockdown of 5-HT1A autoreceptors on raphe 5-HT neurons (Pet1-tTS; Htr1atetO/tetO mice). In these mice, 5-HT1A knockdown dis-inhibits raphe 5-HT neurons and increases 5-HT release in terminal projection areas, such as the hippocampus. To examine if hyperactivity of the vDG leads to reduced fear discrimination, we used inhibitory DREADD virus to reduce granule cell activity in the vDG during novel context exposure on day 2. Data were analyzed using 2-Way ANOVA with Tukey's post-hoc test.

Results: We found that ELA-exposed females, but not males, have reduced excitability of 5-HT neurons in the MRN, but not the DRN, at P56 (Control MRN: 16.12 ± 2.5 n = 11; ELA MRN: 8.26 ± 1.42; interaction $F(1,42) = 6.43$ *$p = 0.015$; post hoc test: Control MRN vs. ELA MRN *$p = 0.01$). This finding was not seen at P35, indicating an adult-onset impairment in 5-HT neuron activity following ELA exposure. At the behavioral level, we found that ELA-exposed females, but not males, overgeneralize between a shock associated context and a safe context at P56, an effect that

was rescued by 5-HT1A knockdown (Wild-Type (WT) control: 0.63 ± 0.04 n = 26; WT ELA: 0.34 ± 0.1 n = 14; 5-HT1A knockdown ELA: 0.66 ± 0.06 n = 11; interaction F(1,55) = 7.7, *p = 0.01; post hoc: WT control vs. ELA p = 0.01; WT ELA vs. 5-HT1A knockdown ELA *p = 0.02). This effect was not observed at P35. On day 1 of CFD, WT ELA-exposed adult females had a hyperactive granule cell response to a shock compared to controls and ELA-exposed females with 5-HT1A knockdown (WT control: 4061 ± 761 n = 9; WT ELA: 8911 ± 1806 n = 6; 5-HT1A knockdown ELA: 3551 ± 551 n = 5; interaction F(1,20) = 4.72, *p = 0.04; post hoc: WT control vs. ELA p = 0.03 and WT ELA vs. 5-HT1A knockdown ELA *p = 0.04). This increase in the vDG granule cell response to a shock negatively correlated with discrimination ability on day 2 (Spearman correlation r = -0.5; *p = 0.01). Granule cell hyperactivity was not seen in males, suggesting sex-specific effects of ELA on vDG activity during fear encoding and generalization. To test if the ELA-induced vDG hyperactivity causes fear overgeneralization behavior, we inhibited vDG granule cells using DREADDs and found that vDG inhibition during novel context exposure rescued fear generalization in ELA-exposed adult females (ELA hM4Di: 0.27 ± 0.06 n = 8; ELA mCherry: 0.79 ± 0.09 n = 7; interaction F(1,26) = 7.74 *p = 0.01; post hoc: ELA hM4Di vs. ELA mCherry **p = 0.001).

Conclusions: Our findings show that ELA causes sex-specific impairments in the activity of MRN 5-HT neurons, resulting in less 5-HT terminal release and elevated granule cell activity in the female vDG. Disinhibiting 5-HT neurons using 5HT1A autoreceptor knockdown, and inhibiting vDG hyperactivity using hM4Di DREADDs, both rescue ELA effects on fear overgeneralization, suggesting 5-HT regulation of vDG granule cell activity as a novel cellular mechanism mediating ELA effects on fear generalization. Overall, our results provide new insight into long-lasting circuit impairments following ELA with relevance for the pathogenesis of psychiatric disorders that have their origin early in life.

Keywords: Early-Life Adversity, Serotonin, Dentate Gyrus, Early Life Stress (ELS), Neural Circuits

Disclosure: Nothing to disclose.

P386. Roles of Glutamate, GABA, Dopamine, and Norepinephrine in Pathological Basis of Treatment-Resistant Depression: A Multimodal MRI Study

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Background: Approximately 30% of patients with major depressive disorder (MDD) fail to respond to two different antidepressants, the definition of treatment-resistant depression (TRD). Despite previous studies indicating different brain structures and functional connectivities between TRD and non-TRD, results have been inconsistent (Drysdale et al., 2016). The pathophysiology of MDD, including TRD, is suggested to involve abnormal neural systems consisting of mediators such as gamma-aminobutyric acid (GABA) and glutamate, as well as modulators such as dopamine (DA) and norepinephrine (NE). These neurotransmitter systems interact within the brain, yet no studies have comprehensively investigated these systems in patients with TRD. Thus, the present study compared GABA and glutamate+glutamine (Glx) levels in the anterior cingulate cortex (ACC) between patients with TRD and healthy controls (HCs) using proton magnetic resonance spectroscopy (1H-MRS). The ACC was chosen as a region of interest, being potentially involved in the pivotal pathological neural basis of MDD (Mayberg et al., 2003). Additionally, we measured neuromelanin (NM) signals in the substantia nigra (SN) as a surrogate marker of DA activity and NM signals in the locus coeruleus (LC) as an index of NE activity between the two groups, employing NM-sensitive magnetic resonance imaging (NM-MRI).

Methods: This study was approved by the ethical committee at Keio University School of Medicine and the Keio Certified Review Board. All participants provided written informed consent. Patients with TRD were recruited from Keio University Hospital (Tokyo, Japan), and age- and sex- matched HCs from the general population. The criteria for TRD in this study were based on depression severity at entry, showing a score of 18 or higher on the Montgomery Åsberg Depression Rating Scale. We used a 3T Siemens MRI with a 32-channel head coil and applied 1H-MRS (MEGA-PRESS, 256 averages, TR = 1500 ms, TE = 68 ms) to measure GABA and Glx levels in the ACC. We also measured NM signals using NM-MRI (2D GRE, TR = 427 ms, TE = 4.48 ms). GANNET 3.0 was used for detecting GABA and Glx levels, and a toolbox for batch processing NM-MRI using MATLAB for NM signals (Wengler et al., 2020). For statistical analyses, we compared these outcomes between patients with TRD and HCs. Subsequently, we performed correlation analyses to explore relationships among GABA and glutamate levels, and NM signals within each group.

Results: After quality checks, data from 73 patients with TRD (44.2 ± 13.3 years old, 33 females) and 69 HCs (43.9 ± 15.0 years old, 29 females) were used for the MRS analyses. Data from 49 patients with TRD (41.0 ± 10.9 years old, 21 females) and 49 HCs (41.7 ± 13.4 years old, 21 females) were used for the NM-MRI analyses.

We found that the ACC Glx levels were lower in the TRD group than in the HC group (F1,147 = 6.87, p = 0.01), while no group difference was found in the ACC GABA levels or NM signals in the SN and LC. The correlation analyses for participants who underwent both 1H-MRS and NM-MRI showed interrelationships between the NM signals in the SN and LC (r = 0.60, p < 0.01) as well as between the levels of the ACC GABA and ACC Glx (r = 0.60, p < 0.01) within HCs. However, no significant correlations were detected in patients with TRD.

Conclusions: Our findings revealed lower Glx levels in the ACC of patients with TRD relative to HCs, with no group differences in the GABA levels or NM signals. We also found a relationship between the Glx and GABA levels in the ACC of HCs and between DA activity in the SN and NE activity in the LC of HCs, while these relationships were not observed in patients with TRD. Strengths of our study include a larger TRD sample size and consideration of neurometabolite level variations due to brain volume differences.

Few studies have examined both GABA and Glx levels in patients with TRD, including one study for the dACC (n = 18) (Baeken et al., 2017) and another for the pregenual ACC (pgACC) (n = 15) (Price et al., 2010). Neither of them reported statistically significant results compared with HCs. However, Price et al. found a trend-toward decrease in pgACC Glx levels in the TRD group compared to the HC group. A meta-analysis indicated that ACC Glx levels were lower in those with MDD than HCs, suggesting that ACC Glx levels may not normalize with standard treatment in the TRD group. Regarding GABA, our results are consistent with those two studies. In contrast, among three 1H-MRS studies on GABA in MDD, two demonstrated lower ACC GABA levels, while the remaining one reported null results. Taken together, lower ACC GABA levels may be a marker of favorable outcomes in MDD. Considering the limited number of studies on this topic, future research is needed to investigate the dynamics of ACC GABA and Glx in TRD.

According to our correlation results between GABA and Glx, while the levels of GABA and Glx mutually correlated in HCs, such an excitatory and inhibitory (E/I) balance was disturbed in TRD. Given our null results of the ACC GABA levels, the E/I imbalance in TRD may be due to glutamatergic dysfunction in the ACC.

Since our analysis revealed no significant impairment of NE activity in LC or DA activity in SN in the TRD group, it is possible that the E/I imbalance is more closely involved in TRD beyond the monoamine hypothesis. Finally, the small number of participants in the study who underwent both 1H-MRS and NM-MRI imaging warrants further research.

Keywords: Treatment Resistant Depression, MR Spectroscopy, Neuromelanin-Sensitive MRI

Disclosure: Nothing to disclose.

P387. Psilocybin Causes Persisting Decrease in Hippocampal-Cortical Connectivity

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Background: Psychedelic drugs induce large acute changes in brain function as well as persisting changes in behavior and psychiatric symptoms. This has led to growing interest in potential clinical applications. But the relationship between persisting neurobiological, and clinically-observed effects of psychedelics is not understood. The precision functional mapping (PFM) fMRI strategy, with precise measurement of brain networks, control for individual differences, and repeated longitudinal sampling, is ideally suited for this.

Methods: In this randomized crossover study, we use a longitudinal precision connectomic approach to acute and persisting effects of psilocybin in the cortex, basal ganglia, hippocampus, and cerebellum. Healthy adults ages 19-45 received psilocybin (25mg, oral) or methylphenidate (40mg, oral) spaced 1-2 weeks apart. Participants ($N = 7$) underwent numerous MRI visits (15.9 visits/participant avg) before, during, and for two weeks after oral psilocybin or methylphenidate (MTP, placebo). Participants ($N = 4$) returned 6-12 months later to repeat an abbreviated imaging protocol with a second psilocybin dose. Task fMRI and physiological monitoring (respiration, pulse oximetry) were measured, in addition to resting fMRI, to control for brain state and physiological confounds. Hippocampal connectivity change was assessed using a linear mixed effects model which included fixed effects for class (baseline drug, after drug), task/rest, and head motion, and random effects for subject.

Results: The PFM approach enabled us to acquire greater quality and quantity of fMRI data than prior psychedelics studies. We found that psilocybin, but not methylphenidate, induced persistent decrease in functional connectivity between the anterior hippocampus and cortex (mixed effects model: $P = 5.1e\text{-}5$) in all subjects, lasting for at least two weeks but normalizing after 6 months. Large decreases were observed between anterior hippocampus and default mode network (DMN) in particular.

Conclusions: Using PFM to precisely measure brain network change, this work localizes persisting changes in hippocampal-cortical connectivity which may tie to behavioral and clinical observations. Hippocampal-DMN connectivity represents a candidate neuroanatomical and mechanistic correlate for psilocybin's pro-plasticity and anti-depressant effects.

Keywords: Psilocybin, Hippocampal Connectivity, Resting and Task fMRI, Psychedelics, Precision Imaging

Disclosures: Usona: Other Financial or Material Support (Self). Silo: Advisory Board (Self).

P388. Sensitivity to Distinct Types of Regret Recruits Separate Striatal Networks

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Background: Regret describes recognizing that an alternative action could have led to a better outcome. Recently, we discovered that there may exist fundamentally distinct types of regret processed in separable circuits. These types are defined by specific actions that lead to unique economic violations. Regret-related computations involve the integration of multiple information streams and as such, large-scale neural data is necessary to fully grasp the breadth of how several circuits converge in order to drive complex behavior.

Methods: Here, we leveraged brain-wide activation data to discover pathways encoding complex decision variables and harnessed the power of unbiased imaging data to reveal circuits implicated in counterfactual thinking. We characterized 40 outbred Swiss Webster male mice on the neuroeconomic task, "Restaurant Row." Mice had 45 min to forage for their daily source of food investing in rewards of varying costs (delays, 1-30 s signaled by tone pitch) and value (unique flavors). As previously published, regret trials were characterized by economic violations following atypical decisions either to reject high-value offers (type 1) or accept low-value offers (type 2). Immediately following these decisions, when mice were subsequently presented with low-value offers on the next trial (read-out trial), we measured regret-related behavioral sensitivity as the change in choice probability on the read-out trial relative to non-violation sequences. On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene. Brain harvesting was timed to task engagement and normalized to mice who did not perform the task but were equally food restricted and post-prandial.

Results: We found a wide range of individual differences in regret sensitivity. We found sensitivity to type 1 vs. type 2 economic violations was negatively correlated. PCA analysis found that 78.4% of variance was explained by PC1 with mice that were most sensitive to either type 1 or type 2 scenarios occupying opposite ends of this spectrum. iDISCO+ revealed that the most robust bidirectional change in c-Fos+ cell counts was found in the amygdala (increased in type 1 / decreased in type 2 sensitive mice). This was strongly correlated with accumbens activation in type 1 sensitive mice only. In contrast, orbitofrontal and hippocampus activation was strongly correlated with accumbens activation in type 2 sensitive mice only.

Conclusions: These data implicate the involvement of multiple regions in dissociable roles of action-specific forms of counterfactual thinking. Our findings suggest that the ways in which regret-processing could become dysfunctional is multifactorial and stem from distinct circuits in the brain.

Keywords: Decision Making, Neuroeconomics, Mice, Whole-Brain Rodent Imaging, Affective Behavior

Disclosure: Nothing to disclose.

P389. Frontocortical Circuits Encode Reward- and Effort-Related Information and are Affected by Chronic Forms of Stress

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Background: The ability to integrate information to drive high utility behavior is critical for survival. Individuals must continually update and weigh the value of rewards available in the environment against real and perceived effort costs and select appropriate actions. A deficit in this process, known as effort valuation (EV), is characteristic of anhedonia, a core symptom of several neurological and neuropsychiatric conditions including depression. Chronic stress is a significant risk factor for depression in patients and elicits anhedonia in animal models. Understanding the circuit and molecular mechanisms that contribute to anhedonia is integral to the development of more efficacious therapeutic strategies.

Methods: We employed two parallel approaches to examine the contribution of prefrontal circuits in supporting effort valuation: A barrier T-maze task integrated with fiber photometry recording and optogenetic inhibition allowed us to probe effortful choices in males ($N = 16$-29), while a head-fixed EV task enabled the measurement of anticipatory and consummatory responses to reward- and effort-predictive stimuli along with single cell activity recording in males and females ($N = 27$-51).

Results: We found that corticostriatal signaling is necessary for maintaining future effortful reward seeking ($N = 29$; $F(2,54) = 10.49$; $p < 0.0001$). High-effort, high-reward choice is reduced and circuit activity is diminished with exposure to chronic neuroendocrine stress ($N = 25$; $F(2,46) = 24.09$; $p < 0.0001$. Mice learned to modulate lick responses by effort requirement and concurrent 2-photon calcium imaging revealed that distinct prefrontal projection neurons exhibit heterogenous responses to reward- and effort-predictive cues and varied feature selectivity at baseline, with coding of reward anticipation and consumption represented within each recorded population ($N = 29$; ~2100 neurons). Exposure to chronic social stress diminishes high effort reward seeking ($N = 30$; $p = 0.0044$) and alters the selectivity of individual corticostriatal neurons and the accuracy of decoding trial features from population activity ($N = 19$; ~1500 neurons).

Conclusions: Together, these results suggest that stress may bias animals toward low-effort responding in part by diminishing the coding efficacy of learned reward- and effort-related information in a corticostriatal pathway.

Keywords: Anhedonia, Effort Based Decision Making Task, Anterior Cingulate Cortex (ACC), Reward Processing

Disclosure: Nothing to disclose.

P390. Linking Brain-Wide Activity Patterns During Neuroeconomic Decision Making to Aggression

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Background: Aggression is an evolutionarily conserved response to a perceived threat that spans a large range of diverse behaviors, including those that may be adaptive and protective as well as those that may be pathological and dangerous to others. Circuits recruited during the expression of aggression, in addition to circuits known to subserve social interactions themselves, are critical nodes of the brain's reward system. However, it is unclear how pathological aggression may "hijack" key reward circuits in the brain, contributing to maladaptive reinforcement of aggression.

Methods: Because the brain has evolved to use multiple decision-making systems, simple tests of reward value may be unable to access computational subtleties that may be altered in the brains of aggressive individuals. We characterized decision-making profiles of 40 outbred Swiss Webster mice screened for aggression and then tested on the neuroeconomic task, "Restaurant Row." Mice had limited time each day to forage for their sole source of food investing in rewards of varying costs (delays from 1-30s signaled by tone pitch) and value (unique flavors tied to four spatially cued locations). On the final day of testing, mice engaged the task before being prepped for whole brain iDISCO+ tissue clearing and staining in 275 distinct brain regions for c-Fos expression, an activity-dependent immediate early gene.

Results: We found that the majority of brain regions revealed decreased levels of c-Fos expression in highly aggressive animals versus non-aggressive animals. Using an unbiased, open-ended analysis approach, top region hits revealed strong negative correlations between aggression and c-Fos expression, regions that lie in the medial wall of the prefrontal cortex (mPFC) (including the anterior cingulate, prelimbic, and infralimbic cortex) and are known to be engaged by the Restaurant Row task. Using this approach, we also found that several regions across the limbic system covaried with numerous key metrics from the Restaurant Row task, suggesting specific regions may be interacting in order to give rise to complex decision-making profiles. Using a focused analysis, we found that individual differences in subjective value covaried with c-Fos expression in the mPFC, scaled along its dorsoventral axis.

Conclusions: These data reveal how brain-wide studies of aggression may reveal changes in circuits affecting only certain types of decision being processed. These findings set the stage for future experiments manipulating circuit-specific computations, including within functional subregions of the mPFC, in order to augment multiple valuation algorithms underlying aggression.

Keywords: Aggression, Decision Making, Whole-Brain Rodent Imaging, Neural Circuit and Animal Behavior, Social Behavior

Disclosure: Nothing to disclose.

P391. Digital Homecages for Mice: A Novel 24/7 System for Multi-Week Monitoring of Mouse Behavior and Brain Electrophysiology

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Background: The neurobiology of phenomena underlying and contributing to stress response and depression are not fully understood. The development of further models and systems to study these in rodents can lead to mechanistic biological explanations that link to possibly translatable behavioral and physiological phenotypes.

Methods: Our strategy was to improve the resolution of behavioral monitoring in rodents over long time periods (weeks) in C57BL6 mice to both develop improved behavioral phenotypes

and to link those to brain mechanism. We focus on both behavioral resolution and temporal resolution over weeks. Our system classifies sub-second resolution data into one of dozens of behaviors via automated video analysis combined with instrument-based measurements of eating, drinking, food choice, sucrose preference and wheel running. Our custom system is able to record 16 mice simultaneously, each in a modified version of a standard homecage with 24/7 video and device monitoring. We have also designed data intake and processing streams to both handle and graph data on a secure webserver for daily checks and ongoing monitoring before diving into deeper analyses. We have also integrated recording of electrophysiology over weeks with automated analytics pipelines being built.

Results: We have studied two cohorts of mice. The first was a proof of principle cohort where circadian rhythms were studied by inverting the timing of the daily 12:12 hour lighting. In this cohort we found 12 hour shifts of behavioral markers as predicted, validating our system. In a second cohort we gave corticosterone in the drinking water and initial results have indicated changes in sucrose preference and wheel running. We also see remarkable inter-individual variation even at baseline indicating we may have a system that is able to better capture human-like individual variance.

Conclusions: Our Mouse Digital Phenotyping system has been developed and shown to work for deep characterization of circadian rhythms and initial results show that it can also measure effects of a chronic stress model. We look forward to deepening our characterization of circadian rhythms, sleep and stress - and how those link to brain electrophysiologic activity.

Keywords: Chronic Stress, Mouse Models, Electrophysiology, Circadian Rhythms, Sleep

Disclosure: Nothing to disclose.

P392. Voluntary Exercise Potentiates Myelin Repair in a Mouse Model of CNS Demyelination

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Background: Central nervous system (CNS) demyelination is a hallmark of several neurological and neurodegenerative diseases, an archetype being multiple sclerosis (MS). Myelination of axons is a pivotal component of efficient neurotransmission and provides trophic support to neurons. The loss of myelin, as occurs in demyelinating diseases, impairs neuronal conduction and renders axons susceptible to degeneration. Studies involving people living with MS suggest that the efficiency of remyelination following a demyelinating episode is correlated with improved clinical prognosis. On this basis, it is believed that clinical interventions that enhance timely and efficient remyelination are likely to be critical for combating disease progression and improving disease outcomes. Thus, identifying effectors that potentiate myelin repair could lead to improved therapeutic interventions.

Methods: We investigated whether a naturalistic behavior that increases the activity of transcallosal projection neurons could potentiate myelin repair by enhancing the generation of new myelin-forming oligodendrocytes following cuprizone-induced demyelination in adult mice. Previous research has demonstrated that voluntary exercise (VE) on the complex running wheel (CW) increases oligodendrogenesis in healthy adult mice. To explore whether increasing physical activity following demyelination enhances myelin repair following a demyelinating insult, male ($n = 5$-6/group) and female ($n = 5$-6/group) mice were challenged with cuprizone to induce demyelination for five weeks and then underwent VE on the CW for two weeks during early remyelination. We have previously demonstrated that remyelination is mediated by both oligodendrocyte progenitor cells (OPCs) and by neural progenitor cells (NPCs) that derive from the ventricular-subventricular zone (SVZ). Accordingly, we assessed the relative contribution of each population to remyelination by conducting genetic fate-mapping of NPC- and OPC-derived oligodendroglia in both runners and non-runner controls.

Results: After two weeks of CW running, runner mice exhibited improved sensorimotor co-ordination and enhanced oligodendrogenesis in the corpus callosum compared to non-runner mice (e.g. mean latency to fall on rotarod: non-runners, 157.2 ± 5.97 sec vs runners, 230.20 ± 12.89 sec; $p < 0.0001$). With an additional five weeks of recovery, acute brain slice multielectrode array analyses revealed that mice who ran on the CW during early remyelination exhibited increased synchronous transcallosal neuronal firing and these axons had a greater ability to recover from refractoriness. These results suggest that heightened physical exercise during early remyelination has positive effects upon remyelination and axonal health long term. By utilizing immunoelectron microscopy and Tokuyasu method of tissue processing, we found that the myelin ensheathing the callosal axons of runner mice was thicker (lower g-ratio, $p < 0.0001$), despite an increase in myelin compaction ($p < 0.05$), due to a significant increase in the number of myelin lamellae ($p < 0.005$). In addition, g-ratio analyses of transcallosal axons from both runner and non-runner mice revealed that the myelin sheath elaborated by NPC-derived oligodendrocytes was significantly thicker ($p > 0.0001$) than myelin elaborated by OPC-derived oligodendrocytes.

Conclusions: Our data provide compelling evidence that complex wheel running following a demyelinating episode accelerates myelin regeneration and substantially increases the generation of newborn oligodendrocytes that derive from both NPC and OPC lineages. We also provide evidence that myelin ultrastructure from NPC-oligodendrocytes is distinct from that of OPC-derived oligodendrocytes, and is influenced by CW running. Together, these findings support the notion that voluntary exercise could be harnessed as a cogent strategy for potentiating myelin repair following a demyelinating injury.

Keywords: Oligodendrocytes, Regeneration, Multiple Sclerosis, Adult Stem Cells

Disclosure: Nothing to disclose.

P393. CEY-1/YBX RNA-Binding Protein Dysfunction Leads to Impairments in Memory and Cognition

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Background: Cognitive processes, such as learning and memory, require the precise control of mRNA translation and new protein synthesis. One class of proteins that regulates mRNA translation are RNA binding proteins, the dysfunction of which are becoming increasingly associated with neurological disorders. However, despite their biological significance, the role of many RNA binding proteins in neuronal phenotypes such as cognition remains unknown. Using the model organism C. elegans, we sought to identify conserved RNA binding proteins that exhibit neuronal expression, but remain functionally uncharacterized with regards to nervous system phenotypes, particularly complex behavior. Cross-referencing publicly available C. elegans, mammalian, and human datasets, we found that the C. elegans CEY family, and their mammalian orthologs in the YBX family (specifically YBX1 and YBX3), are abundant throughout the nervous system across

species. Mammalian YBX family members are abundant in the hippocampus, and highly expressed in C. elegans neurons known to control associative behaviors. In non-neuronal cell types, YBXs regulate polysome and ribonucleoprotein complex formation, a function conserved with the worm CEY proteins. Based on their expression patterns and established role in RNA and translational regulation, we hypothesize that CEY/YBX proteins are involved in associative learning and memory.

Methods: C. elegans maintenance: Wild-type and mutant animals were maintained under standard laboratory conditions and fed the E. Coli strain OP50 ad libitum. Synchronized populations for behavior assays were generated by standard hypochlorite treatment.

RNAi Treatment: Standard RNAi by feeding was performed to achieve gene knockdown. To knock down genes specifically in adulthood, animals were fed RNAi at the L4 larval stage, after terminal nervous system differentiation. To achieve RNA-knockdown selectively in neurons, experiments were performed in a transgenic C. elegans strain that expresses a double stranded RNA transporter exclusively in neurons.

Behavior Assays: Standard positive olfactory association assays were performed. These assays pair the neutral odorant butanone with food (E. coli) so that animals form a positive butanone association. Learning and memory were assayed as a training-dependent increase in preference for butanone as measured by population chemotaxis assays (~100 animals per assay) to obtain a chemotaxis index. Memory performance was calculated by Performance Index (Chemotaxis_Index(trained) - Chemotaxis_Index(naive/untrained). For all behavioral assays, 10-15 replicates were used, and either one- or two-way ANOVA followed by Bonferroni post-hoc tests were performed.

Microscopy: C. elegans expressing fluorescently tagged proteins were imaged via confocal microscopy using a Nikon A1 Spinning Disk Confocal at 100x magnification to examine protein expression patterns. 20-30 animals were imaged per experiment.

Protein Alignment: C. elegans and mammalian proteins were aligned with MultiAlin, and domains annotated according to SMART domain prediction and previous literature.

Genetic Database Analysis: Publicly available DECIPHER, gnomAD, and Baylor Genetics databases were mined for variants in human Ybx genes. Variants were manually curated to identify de novo mutations in Ybx genes in patients using the UGSC Genome Browser. De novo mutations were assessed for pathogenicity using CADD, REVEL, and GERP to assign scores. PolyPhen2 was used to predict the tolerability of specific variants.

Results: We find that of the four C. elegans CEY family members, CEY-1, is most closely related to mammalian YBXs, and is more closely related to mammalian YBXs than other CEY family members. Microscopy analysis of endogenous fluorescently tagged CEY-1/YBX shows that the RNA-binding protein is abundant in the nervous system, confirming previous transcriptomic results. We find that two different C. elegans cey-1 reduction- or loss-of-function mutants exhibit deficits in associative learning and memory ($p < 0.05$). Adult-only, neuron-specific knockdown of cey-1/Ybx using RNAi recapitulates the memory deficits observed in mutants ($p < 0.05$), indicating that cey-1/Ybx is necessary in the nervous system for associative behaviors. Conversely, overexpression of neuronal CEY-1/YBX enhances associative memory ($p < 0.05$), suggesting that it is indeed a memory-promoting molecule.

We next examined whether dysfunction of human YBXs are potentially associated with neurological symptoms in patient populations. Using a combination of publicly available, as well as institute specific human variant datasets, we found that over 80% of patients with single nucleotide variants in any YBX have severe neurological symptoms. Interestingly, the most common symptom among patients is intellectual disability, mirroring our behavioral findings in C. elegans. In ongoing work, we are investigating the functional significance of specific human YBX variants using "humanized" C. elegans strains, and examining which biological pathways are altered when CEY/YBX function is disrupted.

Conclusions: In summary, we have uncovered a new role for the CEY/YBX RNA-binding proteins in the nervous system as regulators of memory and cognition. Our studies in C. elegans can inform the molecular underpinnings of any potential YBX -related neurological symptoms in human patients and underscore the importance of neuronal RNA binding proteins in cognition.

Keywords: Memory and Learning, RNA Binding Protein, Molecular Genetics, Model Systems

Disclosure: Nothing to disclose.

P394. Intersectional and Transcriptomic Approaches for Probing Molecular Mechanisms of Dopamine Neuron Resilience in Distinct Dopamine Neuron Subpopulations

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Background: Loss of dopamine (DA) neurons in Parkinson's disease (PD) is not uniform. DA neurons in the substantia nigra pars compacta (SNc) are more vulnerable while cells in the ventral tegmental area (VTA) are more resilient. Yet, the mechanisms for these region-specific differences remain unknown. The subpopulation of medial VTA DA neurons that co-transmit glutamate and express the vesicular glutamate transporter 2 (VGLUT2) offer key clues for mechanisms of DA neuron resilience in PD. We find VGLUT2+ DA neurons are likelier to survive neurotoxic insults compared to VGLUT- DA neurons. Conversely, increasing DA neuron VGLUT2 expression enhances rodent DA neuron resilience in PD models. VGLUT2 also modulates sex differences in DA neuron resilience where females express more VGLUT2 in DA neurons versus males and are more protected from PD-induced DA neurodegeneration.

Hypothesis: DA neuron VGLUT2 expression is part of a conserved, sexually dimorphic neuroprotective response to DA neuron injury in PD.

Methods: Mouse Procedures and Brain Dissections: 14 male, 12 female VGLUT2-IRES-Cre; TH-2A-Flpo mice (7-11 wk-old) were injected with INTRSECT2.0 viruses (AAV8-nEF-CreON,FlpON-EYFP, and AAV8-nEF-CreOFFFlpON-mCherry) into medial VTA. Brains from injected mice as well as DAT-Cre;Td-Tomato mice (4 males, 6 females) were collected ~5 wks post-injection.

Mouse Midbrain Fluorescent Activated Cell Sorting (FACS): Midbrain neurons from were dissociated via a Miltenyi Neural Dissociation kit. Dissociated cells were resuspended and FACS-sorted using an Aria2 FACS instrument. Cells were sorted based on viability, cell size, CD4/CD11b immunoreactivity, and fluorophore expression.

Mouse Bulk RNA Sequencing: RNA from sorted cells was extracted using the Qiagen RNeasy Plus Micro extraction kit. RNA quality was assessed via the High sensitivity RNA kit. Library preparation was performed using the Illumina Nextera XT kit. Libraries were assessed using an Agilent High sensitivity NGS kit and then normalized and pooled by calculating the nM concentration based on the fragment size and the concentration. Libraries were sequenced on a NovaSeq 6000 at UPMC Genome Center on an S2 100 cycle flow cell, 2 × 50 bp, for an average of ~30 million reads/sample.

RNA Sequencing Analysis: Transcripts with p2) and log2 fold change (FC) > 0.26 were considered differentially expressed (DE) in VGLUT2+ DA neurons compared to VGLUT2- DA neurons. We

specifically compared EYFP+/VGLUT2+ DA neurons with DAT;-CreTd-Tomato+/VGLUT2- DA neurons. DE gene lists were entered into Metascape and assessed for pathway overrepresentation with expressed transcripts as background. Additional analyses of mitochondrial pathways used MitoCarta3.0 and MitoXplorer software packages.

Results: We used the AAV-based intersectional genetic INTRSECT2.0 approach to selectively label VGLUT2+ DA neurons that co-express DA marker tyrosine hydroxylase (TH+/VGLUT2+) in adult male and female mouse VTA. We also labeled non-glutamatergic DA-only neurons in the same brains with mCherry (TH+/VGLUT2-). Imaging of these labeled whole brains demonstrated strong striatal innervation by mCherry+ TH+ neurons originating in the VTA. In parallel, we compared our findings with DA neurons labeled via genetically-encoded DAT-Cre-driven tdTomato. We FACS-sorted the respective labeled neurons followed by analysis of gene expression via bulk RNAseq. Gene set enrichment analysis of genes differentially enriched in VGLUT2+ DA neurons revealed a substantial number of genes associated with mitochondrial bioenergetics, vesicular trafficking, and transcriptional regulation. We also found significant differences in differential gene expression within TH+/VGLUT2+ neurons across males and females.

Conclusions: 1.RNAseq in mice reveals differentially expressed genes in VGLUT2+ versus VGLUT2- DA neurons. 2.Screen hits comprise genes associated with transcription factors, mitochondrial metabolism, and protein trafficking. 3.Gene expression in TH+/VGLUT2+ DA neurons differs between males and females, providing a basis for future work examining sex differences in PD DA neuron resilience.

Keywords: Parkinson's Disease, Dopamine, Neurodegeneration, Vesicular Glutamate Transporter (VGLUT), RNAseq

Disclosure: Nothing to disclose.

P395. Using 'Optical Field Potentials' to Probe Synaptic Plasticity in the Adult Prefrontal Cortex in Mouse Models of Neurobiological Disorders

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Background: Deficits in synaptic plasticity in the adult prefrontal cortex (PFC) are thought to underlie social and cognitive impairments in multiple neurobiological disorders. Yet there is increasing awareness of the experimental challenges involved in investigating synaptic plasticity in adult rodent PFC. Experimental paradigms which yield robust long-term potentiation (LTP) in the hippocampus, such as theta burst stimulation and spike timing dependent plasticity, are inefficient in adult PFC. While new interventions directed at harnessing mechanisms of behavioral timescale plasticity appear promising, their reliance on whole cell recording limits characterization of synaptic plasticity to a single neuron at a time. Since evaluating prefrontal plasticity strategies at the neural population level would be more efficient, we propose a novel technique using wide-field calcium imaging to measure the 'optical field potential' in response to synaptic stimulation.

Our induction paradigm takes advantage of the phenomenon of dendritic plateau potentials, considered essential for eliciting LTP in prefrontal cortex in vivo. These potentials arise from integration of synaptic stimuli arriving close together in space and time, triggering dendritic calcium spikes through NMDA receptors. Therefore, as proof of concept, we contrast the ability of electrophysiological and optical approaches to detect synaptic plasticity differences in the adult PFC between wild-type mice and a model with genetically-disrupted NMDA receptors.

Methods: First, we reviewed the literature to assess the efficacy of conventional plasticity paradigms (spike timing dependent potentiation, STDP, or theta burst stimulation, TBS) at inducing long term potentiation in the adult rodent PFC. Then we experimentally contrasted two approaches in prefrontal cortex of adult mice to assess differences in synaptic plasticity associated with an NMDA receptor genetic variant: an electrophysiological approach with spike timing dependent plasticity and an optical approach with wide-field calcium imaging. Optical field potentials were measured using wide-field calcium imaging in prefrontal brain slices from adult (>P60) compound Thy1-GCaMP6f mice of both sexes. Synaptic stimulation was delivered to the apical dendritic field of the major output neurons of prefrontal cortex by a superficial field electrode. Images were analyzed with ImageJ and MatLab. Additional electrophysiological recordings were performed with intracellular indicator to visualize dendritic calcium spikes evoked by plateau potentials in individual neurons.

Results: The systematic review demonstrated that most studies reporting successful LTP in adult animals require the use of non-physiologically strong stimulation or blockers of GABA receptors, supporting the hypothesis that potentiation is challenging to achieve in PFC. Next, we tested our conclusion experimentally with electrophysiological experiments comparing NMDA receptor variant mice to their wild-type littermate controls. As predicted, we found that the highly variable outcomes of STDP in PFC obscured the detection of differences in synaptic plasticity between the genotypes. Next, we tested these mice using the optical field potential to assess responses to dendritic plateau potentials. We found this approach captured significant differences in PFC between wild-type mice and those with a GluN1 NMDA receptor mutation. Ongoing work is pursuing refinements of stimulation protocols to elicit long-term synaptic plasticity in models of neurobiological disease.

Conclusions: Optical field potentials show clear benefits in revealing synaptic and dendritic deficits. We demonstrate that this approach demonstrates greater promise than a traditional single cell plasticity paradigm towards identifying synaptic deficits in adult PFC of animals with a genetic mutation in the NMDA receptor. Wide-field imaging achieves greater sensitivity for the detection of relevant events at the neural population level. Thus, it presents a strategic advantage in developing and refining preclinical stimulation paradigms to induce plasticity in the adult prefrontal cortex.

Keywords: Medial Prefrontal Cortex, Synaptic Plasticity, NMDA Receptor, GRIN-Related Disorders, Calcium Imaging

Disclosure: Nothing to disclose.

P396. Unrestrained Dendritic Excitation and Epilepsy Caused by GRIN1 Patient Variant Can Be Prevented by Boosting Negative Feedback Regulation of NMDA Receptors

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Background: Mutations in NMDA receptor (NMDAR) encoding GRIN genes are an emerging cause of epileptic encephalopathy, characterized by profound developmental delay and epilepsy. Patient-specific GRIN mutations cause varying symptom severity and neural deficits, complicating a general understanding and treatment of GRIN disorders. While previous studies of GRIN mutations focus on heterologous expression systems or synaptic NMDARs, the impact on extrasynaptic NMDARs that have dynamic interactions with vital dendritic ion channels remains unknown. To obtain a broad understanding of neurophysiological changes and identify potential treatments, we studied a mouse model carrying

the Y647S patient mutation in the obligate GluN1 NMDAR subunit. Grin1 Y647S+/- mice recapitulate key behavioral features of the patient, including prominent seizures and cognitive disability. Our neurophysiological investigation reveals a dendritic mechanism involving loss of negative feedback on NMDARs leading to prolonged excitation, which can be successfully targeted to prevent seizures in Y647S+/- mice.

Methods: Transgenic mutant (Grin1 Y647S+/-) and wildtype littermate adult mice (>P60) of both sexes were used for patch clamp electrophysiology of layer 5 pyramidal neurons in the prefrontal cortex. Thy1-GCaMP6f mice were bred to express the Grin1 Y647S+/- mutation for widefield calcium imaging experiments. Seizure incidence in Y647S+/- mice administered with treatment or vehicle control was measured for 2 months to assess the efficacy of our treatment strategy developed from neurophysiology insights. Unpaired t-tests and two-way ANOVA were used to assess genotype or pharmacological effects.

Results: Electrophysiology experiments revealed complex synaptic and dendritic mechanisms causing pathological hyperexcitability in Grin1 Y647S+/- mice. While there was a significant reduction in synaptic NMDAR currents (Genotype effect: $F(1, 192) = 37.78$, $P < 10\text{-}4$), extrasynaptic NMDAR-dependent dendritic plateau potentials were aberrantly prolonged ($t(17) = 2.691$, $P = 0.015$) in Grin1 Y647S+/- mice. Calcium imaging experiments to assess dendritic excitability at the neural population level revealed prolonged and unrestrained dendritic excitation in Y647S+/- mice, which may initiate seizures. We hypothesized that this pattern is consistent with the failure of a negative feedback mechanism that prevents unrestrained excitation via NMDAR recruitment of calcium-activated SK channels which restores Mg2+ block of NMDARs. Consistent with our hypothesis, boosting SK channel activity reduced hyperexcitability by restoring appropriate timing to dendritic plateau potentials, whereas reducing extracellular Mg2+ levels caused disproportionate hyperexcitation due to insufficient negative feedback in Y647S+/- mice. Based on these results, we developed a treatment strategy to boost negative feedback of NMDARs that was highly effective in suppressing seizures in Y647S +/- mice at up to 8 weeks of treatment.

Conclusions: Our work reveals fundamental dendritic mechanisms underlying seizures in a GRIN1 patient variant, that can be successfully treated by targeting negative feedback mechanisms to restore Mg2+ block to NMDARs. We develop a highly effective and patient-specific treatment strategy to prevent seizures in GRIN disorder based on careful neurophysiological examination. This highlights the importance of evaluating NMDAR function in intact neural circuits to determine treatment strategies for GRIN disorders.

Keywords: GRIN1 Mutation, NMDA Receptor, Epilepsy, Slice Electrophysiology, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

P397. The Effects of Transcranial Photobiomodulation on Regional Intrinsic Brain Activity in Early Alzheimer's Disease

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Background: Impaired mitochondrial function, and therefore impaired cerebral metabolism, is evident in individuals with Alzheimer's disease [AD]. Fractional amplitude of low frequency fluctuations (fALFF) is a noninvasive neuroimaging measure of regional, voxel-wise, spontaneous fluctuations of the fMRI BOLD signal, which reflects variations in intrinsic brain activity over time and space. Magnetic resonance imaging (MRI)-derived fALFF values correlated most strongly ($r = .79$) with regional positron emission tomography (PET) measurements of metabolism. Transcranial photobiomodulation (tPBM) is a novel, noninvasive, and non-pharmacological treatment that uses red and/or near infrared light to penetrate the cortex and is believed to alter cerebral metabolism and enhance cognition. While a growing number of studies are using tPBM in various populations, including early AD, no studies have examined the influence of tPBM on regional fALFF, which may serve as a modifiable treatment target in early AD patients.

Methods: We examined the change in fALFF in frontal regions directly irradiated by tPBM. We recruited 35 participants at two sites; 16 were excluded from the final analyses due to excessive motion during the scan. The 19 participants (NYU/NKI $n = 16$ and MGH $n = 3$) included in analyses were between ages 65 and 85 (mean 74.3 years, 63% male, 74% White and 79% non-Hispanic/Latino), and met Petersen criteria for early AD, as determined by Clinical Dementia Rating Scale and Functional Assessment Staging Tool. Then, they underwent three sequential resting state MRI scans (3T Siemens Trio and 12 channel head coil). Multi-echo echo planar imaging (EPI) was acquired pre-tPBM (baseline), during tPBM, and immediately post-tPBM. EPI parameters were: $TR = 2.5s$; $TE = 12.8,33.01,54.02$ ms for MGH and $TE = 12.8,32.33,51.04$ ms for NYU/NKI; slice thickness 2.5 mm. tPBM was delivered via laser probes (808 nm) placed over the forehead bilaterally. Specific standard EEG electrode positions were directly irradiated (F4, F3, Fp2, Fp1, Fz, Fpz). fMRI data were pre-processed using afni_proc.py customized for multi-echo EPI and FreeSurfer was used to pre-process the structural T1. fALFF was calculated using afni 3dRSFC and was extracted from regions of interest (ROI) using Marsbar. The ROIs were created as 5mm spheres centered on the cortical MRI coordinates of the bilateral irradiated regions. All statistical tests were computed in R studio.

Results: In prefrontal ROIs illuminated by tPBM, paired t-tests showed significant changes from baseline fALFF during and after tPBM (uncorrected). fALFF decreased during tPBM in F3 ($t = -2.290$, $p = .034$, Cohen's $d = .768$), F4 ($t = -2.778$, $p = .012$, $d = .925$), Fp1 ($t = -2.460$, $p = .024$, $d = .833$), Fp2 ($t = -3.576$, $p = .002$, $d = 1.169$), and Fz ($t = -2.400$, $p = .027$, $d = .779$). fALFF decreased from baseline to post-tPBM in F3 ($t = -2.212$, $p = .040$, $d = .580$), F4 ($t = -2.410$, $p = -.027$, $d = .684$), and Fp2 ($t = -2.909$, $p = .009$, $d = .779$). Trends were also seen in Fp1 ($t = -2.094$, $p = .051$, $d = .583$) and Fz ($t = -2.078$, $p = .052$, $d = .456$). We did not see significant changes in fALFF from baseline in Fpz during ($t = -.935$, $p = .360$, $d = .214$; mean = -.056, SD = .26) or after tPBM ($t = -.551$, $p = .589$, $d = .148$; mean = -.038, SD = .30).

Conclusions: Despite a small sample size, effect sizes for the change from baseline fALFF in the target regions during and post-tPBM were medium-to-large. Effect sizes were larger during versus after tPBM, suggesting that targets were engaged most robustly during tPBM with effects diminishing somewhat after. We suspect the lack of significance in Fpz reflects its high variability as it is close to the edge of the anterior midline and susceptible to noise and signal drop out. Future studies should compare regional changes in fALFF to changes in PET metabolism pre- and post-tPBM. Such work could also inform on the biological interpretation of fALFF, which is non-invasive and more accessible than PET. These results also suggest that fALFF could be useful in exploring diverse tPBM parameters to further enhance target engagement. These data are part of an ongoing multi-site clinical trial, therefore this is only the first stage of analysis. Outcome variables will be correlated with these findings after study completion.

Keywords: Alzheimer Disease, Multi-Echo fMRI, Transcranial Photobiomodulation, Neuromodulation

Disclosure: Nothing to disclose.

P398. Sustained Improvements in Chorea Associated With Huntington Disease With Once-Daily Valbenazine: Interim Results From a Long-Term Open-Label Study

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Background: In a recently published Phase 3 trial (KINECT™-HD; NCT04102579), once-daily treatment with valbenazine significantly improved chorea versus placebo in adults with Huntington disease (HD). Individuals who completed KINECT-HD, along with de novo participants, were allowed to enroll in KINECT™-HD2 (NCT04400331), the first long-term study of once-daily valbenazine for chorea associated with HD. Pre-planned interim analyses from this ongoing study were conducted to evaluate the maintenance of valbenazine's effect on chorea and its long-term safety in adults with HD.

Methods: All KINECT-HD2 participants start valbenazine at 40 mg with increases to 60 mg (Week 2) and 80 mg (Week 4); target maintenance dose is 80 mg once daily until end of treatment (up to 156 weeks). Concomitant antipsychotic medications are allowed. Efficacy outcomes, analyzed by study visit, include mean changes from baseline in Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score and response status for Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C). Responders are defined as participants with a score ≤2 (rating of "much improved" or better). Efficacy outcomes up to Week 50 (~1 year) are reported. Treatment-emergent adverse events (TEAEs) are presented for all participants who received ≥1 dose of study drug, regardless of time in study (2 to 104 weeks). All interim outcomes were analyzed descriptively.

Results: Of 127 participants enrolled at the time of analysis, 98 (77.2%) had completed KINECT-HD and 29 (22.8%) were newly enrolled. Of 125 participants who received treatment, 65 (52.0%) were female and 118 (94.4%) were white; mean age (±SD) was 54.8 (±11.5) years. A mean reduction in TMC score was observed by Week 2 with valbenazine 40 mg (-3.4 [±3.1], n = 118); mean reductions were sustained from Week 8 (-5.6 [±3.6], n = 110) to Week 50 (-5.8 [±4.1], n = 66) (all valbenazine doses). At Week 50, 76.9% (50/65) of participants met the pre-defined threshold for CGI-C response; 74.2% (49/66) met the threshold for PGI-C response. Analyses in participants taking concomitant antipsychotic medications are ongoing and will be presented at the meeting. Of the 125 participants who received treatment, 119 (95.2%) reported at least 1 TEAE and 17 (13.6%) discontinued due to a TEAE. The most commonly reported TEAEs were falls (30.4%), fatigue (24.0%), and somnolence (24.0%).

Conclusions: Interim TMC data from KINECT-HD2 indicated chorea improvement with once-daily valbenazine by Week 2 (-3.4 [±3.1] with 40 mg), similar to KINECT-HD Week 2 results (-2.9 [±3.0]). The interim analyses also indicated that long-term treatment with valbenazine was well tolerated and provided clinically meaningful improvement in chorea severity for up to ~1 year.

Keywords: Huntington's Disease, Valbenazine, Chorea, KINECT-HD2

Disclosure: Neurocrine Biosciences, Inc.: Employee (Self).

P399. New Drug Development in Alzheimer's Disease

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Background: Therapies for Alzheimer's Disease are rapidly progressing with many new treatments being tested in clinical trials and getting approved each year. This year alone in the United States, there were at least 2 drugs that have been early approved by the FDA: Lecanemab, and Donanemab[5]. These drugs all work to reduce beta amyloid levels in the brain, which have been proven to significantly decrease in various clinical trials [6]. Both of these treatments are intravenous infusions that can be administered monthly, or every two weeks. The duration of treatment can be for years at a time to obtain a sufficient diminishment of amyloid. They fall under the drug class of monoclonal antibodies and are most commonly used for patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease. This is because these drugs are meant to change the progression of disease and delay onset, sometimes as much as 35%. The current line of treatment for Alzheimer's Disease and dementia typically are medications that only treat the symptoms of disease, instead of targeting the cause. As technological capabilities advance, there are more tools that can help detect susceptibility to Alzheimer's as well as catching the disease in its early stages. This can be done with tests like the Precivity Assay, which can detect clinically significant levels of amyloid in the blood before memory loss can present as a symptom [2]. With a tool like this, it will be possible to identify patients with a family history of Alzheimer's disease to seek treatment and attempt to delay the progression of disease with the new treatment options that are becoming increasingly available. With an indication of this nature, preventing progression before pronounced outcomes like memory loss and other neuropsychiatric symptoms can prove to be invaluable. In addition to amyloid antibody therapy, there is also further research that includes anti-tau antibodies, antigens, and vaccines. This is because the amyloid hypothesis has long been the primary mechanistic cause of AD, and in more recent years it has been shown that tau aggregation is what leads to cell damage and neurofibrillary tangles [4]. Current clinical trials testing anti-tau drugs include Janssen JNJ-63733657, a humanized IgG1 monoclonal antibody that binds to aggregated phosphorylated tau [1]. There is also Merck MK2214, which is another humanized monoclonal tau antibody that targets specific parts of pathological tau which is theorized to prevent extracellular spread from neuron to neuron (Merck Sharp and amp; Dohme LLC, 2023). Also in development are anti-inflammatory drugs, such as that of Cassava Sciences, simufilam, which binds to an altered conformation of filamin A, which is related to elevated levels of beta amyloid [3]. The altered filamin A prevents various toxic signaling cascades as seen in the AD brain.

Methods: Poster and literature review.

Results: Poster and presentation review.

Conclusions: We are entering an exciting era in new drug development in AD.

Keywords: Alzheimer's Disease, Drug Development, Emerging Therapies

Disclosure: Nothing to disclose.

P400. Psilocybin Therapy for Depression and Anxiety Associated With Parkinson's Disease: A Pilot Study

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Background: Depression and anxiety are common in PD, often treatment-resistant, and linked to reduced quality of life as well as accelerated physical and cognitive decline. Evidence suggests that psilocybin may be a promising intervention for treatment-resistant depression and mood dysfunction in people with terminal cancer. However, no prior psilocybin trials have enrolled participants with PD or any other neurodegenerative illness. We aimed to investigate the safety, tolerability, and preliminary efficacy of psilocybin administration paired with psychotherapy among people with PD and comorbid mood dysfunction.

Methods: This open-label single-arm pilot study enrolled people ages 40 to 75 with idiopathic PD (Hoehn and Yahr stages 1-3) also meeting criteria for a depressive and/or anxious disorder. In a monitored setting, participants received a 10 mg dose of psilocybin orally followed ~2 weeks later by a 25 mg dose. Participants completed psychotherapy sessions before and after each drug session. Primary outcomes were safety and tolerability measured by the incidence, severity, and treatment-relatedness of adverse events (AEs). Exploratory efficacy outcomes were severity of depression and anxiety at 7 (primary) and 30 days following the 25mg session.

Results: 12 people (M = 63 years old, SD = 8.8; 5 women) with mild to moderate disease severity (M = 4.4 years since PD diagnosis, SD = 3.8) enrolled. All completed 100% of study visits including both psilocybin sessions. Treatment was well-tolerated with no serious AEs, no worsening of suicidality, and no increase in psychotic symptoms. Treatment-related AEs included nausea, hypertension, tachycardia, anxiety, and headache. Relative to baseline, we observed improvements in motor exam scores (7 days: $p = .02$, Hedge's $g = -0.29$; 30 days: $p = .006$, $g = -0.35$), motor symptoms (7 days: $p < .001$, $g = -1.11$; 30 days: $p < .001$, $g = -1.21$), non motor symptoms (7 days: $p < .001$, $g = -3.17$; 30 days: $p < .001$, $g = -3.00$), depression (7 days: $p = .002$, $g = -0.93$; 30 days: $p = .01$, $g = -1.00$), and anxiety (7 days: $p = .007$, $g = -0.88$; 30 days: $p = .13$, $g = -0.54$).

Conclusions: This study provides the first data on the clinical potential of psilocybin therapy for people with PD and comorbid mood dysfunction.

Keywords: Psychedelics, Parkinson's Disease, Clinical Trial, Psilocybin, Neurodegenerative Disease

Disclosure: Nothing to disclose.

P401. Altered Expression of Circadian Clock Genes in Saliva of Children With Fetal Alcohol Spectrum Disorder

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Background: Fetal alcohol spectrum disorders (FASD) are a combination of developmental, cognitive, and behavioral abnormalities in children with prenatal exposure to alcohol. The prevalence of FASD is estimated to be 2-5% of children in the U.S. Children with FASD exhibit altered sleep and eating patterns, which suggest possible alcohol-mediated disturbances in circadian rhythms. Elucidation of mechanisms for disrupted circadian rhythmicity is critical for understanding the impact on behavioral and physiological outcome, as well identifying effective interventions for FASD. Human saliva offers an emerging and easily available physiological fluid that can be used to study circadian rhythms and may also provide biomarkers that can help identify individuals with FASD early, so that interventions can be implemented when most effective.

Methods: Saliva samples were collected from 49 children aged 6-10 years old with (prenatal alcohol-exposed [PAE] = 12 males, 10 females) and without prenatal alcohol exposure (control [CON] = 16 males, 11 females) at 2 timepoints during the light cycle (between 08:30-17:30 h). Subjects were recruited concurrently with recruitment for other studies at the Genetics and Dysmorphology Clinic at Rady Children's Hospital-San Diego (RCHSD), the UCSD Center for Better Beginnings and FASD Research Registry, and the SDSU Center for Behavioral Teratology. Saliva was mixed with RNA stabilizing solution (DNA/RNA shield reagent, Zymo Research) and transported to Rutgers for analysis. RNA was isolated from the samples and the expression patterns of core clock genes and clock-regulating genes were measured using the human specific primers with qPCR array.

Results: Clock gene expression levels were significantly altered in saliva samples from children with PAE and age-matched controls, including core-clock BMAL1, CLOCK and PER1-3. We did not find any sex difference in the levels of most of the clock genes in PAE and CON groups, with exception of CLOCK gene in PAE group. Importantly, cosinor analysis to calculate the rhythmic patterns of these clock genes identified a diurnal pattern in the levels of core clock genes in the CON but not in the PAE group, suggesting that PAE severely disrupts the circadian rhythmicity of clock gene expression. Altered expression patterns were also observed in clock regulatory genes in PAE groups as compared to control group.

Conclusions: Overall, these findings provide evidence that prenatal alcohol exposure disturbs the circadian patten expression of core clock genes in saliva that may contribute to an altered sleep cycle and behavioral problems observed in children with FASD.

Keywords: Fetal Alcohol Spectrum Disorder, Circadian Rhythm, Epigenetic

Disclosure: Nothing to disclose.

P402. SMRI and Cognitive and Neuropsychiatric Symptoms in Post-Acute Sequelae SARS-CoV-2 Infection (PASC

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Background: Approximately 30% of COVID-19 patients exhibit symptoms of post-acute sequelae of SARS-CoV-2 infection (PASC), or long COVID, and 90 % of those present with neuropsychiatric symptoms. As of January 2023, there have been 660M confirmed cases of COVID-19 worldwide as per the World Health Organization (WHO). In this pilot study, we examined imaging results of the blood-brain barrier, as well as structural and functional brain measures from magnetic resonance imaging (MRI) analysis to obtain linkages between PASC and neuropsychiatric and cognitive symptoms.

Methods: We recruited a total of 36 subjects through our Post-COVID clinic at UCLA with 4-6 weekly referrals of new patients), thus demonstrating feasibility of recruitment for the current study. The mean age of these COVID+ participants (22 females; 19 Caucasian, 11 Hispanic, 2 African American, 4 Asian) was 43.4 (SD = 15.5) years; 18 patients are COVID+/NP+, 8 patients are COVID+/NP-, 4 participants are COVID-/NP+, and 4 participants had no symptoms The COVID+/NP+ participants exhibited significantly more depressive symptoms, greater fatigue, more trouble participating in social activities, and worse sleep quality compared to COVID+/NP- participants, and other controls. All subjects underwent MR scanning using a 32-channel head coil on a 3T Siemens MAGNETOM PRISMA (Siemens:T2-weighted image comprised a repetition time (TR = 3200 ms), echo time (TE = 564 ms), field of view = 256 × 256 mm2, and an isotropic voxel resolution of 0.8 × 0.8 × 0.8 mm3). Behavioral measures

included measures of depression (BDI), Anxiety (HAMA) and cognitive battery of tests.

Results: We found significant (uncorrected for multiple comparisons) correlations between ROI cortical thickness for the posterior cingulate ($r = 0.57$, $p = 0.0070$) with CDRISC, insula ($r = 0.46$, $p = 0.034$) with HAMA, entorhinal cortex with HAMA ($r = 0.47$, $p = 0.031$), and the postcentral gyrus with CDRISC ($r = 0.55$, $p = 0.031$) respectively. These ROIs except the insula showed an increasing relationship of thickness with the CDRISC and HAMA. Cognitive performance data did not show any significant difference between any of the groups.

Conclusions: Our results report an increase in gray matter thickness in long COVID patients compared to the COVID negative group. Future studies will address fMRI measures sensitive to BBB function.

Keywords: COVID-19, Multimodal Neuroimaging, Brain Based Markers for Depression, Cognition

Disclosure: Nothing to disclose.

P403. Rapid and Minimally Invasive Screening for Alzheimer's Immunotherapy: A Comparative Analysis of Plasma P-Tau217 and Amyloid PET/CSF Testing to Improve Treatment Access

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Background: Access to novel disease modifying treatments (DMTs) for Alzheimer's disease (AD) hinges upon early and efficient detection of cerebral amyloidosis in patients with early-stage disease. The recent approval of amyloid-lowering immunotherapies, such as aducanumab and lecanemab, necessitates the optimization of screening techniques, which currently represent a major barrier to treatment due to reliance on positron emission tomography (PET) or cerebrospinal fluid (CSF) to confirm amyloid status in all patients. While previous studies have demonstrated blood biomarkers, such as P-tau217, can detect amyloidosis in early AD, more work is needed to understand how they can be used alongside other testing modalities to aid in determining treatment eligibility. This retrospective, cross-sectional observational study aims to assess the predictive value of P-tau217 compared to the current "gold standard" of amyloid PET/CSF testing in memory clinic patients who are potential candidates for aducanumab treatment.

Methods: Participants from the Butler Hospital Memory and Aging Program Prevention Registry, diagnosed with MCI or mild dementia and with confirmed amyloid status using amyloid PET/CSF, were included in the study. The primary outcome measured was the diagnostic performance of P-tau217 in predicting amyloid status by PET/CSF. Secondary outcomes included rate of subsequent aducanumab initiation in amyloid-positive individuals. Demographic data were calculated and reported as mean (SEM) or frequency (%). Missing data were imputed, then receiver operator characteristic (ROC) analysis was performed in R using an iterative, randomized train-test approach, reported as area under the curve (AUC [95% CI]). Positive predictive value (PPV) and negative predictive value (NPV) were calculated at Youden's cutoff. All study procedures were performed in compliance with the Butler Hospital Institutional Review Board.

Results: Participants ($n = 74$) were 54.1% male, with a mean age of 69.9 (0.86) years, MMSE score of 25.7 (0.36), 82.4% of whom were amyloid-positive by PET/CSF testing. We found that plasma P-tau217 significantly predicted amyloid status (AUC 0.94 [0.89, 0.99], $p < 0.001$), corresponding to a PPV = 99.3% and NPV = 61.45%. A total of 32.7% of amyloid-positive participants ultimately elected to initiate treatment with aducanumab.

Conclusions: Similar to previous studies, our results support the utility of plasma P-tau217 as a clinically useful biomarker for detecting amyloidosis in symptomatic patients with early AD. Incorporation of additional socio-demographic and genetic variables alongside P-tau217 may further improve model sensitivity. Intermediate P-tau217 values must be interpreted with caution, as lower sensitivity of this biomarker could result in the inappropriate exclusion of patients from treatment, and may require reflex confirmatory testing with alternative diagnostic modalities. Limitations of the study include the retrospective design and limited generalizability due to a relatively high prevalence of amyloid positivity, likely due to participant self-selection in the memory clinic setting.

Keywords: Alzheimer Disease, Biomarker Analysis, Immunotherapy

Disclosure: Nothing to disclose.

P404. TRV045, a Novel and Selective S1P1 Receptor Modulator is Efficacious in Acute, Chronic and Prevention in Mouse Models of Chronic Neuropathy, Without Causing Lymphopenia

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Background: Chemotherapy-induced peripheral neuropathy (CIPN) occurs in up to 70% of oncology patients undergoing chemotherapy. There is an unmet medical need for prophylactic and symptomatic treatment of CIPN. Previous studies have suggested a beneficial role for non-selective sphingosine 1-phosphate receptor subtype 1 (S1PR1) modulators in treating neuropathic pain. However, at doses which produce analgesia, these compounds also affect lymphocyte trafficking, resulting in profound reductions in circulating peripheral lymphocytes. This limits their utility for use in clinical conditions, like CIPN, where immunosuppression would not be desirable. The objective of the work reported here is to evaluate TRV045, a newly developed selective S1PR1 modulator that does not cause lymphopenia, following single or repeat oral dosing in a mouse model of CIPN induced by paclitaxel.

Methods: C57BL/6J young adult male mice were injected with paclitaxel (8mg/kg i.p.) or its vehicle at days 1, 3, 5, 7. At Day 15, mice were treated with TRV045 (0.1, 0.3, 3, 10 mg/kg, p.o.) or fingolimod (1 mg/kg, p.o.) or vehicle. Mechanical and cold hypersensitivity were tested at 1, 3, and 6 hours after drug administration for reversal studies. TRV045 was also evaluated for CIPN prevention. C57Bl/6J young adult male mice were treated with TRV045 (0.3, 3, 10, 100 mg/kg, p.o.) or vehicle once daily from day 1 through day 14. Mice were injected with paclitaxel (8 mg/kg i.p.) or its vehicle at days 3, 5, 7, and 9. At day 15 (24 hours after last TRV045 dose) and day 21 (168 hours after last TRV045 dose), mechanical and cold hypersensitivity were tested.

Results: In the reversal experiments, TRV045 at 10 mg/kg reduced mechanical hypersensitivity at 1, 3, and 6 hours after treatment. TRV045 at 3 mg/kg and fingolimod at 1 mg/kg only showed efficacy at the 3 hour timepoint. In the cold hypersensitivity test, TRV045 at 3 and 10mg/kg and fingolimod (1 mg/kg) showed efficacy at 1 and 3 hours only. Other TRV045 dosages produced no effects. In the prevention experiment, at 24 hours, TRV045 (100 mg/kg but not 0.3, 3 and 10 mg/kg) reduced both mechanical and cold hypersensitivity. At 168 hours, TRV045 (100 mg/kg) reduced cold hypersensitivity but not mechanical hypersensitivity, whereas other doses had no effects.

Conclusions: Oral administration of TRV045 reduced the stimulus-evoked nociception in a dose-related manner in a mouse model of chemotherapy-induced peripheral neuropathy. Our experiment in the preventive paradigm suggests TRV045 may have potential disease or pathology-modifying effects on pain transmission processes detectable by the cold hypersensitivity test, with the reasonable assumption that at 168 hours, no detectable levels of TRV045 remain in circulation. Whether the efficacy seen at 24 hours was attributable to residual tissue TRV045 or results of disease prevention remains to be determined. TRV045 is an experimental drug not approved by the FDA.

Keywords: Sphingosine 1-Phosphate Receptor, Neuropathic Pain, Animal Models

Disclosure: Trevena, Inc.: Employee (Self).

P405. Discovery and Preclinical Characterization of the Phenylalkylamine, CYB210010, a Potent and Long-Acting Serotonin 5-HT2A Receptor Agonist

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Background: Phenethylamine psychedelics offer an alternative treatment approach to the classical tryptamine psychedelics such as psilocybin and dimethyltryptamine. Most of the early research efforts in psychedelic phenethylamine drug development focused on mescaline and MDMA, and there has been less focus on developing compounds from the 2C-X series, discovered by Shulgin (see Shulgin and Shulgin, 1991). The purpose of these studies was to synthesize novel analogs of 2C-X compounds with the objective of identifying candidates with improved safety and therapeutic profiles. The Structure-Activity Relationship (SAR) of 4-thio analogs was investigated to identify molecules for potential clinical development that have unique pharmacodynamic (PD) and pharmacokinetic (PK) properties.

Methods: Iterative chemical synthesis and SAR studies resulted in the profiling of over 40 novel molecules. Using a classic drug discovery screening cascade, molecules were first profiled for in vitro activity at the serotonin 5-HT2A, 5-HT2B, and 5-HT2C receptor subtypes using in vitro binding and/or functional assays. Compounds exhibiting < 100 nM affinity (Ki) and/or functional potencies (EC50) < 1 μM at the 5-HT2A receptor, were then screened for in vivo activity (3 mg/kg subcutaneous dose) in the C57BL/6J mouse head-twitch response (HTR) model of central 5-HT2A receptor activation. The HTR model was adapted to include an evaluation of duration of activity with HTR measured both 0-15 min and 160-170 min post-administration. Compounds exhibiting robust and durable HTRs were tested in rodent pharmacokinetic studies to understand peripheral and central exposure, as well as 5-HT2A receptor occupancy in mouse frontal cortex. Finally, a lead candidate molecule was tested for effects on the expression of several genes implicated in the regulation of neurogenesis and neuroplasticity, processes potentially underlying the beneficial effects of psychedelic 5-HT receptor agonists.

Results: Several novel potent and selective 5-HT2A receptor agonists were identified, and an expanded profiling was completed on one phenylalkylamine, 2,5-dimethoxy-4-(trifluoromethyl)thio-phenethylamine (CYB210010). CYB210010 exhibited high agonist potency at 5-HT2A (EC50 = 4.1 nM) and 5-HT2C (EC50 = 7.3 nM) receptors, with full agonist activity, modest agonist selectivity over 5-HT2B, 5-HT1A, 5-HT6, and adrenergic α2A receptors, and >100-fold binding selectivity over 70+ other proteins, including monoamine transporters. CYB210010 dosed either subcutaneously or orally (0.1-3 mg/kg) elicited a robust, dose-dependent HTR, and could be administered sub-chronically at a threshold dose (0.3 mg/kg) without any behavioral tolerance. In studies measuring target engagement and gene expression, CYB210010 occupied frontal cortical 5-HT2A receptors and increased the expression of genes implicated in neuroplasticity in the frontal cortex, but not the hippocampus, following acute administration of a 3 mg/kg dose, and sub-chronic administration of a 0.3 mg/kg dose. Pharmacokinetic studies demonstrated that CYB210010 was orally bioavailable in three species (mouse, rat, dog), exhibited high brain penetration (rat brain-to-plasma ratio > 15), and similar pharmacokinetic profiles in three compartments; plasma, brain, and CSF.

Conclusions: Based on these properties, CYB210010 represents an important molecule for investigating the downstream effects of serotonergic receptor activation and the therapeutic potential of serotonin 5-HT2 receptor agonists administered via sub-psychedelic, chronic dosing regimens.

Shulgin A., Shulgin A. (1991) PiHKAL: A Chemical Love Story. Transform Pre

Keywords: 5-HT2A Receptors, Psychedelic, Neuroplasticity, Behavioral Pharmacology, Neurological and Psychiatric Disorders

Disclosures: Cybin, Inc.: Consultant (Self). Palfreyman BioPharm Advisors, LLC: Founder (Self).

P406. Targeting Synaptic Downscaling to Alleviate SNAP25 Encephalopathies

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Background: Synaptic vesicle fusion requires soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, SNAP25, synaptobrevin-2, and syntaxin-1. Neurotransmitter release can take place spontaneously, without an external stimulus, or can be triggered by an action potential resulting in fast and synchronized synaptic vesicle fusion. Mutations in different components of the SNARE machinery can differentially affect spontaneous or evoked release and result in severe neurodevelopmental phenotypes. Among these, SNAP25 encephalopathies are a group of neurodevelopmental disorders characterized by impaired synaptic function due to mutations in the SNAP25 gene. Among various pathogenic SNAP25 variants, our initial analysis showed that L50S, V48F, and D166Y amino acid variations largely result in aberrant spontaneous release that results in abnormal network activity. Patients harboring these mutations experience recurrent treatment-resistant seizures, in addition to various abnormal neurobehavioral phenotypes.

Methods: We used human induced-neurons (iN cells) and primary rat hippocampal cultures and expressed mutant SNAP25 constructs (L50S, V48F, or D166Y) through lentiviral transduction. We assessed the effects of conventional antiepileptic treatments compared to chronic treatment with lithium, previously shown to downscale postsynaptic synaptic responses, on aberrant synaptic transmission and network activity using whole-cell patch clamp electrophysiology.

Results: We found that although conventional antiepileptics did not significantly improve the abnormal network activity nor synaptic transmission elicited by these variants, lithium showed significant improvement in the neuronal resting membrane potential, action potential kinetics, and spontaneous neurotransmission.

Conclusions: Patients diagnosed with SNAP25 encephalopathies experience treatment-resistant epilepsies that do not respond to standard antiepileptic treatments. Our results highlight

the use of conventional antiepileptics that usually target voltage-gated ion channels might not be effective in treating epileptic encephalopathies that stem from aberrant spontaneous release, supporting the clinical observation. Alternative treatment options, such as lithium, normalize the abnormal activity by targeting homeostatic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor downscaling and may represent a novel treatment approach to explore.

Keywords: SNAP25, Epilepsy, Lithium, Spontaneous Release

Disclosure: Nothing to disclose.

P407. Pharmacological Characterization of Rat Models of Vascular Headache and Trigeminal Sensitization in Support of the NIH Heal Initiative Preclinical Screening Platform for Pain (PSPP)

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Background: The National Institutes of Health Helping to End Addiction Long-termSM Initiative, or NIH HEAL InitiativeSM, Preclinical Screening Platform for Pain (PSPP) program aims to accelerate the discovery and development of novel non-opioid, non-addictive pain therapeutics. Under the HEAL initiative, the NIH is collaborating with PsychoGenics, Inc. to screen and profile novel assets in vivo in rat models of pain to determine efficacy, and in additional tests to examine potential adverse effects and abuse liability. Efforts in the PSPP program are also focused on the characterization and optimization of disease-specific models to provide support for specific pain indications. Here, we describe one such effort to characterize and validate rat models of vascular headache and trigeminal sensitization involving systemic administration of nitric oxide (NO) donors or dural infusion of inflammatory soup (IS).

Methods: Adult male and female Sprague Dawley rats ($n = 10$, each sex) were used in these studies. For the model of vascular headache, the nitric oxide donor isosorbide dinitrate (ISDN; 10 mg/kg) was injected intraperitoneal (i.p.). For the model of trigeminal sensitization, rats received single or multiple infusions of inflammatory soup (IS; 2 mM serotonin, histamine, bradykinin, 0.2 mM PGE2) onto the dura under acute isoflurane anesthesia. Facial allodynia was measured by applying calibrated von Frey filaments to the periorbital region of the face and determining facial sensitivity thresholds (facial swipe/head withdrawal). Pharmacology was examined by evaluating the effects of pretreatment with the reference analgesics morphine sulfate (6 mg/kg), naproxen (30 mg/kg), sumatriptan (1 mg/kg), olcegepant (1 mg/kg) and SNC80 (30 mg/kg).

Data were analyzed using two-way repeated measures ANOVA with Bonferroni's or Dunnett's post hoc test when appropriate. Study groups were randomized and were sufficiently powered based on previous analysis to ensure adequate power for F-tests for two-way interactions. Effects $p < 0.05$ were considered statistically significant.

Results: For the model of vascular headache, administration of ISDN produced a transient facial allodynia which persisted for 2-3 hours in male and female rats. Facial allodynia was recorded as a decreased facial swipe or head withdrawal threshold to von Frey filament stimulation of the periorbital area. For the model of trigeminal sensitization, a single infusion of IS onto the dura produced a transient facial allodynia which persisted for 1-2 hours. Multiple infusions of IS onto the dura once per day for 5 consecutive days resulted in a persistent facial allodynia which was robust and continued following the discontinuation of the IS infusions.

Reference analgesic compounds were evaluated by pretreating rats prior to induction of vascular headache or trigeminal sensitization. Administration of the mu opioid receptor agonist morphine sulfate (6 mg/kg) or delta opioid receptor agonist SNC80 completely prevented the development of facial allodynia. Pretreatment with the 5-HT1B/1D receptor agonist sumatriptan (1 mg/kg) or CGRP receptor antagonist olcegepant (1 mg/kg) partially prevented the development facial allodynia, while pretreatment with the NSAID naproxen (30 mg/kg) was ineffective.

Conclusions: The data demonstrate that clinically effective treatments for headache and migraine can prevent the development of facial allodynia in rat models of vascular headache and trigeminal sensitization. Additional potential therapies for headache and migraine are currently being evaluated to further understand the pharmacology associated with these models, and to support the use of these models to accelerate the development of novel treatments for headache and migraine.

Keywords: Headache, Migraine, Preclinical Pharmacology, Behavioral Model

Disclosure: Nothing to disclose.

P408. Targeting the α5-GABAA Receptor Alleviates Cognitive Deficits and Reverses Neuronal Atrophy Across Animal Models of Brain Disorders

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Background: Reduced GABA/somatostatin (SST) signaling is reported in psychiatric, stress-related, and neurodegenerative disorders. SST+ interneurons from cortical layers and the hippocampus inhibit the dendrites of excitatory neurons, largely through α5-containing GABAA receptors (α5-GABAAR). Recently, we showed that an α5-positive allosteric modulator (α5-PAM) alleviates working memory deficits and reverses neuronal atrophy in old mice. We then started to investigate the behavioral and neurotrophic effects of this α5-PAM in animal models of aging, chronic stress, β-amyloid load, and tauopathy.

Methods: Four studies are presented, with ~12 mice/group, 50% female: 1) Young C57BL6 subjected to unpredictable chronic mild stress (UCMS) to induce cognitive deficits. 2) 22 month-old C57BL6 developing an age-related cognitive decline. 3) 5xFAD transgenic mice with progressive amyloid-related cognitive decline. 4) PS19 transgenic mice developing tauopathy and associated cognitive decline. In all studies, efficacy of chronic administration of GL-II-73 (30mg/kg, p.o, for 4 weeks) at rescuing cognitive deficits across 3 domains was assessed. Working memory was assessed in an alternation task, spatial memory in the water maze, and cognitive flexibility in a set-shifting assay. Brains were then stained using Golgi-Cox technique ($n = 4$brain/group; 8cell/brain) for quantification of dendritic length and spine density in the prefrontal cortex and hippocampus (NeuroLucida).

Results: Chronic treatment in all models reversed cognitive deficits across domains (ps < 0.01), with a strong effect on working memory. Chronic treatment also significantly reversed UCMS-, age-, amyloid- or Tau-protein-induced dendritic shrinkage and reduction of spine density at apical and basal dendrites ($p < 0.001$ in PFC and CA1).

Conclusions: Together, results support that selective α5 targeting of GABAA receptors overcomes chronic stress-, aging-, amyloid- or tau-related cognitive deficits and detriments in

neuronal morphology. This represents the first intervention targeting the GABAergic system to have a symptomatic and disease-modifying therapeutic potential and could represent a major avenue for clinical development for patients suffering from cognitive deficits across brain disorders.

Keywords: Cognition, α5 GABAA Positive Allosteric Modulator, Somatostatin, Alzheimer Disease, Early Phase Drug Development

Disclosure: Damona Pharmaceuticals: Consultant (Self).

P409. Differential Effects of Enantiomers (S)- and (R)-Tianeptine on Neurite Outgrowth and Mitochondrial Activity in Cultured Glutamatergic Neurons

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Background: Tianeptine is an atypical antidepressant marketed in Europe, Asia, and South America. While tianeptine's mechanism of action (MOA) in depression has been elusive, it is known to promote neuronal growth, survival, and plasticity and to modulate glutamatergic activity in brain regions such as hippocampus. Tianeptine's plastogenic activity in hippocampus is known to be more active in stressed than in non-stressed animals, consistent with targeting the deleterious effects of a considerably activated hypothalamic-pituitary-adrenal axis. Tianeptine contains a chiral center, and the currently marketed product ex-US consists of a 1:1 racemic mixture of (S)- and (R)- isomers. We have studied the purified isomers and recently found that (S)-tianeptine activates PPAR-β/δ and is active in the rat Novel Object Recognition test, whereas (R)-tianeptine is a weak μ-opioid receptor agonist and is active in reducing immobility in the mouse Forced Swim Test. Since the differential effects of the (S)- and (R)-tianeptine isomers on neuroplasticity, neurite outgrowth, mitochondrial distribution, and mitochondrial activity were unknown, we studied their effects in cultured glutamatergic neurons.

Methods: iCell Glutaneurons (Fujifilm CDI) were seeded, and on day 5 in culture, cells were treated with (R)- and (S)-tianeptine (0.1, 1, and 10 μM each), dexamethasone (0.001, 0.01, 0.1, 1, 10, and 100 μM), and matrixed concentrations of all doses of dexamethasone with all doses of (R)- and (S)-tianeptine. Treatments were refreshed on day 7 in culture. Plates were treated with staurosporine (0.02, 0.063, 0.2, and 0.63 μM), an inhibitor of ATP binding to protein kinases, and vincristine (0.2, 2, and 20 μM), a microtubule inhibitor, on day 9 for a total of 24 hours. At 22 hours post-staurosporine and vincristine treatment, plates were treated with FCCP (6.2 and 62 μM), an uncoupler of oxidative phosphorylation, for a total of 2 hours. MitoTracker CMXRos (Thermo Fisher Scientific) was added 45 minutes prior to the end of the treatment period and plates were fixed at the treatment endpoint. Cells were stained with Hoechst (Thermo Fisher Scientific) and CellMask Green (Thermo Fisher Scientific). Image acquisition was performed on the Yokogawa CQ1. Image analysis was performed using the Neuronal Profiling protocol in HCS Studio Cellomics, Version 6.6.2.

Results: Morphometric image analysis of iCell Glutaneurons cultured for 10 days with (S)-tianeptine revealed significant increases in all parameters of neurite outgrowth, including neurite length, width, area, count, staining intensity, and branching ($p < 0.05$ in all cases). In contrast, (R)-tianeptine produced no significant changes in neurite metrics except for a modest increase in neurite count observed at a concentration of 1.0 μM. (S)-tianeptine produced significant increases in mitochondrial staining in neurite processes ($p < 0.05$) and no changes in mitochondrial staining in cell bodies. In contrast, (R)-tianeptine produced no significant changes in mitochondrial staining in neurite processes, but significantly decreased mitochondrial staining in cell bodies ($p < 0.05$). In the iCell Glutaneuron model, we found that dexamethasone alone positively affected dendrite outgrowth metrics ($p < 0.05$). Combining (S)-tianeptine and dexamethasone resulted in larger effects on neurite outgrowth and mitochondrial staining in neurites than with either compound alone. (R)-tianeptine, in combination with dexamethasone, showed no evidence of additive effects.

Conclusions: Comparison of (S)- and (R)-tianeptine treatment of iCell Glutaneurons revealed significant differences in their effects on neurite outgrowth metrics and measures of mitochondrial function. (S)-tianeptine significantly increases neurite growth and synaptic connectivity in this in vitro neuronal system. (S)-tianeptine also increases mitochondrial staining in neurites, which may reflect increased activity or transport of mitochondria into growing neurites. In contrast, (R)-tianeptine does not induce neuroplasticity, and there is preliminary evidence for reduced mitochondrial activity at the level of the neuronal cell body. Dexamethasone also exhibits pro-trophic effects on neurite metrics and positive effects on neurite mitochondria, consistent with in vitro modeling of in vivo effects of mild, acute stress. The combination of dexamethasone and (S)-tianeptine showed additive effects and produced the largest changes in neurite metrics and neurite mitochondrial staining. The additive effects of dexamethasone and (S)-tianeptine are consistent with (S)-tianeptine's reported effects on neuroplasticity in stressed animals. In summary, our results indicate that (S)-tianeptine, but not (R)-tianeptine, is responsible for the pro-trophic effects on neuronal growth, survival, plasticity, and connectivity reported for racemic tianeptine in in vivo rat studies. Reductions in neuroplasticity and neurite bioenergetic activity appear to be central to disorders of mood and neurodegeneration. Further investigation of (S)-tianeptine as a therapeutic for these disorders is warranted.

Keywords: Neuroplasticity, Tianeptine, Mitochondria, Antidepressant, Hippocampus Shrinking

Disclosure: Tonix Pharmaceuticals, Inc.: Employee (Self).

P410. Associations Between Symptom Profiles, Structural and Functional Neural Circuitry, and Quality of Life Among a Large Cohort of Trauma Survivors

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Background: The relationship between symptom heterogeneity among trauma survivors and neuroimaging biomarkers and later quality of life remains unclear. We hypothesized that trauma survivors experiencing a greater burden of somatic symptoms two weeks after trauma that are traditionally considered traumatic brain injury (TBI) symptoms would exhibit greater disruption in structural and functional connectivity, and would report worse physical and mental health related quality of life six months after trauma.

Methods: Participants aged 18-75 years were recruited from participating emergency departments (EDs) to the multisite AURORA study. Inclusion criteria included presentation to the ED within 72 hours of qualifying traumatic events (e.g., motor vehicle collisions, sexual assault, physical assault, falls from >10 feet). Participants completed follow-up assessments two weeks, eight weeks, three months, six months, and 12 months post-trauma. These follow-up assessments included a modified Rivermead Post-Concussion Questionnaire, which assesses severity of 12 somatic symptoms traditionally associated with TBI, and the 12-Item Short

Form Health Survey, which generates normative scores for physical and mental health related quality of life.

Individuals who reported that they met traditional TBI criteria, i.e., hit head and experienced loss of consciousness, amnesia, or feeling dazed or confused after the trauma (N = 842), were included in the following analyses. This sample included 119 participants who completed a neuroimaging assessment two weeks after trauma that included 64-direction diffusion weighted images, 7 non-weighted images, and a 9-minute resting-state functional MRI scan (TR = 2.36 sec, 230 volumes). Site-specific effects were removed from the mean fractional anisotropy values and the z-transformed internetwork connectivity values using ComBat-GAM. Latent profile analysis was performed using the "mclust" R package to identify profiles of somatic symptoms at two weeks post-trauma. Models were compared using the Bayesian information criterion and the Integrated Completed Likelikood criterion. The effects of profile group on white matter tract integrity (genu and splenium of the corpus callosum; cingulum; posterior, anterior, and superior corona radiata; and the internal capsule) and internetwork connectivity strengths (between the visual, default mode, frontoparietal, limbic, and dorsal attention networks) were assessed using a series of one-way ANCOVA models, adjusting for age and sex. In addition, one-way ANCOVAs were used to assess the effect of profile group on physical and mental health related quality of life at six months post-trauma, adjusting for age and sex.

Results: A total of 730 participants met traditional TBI inclusion criteria and had complete data regarding Rivermead somatic symptom domains at two weeks. Latent profile analysis of these somatic symptom domains identified 3 subgroups: 1) mild headache (n = 132, 18.1%), 2) moderate headache and cognitive symptoms (n = 514, 70.4%), and 3) severe headache, cognitive symptoms, and visual/vertigo-related symptoms (n = 84, 11.5%). Neither mean FA values for selected tracts nor inter-network functional connectivity strengths differed by profile group. Both physical and mental health related quality of life differed significantly by profile group (physical: $F(2) = 11.6$, $p < .001$, $\eta 2 = 0.03$; mental: $F(2) = 17.7$, $p < .001$, $\eta 2 = 0.05$). Pairwise comparisons revealed that the participants who reported severe headache, cognitive symptoms, and visual/vertigo-related symptoms at two weeks also reported worse physical and mental health related quality of life at six months post-trauma. The participants who primarily reported mild headaches experienced better quality of life at six months post-trauma.

Conclusions: Among AURORA participants who reported loss of consciousness, amnesia, or being dazed or confused in the immediate aftermath of trauma, profiles of traditional TBI somatic symptoms included in the Rivermead Post-Concussion Questionnaire at two weeks post-trauma were not related to concurrent structural and functional connectivity. However, participants who were more symptomatic, particularly for visual/vertigo-related symptoms, reported significantly worse physical and mental health related quality of life at six months post-trauma. These preliminary results suggest that while somatic symptom profiles were not related to neural circuitry, symptom profiles were associated with later functional outcomes. Further investigation is needed to understand how symptom heterogeneity relates to neural connectivity.

Keywords: Mild Traumatic Brain Injury, Acute Traumatic Stress, Emergency Department

Disclosure: Nothing to disclose.

P411. Cell Specific cAMP Signaling Dynamics During Striatum-Dependent Learned Behaviors

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Background: Striatal neuromodulators play crucial roles in motor control and decision-making. These neuromodulators exert their functions through G-protein-coupled receptors (GPCRs) located on striatal medium spiny neurons (MSNs) that activate second messenger intracellular cascades to affect neuronal signaling. Each subpopulation of MSNs, D1 and D2, contains pairs of receptors that can oppositely control the cAMP-PKA signaling pathway. Understanding how neuromodulatory information is decoded by intracellular signaling molecules to influence synaptic transmission and circuit functions is important in understanding complex behaviors. However, the spatiotemporal changes in striatal intracellular molecules that occur following GPCR activation during complex behaviors remains unclear.

Methods: In this study, we used a genetically encoded fluorescent cAMP biosensor, cAMP Difference Detector in situ (cADDis) and slice photometry to measure MSN-cAMP signaling in brain slices in response to electrical stimulation. To examine MSN-cAMP signaling during learned behaviors, we used fiber photometry and mice expressing cADDis during rotatrod and other striatum dependent behaviors.

Results: MSN-cAMP transients can be modulated by varying the afferent stimulations and are blocked by tetrodotoxin, indicating that these transients are activity driven. Application of adenylyl cyclase activator and/or phosphodiesterase inhibitor increased baseline cAMP fluorescence in both subtypes of MSNs. Using fiber photometry and cADDis, we observed real-time movement- and trial-related changes in MSN-subcellular cAMP signaling during motor-skill learning on the accelerating rotarod.

Conclusions: Our findings show that dynamic changes in cAMP signaling occur during skill learning on the rotarod, which may primarily be driven by dopamine. Similar changes in cAMP-PKA dynamics have been implicated in complex procedural learning, thus we are beginning to examine subcellular changes during goal-directed behaviors.

Keywords: cAMP Signaling, In Vivo Fiber Photometry, Dorsal Striatum, Genetically Encoded Sensor

Disclosure: Nothing to disclose.

P412. Sensory Circuits Contribute to Motor Recovery After Pediatric Strokes: A Clinical to Preclinical Study

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Background: Neonatal stroke resulting in hemiparesis affects approximately 2/1000 people and produces largely unilateral impairment of hand function and walking. The majority of research investigating movement recovery has focused on the motor cortex and the corticospinal tract. However, our previous pediatric patient study demonstrated that sensory system disruption contributes more to hand dysfunction than motor system injury. The current project aims to investigate the role of sensory circuits in motor function in preclinical rodent models of pediatric hemiplegia and test the hypothesis that lesion to the sensory circuits will result in impaired forelimb function because of decreased sensory inputs for motor learning.

Methods: All animal care and handling procedures were approved by the Columbia University Institutional Animal Care and Use Committee (IACUC) with compliance to the National Institutes of Health guidelines for the care and use of laboratory animals. Male and female Sprague-Dawley rats were used for experiments. We tested three different models of pediatric stroke to determine reproducibility and specificity of sensory circuit targeting: 1. periventricular heme injection; 2. photothrombosis

ischemic lesion; and 3. electrolytic lesion of the thalamocortical sensory tract. For sensory tract analysis, a retrograde green fluorescence protein viral vector was targeted to the primary sensory cortex. For behavioral testing, the cylinder exploration test was used to test the hypothesis that sensory system lesions correlated with impaired forelimb function.

Results: With regards to preclinical model development, we found that electrolytic lesions of the thalamocortical tract produced the most specific and reproducible sensory system lesions when compared to periventricular heme injections and photochemical lesions. Electrolytic lesions disrupted up to 50% of the sensory circuits, while sparing motor circuits and there was a strong correlation ($R = 0.84$, $p = 0.009$) between lesion size and sensory circuit disruption. In terms of behavior, we found that lesions to the sensory circuit were associated with decreased use of the affected forelimb ($n = 8$, 4M and 4F, $p = 0.004$, paired t-test).

Conclusions: Overall, specific sensory system lesions of the thalamocortical tract impair motor function and forelimb use, suggesting a key role of sensory circuits in motor recovery. Future experiments will specifically modulate sensory circuits with inactivation to test necessity and activation for repair of sensory circuits and recovery of motor function. The current study provides insight into the specific neural circuits that contribute to functional recovery after pediatric strokes and provide an avenue for therapeutic intervention to enhance outcomes after neonatal brain injury.

Keywords: Stroke, Pediatric, Motor Learning, Sensory Processing

Disclosure: Nothing to disclose.

P413. Habit Reversal via Smartphone App: A Novel Psychological Approach to Treat Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a disabling psychiatric illness affecting 1-3% of the worldwide population. Current most effective treatments are high doses of selective serotonin reuptake inhibitors and cognitive-behavioural therapy involving exposure and response-prevention (ERP). The latter, albeit considered the first line treatment, is only effective in 40%–60% of patients and does not generally achieve full remission. Dropouts are high and mainly caused by patients' failure to tolerate the exposure aspects of the treatment. Novel treatment approaches are thus warranted. Habit-reversal therapy (HRT), a recognised behavioural intervention for treating tic and hair-pulling disorders, provides a possible new approach for delivering ERP for OCD. It involves learning a non-pathological habitual behaviour and applying it as a substitute for the compulsive behaviours. Such practical approach aligns with the recent conceptualisations of OCD being a product of maladaptive habit learning and of an imbalanced fronto-striatal neural circuitry in control of goals and habits, favouring the latter. This study aimed to investigate the feasibility and utility of introducing HRT to augment ERP in OCD. We trained patients to perform a neutral action using a smartphone app (phase 1), which was then used, once automatic and habitual, as a competing motor response to compulsions (phase 2, during the administration of HRT enhanced ERP). We hypothesised that introducing this habit to facilitate compulsion extinction, via habit reversal, would promote better clinical outcomes as compared to the standard ERP treatment.

Methods: We conducted a randomised controlled proof of concept study within the NHS services. Patients with DSM-5 OCD were recruited and randomly allocated to either 12 weeks of standard ERP treatment ($N = 23$: 17 Female) or 12 weeks of combined ERP/HRT treatment ($N = 22$: 14 Female). The latter included an initial 6-week training phase, in which the neutral action (termed 'habit') was developed and strengthen. The training consisted of a daily practice of two sequences of finger tapping movements, akin to playing the piano, on a smartphone application. Each sequence comprised six moves and was performed using three fingers of the dominant hand. Once automaticity was attained, patients began the treatment phase. Assessments were performed by a blinded-rater and included the evaluation of OCD severity (Yale-Brown Obsessive Compulsive Scale - Y-BOCS). Kruskal-Wallis and Wilcoxon tests were conducted to assess group differences. This study was approved by the East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (18/EE/0281) and was registered as a clinical trial in the ISRCTN registry (Trial ID: ISRCTN69935306).

Results: Of the 45 patients randomised to each treatment group, 28 completed the study, with a numerically but not significantly greater number of dropouts in the ERP/HRT arm [ERP/HRT = 11 (8 Female); ERP = 17 (13 Female]. Patients in both arms improved significantly on the Y-BOCS scores from beginning to the end of the treatment [Kruskal-Wallis test using the last observation carried forward analysis: main effect of Time ($p < 0.001$) but there was no group effect ($p = 0.31$). However, the ERP/HRT group unexpectedly improved significantly during the 6 weeks app training (phase 1) ($p = 0.013$) The ERP group, conversely, improved progressively across the treatment.

Conclusions: In this first of its kind study, application of a learnt habit to augment ERP for OCD was feasible within clinical services, acceptable, and resulted in clinical improvement. Unexpectedly, simple habit training produced positive symptomatic results. Further exploration of efficacy, tolerability, and mechanisms of effect of habit reversal techniques in OCD is indicated.

Keywords: Obsessive Compulsive Disorder, Habit Reversal Therapy, Smartphone-Based App, Habit

Disclosure: Nothing to disclose.

P414. A Reliable and Replicable Endogenous Functional Connectivity Marker of Harm Avoidance in OCD

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Background: Obsessive-compulsive disorder (OCD) is characterized by persistent avoidance behaviors even in the absence of actual threat. The impact on quality of life and the considerable heterogeneity in OCD symptoms emphasize the necessity of identifying novel brain-behavior-based intervention targets. Drawing insights from mechanistic studies in rodents and non-human primates, this study aimed to investigate whether specific connections within a pre-defined persistent avoidance neural network could predict harm-avoidance (HA), a trait measure of persistent avoidance, in individuals with OCD. We hypothesized

that 1) HA, rather than diagnostic group, would be linked to altered endogenous connectivity in at least one direct connection within the network; 2) the findings would remain robust even after accounting for co-morbid OCD symptoms; and 3) the results would replicate in an independent sample.

Methods: The study included 103 adults (M Age(SD) = 23.73(4.27); n OCD = 52; n HC = 51). The two groups did not differ significantly in age or motion. The data were divided into group-stratified training (70%; n OCD = 37, n HC = 36) and testing samples (30%; n OCD = 15, n HC = 15). Participants completed a resting-state functional MRI scan, clinically-relevant measures/interviews, and the NARRT-R for premorbid IQ assessment. The sub-samples were not statistically different on any clinical measures, age, IQ, gender, medication status, or motion (all ps > .1).

Regions of interest were selected based on mechanistic studies of persistent avoidance and devaluation learning in rodents and non-human primates (NHP). Spherical 4mm ROIs were drawn separately for the left and right hemispheres using standard MNI template coordinates, and raw mean time series were extracted. The extracted signals were smoothed, denoised, band-pass filtered, and standardized. Subject-level pairwise Pearson correlations (r-z' transformed) were performed between regions with known direct anatomical projections based on NHP tracing data and human tractography, and that had been mechanistically implicated in persistent avoidance. Left and right ROIs were kept separate (87 total functional connections).

A 10-fold cross-validated Poisson elastic net model was used with 9 levels of alpha (.1-.9) for feature selection in the training sample. The dependent variable (DV) was OCTCDQ HA score, and the potential predictors included all direct pairwise connections (87 total), age, motion, gender, and IQ. A min-lambda threshold was employed to determine which non-zero features to include in the GLM analyses. The procedures were repeated with DV = diagnostic group and DV = OCTCDQ trait incompleteness to ascertain if feature selection was specific to HA. For GLMs, a Bonferroni correction was applied for multiple comparisons within each dataset (n = 2 models; alpha = .025).

Results: Two connections were consistently associated with HA across the entire sample. None of the network connections reliably distinguished between HC-OCD groups or predicted HA-associated trait incompleteness scores, indicating the specificity to HA. Stronger inverse connectivity between R_dACC—R_BLA (Beta = -1.78, SE = .182, t(70) = -9.78, p < .0001) and stronger positive connectivity between R_valns—L_VS (Beta = 1.49, SE = .199, t(70) = 7.49, p < .0001) were both associated with greater HA across groups. Only the dACC—BLA connection remained robust after controlling for co-morbid symptoms/medication status in OCD, and it also predicted HA in the testing sample (Beta = -1.08, SE = .279, t(27) = -4.02, p < .0001; B = -1.36, SE = .293; t(23) = -4.64, p < .0001 after excluding n = 3 on medication and controlling for motion). Overall, two-feature models significantly fit both the training (Chisqrd = 132, p < .0001; Deviance of Fit = .14) and testing samples (Chisqrd = 17.7, p = .0001; Deviance of Fit = .086).

Conclusions: Stronger inverse dACC—BLA connectivity was specifically, robustly, and reliably associated with greater HA across groups and in OCD. The methods and results highlight the value of measures that capture variance in both healthy and clinical samples, with evidence that dACC--BLA connectivity was associated with tendency to avoid harm within and across both groups. Results support the relevance of a cross-species persistent avoidance network to OCD, with implications for precision-based approaches and treatment.

Keywords: Persistent Avoidance, Obsessive-Compulsive Disorder (OCD), Obsessive-Compulsive Personality Traits, Resting State Functional Connectivity, Precision Psychiatry

Disclosure: Nothing to disclose.

P415. Effective Connectivity in Cortical and Subcortical Visual Threat Networks During Fearful Face Processing in Body Dysmorphic Disorder

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Background: Body dysmorphic disorder, or BDD, is a relatively common and debilitating psychiatric disorder involving preoccupations with misperceived appearance defects, which may be related to deficits in visual processing. Prior studies in BDD have also shown that BDD is associated with threat processing biases, and work from our group has demonstrated a relationship between anxiety and activation in ventral visual pathways in BDD. However, it is unclear whether visual processing abnormalities are specifically related to problems processing fear. In this analysis, we hypothesized that individuals with BDD would display abnormal effective connectivity of specific regions within a visual threat network, compared to HCs, including aberrant connectivity with the Pulvinar, between the Right Rusiform Face Area (FFA) and Right Amygdala, and between the right Amygdala and Medial Orbitofrontal Cortex (mOFC). We further expected that connectivity differences would scale with BDD symptom severity.

Methods: We recruited participants with BDD (n = 32) and HCs (n = 37) who were matched based on age, sex, and education. While undergoing fMRI, participants completed a gender-labeling fearful face processing task in which equal numbers of male and female faces were presented as either scrambled images (scrambled trial), where the face was distorted, or an unobstructed image of an angry face (fearful trial). Participants were instructed to identify the gender of the face to ensure vigilance without emotional processing during the task. Dynamic Causal Modeling (DCM) was used to estimate the effective connectivity between a priori regions believed to be implicated in fearful face processing in this task: the Bilateral Pulvinar, Amygdala, FFA, and mOFC.

Results: We compared models that differed by how stimuli drove regional activity and directionality between our predefined regions, defining the best fit model for each group separately prior to investigating group differences. We verified through Bayesian model selection that both groups were best fit by a model where scrambled faces drive the Bilateral Pulvinar and fearful faces drive both the Bilateral Pulvinar and Bilateral Amygdala. We then tested models with varying directionality of connections and found that both groups were best fit by a bidirectional model, in which all regions had reciprocal connections, rather than feedforward or feedback connections only. Using this best fit model for both groups, we tested the ability of these connections to predict group (either BDD or HC) using a logistic regression. We found using sequential feature selection that the highest model accuracy (as determined through using 10-fold cross-validation) was yielded by a model with two input connectivities: the connection from the Left Amygdala to the Left mOFC and the connection from the Right Amygdala to the Right Pulvinar. Notably, model accuracy was highest when both connectivities were inputted as features in a multivariate regression, rather than individually. These connections significantly predicted the participant group in the multivariate regression, although neither connectivity measure survived corrections for multiple comparisons. Correlations between connectivity estimates and BDD-YBOCS scores in the BDD group were not significant.

Conclusions: Our hypotheses were partially confirmed, as we found aberrant effective connectivity from the amygdala to the mOFC in the BDD group suggestive of enhanced limbic-prefrontal connectivity, although only for the left, not right hemisphere. We also observed reduced connectivity strength between the Right

Amygdala and Right Pulvinar in participants with BDD. Groups were best fit by the same structural connectivity model, with bidirectional connections between regions, suggesting that connectivity differences between groups may be a matter of degree, rather than kind. Further, exploratory prediction analyses revealed that multivariate combinations of connectivity patterns may distinguish groups better than individual connections. Our study may have been underpowered to detect group differences. Future research is needed to replicate these findings in a larger sample.

Keywords: Body Dysmorphic Disorder, Dynamic Causal Modeling, Fear Processing, Effective Connectivity

Disclosure: Nothing to disclose.

P416. Latino OCD: Strategies to Improve Equity in Psychiatric Genetic Studies

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Background: Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder of unknown etiology. Genome-wide association studies (GWAS) of psychiatric disorders have enabled the identification of variants related to psychiatric disorders and other relevant traits. GWAS of obsessive-compulsive disorder (OCD) have lagged other psychiatric disorders primarily due to small sample sizes. Recent efforts by the Psychiatric Genomics Consortium (PGC) OCD Working Group have substantially expanded the number of samples under analysis and now include ~46,500 diagnosed cases and over a million controls. Unfortunately, this sample is far from diverse, with 95% of cases being of European ancestry (EA). Incorporating non-European and mixed-ancestry populations in genetic analyses can help to identify genetic effects that generalize across populations, pinpoint causal genetic variants, and ascertain population-specific genetic variants. Despite the fact that admixed populations, such as Latin Americans, represent more than a third of the US population, they are markedly understudied in medical and psychiatric genetics. We sought to address diversify OCD genomics through a team science approach that would enable us to collect a large and diverse sample, and to perform careful genetic analyses.

Methods: The Latin American Trans-Ancestry Initiative for OCD genomics (LATINO) is a new network of investigators from across Latin America, the USA, and Canada, that aims to diversify OCD research by collecting a large, ancestrally-diverse and well-phenotyped sample of Latin American OCD cases for genomic analyses. Individuals with OCD and their relatives (ages 7-89 years) are being recruited from a network of specialist institutions/clinics across the US, Mexico, Canada, and Latin America. Extensive phenotypic analysis is performed by trained researchers and saliva is collected for DNA isolation and future genomic analysis. Our partners across the region are deploying diverse recruitment strategies tailored to their specific communities to implement the LATINO study and increase awareness on OCD.

Results: LATINO includes over 45 sites distributed across 13 countries, and has begun collection in a culturally sensitive and ethical manner. Recruitment is ongoing across the region and as of submission 732 subjects have already been recruited.

Conclusions: We hope that LATINO will strengthen research capacity in Latin America through virtual and in-person training activities, and improve our understanding of the diversity of OCD's clinical presentation across cultures.

Keywords: Obsessive Compulsive Disorder, Psychiatric Genetics, Diverse Populations, GWAS

Disclosure: Nothing to disclose.

P417. Examining the Role of Mitochondrial Genetic Variation in Obsessive-Compulsive Disorder

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Background: Obsessive-compulsive disorder (OCD) is a severe neuropsychiatric disorder, in which the genetic risk factors are not yet fully understood. Gene candidate and genome-wide association studies have mainly implicated serotonergic, dopaminergic and glutamatergic systems to be involved in OCD. However, there is currently a significant gap between the degree of genetic risk suggested by segregation studies, and the modest risk conveyed by identified common variants to date, suggesting that other genetic mechanisms of risk merit exploration. Mitochondria play important roles in sustaining complex high-energy requiring brain functions and therefore should be considered in the pathophysiology of neuropsychiatric disorders generally. It is therefore unsurprising that comorbidity between mitochondrial diseases and neuropsychiatric symptomatology has been reported Noteworthy, cases of OCD occurring in patients with primary mitochondrial disease were also reported. With regard to OCD, there has been limited exploration of the mitochondrial system to date. A few studies have suggested a role for excess of free radicals in the pathogenesis of the disorder. Here we tested the hypothesis that mitochondrial genetic variation is associated with OCD risk and related clinical phenotypes. In exploring the role of mitochondrial genetics, it is important to explore both the variation in mitochondrial DNA directly (mDNA), as well as nuclear-encoded mitochondrial genes. We therefore selected a set of nuclear-encoded mitochondrial genes that includes 12 genes that are OXPHOS subunits and 16 genes involved in oxidative stress, mitochondrial biogenesis, inflammation, and apoptosis to interrogate the nuclear (autosomal) genome. Additionally, we explored the 37 genes located in the mtDNA.

Methods: Here we first examined the association of a set of 59 mitochondrial genetic single nucleotide polymorphisms (SNPs) with OCD risk and with clinical phenotypes. These SNPs are located inside of 28 nuclear-encoded mitochondrial genes involved in oxidative phosphorylation, oxidative stress, mitochondrial biogenesis, inflammation, and apoptosis. We used logistic regression to test the association of the SNPs with OCD risk using sex as a covariate. We also tested for association with age at onset (AAO) and symptom severity using the Yale Brown Obsessive Compulsive Scale (YBOCS). To further examine mitochondrial genetic variation in OCD risk, we focused on the mitochondrial DNA (mtDNA), the circular genome located inside each mitochondrion. We extracted mtDNA genotypes from Illumina Human610-Quadv1_B SNP array for the Psychiatric Genomics Consortium (PGC) OCD working group (wave 1 data) for Toronto sample only. The 1000 Genomes European sample (N = 485) was used as control group. Next, replication was conducted using the PGC-OCD sample (N = 1693; remain sample after extraction of Toronto sample) and the Welcome Trust NBS sample (N = 2619) as used health controls. We used logistic regression to test the association

of the SNPs with OCD risk using sex as a covariate (both sexes were included). There were 64 mtDNA variants available for analysis in both datasets. Meta-analysis was used to compare data between discovery and replication mtDNA OCD datasets.

Results: For nuclear-encoded mitochondrial genes, we found a nominally significant association for rs4011457 in the NDUFS7 gene and OCD risk (N = 856, Puncorrected = 0.004) and for rs3820189 in the 5′ of the MFN2 gene with YBOCS total score (N = 346; Puncorrected = 0.002). We also performed a permutation-based statistical test of all 59 SNPs jointly and found a significant association with OCD risk (Pperm = 0.003). For mtDNA analysis, meta-analysis across the significant mtDNA variants shared between both samples revealed two SNPs significantly associated with OCD risk: NC_012920.1:m.1189T>C (P = 0.0004) and NC_012920.1:m.11914G>A (P = 0.0026) following multiple testing correction.

Conclusions: In conclusion, to the best of our knowledge, this is the first study to report associations of mitochondrial genetic variants in OCD. Our findings add evidence that mitochondrial variants in nuclear and mtDNA genes may influence OCD risk and clinical severity.

Keywords: Mitochondria, Mitochondrial DNA, OCD

Disclosure: Nothing to disclose.

P418. The Network Impact of DBS for Refractory OCD

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Background: Deep brain stimulation (DBS) is a treatment for severe, refractory obsessive compulsive disorder (OCD) that applies direct electrical stimulation to the anterior limb of the internal capsule (ALIC). To examine the difference between therapeutic and nontherapeutic DBS, we compared BOLD response when DBS was cycled ON and off in different DBS electrode contact configurations. We hypothesized that the optimal therapeutic targets for DBS would be strongly connected to and cause suppression in the areas most strongly implicated as components of the OCD cortico-striato-thalamo-cortical (CSTC) circuit: the anterior cingulate (ACC), caudate, and thalamus.

Methods: Subjects: Five subjects with severe, refractory OCD were implanted with an MRI-compatible Medtronic Percept DBS stimulator as part of clinical care. Quadripolar leads were implanted bilaterally within the ventral capsule/ventral striatum and bed nucleus of the stria terminalis. Three subjects were classified as treatment responders based on clinical response to DBS. Among responders, contact configurations were classified as therapeutic and nontherapeutic based on long-term clinical response.

MRI: MRI scans were acquired on a GE Discovery MR750 3 Tesla scanner. We collected T1-weighted structural scans and DWI pre- and post-implantation (55 direction HARDI, b-1000). Gradient-echo fMRI was acquired in low-SAR mode with a 32-channel head coil, TR/TE = 2s/30ms, voxel size = 3.75 × 3.75.4xm, flip angle = 86, FOV = 24 cm. For each 6-minute fMRI scan, we selected one of 12 bipolar contact configurations to deliver stimulation that was cycled ON/OFF for 1-minute blocks.

fMRI Processing: T1 and fMRI were preprocessed with fMRIprep, a standardized pipeline that combines tools from AFNI, ANTs, FreeSurfer, FSL, and Nipype. A T1w weighted patient space template was generated from intensity normalized, skullstripped and co-registered T1w anatomical scans, which was then registered to MNI template. BOLD runs were slice-time corrected and resampled back to their native space with head-motion correction, then registered and resampled to MNI space. ICA-AROMA was performed after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM. Components were manually reviewed by two expert raters, and those classified as noise by both raters were removed. Using AFNI, motion outliers (FD>0.2) and additional polynomial drift terms were removed, and ON-off contrasts were generated.

Electrode reconstruction and DWI processing: Diffusion-weighted scans were also preprocessed using QSIprep. MP-PCA denoising as implemented in MRtrix3's dwidenoise was applied with a 5-voxel window, then Gibbs unringing was performed using MRtrix3's mrdegibbs B1 field inhomogeneity was corrected using dwibiascorrect from MRtrix3 with the N4 algorithm. FSL's eddy was used for head motion correction and Eddy current correction. Shells were aligned post-eddy. Eddy's outlier replacement was run. The DWI time-series were resampled to ACPC, generating a preprocessed DWI run in ACPC space with 1mm isotropic voxels. Using Lead-DBS, a MATLAB toolbox for DBS electrode reconstruction and simulation of DBS stimulation, CT, T1 and DWI scans were co-registered and normalized using ANTs (CT-MRI) and SPM (MRI-MRI), after which DBS electrodes were reconstructed and manually localized. White matter tracts were reconstructed from diffusion imaging data using generalized q-sampling. The volume of activated tissue (VAT) was modeled for bipolar contact pairs, and the VAT was used as seeds to generate connectivity to parcels from Schaefer cortical and Melbourne subcortical atlases.

Results: We compared stimulation ON and off across subjects for contact pairs that had therapeutic (n = 6 runs, 3 subjects) vs nontherapeutic (n = 11 runs, 3 subjects) stimulation. In therapeutic compared to nontherapeutic configurations, DBS stimulation correlated with significant BOLD suppression ($p < 0.05$) in areas related to OCD, including the right orbitofrontal cortex, bilateral dorsomedial prefrontal cortex, and right thalamus. These suppressions were distant from the sites of the active electrode contacts. We also examined the relationship between DBS stimulation and canonical resting-state fMRI networks. Comparing stimulation ON vs off, we found a significant ($p < 0.05$) difference in BOLD signal change between therapeutic and all other contacts bilaterally in the default mode network, and in the control network in the right hemisphere. In the diffusion data, a significant percentage of streamlines seeded from therapeutic electrode VAT ROIs connected to areas of the default mode and limbic networks.

Conclusions: Our findings suggest that relief of OCD symptoms by DBS may be mediated by suppressions within the OCD network, as well as in the default mode network through structural connections to the network. This combination of stimulation-based fMRI and diffusion imaging approach to characterizing the impact of DBS on networks may provide a novel method for optimizing contact locations and parameters to treat severe OCD. We aim to explore these network-based changes as a potential biomarker and treatment target for therapeutic DBS stimulation in OCD.

Keywords: DBS, OCD, BOLD fMRI Signal, Default Mode Network (DMN)

Disclosure: Nothing to disclose.

P419. Cognitive Behavioral Therapy Effects in Cognitive Function in Adults With Hoarding Disorder: Behavior and Neuroimaging Data

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Background: Hoarding disorder (HD) has a prevalence of 2.5% of the general population, and it is characterized by difficulty parting with possessions, leading to clutter that congests living spaces and disruption of social, occupational, or other important areas of functioning. A large percentage (92%) of HD patients present signs of excessive acquisition. Acquisition is one of the first target symptoms in being treated, and it has been associated with information processing problems and compulsive behaviors that are associated with inhibitory control. There are no FDA-approved drugs to treat HD. However, cognitive behavioral therapy and the Buried in Treasures (BIT) workshop, a highly structured, short-term, skills-based group using CBT principles, have been shown to be promising to treat HD severity symptoms in discarding and acquiring. Different from cognitive behavioral therapy (CBT), the BIT workshop could be led by non-professional facilitators, making it accessible to those who can afford the cost of CBT. However, adding home uncluttering could enhance the benefits of BIT therapy. Further, to our knowledge, there are no neuroimaging analyses showing neural activity changes after any HD treatment.

Methods: Because participants struggle with home uncluttering, we used the BIT workshops, but also added in-home uncluttering sessions (BIT+) to augment BIT group sessions. In order to understand the effects of BIT+ in the cognitive network in HD patients, we scanned BIT+ participants prior and after ($n = 9$) the BIT+ sessions. Specifically, we scanned the participants while they performed a Go/No-Go task, a well-known task for measuring response inhibition to look at differences in inhibitory control. Neuroimaging data were acquired on a General Electric (GE) Discovery MR750 whole-body 3.0 Tesla MRI scanner (GE Healthcare, WI, USA) at the Stanford Lucas Center. Go trials (which displays the word "press" in green) requires subjects to respond as quickly as possible, while in the No-Go trials (which displays the word "press" in red) subjects have been instructed to withhold responses. 180 Go and 60 No-Go stimuli were presented in pseudorandom order; 500 ms each with an interstimulus interval of 750 ms.

Results: As a result, BIT+ participants showed to benefit more than waitlist controls on post-treatment reduced hoarding severity (Cohen's $d = 1.5$, $p < 0.001$). Participants also reported improvement reductions in their Saving Inventory–Revised scale (SI-R) total scores including in each subscale (clutter, difficulty discarding, and acquisition). We did not observe statistical differences after the BIT+ interventions in the performance of the Go/NoGo task or in the Neural activity in regions of the cognitive network, like the insula and the anterior cingulate cortex.

Conclusions: BITS+ showed to be a promising treatment to decrease the severity of hoarding symptoms, but did not impact the inhibitory control in HD patients or had significant effects in the cognitive control network activity.

Keywords: Hoarding Disorder, Inhibitory Control, Cognitive Control Network

Disclosure: Nothing to disclose.

P420. A Randomized, Controlled Trial of Psilocybin and Psychedelic Mushroom Extract in the Treatment of Obsessive Grooming and Self-Mutilation in SAPAP3 KO Mice

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Background: Synapse associated proteins (SAPAPs) are a family of proteins that are expressed in the brain and are highly concentrated in the postsynaptic density (PSD), an extensive complex of proteins associated with postsynaptic membranes of excitatory synapses. SAPAP3 proteins are postsynaptic excitatory proteins, localized at the postsynaptic density and are the only member of the SAPAP protein family that is highly expressed in the striatum, an area in which cortico-striatal synapses make up most of the glutamatergic synapses. SAPAP3 KO mice manifest a phenotype that resembles obsessive compulsive disorder (OCD) in humans. By the age of 4-6 months, homozygous SAPAP3 KO mice develop a unique phenotype that includes excessive self-grooming, self-injuries and formation of skin lesions on the snout, neck and head, and, in addition, head-body twitches. The phenotype worsens over time and is attenuated by chronic treatment with an SSRI e.g., fluoxetine. In humans the SAPAP3 gene is related to OCD spectrum behaviors, such as pathological grooming.

Methods: We have successfully established a SAPAP3 null KO breeding colony that is based on founders provided by Dr. G. Feng of MIT. The focus of the current project is on the effectiveness of psilocybin (PSIL) and psychedelic mushroom extract (PME) in alleviating the OCD-like behavioral phenotype of SAPAP3 null mice. The experiment is focused on the adult phenotype of SAPAP3 KO mice and is conducted as a clinical trial based on the individual phenotype of each mouse. Adult mice aged >6 months homozygous for the null mutation undergo a battery of behavioral tests before treatment (compulsive behavior, general activity, anxiety level and cognitive function) and documentation of self-grooming and head twitches over one hour by video with blind assessment by two observers. The homozygous mice are then randomly assigned to one of three treatment groups- Saline Vehicle (VEH), PSIL and PME - with a balanced ratio of males to females maintained between the treatment groups. PSIL is administered at a dose of 4.4 mg/kg i.p. and PME at the same psilocybin dose in mg/kg. Behavioral tests and documentation of self-grooming are repeated 48 hours and 12 days after treatment.

Results: Assessment prior to treatment showed significantly higher levels of total grooming ($p = 0.02$), short ($p = 0.02$) and long ($p = 0.009$) grooming bouts and body twitches ($p = 0.02$) in KO compared to wild type SAPAP3 mice. We conducted an interim assessment after 28 mice completed 12 days of treatment (VEH, $N = 8$; PSIL, $N = 10$; PME, $N = 10$). Analyses were conducted by analysis of variance with repeated measures followed by Sidak's test for multiple comparisons using Graphpad Prism. In mice treated with PSIL, total grooming over one hour was reduced by 7.2% 12 days after treatment as compared to VEH treatment 12 days after treatment in which total grooming was increased by 43.8% ($p = 0.009$, PSIL vs. VEH). In mice treated with PME, total grooming decreased by 14.7% ($p = 0.003$ vs. VEH). The primary contribution to the reduction in total grooming was a reduction in long grooming bouts which was significant for PSIL 48 hours after treatment ($p = 0.02$) and for both PSIL ($p = 0.03$) and PME ($p = 0.01$) 12 days after treatment. There were trends for short grooming bouts and head twitches to be reduced by both treatments but these did not reach statistical significance. A trend for PME effects to be slightly stronger than those of PSIL was also observed but did not approach statistical significance. It should be noted that 2 mice were withdrawn from the trial because they developed severe skin lesions. Last observations were carried forward in all analyses.

Conclusions: Even at a relatively early stage of this trial, interim results indicate a significant effect of chemical psilocybin and of psychedelic mushroom extract to reduce self-grooming, the key compulsive-like phenotype that is manifested by SAPAP3 KO mice. Our findings have important implications for the potential use of psilocybin and psychedelic mushroom extract to treat disorders with a similar phenotype in humans. Whether there are differences between the effect of psilocybin and psychedelic mushroom extract on the phenotype is a key question that awaits inclusion of additional mice in the trial. We are also gathering data on longer term effects by following up mice who have responded

to treatment and by crossing over non-responders 12 days after treatment to the alternate treatment. Furthermore, the mice in this study are undergoing pre- and post-treatment FDG-glucose PET and correlations of findings with treatment outcome will be examined.

Keywords: Psychedelic Effects, Psilocybin, Obsessive Compulsive Disorder

Disclosures: Back of the Yards Algae Sciences (BYAS): Founder (Self). ParowBio: Founder (Self).

P421. Synaptic Plasticity Via Receptor Tyrosine Kinase and G Protein-Coupled Receptor Crosstalk

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Background: Cognition and mood regulation are higher order functions of the brain that arise from the proper regulation of neuronal circuits and synaptic activity. Dysfunctional synaptic receptors binding neurotransmitters, such as glutamate, and neurotrophic growth factors, such as brain-derived neurotrophic factor (BDNF), have been associated with aberrant synaptic plasticity and neural circuits underlying psychopathology. Abnormal plasticity mediated by the metabotropic glutamate receptor 5 (mGluR5) is driven by accentuated mGluR5-mediated long-term depression (LTD), correlated with decreased dendritic growth and increased synapse loss. This leads to disruptions in learning, planning and execution of goal-directed activities, and mood regulation. Similarly ubiquitous as mGluR5, tropomyosin receptor kinase B (TrkB), the predominant CNS neurotrophin receptor that binds BDNF, promotes long-term potentiation (LTP), increasing dendritic growth and promoting synapse stabilization. Normalizing aberrant BDNF-TrkB signaling is believed to be critical for treatment strategies for neuropsychiatric diseases. Intriguingly, growing evidence has implicated functional interactions between the glutamate system and the neurotrophin system. While evidence exists that receptor tyrosine kinases (RTKs) can be indirectly regulated by GPCRs, it is unknown whether RTKs can potentiate or attenuate GPCR signaling. Given mGluR5 and TrkB's essential roles in synaptic plasticity, as well as their shared associations with neuropsychiatric disorders, we hypothesized that TrkB engages mGluR5 to augment a distinctive profile of intracellular signaling to mediate BDNF-induced potentiation in the hippocampus.

Methods: Using acute slice electrophysiology and primary neuronal cultures, we probe the functional and structural plasticity induced by BDNF. We primarily focus on a chemically induced form of LTP, known as BDNF-LTP, in which we perfuse recombinant BDNF protein onto an acute hippocampal slice and measure field excitatory postsynaptic potentials (fEPSP) within the CA3-CA1 synapse. We used specific pharmacological agents to inhibit and enhance activity of mGluR5 on acute hippocampal slices and primary neuronal cultures to assess BDNF-LTP and BDNF-induced spine density changes. We also injected AAV5-CamKII-mCherry-Cre into the dorsal CA1 of the hippocampus in mGluR5 FL/FL mice to mediate a region-specific genetic mGluR5 knockout to establish the necessity of TrkB/mGluR5 crosstalk to achieve LTP. We then performed a series of mutagenesis signaling studies of the two receptors in HEK 293 cells to pinpoint the mechanism of this signaling crosstalk. Finally, we use a series of G protein manipulations in acute slice electrophysiology, primary neurons, and HEK 293 cells to pinpoint the mechanism of the TrkB/mGluR5 crosstalk in modulating intracellular calcium signaling and hippocampal functional and structural synaptic plasticity.

Results: Through pharmacological ($n = 10$ mice/group, $p < 0.001$) and genetic manipulations of mGluR5 ($n = 6$-8/group, $p < 0.01$), we found that BDNF-TrkB-induced potentiation is dependent on mGluR5. This dependence of BDNF-TrkB-induced potentiation in acute hippocampal slices correlated with structural plasticity changes in spine density in primary neuronal cultures ($n = 40$-60 neurons/group, $p < 0.001$). We then show that BDNF-induced neuronal calcium response is diminished with pharmacological inhibition of mGluR5 ($n = 6$ neurons/group, $p < 0.001$) and enhanced with positive allosteric modulation of mGluR5 ($n = 6$ neurons/group, $p. < 0.05$). Similarly in HEK 293 cells, activation of TrkB by BDNF enhanced the constitutive mGluR5 activity in HEK 293 cells ($n = 10$-18/group, $p < 0.001$). When TrkB and mGluR5 are co-expressed, BDNF leads to a mode-switch to a sustained, oscillatory calcium signaling, characteristic of mGluR5-mediated calcium signaling. Positive allosteric modulation of mGluR5 also led to an enhancement in BDNF-induced oscillatory calcium signaling ($n = 6$/group, $p < 0.001$) as well as enhanced MAPK activation ($n = 7$ preps/group). Finally, through pharmacological and genetic manipulations in HEK 293 cells, primary neurons, and acute hippocampal slice electrophysiology, we show that this TrkB-mGluR5 crosstalk is mediated by synergy between the G-beta-gamma subunit released by TrkB and the Gq-GTP released by mGluR5. This BDNF-mediated crosstalk between these two ubiquitous synaptic proteins highlights physiologically relevant RTK/GPCR crosstalk that has been previously uncharacterized.

Conclusions: We have identified a novel mode of RTK/GPCR crosstalk, with a specific focus on understanding BDNF-induced TrkB/mGluR5 crosstalk in the hippocampus. Our findings support a new synergistic model, in which activation of both an RTK and a GPCR drives non-linear signal summation to shape the long-term consequences of receptor activation. Both mGluR5 and TrkB-mediated signaling have been shown to have broad clinical relevance. Enhanced mGluR-induced LTD as well insufficient BDNF-TrkB-induced LTP have been both shown to be underlying negative mood and cognitive processes seen across the lifespan, such as in depression, autism spectrum disorders, and Alzheimer's disease. Our study defines this important interplay between these two systems, which is crucial to understanding mechanisms of how pharmacological agents can be designed to work in concert with one another to produce maximal therapeutic benefits.

Keywords: Synaptic Plasticity, Neurotrophins, GPCR, Calcium Imaging, Receptor Tyrosine Kinase

Disclosure: Nothing to disclose.

P422. Sex-Specific Mechanisms Underlie Plasticity at Hippocampus-Nucleus Accumbens Synapses

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Background: The ability to make associations between contextual information and rewards are key for guiding motivated behaviors, while disruptions in reward drive as well as learning and memory are commonly observed in psychiatric disorders like depression or substance use disorders. Our previous work demonstrated that the regulation of the strength of hippocampus-nucleus accumbens synapses (Hipp-NAc) is critical mediator of reward related behaviors. Long-term potentiation (LTP) of Hipp-NAc synapses induced by high frequency stimulation (HFS) in vivo induces conditioned place preference in the absence of an extrinsic rewarding stimulus, suggesting that potentiation of these

synapses is intrinsically rewarding and mediates contextually-based reward-related behaviors. Given the important role of Hipp-NAc synapses in influencing motivated behavior, we sought to identify the molecular mechanisms underlying plasticity at this synapse in male and female mice.

Methods: We used whole-cell electrophysiology to record from medium spiny neurons in the NAc while stimulating hippocampal terminals in ex vivo brain slices. Slices were taken from male and female D1dr-tdtomato mice allowing us to differentiate between D1- and D2-expressing neurons. We used pharmacological blockade to interfere with molecules implicated in LTP induction and expression. Vehicle treated slices were used as controls.

Results: When comparing excitatory synaptic strength, we found that the strength of Hipp-NAc synapses is similar between males and females ($n = 10$-13; $p>0.05$). Further, we found that LTP in response to HFS occurs at a similar magnitude in both sexes ($n = 14,9$; $p>0.05$). The locus of this plasticity appears to be postsynaptic ($p>0.05$) in both sexes, however the molecular mechanisms underlying LTP differ between males and females. While LTP in males requires N-methyl-D-aspartate (NMDA) receptors ($n = 14,11$; $p = 0.0127$), LTP in females is NMDA receptor independent ($n = 9,12$; $p>0.05$), and instead utilizes a mechanism dependent on postsynaptic voltage gated calcium channel activity.

Conclusions: Our results reveal that while the strength of Hipp-NAc synapses is similar between males and females, the mechanisms by which synaptic strength is regulated differs between the sexes. This presents an interesting convergent mechanism for regulating plasticity in males and females and a potentially useful target for understanding sex differences in motivated behavior and related disorders.

Keywords: Synaptic Plasticity, Sex-Specific Effects, Excitatory Synapses

Disclosure: Nothing to disclose.

P423. Investigating the Relationship Between Hippocampus/Dentate Gyrus Volume and Hypothalamus Metabolism in Participants With Major Depressive Disorder

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Background: Reduced hippocampal volume has been reported in major depressive disorder (MDD), potentially due to glucocorticoids from overactivation of the hypothalamus-pituitary-adrenal (HPA) axis. Extended exposure to glucocorticoids causes dendritic retraction in the hippocampus, a reversible form of volume loss that causes the hippocampus to be vulnerable to cell death.1 Further, an animal model of an anxiety/depressive-like state suggests that cortisol hampers proliferation of progenitor cells in the hippocampus.2 Partially supporting this glucocorticoid hypothesis, patients with depression report a higher rate of stressful life events3 and long-term stress is associated with volume loss in the hippocampus.4 To examine this in humans, hippocampal volume and hypothalamus (HPA axis) activity was quantified in participants with MDD before and after antidepressant treatment. As females with MDD have been shown to exhibit higher levels of HPA hyperactivity and greater incidences of hypercortisolism, sex differences were also investigated.

Methods: 65 participants ($n = 24$ males, $n = 41$ females) with MDD were treated in a double-blind, randomized clinical trial of escitalopram. Participants received simultaneous positron emission tomography (PET) / magnetic resonance imaging (MRI) before and after treatment. For the MRI, a magnetization-prepared rapid gradient-echo (MP-RAGE) T1-weighted structural image was acquired with voxel size $= 0.87 \times 0.87 \times 0.87$ mm. Freesurfer was used to extract whole hippocampus and dentate gyrus volume from MRI. Metabolic rate of glucose uptake in the hypothalamus was quantified from dynamic 18F-fluorodeoxyglucose (FDG)-PET images collected for 60 min. Frames were corrected for motion and co-registered to MRI. Regions delineated on the MRI were transferred to the PET images through the co-registration. The Patlak graphical approach was used to estimate metabolic rate of glucose uptake (MRGlu) from the time activity curve while correcting for blood glucose and the lumped constant, using Simultaneous Estimation and a single venous sample, as previously described.5 The 17-item Hamilton Depression Rating Scale (HDRS-17) was administered in proximity to imaging. Remission was defined a priori as post-treatment HDRS-17 less than or equal to 7. Linear mixed models were utilized to examine the relationship between hippocampus/dentate gyrus volume and hypothalamus metabolism. Chi-squared tests and multivariable logistic regression examined the association between hippocampus/dentate gyrus volume change and hypothalamus activity change direction with treatment. Multiple linear regression was used to compare these changes between remitter and non-remitter groups. Covariates included age, sex and treatment type.

Results: No significant linear association was found between hippocampus/dentate gyrus volume and hypothalamus metabolism. 62% (38 of 61) of participants experienced a decrease in hypothalamus metabolism while 43% (27 of 63) of participants demonstrated an increase in hippocampus volume (51% [32 of 63] for the dentate gyrus) following treatment. Although participants with decreased hypothalamus metabolism were more likely to experience an increase in hippocampus/dentate gyrus volume, the odds were not statistically significant (hippocampus: odds ratio [OR] $= 1.87>1$, 95% confidence interval [CI]: [0.6, 5.9], p-value $= 0.28$; dentate gyrus: OR $= 1.12>1$, 95% CI: [0.4, 3.6], p-value $= 0.85$). No significant association was found between change in hypothalamus activity and change in hippocampus/dentate gyrus volume with treatment, and this association did not vary by sex, medication or remission status.

Conclusions: No statistically significant association was found between hypothalamus metabolism and hippocampus/dentate gyrus volume; therefore, the complexity of treatment-induced hippocampal volume changes likely requires examination of a more comprehensive circuitry of anatomy. Interestingly, however, no sex differences were found in these relationships suggesting that at least the relationship between hypothalamus activity and hippocampus volume does not underlie sex-effects in this system.

Keywords: Major Depressive Disorder, MRI, PET

Disclosure: Nothing to disclose.

P424. A 14-Week, Randomized, Placebo-Controlled Cross-Over Study of Multilayer Release Methylphenidate in Adult ADHD With and Without Anxiety Disorder Comorbidity

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Background: Adult Attention-deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder which is highly comorbid, with 85% of patients having at least one psychiatric comorbidity, and 60% having at least two [1]. Common comorbid conditions include anxiety and mood disorders and substance use disorders [2]. The presence of anxiety comorbidity in adult ADHD

has been associated with more global impairment, poorer outcome, greater resistance to treatment and increased costs of illness [3]. Although stimulant medications are effective first-line ADHD treatments, the bulk of treatment literature has examined populations without comorbidity. The literature is equivocal on the effects of stimulants on comorbid anxiety symptoms, with some studies indicating a worsening of anxiety symptoms and more recent studies showing either a negligible or beneficial effect [4]. It has been reported that individuals who have ADHD with a comorbid disorder may have more severe ADHD symptoms and may respond differently than individuals without comorbidity [5]. Despite these potential differences in response, no study has directly compared populations with and without comorbidity. This study aims to address these gaps in the literature. The results in this abstract are preliminary and will be presented in full when the poster is presented.

Methods: A 2-site, 14-week, double-blind, placebo controlled, flexible-dose (25-100mg/day), cross-over evaluation of multilayer release methylphenidate (MLR-MPH) in the treatment of moderate DSM-5 Adult ADHD with and without anxiety disorder comorbidity. Comorbid anxiety disorders included Panic disorder, Agoraphobia, Generalized Anxiety Disorder or Social Anxiety Disorder. Following a 1-week placebo run-in, consenting, eligible participants were randomized to MLR-MPH or placebo (PBO); the dose was titrated to the maximally tolerated dose over 4 weeks and maintained for 2 more weeks (Phase I); a 1-week PBO cross-over occurred at week 7; participants were then switched to the other condition for 6 weeks (Phase II). Primary efficacy was change from baseline on the clinician-rated ADHD Rating Scale (ADHD-RS). Secondary outcome measures included clinician-rated Clinical Global Impression – Severity and Improvement Scales (CGI-S, CGI-I), Hamilton Anxiety Rating Scale (HAM-A), as well as a battery of self-rated scales measuring ADHD severity, anxiety disorder and depression symptom severity, functional impairment and deficits in executive functioning. Response was defined as a ≥ 30% drop in ADHD-5-RS plus a CGI-I score of ≤ 2.

Results: In total, 66 participants were enrolled, 57 were completers and 61were included in the LOCF analyses. The mean age was 31.8 ± 9.9; 55.7% female; 49.2% had anxiety disorder comorbidity. The mean dose at endpoint in both Phase I and II was 100 mg/day. At Phase I baseline, the mean ADHD-RS score was 41.02 ± 7.8 (severe) and the mean CGI-S score was 5.49 ± 1.2 (moderate-severe). There were no significant differences in ADHD-RS or CGI-S severity between the comorbid and non-comorbid groups. The mean HAM-A score was significantly higher in the comorbid group ($p = .01$) but was considered mild 12.5 ± 4.0. Paired sample analyses revealed significant improvement in both MLR-MPH groups when compared to PBO, ($p < .01$). Effect sizes were moderate: Cohen's $D = 0.46$ for Phase I and Cohen's $D = 0.59$ for Phase II. In addition, the proportion of responders in the MLR-MPH group was significantly greater than those in the placebo group in both Phase I (24.2% vs. 0%; $\chi2$ 7.8, $df = 1$ $p = .005$) and Phase II (38.5% vs.3.3%, $\chi2$ 10.9, $df = 1$ $p < .001$). No significant differences were found between those with and without comorbidity on change scores from Phase 1 baseline to end of Phase 1 or between Phase 2 baseline to the end of Phase 2, on either primary or secondary outcomes. No serious adverse events were reported. Adverse events associated with MLR-MPH were decreased appetite (7.8% vs. 0% PBO), insomnia (6.9% vs. 5.0% PBO), nasal congestion (4.9% vs. 0% PBO), headache (2.9% vs. 12.5% PBO, $p < .05$) and dry mouth (3.9% vs. 10% PBO).

Conclusions: In the first study to compare ADHD with and without anxiety comorbidity, our results suggest that there are no differences in rates of response to ADHD treatment with MLR-MPH. Contrary to some reports in the literature, comorbidity did not lead to differences in ADHD treatment outcome. This is an important finding, given the high rates of ADHD and anxiety disorder comorbidity and that this population has been excluded from most clinical trials.

Keywords: ADHD, Anxiety Disorders, Comorbidity, Psychostimulant, Clinical Trial

Disclosures: Abbvie, Bausch Health, Biogen, Biron, Boehringer Ingelheim, Elvium, Jazz, Vistagen: Advisory Board (Self). Abbvie, Elvium, Lundbeck, Otsuka, Pfizer, Sunovion, Takeda: Speakers Bureau (Self). Elvium, Canadian Institute for Health Research, Michael G. DeGroote Centre for Medicinal Cannabis Research: Grant (Self). Otsuka, Biohaven, Clairvoyant: Contracted Research (Self).UpToDate: Honoraria (Self).

P425. Early Clinical Development of a Deuterated N,N-Dimethyltryptamine (DMT) Analog for the Treatment of Mental Health Conditions

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Background: N,N-dimethyltryptamine (DMT) is a naturally occurring psychedelic and the main active ingredient of ayahuasca. Studies have shown that DMT/ayahuasca can improve various mental health outcomes. DMT is a potent agonist at the serotonin 5-HT2A receptor, through which it exerts many of its subjective and potentially therapeutic effects. As DMT is not orally active, it is administered via intravenous (IV), intramuscular (IM), or inhaled routes. DMT's effects are evident within seconds to minutes but dissipate rapidly as it is quickly metabolised by monoamine oxidase. Consequently, an optimal parenteral dosing regimen and pharmacokinetic/pharmacodynamic (PK/PD) relationship for DMT has not been accurately characterised, which limits the ability to generate large scale clinical data on the therapeutic utility of DMT.

Selective deuteration has been shown to decrease metabolism, reduce pharmacokinetic variability and improve bioavailability. This could improve the PK profile of DMT while maintaining its desired PD effects. Cybin is developing CYB004, a deuterated analog of DMT and has designed and conducted a series of clinical studies (CYB004E Parts A, B, and C) that have explored the PK, PD, and safety of DMT and CYB004.

Methods: Part A: CYB004E Part A was a randomised, double-blind, placebo-controlled, single ascending dose study of DMT to evaluate the safety, PK and PD of a 90-minute infusion of DMT in healthy smokers at dose levels of 0.12 mg/kg, 18.2, 36.4, and 72.8 mg DMT hemifumarate.

Part B: CYB004E Part B evaluated DMT IV as a bolus over 5 min followed by an infusion over 55 min, in an open label, fixed order, 2-way crossover rising dose design in healthy non-smokers. The duration of infusion was selected to optimise the time of on-target effects. The infusion scheme selected for the first dosing period (18.2 mg in 5 min + 44.5 mg in 55 min IV) was expected to provide a mean steady state DMT concentration of approximately 40 ng/mL, a concentration level that was reported previously in the literature to be associated with robust psychedelic effects. Doses for the second treatment period (18.2 mg in 5 min + 71.2 mg in 55 min IV) were selected based on safety, PK and PD data from the first dosing period.

Part C: Based on data from Parts A and B, Part C was designed as a first-in-human dosing of deuterated DMT (CYB004) in healthy volunteers. Part C, cohort 1 ($n = 12$), a double-blind, randomized, crossover study is evaluating IV dosing regimens (5 min bolus ± 30 min infusion) that result in a rapid onset of psychedelic effects that are sustainable for 60 minutes and achieve mean

steady state plasma DMT concentrations between 40-60 ng/mL. A shorter infusion, compared with Part B, was selected based on PK and PD profile of CYB004 predicted using animal data.

Cohort 2 (n = 12) will be performed if subjects do not achieve either a minimal median Cmax of 60 ng/ml, or if subjects did not achieve a persistent subjective psychedelic experience of moderate to intense intensity in cohort 1. Part C is currently ongoing and will be completed in the coming months and a full set of data from Parts A, B, and C will be presented at the ACNP meeting.

Results: Part A: 38 participants were recruited across 4 cohorts. DMT was well tolerated; all adverse events (AEs) were mild and self-limiting. Transient increases in blood pressure were noted at doses ≥ 36.4 mg. Statistically significant effects ($p < 0.0001$) were only observed at the highest dose (72.8 mg) on the Mystical Experiences Questionnaire-30 (MEQ-30) total score, visual analogue scale (VAS) feeling high, hallucinogen rating scale (HRS) subscales cognition, intensity, perception and somaesthesia. No relevant effects were noted on measures of smoking. Plasma concentrations of DMT increased in a dose proportional manner, albeit with high variability. When compared with published data, higher maximum plasma concentrations were observed (mean ± SD of 81.5 ± 34.3 ng/mL at 72.8 mg), although, psychedelic effects remained moderate. We concluded that not only the peak concentrations, but also the rate at which Cmax is attained, contributes to the psychedelic effects. Based on this we decided to explore IV bolus, followed by infusion in Part B.

Part B: 10 healthy non-smokers were enrolled in Part B. In period 1, all AEs were mild and self-limiting. Transient increases in blood pressure and heart rate were noted. Intense psychedelic effects were reported by subjects during the 5-minute bolus, changing to moderate intensity during the infusion. Median plasma Cmax was 37.7 ng/mL with a median Tmax at 5 min, while AUClast values ranged from 1006 to 2763 min*ng/mL. In period 2, AEs and effects on blood pressure and heart rate were similar to those seen in period 1. Median plasma Cmax was 55.1 ng/mL with a median Tmax at 48 min, while AUClast values ranged from 1602 to 3762 min*ng/mL. Psychedelic effects were similar in intensity to period 1, during the 5-minute bolus but more intense and longer lasting during the 55-minute infusion. In general, psychedelic effects in Part B were more intense compared to Part A.

Conclusions: Escalating doses of DMT were well tolerated with high variability in plasma levels. Robust psychedelic effects were produced and were related to the rate at which Cmax was achieved. A bolus + infusion dosing regimen may provide sustained therapeutically relevant psychedelic effects over an extended period.

Keywords: DMT, Dimethyltryptamine, Psychedelics, Pharmacokinetics

Disclosure: Cybin IRL Limited: Employee (Self).

P426. Standards for Designing Optimal Outcomes Strategies for Drug Development – Survey on the Challenges in Neurosciences

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Background: Despite major advances in neuroscience, clinical trials for neurological and psychiatric conditions continue to have notoriously high failure rates. The use of innovative clinical outcome assessments (COA) grounded in translational research is key to maximize the likelihood of identifying promising new treatments in early phase clinical trials and discarding compounds that do not warrant further development efforts. However, the field has lacked standardized best practice guidelines for optimal selection of COAs for early trials in neuroscience drug development. The Outcomes Research Working Group was established to develop a consensus-based outcomes decision- making process.

Methods: A review of existing methods was conducted including analysis of completed projects on core outcomes sets (COS) in several disciplines. Existing standards were considered and tailored to neurosciences field applicable to interventional trials. This setting of the process guided the consensus-based development of a standard process for COA selection for early interventional neuroscience trials. An open-ended survey questionnaire then was distributed to the Group members to solicit feedback on potential risks associated with not following the standard process and the potential impact on drug development and marketing of new drugs. The responses were categorized and tabulated, providing risk assessment considerations for end-users.

Results: A 7-Step process was established by the diverse stakeholders in the Group to facilitate optimal outcomes selection, covering activities for evidence generation supporting the content validity of patient-centred outcomes, validity requirements and considerations for regulatory acceptance. The 7-Steps are: (S1) Description of the disease impact model and therapeutic background, (S2) Definition of the scope of use for the COS/Outcomes, (S3) Decision on stakeholder involvement, (S4) Determine "What to Measure" in terms of domains/ concepts of interest, (S5) Determine "How to Measure" the outcomes, (S6) Make final generic recommendations for optimal COS measurement in the specific program, (S7) Draw final conclusions concerning gap analysis and future steps in the therapeutic field.

Surveys results showed that the risks considered relevant by for each step, and indicated strong alignment among experts in neuroscience clinical trial design that all seven steps are necessary. They also revealed several risks associated with reducing the seven-step processes. Most frequently reported concerns related to missing or inaccuracy on the standard process were; for S1 If a disease impact model is not provided, the user may "miss relevant information about the disease" and additional issues related to the inadequacy of measuring outcomes" may arise. S2 to set the scope for the use of the outcomes is critical, otherwise there is the risk of distorting the final application of the study results in several ways. e.g., outcomes for clinical practice might not be suitable for clinical trials being developed or not using appropriate instruments for the stage of the disease. S3 In many cases, missing stakeholders were reported to negatively impact the final approval/authorization, reimbursement, or drug access to the country market. S4 If this step is missed; the most critical concepts/domains of the disease may not be evaluated. S5 The lack of a comprehensive analysis of measurement instruments quality, involves the risk of using instruments that are poorly sensitive to changes in clinical response or using instruments that do not meet technical or regulatory requirements for outcomes assessment. S6 and S7 are key to avoid repletion of past assessment errors and for providing strong evidence supporting the choice of endpoints, and an understanding of how the results translate to benefits for patients. Overall, the output from this Working Group found alignment regarding recognition of risks to outcomes development. The multiple viewpoints provided are valuable for consideration for early-phase neuroscience trial development.

Conclusions: The 7-Step standard method for setting COAs strategy is a key reference for any type of research in neuroscience that aims to prove the efficacy and safety of new interventions. Each step accounts for generating evidence useful to the different

levels of the value chain for COA strategy in the development of a new drug. The 7-Step process must take place before COAs are implemented in a PoC/ph2 or pivotal trial. COAs in neurosciences offers particular value for their potential to prove the mechanism of action of new drugs i.e., cognitive functioning.

A full understanding of the standard COA decision process can empower trial designers to mitigate the risks of failure, thereby increasing the likelihood of success in the development of new treatments for neuroscience conditions. This method provides a consensus-based approach for clinical outcomes selection to maximize the efficiency of clinical research and is now available to researchers in industry and academia.

Keywords: Outcomes, Patient Reported Outcomes, Novel Endpoints, Innovative Methods, Translating Innovation

Disclosures: Sanofi: Consultant (Self). Neuropsychological Research Organization s.l (Neuropsynchro): Owner (Self).

P427. Kappa and Mu Opioid Receptors in the Paraventricular Thalamus Reveal Enigmatic Roles in Assimilation, Integration, and Processing of Aversive and Rewarding CNS Signals

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Background: Kappa opioid receptors (KOPr) encode the dysphoric component of stress and are involved in stress-and reward-related psychopathologies, such as depression and substance abuse. The paraventricular thalamus (PVT) is believed to integrate stress- and reward-related information and, therefore, may be a pivotal node in developing these maladaptive behaviours. We investigated PVT KOPr on 3 levels: postsynaptically, presynaptically, and within network effects. Postsynaptic: we determined KOPr distribution (i) within the PVT, (ii) between sexes, and (iii) co-expression with mu opioid receptors (MOPr). KOPr effects on presynaptic neurotransmitter release were inferred from KOPr-induced effects on excitatory and inhibitory postsynaptic currents (EPSCs; IPSCs). Thirdly, the PVT is a well-connected node with a major output to nucleus accumbens (NAc). PVT-NAc pathway has a dual role in reward- and aversive-related behaviour, and we studied KOPr and MOPr on PVT-NAc neurons.

Methods: Young C57BL/6J mice (20 male; 25 female) were used. Brains were removed under anaesthesia and coronally sectioned in 300μm slices in warm aCSF saturated with 95% O2/ 5% CO2. Slices containing PVT were equilibrated at 32°C for 30 min before recording. Anatomical locations were determined by Paxinos and Watson Brain Atlas.

Whole-cell voltage-clamp recordings were made of PVT neurons using electrodes of 4-6 MΩ. For postsynaptic currents, neurons were clamped at -60mV and perfused with KOPr agonist spiradoline (30 μM), KOPr antagonist norBNI (1 μM), mu opioid receptor (MOPr) agonist met enkephalin (10 μM), and MOPr antagonist CTAP (1 μM).

Presynaptic recordings: slices were perfused with KOPr agonist dynorphin-A (1-13) (10 μM) and norBNI (1 μM). EPSCs were measured after clamping the neuron at -60mV in the presence picrotoxin (100 μM). IPSCs were recorded at a holding potential of 0mV.

KOPr and MOPr expression on PVT neuronal projections were recorded after inter-NAc injection of Lumafluor retrobeads. Postsynaptic opioid currents were measured in retrobead positive PVT neurons using the postsynaptic protocol above.

Current amplitudes compared across anatomical locations by 1-way ANOVA. Co-expression of KOPr and MOPr analysed by Chi-square test. EPSC and IPSC effects analysed by repeated measures (rm) ANOVA for baseline, agonist effects, and antagonist reversal. Data shown as mean±SEM; significance $p < .05$ (two-tailed).

Results: In 40 postsynaptic KOPr recordings, 29 neurons responded to spiradoline (30 μM) by producing a G protein-gated inwardly rectifying K+ (GIRK)-mediated current of 14.1 ± 1.8pA. KOPr currents changed across anterior-posterior axis of PVT ($F(2,26) = 3.7$, $p = 0.039$) ($n = 4$-13 per group) with smaller currents in medial PVT versus more anterior regions (mean difference±SEM) (8.95 ± 3.46pA, $p = 0.040$). There were no differences between sexes ($p = 0.67$) ($n = 13$-16 per group).

In 29 neurons perfused with KOPr and MOPr agonists, 95% of neurons showing a KOPr agonist response also exhibited a MOPr agonist current ($\chi 2 = 30.7$, $df = 3$, $p < 0.0001$) indicating these neurons functionally co-express both opioid receptor subtypes. KOPr response was smaller than MOPr response (1-sample t-test of %KOPr current of MOPr current against 100%: $t = 8.9$, $df = 19$, $p < 0.0001$) ($n = 20$).

In 8 recordings studying effects of KOPrs on glutamatergic nerve terminals, EPSCs were modulated by KOPr agonists ($F(2,7) = 7.40$, $p = 0.016$): dynorphin-A (1-13) decreased frequency of EPSCs by 45.6 ± 6.0% ($t = 7.56$, $p = 0.0003$) ($n = 8$). GABAergic IPSCs on inhibitory synapses were also modulated by KOPr agonists ($F(2,6) = 8.05$, $p = 0.023$): dynorphin-A (1-13) reduced IPSC frequency by 46.4 ± 6.9% ($t = 3.19$, $p = 0.037$) ($n = 7$).

Postsynaptic recordings of PVT neurons containing retrogradely transported fluorescent beads from the NAc found 7/7 neurons produced KOPr currents and 10/10 neurons produced MOPr currents.

Conclusions: Although it is now recognized that the PVT integrates stress and reward-related information, the mechanisms responsible have not been elucidated. KOPrs and MOPrs produce opposing functions in emotional valence with KOPrs mediating aversion and MOPrs mediating reward. We show that: (i) KOPr currents differ across the anterior-posterior axis of PVT, with smaller currents in medial versus anterior regions, (ii) most PVT neurons co-express both KOPrs and MOPrs and both induce hyperpolarising currents. The major neuronal output from PVT is to the NAc, and this pathway drives both aversive and rewarding behaviours. Our findings add further evidence pointing to the pivotal role of the PVT in serving as a "collection, sorting, and distribution centre" for positive and negative emotional processing. We hypothesise that the PVT receives positive and negative emotional signals, integrates these inputs, and distributes them to the appropriate centres within the mesocorticolimbic system for emotional processing where they are functionally consolidated into stress- and reward-related responses. Finally, the observation that KOPrs are strategically located on excitatory and inhibitory presynaptic nerve terminals in the PVT, where they inhibit glutamate and GABA release, indicates the involvement of excitatory and inhibitory signalling pathways in KOPr's mechanism of action.

Keywords: Opioid Receptors, Single-Unit Electrophysiology Ex Vivo, Paraventricular Nucleus of the Thalamus, Reward and Aversion, GPCRs

Disclosure: Nothing to disclose.

P428. Common and Distinct Effects of Incentives on Spatial Working Memory in Schizophrenia and Obsessive-Compulsive Disorder

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Background: Patients with schizophrenia (SCZ) and patients with obsessive-compulsive disorder (OCD) share symptomatology, including motivational and cognitive impairments, suggesting common and distinct associated mechanisms. We analyzed data from SCZ, OCD and typical adults (TA) who performed an incentivized spatial working memory (sWM) task.

Methods: Three groups (SCZ ($N = 27$, $M = 21/F = 6$), OCD ($N = 39$, $M = 18/F = 21$), TA ($N = 34$, $M = 21/F = 13$)) completed an incentivized sWM task during 3T-scanning. Participants kept spatial locations in mind, and also won/lost money depending on sWM performance. Incentives were cued at each trial or presented in a non-cued, contextual manner. Behavioral data examined angular accuracy. Preliminary neuroimaging analyses are presented.

Results: Patients with SCZ had worse baseline sWM performance than patients with OCD and TA (interaction, $p < 0.001$; pairwise, $p < 0.005$), with no difference between OCD and TA. Cued incentives improved sWM in all groups ($p < 0.005$) but there was no interaction between cued incentive sWM performance and group. There was a significant group x non-cued incentive interaction ($p < 0.05$) for sWM performance, with TA showing improved sWM performance during non-cued gain ($p < 0.001$) and loss ($p < 0.05$), and SCZ showing improved sWM performance during non-cued loss only ($p < 0.01$). Patients with OCD demonstrated a trend towards improved sWM performance during non-cued loss ($p = 0.06$). Whole-brain neuroimaging results demonstrated a significant group x sWM interaction (fwep < 0.05, 5,000 permutations) in fronto-parietal regions, with relatively lower BOLD signal during sWM in SCZ, compared to OCD and TA. Compared to TA, OCD had similar prefrontal, but greater parietal, sWM BOLD signal changes. There was a significant group x cued incentivized sWM interaction (fwep < 0.05, 5,000 permutations) in the right dorsolateral prefrontal cortex. In this area, TA had relatively decreased BOLD signal during the cued incentivized conditions, compared to the neutral sWM condition, while OCD and SCZ had similar BOLD signaling across the neutral and cued incentivized sWM conditions. No significant regions were identified for the group x non-cued incentivized sWM interaction.

Conclusions: Patients with SCZ, patients with OCD, and TA demonstrated shared and distinct incentive effects on sWM. Preliminary fMRI data analysis suggests SCZ has lower, while OCD has similar, or higher, sWM activation in fronto-parietal regions, compared to TA. During cued incentivized sWM conditions, patient groups demonstrated a relative lack of BOLD signal deactivation, compared to the TA group in the dorsolateral prefrontal cortex.

Keywords: Working Memory, fMRI, Reward, Schizophrenia, OCD

Disclosure: Nothing to disclose.

P429. The Effects of Oxytocin on Altruistic Cooperation and its Neural Correlates Depend on Childhood Trauma

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Background: Monetary donations to social charities represent a form of altruistic cooperation by which humans show their willingness sacrifice his or her own resources to a stranger in need without receiving anything in return. Only recently has neuroscience begun to dissect the biological components of altruistic cooperation and identified oxytocin (OXT), an evolutionarily conserved peptide signaling pathway originating in the mammalian hypothalamus, to be a key modulator. These insights could be gained because intranasally administered OXT penetrates the brain and alters measures of neural and behavioral response. Seminal studies have shown that exogenous (intranasal) administration of synthetic OXT induces subtle changes in social behaviors; these alterations have often been described as tendencies toward increased sociality, including trust, empathy, and altruism. The prosocial profile of OXT is further enhanced by findings from neuroimaging studies reporting that OXT consistently targets reward-related and fear-related neurocircuits. However, given that OXT-effects are highly sensitive to situational factors and individual personality traits, the peptide does not exclusively promote prosocial behaviors and may interact with contextual- and person-dependent variables. While the effects of OXT on altruistic cooperation have been characterized in behavioral experiments, the neural correlates of altruistic cooperation and their neurobiological basis have been neither precisely understood nor systematically researched.

Methods: In this study we used ultra-high-field (7 Tesla) functional magnetic resonance imaging (fMRI) in a double-blind, randomized, parallel-group trial design to explore the behavioral and neuronal effects of OXT on altruistic donations in 54 healthy male participants. A 7-T whole-body MRI research system (Siemens Healthineers) with a 32-channel head array coil (32Rx/1Tx; Nova Medical) was used to obtain T2*-weighted whole-brain images with blood oxygen level-dependent contrast at 1.7-mm isotopic resolution using an accelerated 3D echo planar imaging sequence. Prior to participating in an established altruistic donation task during the fMRI session, which included 60 authentic case vignettes of strangers in need, subjects received a single nasal dose (24 IU) of synthetic OXT or placebo (PLC). Based on the effect size obtained in our recent OXT dose-response study, we used G*Power to conduct an a priori power analysis for the present project. The study was approved by the Institutional Review Board of the Medical Faculty of the University Hospital Bonn and was conducted in accordance with the Declaration of Helsinki.

Results: The analyses of the behavioral data showed that among individuals with higher scores in childhood trauma (CTQ), those who received OXT donated more money in an altruistic donation task as compared to those who received PLC (OXT: 15.68 EUR ± 10.13; PLC: 8.22 EUR ± 4.62; $t(23) = -2.50$, $p = 0.02$). Among individuals with lower CTQ scores, those who received OXT donated less money than those in the PLC group (OXT: 9.45 EUR ± 6.63; PLC: 20 EUR ± 8.14; $t(27) = -3.70$, $p = 0.001$). Under PLC, the amount donated by CTQ low scorers was more than twice as high as in the amount donated by CTQ high scorers. The analyses of the imaging data revealed functional connectivity between medial prefrontal cortex (mPFC) and the middle cingulate (midCing) region during altruistic donations in which the interacting effects of CTQ and OXT on altruistic donations are reflected in a mirrored effect on functional connectivity between mPFC and a middle cingulate region cluster: under OXT, donations increase, and connectivity decreases with CTQ($R2 = 0.17$, $F(1,25) = 5.01$, $p = 0.003$); while under placebo, donations decrease, and connectivity increases with CTQ ($R2 = 0.28$, $F(1,24) = 9.39$, $p = 0.005$).

Conclusions: This is the first neuroimaging study which explored the neurobiological basis of altruistic cooperation using 7-Tesla fMRI. We found that the effect of OXT on altruistic donations and the functional connectivity between mPFC and midCing is CTQ-dependent. While OXT leads individuals with higher scores in CTQ to donate more money to strangers in need, there was no such effect in those subjects scoring low in CTQ. On a neural level, we found that connectivity increases with CTQ under PLC, but decreases with CTQ under OXT. Taken together, these findings suggest that the connectivity between mPFC and midCing could be associated with inhibiting altruistic behavior in

those individuals with higher childhood trauma. This inhibition is disrupted/reversed under higher concentrations of OXT.

Keywords: Oxytocin, Altruism, Childhood Trauma, 7T fMRI

Disclosure: Nothing to disclose.

P430. The Neural Correlates of Maternal Empathy to Their Children's Emotions - Effects of History of Childhood Emotional Abuse

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Background: Childhood emotional abuse can have far-reaching adverse health effects. In particular, mothers who have experienced adversity such as childhood maltreatment have significant difficulties with parenting. While the literature has largely examined the effects of childhood emotional abuse on parenting using self-report and observational measures, the literature on how maternal neural response in parenting is influenced by mothers' childhood emotional abuse is sparse. The few existing studies have, however, suggested atypical neural activity (both heightened and dampened) when viewing images of their children or hearing their own versus other infant cries among at-risk mothers. The present study examines associations between maternal experiences of childhood emotional abuse and neural responses during a functional magnetic resonance imaging (fMRI) task, namely Child Face Mirroring Task (CFMT), designed to tap into maternal empathy regarding child emotions, a critical aspect of sensitive parenting toward healthy child development.

Methods: In this study, 14 low-income, trauma-exposed mothers (mean age 26 years), who were enrolled during pregnancy in an ongoing longitudinal study on psychosocial risks and parenting, participated in a follow-up lab visit when their children were 5 years old. These mothers underwent CFMT fMRI scanning, during which they were shown pictures of their own and unknown children displaying four emotional expressions (neutral, ambiguous, distressful, and joyful), presented consecutively in a pseudo-random order (4 seconds each picture, 16 seconds per block, 4 blocks per task for each of the Own and Other Child). Mothers were instructed before each block to either "join" (i.e., empathize with and imitate the child's emotions) or "observe" (i.e., observe as unresponsively as possible, trying not to generate any emotion). For this study, the Join-Own-Child > Observe-Own-Child differential responses during CFMT were regressed against severity of maternal childhood emotional abuse (based on the Childhood Trauma Questionnaire). For the main effect of Join-Own-Child > Observe-Own-Child, the whole brain search with cluster-level family-wise correction for multiple comparison was conducted. For associations with maternal childhood emotional abuse history, the threshold for interpretable results was set at $p = 0.005$ uncorrected, masked by functional brain networks based on a priori brain model of parent-child interactions.

Results: For the main effect of Join-Own-Child > Observe-Own-Child, participants on average activated the supplemental motor area (SMA) and right pericentral gyrus (pCG). For associations with maternal childhood emotional abuse scores, participants with higher levels of childhood emotional abuse showed greater Join-Own-Child vs Observe-Own-Child differential responses in the SMA, but not the right pCG, that were implicated in the main effect. In addition, the dorsomedial prefrontal cortex (dmPFC), periaqueductal gray (PAG), middle cingulate cortex (MCC), left temporal poles (TP), and right inferior temporal gyrus (ITG) were also associated with maternal childhood emotional abuse scores. Based on the meta-analytical database (Neurosynth.org), the right pCG, which was not influenced by the emotional abuse history, is typically involved in imitation. Meanwhile, those areas that were influenced by emotional abuse history are typically involved in top-down belief-based mentalization (SMA and dmPFC), pain (PAG and MCC), and autobiographical memory retrieval (TP and ITG).

Conclusions: These results suggest that a history of childhood emotional abuse does not affect maternal Join-Own-Child > Observe-Own-Child responses in the imitation-related right pericentral gyrus, which implies that the sensorimotor responses elicited by the imitation per se were not sensitive to a history of emotional abuse. However, the results also suggested that maternal childhood emotional abuse does influence brain regions underlying belief-based mentalization (dmPFC), which has been found to mediate over-mentalization (explaining away a child's behaviors or feelings based on each mother's own prior model of her child) in our previously published studies. Thus, maternal history of emotional abuse may influence maternal parenting as if it had "colored" maternal perception and understanding of her child with top-down child-oriented beliefs that may have come from automatic retrieval of maternal autographic memory and emotional pain. According to our established prior work, such top-down influences may increase maternal risks of impaired understanding of her child's actual intentions, feelings, and behaviors and disrupt maternal sensitivity. Thus, these results provide evidence to explain symptoms that are commonly found in mothers who are affected by childhood emotional abuse. Understandings of these neural correlates of observed incoherent and contradictory parenting among maltreated mothers may contribute to an allied literature on parenting brain and behavior to optimize psychotherapy treatments and improve mother-child health.

Keywords: Maternal Brain, Child Abuse and Neglect, Emotional Empathy, Functional MRI (fMRI), Maternal Mental Health

Disclosure: Nothing to disclose.

P431. Amygdalo-Orbital Interactions Coordinate Memory Formation in the Orbitofrontal Cortex

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Background: The orbitofrontal cortex (OFC) is a large frontal cortical brain region essential for goal-directed decision making (i.e., making choices based on outcome expectations). Distinct OFC neuron populations become active when mice trained to respond for food encounter unexpected nonreinforcement. These cells are necessary for mice to later adjust their food-seeking strategies; thus, they form memory traces (MTs) for adaptive action. In the current study, we interrogate afferent projections to the OFC that may be necessary for these reward MTs.

Methods: We utilized Fos2A-iCreER ("TRAP2") mutant mice to gain genetic access to activity-defined neuron populations. First, we induced Gi- or Gq-coupled designer receptors exclusively activated by designer drugs (DREADDs) in OFC neurons that were active when reward contingencies changed and assessed their ability to control later goal-seeking behavior. Next, we used retrogradely transported viral vector strategies to label soma in regions projecting to the OFC that were active during the encoding of new reward information. The outcomes led us to lastly use combinatorial viral vector techniques to interrogate the functional role of the basolateral amygdala (BLA) in MT formation. Throughout this project, data were compared using ANOVA, and post-hoc comparisons followed interaction effects. Both sexes were used.

Results: OFC neurons active following new reward information are necessary and sufficient to coordinate later flexible goal-directed behavior. A large population of neurons in the BLA that project to the OFC are active during the encoding of new reward information, suggesting that they may contribute to MT formation. Indeed, MT formation in the OFC requires concurrent excitatory plasticity within the BLA, enabling later adaptive choice.

Conclusions: BLA-OFC connections are necessary for the encoding of new reward information within the OFC, which is retained in the OFC and utilized during later choice behavior. Defining the contribution of OFC neuron populations and their afferent projections to distinct behaviors will advance our understanding of the region's contribution to goal-directed action and improve future efforts to map functionally relevant connections.

Keywords: Decision Making, Orbitofrontal Cortex (OFC), Basolateral Amygdala

Disclosure: Nothing to disclose.

P432. Dopamine Mediates Exploration Via Decision Noise and Encodes State-Based Learning

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Background: In an uncertain world, we must balance two goals: exploiting rewarding options when they are available and exploring potential better alternatives. Since the goal of exploration is information seeking and the goal of exploitation is reward-maximizing, the reward learning during these two states should be different. A key neuromodulatory system that is well positioned to modulate reward learning and exploration is dopamine. Dopamine projection to the ventral striatum is proposed to encode reward prediction error (RPE), which facilitates reward learning. Dopaminergic activities in the striatum have been implicated in mediating exploitative and repetitive behaviors. Past research has also implicated tonic dopamine in modulating exploration. Here, to examine how dopamine modulate exploration, we first pharmacologically up- and down-regulated dopamine receptor activity with a nonselective DA receptor antagonist (flupenthixol) and a nonselective DA receptor agonist (apomorphine) while mice ran a restless bandit task, which encourages balance between exploration and exploitation, and examined how the manipulation affected the level of exploration. Then we measured in vivo dopamine transmission in the nucleus accumbens during the restless bandit task using dLight 1.3b, which is a biosensor for dopamine and identified distinct dopamine signatures associated with reward learning during exploration and exploitation.

Methods: Wildtype mice ($n = 22$, 11 per sex) were trained to perform a spatial restless two-arm bandit task in the touch-screen operant chambers. Mice indicated their choices by nose poking at one of two target locations (left or right). Each location was associated with some probability of reward, which changed independently and unpredictably across trials. The dynamic reward contingencies naturally encouraged the constant transition between exploitation and exploration. In the first experiment, to manipulate dopamine receptor activity, mice received systemic administration of apomorphine (0.1mg/kg)/flupenthixol (0.03mg/kg) or saline (control) before the behavioral task on alternating sessions using a within-subject counterbalance design. In the second experiment, to examine real-time changes in dopamine while the animal performed the task, we used a dopamine sensor, dLight 1.3b, which emits fluorescent signals in response to binding with dopamine. Then we implanted an optic fiber in the nucleus accumbens core (NAcc) to record in vivo dopamine dynamics. We fit a hidden Markov model (HMM) to infer latent exploration and exploitation state from choices. This allowed us to infer whether a trial was exploratory or exploitative on a trial-by-trial basis. We examined how dopamine manipulation influenced the frequency of exploratory choices and the distinct pattern of dopamine transmission during exploration.

Results: We observed a bidirectional modulatory effect of dopamine receptor activity on the level of exploration. When animals were administered apomorphine, we found that animals on average had fewer exploratory trials than when they were on vehicle control, with $55.5\% \pm 12.6\%$ STD of trials labeled as exploratory on apomorphine and $72.3\% \pm 13.6\%$ STD of trials labeled as exploratory on vehicle (GLMM, main effect of drug, $p < 0.0001$, $\beta 1 = 0.174$). In contrast, when decreasing dopamine receptor activity with flupenthixol administration, animals explored more compared to vehicle control, with $58.2\% \pm 12.0\%$ STD of trials being exploratory on flupenthixol and $52.1\% \pm 12.3\%$ STD of trials being exploratory on vehicle control (GLMM, main effect of drug, 0.002, $\beta 1 = -0.062$).

Reward learning was elevated during the exploration state - animals were more likely to stay with the same choice if rewarded and switch if not rewarded during exploration (Figure 1D, main effect of state, $p < 0.0007$; state x outcome, $p = 0.05$), indicating elevated reward learning during exploration. Consistent with behavioral results, we also found a more pronounced dopamine response to both rewarded and non-rewarded cues in the nucleus accumbens during exploration. Dopamine responses were more pronounced to both rewarded and non-rewarded cues during exploration, quantified by the area under the curve (AUC) (2-way ANOVA, outcome x state, $p = 0.0002$; post-hoc t-test, no reward: $p = 0.003$, reward: $p = 0.009$) and peak of the traces (2-way ANOVA, outcome x state, $p = 0.0002$). This result suggests that exploration is a state of elevated learning characterized by more positive dopamine response to reward cue and more negative dopamine response to no reward cue, compared to dopamine response to outcome during exploitation.

Conclusions: In two experiments, we used a combination of pharmacological manipulation, in vivo neural recording and computational models to examine the role of dopamine in modulating exploration. We found a bidirectional modulatory effect of dopamine on exploration: increasing dopamine receptor activity decreased exploratory choices and decreasing dopamine receptor activity increased exploratory choices. With neural recording, we discovered elevated reward learning encoded by dopamine signals during exploration, suggested by the more pronounced dopamine transmission in response to rewarded and non-rewarded cues during the exploration state. Together these results provide neural evidence of explore/exploit state-based learning and identity neuromodulatory systems that mediate exploration.

Keywords: Exploration, Dopamine, Reward Learning, Exploration-Exploitation Tradeoff

Disclosure: Nothing to disclose.

P433. Altered Priors Over Goal-Directed Features and Test-Retest Performance Adults Typed for Autism, ADHD and Depression

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Background: Rigid patterns of behavior exhibited in autism spectrum disorders often manifests as difficulty in generalizing and adapting previous knowledge to a novel context. Heterogeneity along the autism spectrum suggests there are multiple potential drivers of behavioral rigidity. Furthermore, these drivers may also relate to ASD's high comorbidity with attention-deficit hyperactivity disorder (ADHD) and depression. However, we lack a rigorous understanding of cognitive generalization in autism, how that manifests heterogeneously across the spectrum and how it relates to transdiagnostic overlap with conditions such as ADHD or depression. In part this gap arises from our incomplete understanding of how humans in general (both with and without ASD / ADHD / depression) categorize and generalize stimuli and situations.

Methods: We paired commonly used clinical trait questionnaires with newly-developed reinforcement learning tasks to investigate the use of attention during latent-state learning. In addition to self-report of diagnoses, diagnostic rating scales were administered to independently assess symptoms. The tasks investigate how context information drives learning and generalization, based on a new computational model of the cognitive processes driving subject behavior. We pre-registered hypotheses regarding the initial test and retest. Subjects (N = 462 reporting ASD, N = 528 denying ASD) were recruited through Prolific to complete the trait questionnaires. We then recruited a set of those subjects to participate in the tasks (N = 342 reporting ASD, N = 399 denying ASD). A subset of those subjects (N = 256 reporting ASD, N = 328 denying ASD) returned to perform a retest at 4-6 weeks. We then clustered subjects according to:

- Performance. The overall proportion of errors.
- Attention. The bias in their errors towards features with high discriminative informativeness.
- Memory. The difference in proportion of errors between states learned initially and those learned later.

We characterized the clusters according to their reported diagnoses (ASD, ADHD and depression), as well as their trait questionnaire responses.

Results: Our primary pre-registered hypotheses fully replicated:

- Subpopulations that showed error patterns consistent with a prior over features that were goal-directed during initial learning were low in traits for depression, autism spectrum disorder (ASD) behavioral rigidity, and attention deficit hyperactivity disorder (ADHD) inattention.
- A goal-directed attention bias in errors better correlated with ASD trait responses than reported ASD diagnosis.
- At retest, subjects with high trait scores for ADHD inattention and "problems with self-concept" performed worse than the initial test.
- At retest, subjects with high trait scores for ASD rigidity and "pragmatic language" performed better than the initial test, and shifted to a more goal-oriented attention strategy.

Two hypotheses that were based on small initial samples failed to replicate, but failed replication in interesting ways.

- The pre-registered hypothesis was: subpopulation with a choice bias such that there are significantly more errors on the initially learned states, and that these states are confused with each other (forgetting), will be high in ADHD inattention traits and lower in ASD rigidity traits relative to subjects whose errors occur more for recently-learned states, and that these states are confused with each other (anchoring). Instead, we found that subjects who anchored were high in both ASD rigidity and ADHD inattention.
- The pre-registered hypothesis was: A subpopulation with high clinical-trait comorbidity will show error patterns indicating a learning of state representations, but a forgetting of the associated actions. Instead, we found the subjects with that error pattern were high in ASD rigidity traits and reported depression diagnosis, but low in ADHD inattention traits and low in reports of depressive symptoms.

Conclusions: We found ASD rigidity traits were associated with holistic learning of state features, and interacted with ADHD inattention traits to modulate retest behavior. Our results suggest that behavioral rigidity is linked to reduced goal-directed attention priors and improved memory. Comorbid inattention traits reduce the propensity to shift strategies. These results are highly relevant for transdiagnostic insights on ASD, ADHD and depression, as well as specific cognitive mechanisms associated with behavioral rigidity in ASD.

Keywords: Autism and Depression, Attention Deficit Hyperactivity Disorder, Learning and Memory, Behavioral Tasks

Disclosure: Nothing to disclose.

P434. Sex Differences in the Impact of Early Life Adversity on Spatial Memory and Hippocampal Cholinergic Signaling in Rats

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Background: Early life adversity (ELA), including neglect, and stressful situations that exceed a tolerable threshold, has consistently been linked to an increased risk of psychiatric disorders later in life. Individuals with mental illness have impaired cognitive function in addition to emotional and social problems. ELA has an effect on hippocampus neurogenesis and dendritic arborization, and these negative changes may have a long-term influence on mnemonic functions. Here, we examined the impact of ELA on spatial working memory and reference memory in adulthood. Given the neuromodulatory role of acetylcholine (ACh) in regulating hippocampal function, we also assessed the effects of ELA on cholinergic transmission in adult rats.

Methods: This study utilized a limited-bedding and nesting (LBN) model of adversity in rat pups (PND2-9) for ELA as described earlier (Ordones Sanchez et al., 2021). The control pups were raised in standard housing conditions. Young-adult male and female rats (2-4 mo) from control (N = 11) and LBN (N = 12) conditions were tested for spatial working memory using the Y-Maze spontaneous alternation test. Reference memory was assessed two weeks following working memory testing. All trials were recorded using the GoPro recording system and then processed videos were analyzed with Panlab SMART video-tracking software. Following behavioral testing, biosensor-based electrochemical recordings were conducted to assess changes in cholinergic transmission in the dorsal hippocampus.

Results: Data from spatial memory test show a comparable alternation index between the control and ELA animals ($p = .83$). Moreover, splitting the data by sex did not reveal any significant differences on this measure between males and females ($p = .33$). However, sex differences in motor behavior were observed with females exhibiting more arm entries ($F1,19 = 13.22$; $p = .002$) and triplets ($F1,19 = 33.04$; $p < .001$) as compared to the males. Assessment of spatial reference memory revealed a sex x manipulation interaction ($F1,19 = 4.53$; $p = .04$) with deficits in time spent in novel arm for male ELA rats as compared to male controls. This trend was not observed in the females. Overall, no correlation was observed between the two memory measures i.e., alternation index and time spent in novel arm ($r = .03$; $p = .93$). The magnitude of depolarization-evoked ACh release remained comparable between male ELA vs control rats ($p = .68$). However, nicotine-evoked cholinergic signal amplitudes were blunted in ELA males ($0.52 \pm 0.17\mu M$ vs $1.72 \pm .42\mu M$ in control males; $p = .09$).

Conclusions: Although the spatial working memory was neither impacted by the ELA manipulation nor the sex of the animal, an interaction between the two factors in the reference memory test illustrate a heightened susceptibility of ELA to long-term memory deficits in male rats. Because reference memory is dependent on the medial temporal lobe, these functional deficits may involve long-lasting detrimental impact of ELA on hippocampal information processing dynamics. This interpretation also parallels with perturbations in nicotinic cholinergic signaling dynamics observed in male ELA rats. These data together with lack of association between spatial working and reference memory observed in our study may indicate that the detrimental effects of ELA in males may occur in domain-specific neural circuits.

Keywords: Early Life Adversity, Hippocampus, Memory, Cholinergic, Sex Differences

Disclosure: Nothing to disclose.

P435. Longitudinal Assessment of Social Support and Suicidal Ideation and Behavior During the COVID-19 Pandemic Among Brazilian Healthcare Workers

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Background: During the COVID-19 pandemic, several stressors may have increased the risk of suicidal ideation and behavior in Health Care Workers (HCWs). Some studies have reported the importance of social support as a protective factor against suicidal ideation and behavior outcomes in the last decades, but fewer studies have explored its role in HCWs. We aim to investigate the association between social support and suicidal ideation and behavior during the COVID-19 pandemic among Brazilian HCWs.

Methods: This study utilizes data from 10,885 participants who answered the first (time point 1 - between May and June 2020) and the second (time point 2 - between December 2020 and February 2021) assessments of an online, repeated, cross-sectional survey for evaluating the mental health and quality of life of HCWs during the COVID-19 pandemic in Brazil. Social Support was measured by the scores of the Medical Outcomes Study Social Support Survey (MOS-SSS) (overall social support). The question that evaluates social support is, "How often is each of the following kinds of support available to you if you need it?". Support includes emotional and informational support, tangible support, affectionate support, and positive social interaction. Each of the items has a 5-point Likert response (from 0 = "never" to 4 = "always"). Suicidal ideation and behavior assessments were based on the following questions, respectively: "I thought about killing myself, in some moment within the last month" (ideation) and "I tried to kill myself, in some moment within the last month" (behavior). Potential answers for these questions included: "1: strongly disagree; 2: moderately disagree; 3: disagree; 4: neither agree nor disagree; 5: agree; 6: moderately agree; 7: strongly agree. We considered any response from 2: moderately disagree to 7: strongly agree, as a positive answer for the outcome, that is, a presence of suicidal ideation or behavior at the time of the assessment, to be over-inclusive. Logistic regression analysis investigated the relationship between social support as the independent variable (time point 1) and suicidal ideation and behavior as the outcomes (time point 2).

Results: Higher social support was associated with a significantly lower chance of reporting suicidal ideation or behavior in the month preceding assessment, which was taken 6 to 9 months from the baseline (adjusted odds ratio [AOR]: 0.71, CI 95% 0.66 - 0.76 and AOR 0.61, CI 95% 0.54 - 0.68, respectively). These associations were independent of sex, age, a feeling of loneliness, and self-reported psychiatric disorders. The dichotomization of the outcomes using different criteria (considering any response from 5: agree to 7: strongly agree, as a positive answer for the outcome) did not change the main results; that is, higher social support remained significantly associated with a lower chance of presenting suicidal ideation and behavior.

Conclusions: Social support is associated with a lower chance of suicidal ideation and behavior among healthcare workers, a protective role that is probably more evident for suicidal behavior. These findings suggest that evidence-based and scalable strategies to strengthen social support among Brazilian HCWs should be a target for public health system policies.

Keywords: Suicide, Social Support, COVID-19 Pandemic

Disclosure: Nothing to disclose.

P436. Biomarkers of Symptom Improvement Following Treatment With Cariprazine

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Background: Identification of biological factors associated with improvement in symptoms during treatment with psychiatric medications is valuable for tailoring therapies to patients. We are utilizing patient data from two Phase 3 randomized, placebo-controlled studies of adjunctive cariprazine in major depressive disorder (MDD) to identify predictive biomarkers associated with the change in symptoms from baseline following 6 weeks of treatment. Cariprazine is a dopamine D3-preferring D2/D3 receptor partial agonist and serotonin 5-HT1A receptor partial agonist that is approved for the treatment of schizophrenia, bipolar mania, bipolar depression, and as an adjunctive therapy to antidepressants for MDD.

Methods: DNA was collected from participants in two adjunctive cariprazine studies for the treatment of MDD (NCT03738215, NCT03739203). DNA was genotyped using a customized combination of Illumina's Infinium™ Global Screening Array, along with 30K variants from the PsychArray that included markers previously implicated in several psychiatric disorders. Standard quality control and preprocessing were performed for directly genotyped markers, including sample filtering for missing genotypes, sex mismatches, and related pairs, and variant filtering for low-quality or monomorphic variants and those not conforming to the Hardy Weinberg Equilibrium expectations. For each study, two Genome-Wide Association Studies (GWAS1 and GWAS2) were performed independently in patients treated with cariprazine 1.5 mg QD or 3 mg QD (GWAS1: N = 298; GWAS2: N = 340) and those administered placebo (GWAS1: N = 152; GWAS2: N = 164) using linear regression, with sex and the first five principal components as covariates. Genetic association to treatment response was defined using two quantitative phenotypes: 1) percent change from baseline to week 6 in Montgomery–Åsberg Depression Rating Scale (MADRS) total score and 2) percent change from baseline to week 6 in Hamilton Anxiety Rating Scale (HAM-A) total score. Meta-analysis of GWAS results across the two studies was performed for both phenotypes in the cariprazine arm and placebo arm, using Genome-Wide Association Meta-Analysis (GWAMA) software with a fixed-effects model.

Targeted gene-level analysis was carried out by aggregating p-values from individual GWAS summary statistics using MAGMA.

Results: GWAS analysis within each study did not detect any single nucleotide polymorphisms (SNPs) surpassing genome-wide significance ($p < 5 \times 10\text{-}8$) for percent change in MADRS or percent change in HAM-A in either the cariprazine or placebo arms. In addition, GWAS meta-analysis across the two studies did not identify any SNPs surpassing genome-wide significance for percent change in MADRS or percent change in HAM-A. At the suggestive threshold of $p < 10\text{-}5$, SNPs mapping to sodium-potassium transporter ATPase interacting 4 (NKAIN4) were associated with percent change in MADRS in the cariprazine arm (rs111734334; $p = 8.04$ e-7; $\beta = 2.22$), and several SNPs mapping to glutamyl-prolyl-tRNA synthetase 1 (EPRS) and kynureninase (KYNU) were associated with percent change in MADRS in the placebo arm (EPRS rs3767669; $p = 4.69$ e-7; $\beta = -23.107853$/ KYNU rs10207390; $p = 3.05$ e-7; $\beta = -12.15032$). Furthermore, targeted gene-level analysis in GWAS2 confirmed a significant association of choline transporter-like protein 5 (SLC44A5) with percent change in HAM-A in the placebo arm (adjusted $p < 0.05$) and a nominal association with percent change in MADRS (adjusted $p < 0.1$) in the placebo arm.

Conclusions: Improvement in clinical symptoms in patients with MDD may be influenced by genetic variation. We found suggestive associations with disease-relevant genes in our GWAS analyses. Additional analyses of genetic data from cariprazine clinical studies in patients with schizophrenia and bipolar I disorder, and incorporating other types of clinical study data (e.g., baseline clinical scale scores, demographic data) are expected to refine our understanding of predictive biomarkers of symptom improvement in psychiatric patients.

Keywords: Adjunctive Cariprazine, Biomarker Analysis, Genetic Variation, GWAS, Major Depressive Disorder

Disclosure: AbbVie: Employee (Self).

P437. Multivariate Genome-Wide Analysis of Aging-Related Traits Identifies Novel Loci and New Drug Targets for Healthy Aging

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Background: Aging is a complex trait that extends beyond extreme longevity; however, the shared genetic architecture underlying complementary aging-traits is unknown.

Methods: Using data from ~1.9 million participants across 5 longevity-related traits (extreme longevity, lifespan, healthspan, frailty, and epigenetic age acceleration), and employing multivariate GWAS methods leveraging genetic correlation among these traits to increase statistical power beyond conventional single-trait analyses, we construct a multivariate aging-related phenotype modeling the shared genetic architecture of these traits. We then perform extensive bio-annotation and drug-target Mendelian randomization analyses to prioritize therapeutic targets for healthy aging. We also evaluate the impact of psychiatric and substance use behaviors to disentangle potential causal pathways through which those with psychiatric disorders are at risk for shorter lifespans and generally less-healthy aging.

Results: We identified 52 independent single nucleotide polymorphisms (SNPs) in 38 genomic loci. 20 novel SNPs that have not been previously reported in previous longevity-related analyses, including rs268, an exonic SNP in the lipoprotein lipase (LPL) locus. Mendelian randomization (MR) analysis highlighted several risk factors, including apolipoprotein B (Beta = -0.0399, 95% CI, -0.0469, -0.0329, P-value = 6.26x10-29), blood pressure and liver function, as important modulators of aging. Drug-target MR with gene targets of lipid-lowering and antihypertensive therapies suggested inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) (Beta = 0.0409, 95% CI, 0.0242, 0.0576, P-value = 1.62x10-6), angiopoietin-like protein 4 (ANGPTL4) (Beta = 0.0654, 95% CI, 0.031, 0.100, P-value = 2.36x10-4), beta blockers (Beta = 0.00488, 95% CI. 0.0027, 0.00707, P-value = 1.21x10-5), and calcium channel blockers (Beta = 0.00445, 95% CI, 0.00233, 0.00657, P-value = 3.71x10-5), have a beneficial impact on our multivariate aging endpoint. Finally, cis-instrument MR of circulating proteins identified additional novel anti-aging targets such as Colony Stimulating Factor 1 (CSF-1) (Beta = -0.0132, 95% CI, -0.0202, -0.0061, P-value = 2.67x10-4), Matrix Metallopeptidase 1 (MMP-1) (Beta = -0.00335, 95% CI, -0.00489, -0.00291, P-value = 4.5x10-6), and Interleukin 6 Receptor Subunit Alpha (IL6-RA) (Beta = 0.004373, 95% CI, 0.00349, 0.00525, P-value = 4.64x10-22). Single variable MR identified adverse relationships of major depression, and binge drinking, while multivariable MR highlighted an independent effect of smoking, suggesting that the impact of major psychiatric disorders on healthy aging is mediated by comorbid substance use behaviors.

Conclusions: This study will inform future studies for potential therapeutics aimed at improving human aging.

Keywords: Aging, Substance Use, Drug Targets

Disclosure: Nothing to disclose.

P438. nnSVG for the Identification of Spatially Variable Genes and Improved Computational Analyses of Spatial Transcriptomic Data From Postmortem Brain Tissue

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Background: Spatial transcriptomics platforms enable full-transcriptome analyses of gene expression within tissue samples at spatial resolution. Computational analysis workflows for these complex data include steps such as feature selection to identify biologically informative genes and clustering to identify tissue regions corresponding to cell types or spatial domains. While initial analyses have re-used computational methods developed for single-cell RNA sequencing data, new statistical methods that take the spatial coordinates of the measurements into account enable more powerful and robust analyses.

Methods: We have developed a new method, nnSVG, to identify genes with spatially defined patterns of expression that are associated with biological structures of interest, referred to as spatially variable genes, within spatial transcriptomic datasets. The method is based on recent advances in spatial statistical methodology using nearest-neighbor Gaussian process models, which allow fitting statistical models with flexible length scale parameters characterizing the spatial expression patterns per gene, and provide linear computational scalability with the number of spatial coordinates. The method outperforms existing methods as well as baseline methods that do not take spatial coordinates into account, and can be applied to large datasets consisting of thousands of spatial measurement locations per tissue sample, such as from the 10x Genomics Visium platform.

Results: Here, we demonstrate the application of nnSVG for analyses of spatial transcriptomic data from postmortem brain tissue samples from human donors and mice, in brain regions including the locus coeruleus and hippocampus. The method enables improved analyses, including the identification of sets of biologically informative genes in the locus coeruleus and

surrounding region, the identification of genes with spatial gradients of expression within tissue regions, and more precise downstream clustering analyses to delineate biological structures such as known hippocampal layers. We provide freely accessible code and example datasets for our analyses, which can be used to reproduce our analyses and adapt the workflows to new datasets.

Conclusions: nnSVG is freely available as an R software package through the Bioconductor project at https://bioconductor.org/packages/nnSVG. The package includes extensive documentation and tutorials, and is integrated into the Bioconductor framework to facilitate its use within analysis workflows.

Keywords: Spatial Transcriptomics, Statistical Methods, Computational Methods, Software, Postmortem Brain Tissue

Disclosure: Nothing to disclose.

P439. Polygenic Signatures of Medication Prioritization Using Deep Learning: An Analysis of the Spark Autism Study

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Background: Despite the broad availability of FDA-approved drugs for neuropsychiatric indications, psychiatrists often grapple with a paucity of a priori information useful for predicting the optimal first prescription among competing alternatives. This challenge has prompted a growing interest in leveraging genomic information for personalizing treatment. Currently available commercial options for pharmacogenetics typically focus on a restricted set of metabolic or mechanism-of-action genes, despite recent research suggesting that a more integrative genome-wide approach to genetic variation might yield more accurate treatment response predictions. This is analogous to the computing of polygenic scores, which integrates information across the genome to predict individual risk for complex traits and disorders. To address the need for new lines of information useful for prioritizing among FDA-approved options, our study introduces a novel deep learning model that integrates genomic, transcriptomic, and drug perturbation data for improved treatment prioritization.

Methods: Our study utilizes data from 3,321 participants of the SPARK study, a comprehensive autism project offering extensive genotype and Child Behavior Checklist (CBCL) data. The deep neural network (DNN) architecture, grounded in deep neural archetypal analysis, takes the matrix product of imputed brain transcriptomes and drug perturbation profiles as input features. During training, the $k = 50$ archetypes are learned that best represent the diversity of drug response profiles in the sample. These archetypal coefficients are then passed through a decoder network that reconstructs participants' behavior (CBCL), polygenic scores for psychiatric and cognitive traits, as well as the original imputed brain transcriptomes. The model also includes a novel "plausibility loss" that encourages solutions that reflect current drug-indication pairings, while still leaving the model enough latitude to uncover potential new indications for FDA-approved drugs. model predicts individualized behaviors and polygenic scores for major neuropsychiatric conditions. Its unique training process incorporates multiple domain loss functions to constrain the model, ensuring that drugs are largely recommended for their approved indications, while also accommodating for exploration of novel therapeutic applications.

Results: Out-of-sample predictions showed that the trained model, which only uses genomic data as input, successfully recommended simulants to those with behavioral and genetic indices of ADHD, and antidepressants to those with behavioral and genetic indices of depressive symptoms. In addition, potential new applications for approved drugs such as clemastine were uncovered.

Conclusions: This deep learning approach marks a significant advancement in precision psychiatry by utilizing individualized genetic, transcriptomic, and drug data to predict behaviors and therapeutic interventions for neuropsychiatric disorders. Future work will assess the value of incorporating rare variant information into the training process.

Keywords: Deep Learning, Drug Repurposing, Autism

Disclosure: Nothing to disclose.

P440. A Sex-Stratified Analysis of the Genetic Architecture of Human Brain Anatomy

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Background: Large open biobanks have dramatically advanced our understanding of genetic influences on human brain anatomy - but much of this work has combined rather than compared males and females. There are however several reasons to test for sex-differences in genetic influences on brain anatomy. First, there are known sex-differences in the biological factors that influence brain anatomy - particularly from sex-steroids and sex chromosomes - opening up sex-specific domains for the manifestation of genetic effects. Second, sex-differences in the genetic architecture of brain development are a candidate contributor to well-established sex-differences in psychiatric risk. Here, we screen for potential sex-biases in the influence of common genetic variants on brain anatomy.

Methods: T1-weighted magnetic resonance images in the UK Biobank (14301 males, 16054 females of "white British ancestry", age = 64.3 +/- 7.5 yrs) were used to obtain (FreeSurfer) gray matter volume (GMV), surface area (SA) and cortical thickness (CT) for 360 cortical regions (HCP atlas, covaried for total GMV, SA and CT respectively). Additionally, 23 subcortical volumes and mean cortical thickness, total surface area and total brain volume were included. Genotypic data consisted of 17 million SNPs after standard quality control. For each phenotype, I) sex-specific relatedness matrices (GRMs) in GCTA were used to calculate SNP-heritability (h2) for each phenotype in males and females separately; II) GCTA was also used to estimate autosomal genetic correlation (rg) between the sexes, and III) sex-stratified GWASs were performed in PLINK to estimate SNP-level sex-differences. SNPs with significant sex-differentiated effects were mapped to genes using FUMA which in turn were analyzed for enrichment of GO categories. Two p-values cutoffs were used for significance at this step: 1.4e-10 ("stringent" - corrected genome wide and across phenotypes) and 5e-8 ("relaxed" - genome wide).

Results: After correction for multiple comparisons, no individual phenotype showed a statistically significant sex-difference in h2. However, paired t-tests between the sexes revealed that mean h2 for regional GMV and SA tended to be higher in females than males ($p = 6.5e\text{-}10$, $p = 4.3e\text{-}6$ respectively). In GCTA bivariate analyses, 2 phenotypes showed $rg < 1$ between the sexes surviving correction for multiple comparisons (Posterior Insula rg = 046 +/- 0.11, Brodmann area 5m rg = 0.50+/-0.11). Of the two SNPs that showed significant sex-difference in GWAS at the most stringent cut-off, one (chr16:rs113078989; SA of supplementary motor region; male-specific effect) mapped to RBFOX1, a gene linked to multiple neuropsychiatric and neurodevelopmental disorders. Combined enrichment analysis of the genes mapped from SNPs passing the "relaxed" threshold did not show enrichment of any gene ontology category. Notably, sex-biased SNPs were not enriched on the X-chromosome or in sex-steroid related pathways.

Conclusions: This work suggests that common variant influences on human brain anatomy are largely convergent between males and females, with a few exceptions that will guide future research as biobanks continue to grow in size.

Keywords: Sex Differences, Imaging-Genetics, Human Genetics, Neuroanatomy

Disclosure: Nothing to disclose.

P441. Genome-Wide Association Study of Delay Discounting in 134,935 23andme Participants

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Background: Delay discounting (DD) is a heritable transdiagnostic trait, or endophenotype, that has been implicated in multiple psychiatric diseases, including substance use disorders and attention deficit hyperactivity disorder. A prior genome-wide association study (GWAS) of DD identified genetic correlations with these and other traits but was underpowered for genome-wide discovery.

Methods: In collaboration with 23andMe, Inc., we collected responses to a 30-item delay discounting questionnaire from 134,945 research participants and performed a GWAS assuming an additive genetic model that included age, sex, the first five genetic principal components, and indicator variables for genotype platforms as covariates. We further explored the genetic architecture of DD and the pleiotropic mechanisms with other outcomes using an array of genomic tools, such as MAGMA, H-MAGMA, S-MultiXcan and S-PrediXcan, LDSC and LAVA (Local Analysis of [co]Variant Annotation).

Results: We identified 14 significant loci associated with DD, with a SNP-heritability estimated of 9.86% (± 0.57%). Most of these loci (e.g., rs34645063, chr6q16.1, $p = 3.20E-13$; rs3020805, chr16p11.2, $p = 6.50E-10$) have been previously associated with various other behavioral traits, including risk-taking, alcohol consumption, educational variables and cognitive ability, and psychiatric disorders, as well as obesity and BMI. Genetic correlation analyses revealed significant associations with 27 traits, such as educational variables (e.g., years of education $rg = -0.57$, $SE = 0.03$; intelligence $rg = -0.39$, $SE = 0.03$), smoking behaviors (e.g., smoking initiation $rg = 0.32$, $SE = 0.02$; tobacco use disorder (TUD) $rg = 0.33$, $SE = 0.03$), risky behaviors (e.g., externalizing $rg = 0.30$, $SE = 0.03$), and health-related outcomes (BMI $rg = 0.28$, $SE = 0.03$). Local genetic correlation analysis revealed 20 significant bivariate loci between DD and these 27 other traits. Among them, the locus comprising the NCAM1-TTC12-ANKK1-DRD2 gene cluster was positively correlated with 12 traits, including substance use traits (i.e., drinks per week $rg = 0.61$; problematic alcohol use $rg = 0.47$; cannabis initiation $rg = 0.63$; TUD $rg = 0.46$; smoking initiation $rg = 0.31$; cigarettes per day $rg = 0.34$), and psychiatric disorders (schizophrenia $rg = 0.52$). Polygenic analyses in a hospital-based cohort (BioVU, $N = 69,447$) showed that DD polygenic risk score (PGS) was significantly associated with 127 medical traits across 16 categories, the strongest association being with TUD ($p = 1.21E-16$) and mood disorders ($p = 5.26E-10$). Beyond psychiatric disorders, the PGS for DD was also positively associated with medical phenotypes, such as Diabetes Mellitus ($p = 1.75e-06$), ischemic heart disease ($p = 8.51e-06$), hypertension ($p = 1.63e-05$). Secondary analyses stratified by sex and age showed that 62 phenotypes were associated only in females, 16 were only observed in males; and there was a tendency for stronger associations in older individuals.

Conclusions: Our results support the polygenic architecture of DD, identifying novel significant loci and highlighting common genetic factors between DD and other psychiatric and somatic health outcomes. This work further establishes DD as a valuable endophenotype.

Keywords: Impulsivity, GWAS, Delay Discounting

Disclosure: Nothing to disclose.

P442. FDG-PET as a Clinical Diagnostic Biomarker for Repetitive Blast Mild Traumatic Brain Injury

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Background: Blast-related mild traumatic brain injury (blast-mTBI) can result in a spectrum of persistent symptoms leading to substantial functional impairment and reduced quality of life. Clinical evaluation and discernment from other conditions common to military service can be challenging and subject to patient recall bias and the limitations of available assessment measures. The need for objective biomarkers to facilitate accurate diagnosis, not just for symptom management and rehabilitation but for prognostication and disability compensation purposes, is clear.

Methods: The Veterans Affairs Puget Sound Health Care System (VA Puget Sound) and University of Washington Institutional Review Boards approved the study protocol, and all participants provided written informed consent prior to any study procedures. We compared regional brain [18F]fluorodeoxyglucose positron emission tomography ([18F]FDG-PET) intensity-scaled uptake measurements in 79 combat Veterans with retrospectively recalled blast-mTBI, resulting in two or more symptoms meeting American Congress of Rehabilitation Medicine (ACRM) criteria for mTBI, with 41 control participants having no lifetime history of TBI. These images were analyzed on a voxelwise basis using SPM12 with 6mm smoothing in the nonparametric toolbox (SnPM), which implements a single-tailed test, using age as a covariate, and adjusted significance value (pFWE-corrected 5). To identify brain regions affected by blast-mTBI, volumes of interest (VOIs) were extracted from individual images using a standard atlas, segmenting images into discrete neuroanatomical regions. Participants were evaluated by motor (Unified Parkinson's Disease Rating Scale [UPDRS] motor subscale), neuropsychological behavioral (Behavior Rating Inventory of Executive Function-Adult Version [BRIEF-A] and the Frontal Systems Behavior Scale [FrSBe]) and cognitive (working memory by Auditory Consonant Trigrams test [ACT], and prospective memory by Memory for Intentions Test [MIST]) assessments. Self-report assessments for PTSD symptoms (PTSD Checklist-Military version, [PCL-M]), sleep quality (Pittsburgh Sleep Quality Index [PSQI], alcohol use (Alcohol Use Disorders Identification Test-Consumption [AUDIT-C]), and symptoms of depression (PHQ-9).

Results: Using an agnostic and unbiased approach, we found significantly increased left pallidum [18F]FDG uptake in Veterans with blast-mTBI versus control participants, $p < 0.0001$; $q = 3.29 \times 10\text{-}9$. The degree of left pallidum [18F]FDG uptake correlated with the number of self-reported blast-mTBIs, $r2 = 0.22$; $p < 0.0001$. Greater [18F]FDG uptake in the left pallidum provided excellent

discrimination between Veterans with blast-mTBI and controls, with a Receiver Operator Characteristic Area Under the Curve of 0.859 ($p < 0.0001$) and likelihood ratio of 21.19 (threshold:-SUVR≥0.895). The relationship between left pallidum [18F]FDG uptake and the number of blast-mTBIs remained statistically significant after controlling for common covariates using multivariate linear regression (log scale number of blast exposures, $p = 0.038$; motor signs (UPDRS total score), $p = 0.40$; PTSD symptoms (PCL-M total score), $p = 0.031$; age, $p = 0.040$; sleep quality (PSQI total score), $p = 0.75$; overall model $F[5, 96] = 10.11$, $p<0.0001$; adj. $r2 = 0.31$). These results support a dose dependency in left pallidum [18F]FDG uptake related to the number of symptomatic blast-mTBI exposures, a finding that is robust to the effects of age, sleep quality, motor signs, and comorbid PTSD. Deficits in executive function assessed using the BRIEF-A Global Executive Composite T-score were identified in Veterans with blast-mTBI compared to controls, $p < 0.0001$. Regression-based mediation analyses determined that in Veterans with blast-mTBI, increased [18F]FDG uptake in the left pallidum mediated executive function impairments, adjusted causal mediation estimate $p = 0.021$; total effect estimate, $p = 0.039$. Measures of working and prospective memory were negatively correlated with left pallidum [18F]FDG uptake, $p<0.0001$, with mTBI as a covariate. Increased left pallidum [18F]FDG uptake in Veterans with blast-mTBI compared to controls did not covary with dominant handedness or with motor activity assessed using the UPDRS.

Conclusions: Localized increased [18F]FDG uptake in the left pallidum demonstrates potential as a possible biomarker for repetitive blast mTBI, and correlates with clinically relevant chronic postconcussive symptoms. Left pallidum [18F]FDG in those with history of blast mTBI may reflect a compensatory response to functional deficits following blast-mTBI. Limited imaging resolution does not allow us to distinguish subregions of the pallidum, however the significant correlation of our data with behavioral but not motor outcomes suggests involvement of the ventral pallidum, which is known to regulate motivation, behavior, and emotions via basal ganglia-thalamo-cortical circuits. While confirmation of our results by single-subject-to-cohort analyses will be required prior to clinical deployment, this study provides proof-of-concept that [18F]FDG-PET bears promise as a readily available noninvasive biomarker for blast-mTBI.

Keywords: Mild Traumatic Brain Injury, Fluorodeoxyglucose, Pallidum, Positron Emission Tomography

Disclosure: Nothing to disclose.

P443. Vitamin D's Capacity to Increase Amphetamine-Induced Dopamine Release: A Clinical Translational 11C-PHNO PET Study in Healthy Humans

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Background: Dysregulation of dopaminergic tone has transdiagnostic relevance, including attention deficit hyperactivity disorder (ADHD), obesity, binge eating disorder (BED), and cocaine use disorder (CUD). Stimulants are not only approved for ADHD and BED but there is also promising emerging research on stimulants for CUD. However, there are concerns about potential misuse of stimulants. Preclinical research by our group suggests that the active form of vitamin D, calcitriol, increases subcortical tyrosine hydroxylase, D2/3 receptors, and amphetamine-stimulated dopamine (DA) release in rodents.

Methods: Healthy, vitamin-D-sufficient adults ($N = 18$; 32.8 ±6.6 years; 33% female) participated a randomized, double-blind, placebo-controlled design involving same-day, pre- (baseline) and post-amphetamine (0.3 µg/kg) 11C-PHNO PET scans of D2/3 receptor availability (BPND) on both active calcitriol (1.5 µg night before experimental day and 1.5 µg morning of experimental day) and placebo at least six days apart. Parametric images of 11C-PHNO PET BPND were computed using a simplified reference tissue model (SRTM2) with the cerebellum as reference. Blood samples were acquired to measure serum calcitriol, amphetamine, and calcium levels. Regions of interest (ROIs) examined were the dorsal caudate (DCA), dorsal putamen (DPU), ventral striatum (VS), globus pallidus (GP), and substantia nigra (SN).

Results: Calcitriol levels were higher on active (119.2 pg/ml ± 26.4) vs. placebo (69.4 pg/ml ± 23.6) days ($F1,17 = 107.93$, $p < 0.001$). Calcium levels remained within normal limits and did not differ between test days (9.7 mg/dl ± 0.05 on active vs. 9.5 mg/dl ± 0.05 on placebo; $t = 1.5$, $p = 0.1$). Amphetamine levels also did not differ between test days (31.4 mg/ml ± 1.8 on active vs. 33.1 mg/ml ± 1.8 on placebo; $t = -0.4$, $p = 0.6$). For pre-amphetamine scans, there was a medication-by-ROI ($F4,153 = 2.59$, $p = 0.039$) interaction and a main effect of medication ($F1,153 = 4.88$, $p = 0.029$) on BPND, with higher BPND values on calcitriol in the VS ($t = 2.89$, $p = 0.004$) and DPU ($t = 2.15$, $p = 0.033$). There was a main effect of medication on post-amphetamine change in BPND ($F4,153 = 5.93$, $p = 0.016$), with greater decreases on calcitriol in the VS ($t = 3.00$, $p = 0.003$), SN ($t = 2.49$, $p = 0.014$), and DCA ($t = 2.29$, $p = 0.023$).

Conclusions: Current results suggest acute treatment with calcitriol does not lead to temporary hypercalcemia, could upregulate D2/3 receptors, and enhance amphetamine-induced DA release. As such, they provide translational support for vitamin D as a non-addictive agent to target dysregulated dopaminergic tone. Future translational studies among persons with altered dopaminergic regulation are required in order to explore clinical (i.e., food intake, drug intake) and cognitive correlates of PET imaging outcomes.

Keywords: Attention Deficit Hyperactivity Disorder, Cocaine Use Disorder, Dopamine Release, Vitamin D, PET Imaging Study

Disclosure: Nothing to disclose.

P444. Effects of Acute Ethanol Administration on Choroid Plexus Perfusion and Water Exchange

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Background: Alcohol misuse, including binge drinking, is known to be toxic to the brain. A potential novel mechanism is altered fluid flow, including changes in cerebral blood flow (CBF) and the glymphatic system. The glymphatic system uses cerebral spinal fluid (CSF) and lymphatics to remove waste and other toxic agents from the brain. Alcohol misuse has been associated with enlarged ventricles and increased risk of vascular dementia. Using a novel approach based on continuous arterial spin labeling magnetic resonance imaging (CASL-MRI) we studied rats undergoing acute intravenous (IV) administration of ethanol (ETOH). Here we report significantly elevated choroid plexus (ChP) perfusion during acute administration of ETOH.

Methods: To characterize the acute IV administration of ETOH, six 10M old CDF Fischer female rats (Charles River) were assessed. Prior to MRI, a femoral infusion line was placed for intravenous administration of ETOH. The anesthetized rats were placed in a

custom 3D printed rat body holder in prone position while breathing spontaneously through a snout mask under balanced anesthesia with dexmedetomidine supplemented with 1% ISO (DEXM-I) as described previously. The ETOH challenge was comprised of the interleaved acquisition of perfusion weighted (short TE = 23ms) and BCSFB weighted (long TE = 150ms) CASL-MRI as described previously. Following 33 minutes of baseline scans before the administration of ETOH, a continuous infusion of ETOH was commenced at a variable rate to achieve a 33-minute ramp to reach a blood ETOH concentration of 80 mg/dL, where it was maintained for another 33 minutes. CASL-MRI were acquired in 11-minute blocks throughout, totaling ~100 min of scanning time. During the MRI session, respiratory rate, heart rate, mean arterial blood pressure, body temperature, and SPO2 were measured continuously by MRI compatible monitors (SA Instruments, Stony Brook, NY, USA). Body temperature was maintained between 36.5–37.5°C using a heated waterbed system. Image analyses were performed by manually delineating three regions of interest (Choroid plexus (ChP), cortex (CTX), and hippocampus HIP), and semi-quantitative image analysis was performed by calculating the % signal change from the baseline.

Results: We used repeated measures ANOVA to analyze the impact of the ETOH on each physiological parameter. Respiratory rate (51 ± 18 bpm), body temperature (36.7 ± 0.2), SPO2 (99.4 ± 0.7), and mean arterial blood pressure (81 ± 5.5 mmHg) were not affected by the ETOH administration, but the heart rate rose 11%, from 248 ± 24 beats/minute at baseline to 275 ± 20 bpm at plateau. MRI: ChP blood perfusion gradually increased during the ramping phase of ETOH and then peaked ~50% higher above the baseline and stabilized at the same level together with the blood ETOH concentration ($p < 0.0001$). While the BCSFB weighted signals at ChP also exhibit an increasing trend (~20%) during the ramping phase, indicative of upregulation of CSF water secretory function, it was not statistically significant ($p = 0.36$). Similarly, for CTX and HIP perfusion, increasing trends (15~20%) were observed but did not reach statistical significance (0.57 and 0.18, respectively).

Conclusions: As ChP is the primary source of CSF generation, blood perfusion and blood-water exchange to CSF in the ChP hold importance for glymphatic function. Although the sample size is small, the data suggest that acute ETOH exposure alters CNS fluid homeostasis via ChP perfusion and possibly secretory function, as evidenced by marked changes after the administration of ETOH. Further, the much greater increases in ChP perfusion in comparison to ChP water secretion suggest that the effects of acute ETOH are complex in relation to choroid plexus function.

Keywords: Alcohol, MRI, Imaging

Disclosure: Nothing to disclose.

P445. Male Alloparenting is Modulated by Experience and Stress

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Background: Alloparenting, or care provided to young by a non-parent, is prevalent in humans. Recently, neural mechanisms underlying female alloparenting have started to be revealed, but little research on mechanisms for male alloparental care has been conducted. Our lab has previously demonstrated the impact of stress on female alloparenting. Galanin-expressing neurons in the medial preoptic area of hypothalamus (MPOA) have been shown to underlie caregiving behavior in both male and female mice. In the present study, we examined the expression of brain-derived neurotrophic factor in these neurons in relation to male alloparental care with or without stress.

Methods: We examined the stability of infant-directed behavior in virgin male mice using repeated pup exposure (RPE) in 4 test sessions (Screen: initial test; Day 1, 1 week after screen; Day 2, 24 hours after Day 1; and Day 3, 24 hours after Day 2). Across 42 males, we categorized 16 as unstable, 17 as stably non-aggressive, and 9 as stably aggressive toward pups. In the unstable group of 16 mice, 7 males were tested during a period of construction in our animal room. We collected tissue from the medial preoptic area in males exposed to pups acutely or repeated and conducted in situ hybridization for galanin and BDNF to quantify colocalization. In another cohort of males, we used our repeated testing paradigm but subjected a subset of males to acute restraint stress (1 hr) prior to behavior testing on Day 3 ($n = 10$ control; $n = 11$ acute stress).

Results: We find that among non-aggressive males, pup-grooming behavior is significantly enhanced with repeated testing (One-way repeated measures ANOVA $F(3,69) = 5.342$ $p < 0.0023$, Tukey's multiple comparisons Screen vs. Day 2 $^{**}p < 0.0063$, Screen vs. Day 3 $^{**}p < 0.005$, $n = 24$). Males showing infant-directed aggression ($n = 24$) had shorter latencies to aggression or attack on Day 1 and Day 2 (Friedman statistic 16.04 $p < 0.0011$, Dunn's multiple comparisons test Screen vs. Day 1 $^{**}p < 0.0011$, Screen vs. Day 3 $^{*}p < 0.262$, $n = 24$). Preliminary results suggest that BDNF levels are increased in MPOA galanin neurons in alloparental males with RPE. Acutely stressed males showed less alloparental grooming toward pups on Day 3 compared to control males on Day 3 or to the whole unstressed group of males on Day 2 (Mixed effects ANOVA $p < 0.05$, Sidak's multiple comparisons Day 2 vs. Stressed Day 3 $^{*}p < 0.0423$, Control Day 3 vs. Stressed Day 3 $^{****}p < 0.0001$). Analysis is underway to examine BDNF expression in MPOA galanin neurons in this cohort.

Conclusions: Overall, unstressed virgin males show categorically similar behavior toward pups over time, with enhancement of specific behaviors like pup-grooming in non-aggressive males or attack latency in aggressive males with repeated testing. Acute stress dampens the facilitating effect of RPE in males. These behavioral adaptations correlate with expression of BDNF, a marker of neural plasticity, in MPOA galanin neurons. These results further our understanding of alloparenting, a key caregiving strategy in humans, and suggest neurobiological mechanisms that control expression of this critical behavior.

Keywords: Acute Stress, Social Behavior, Hypothalamus, BDNF, Galanin

Disclosure: Nothing to disclose.

P446. Effects of Oral Contraceptive Pills on Resting-State Functional Connectivity

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Background: Oral contraceptive pills (OCPs) are widely used as a form of contraception worldwide. Recent evidence suggests that OCPs have neurobiological effects that extend beyond their primary purpose. While OCPs can have beneficial effects in certain instances, such as the treatment of premenstrual dysphoric disorder, they may also have detrimental effects on individuals who experience adverse emotional effects as a result of OCP use. Individual responses to OCPs, whether positive, negative, or neutral, remain unpredictable. Furthermore, the mechanisms by which OCPs engage neural circuits and their network-level effects

are still not well understood, creating a significant gap in current knowledge.

Methods: To evaluate effects of OCPs on resting-state functional connectivity, we conducted a randomized, double-blind, placebo-controlled crossover study, with counterbalanced random assignment to each starting arm. Twenty-six women (no men) who endorsed regular menstrual cycles and a history of negative emotional reactions in response to OCPs received OCPs containing 0.15 mg levonorgestrel + 0.30 µg ethinyl estradiol, or placebo pills, and self-administered medication at home. Resting-state functional connectivity images were preprocessed and analyzed using the FSL toolbox. Independent component analysis using the MELODIC tool was used to identify the default mode network at the group level. The dual regression tool was used to back-reconstruct individual subject-level maps of the default mode network and difference maps between the OCP and placebo arms were calculated.

Results: Default mode network connectivity with a large cluster concentrated in bilateral occipital cortex was significantly higher during the OCP arm compared to the placebo arm ($p[fwe] = 0.005$; $t[max] = 6.06$, Cohen's $d = 1.19$). Beck Depression Inventory scores were significantly higher during the OCP arm as compared to placebo ($p = 0.02$, Cohen's $d = 0.33$).

Conclusions: These findings suggest that OCPs increase default mode network connectivity with occipital cortex, and can induce negative affective states in some women.

Keywords: Neuroendocrinology, Connectomics, Systems Neuroscience

Disclosure: Nothing to disclose.

P447. Can Transcranial Electrical Stimulation Improve Generalization From Working Memory-Related Cognitive Training in Healthy Adults? Behavioral and Imaging Evidence

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Background: Cognitive training is one of the more promising treatments for patients with serious mental illnesses, however its impact on untrained tests of generalization are small. We tested whether training and near generalization effects increased when using Transcranial Direct Current Stimulation (tDCS) during training to strengthen cortico-thalamic connectivity. Cortico-thalamic connectivity was tested based on evidence that these connections may support generalization of training (Ramsay and MacDonald, 2015).

Methods: In a triple-blind, placebo-controlled study, everyone received 12 weeks of cognitive training focused on working memory and executive control weeks of regular training to assess efficacy. Participants were randomly assigned to: 1) active Left Prefrontal Cortex anodal tDCS (2mA), 2) Right Prefrontal Cortex anodal tDCS, or 3) sham stimulation in these locations. TDCS occurred during training 3 times a week for a total of 12 weeks. The cathode was in the same position on the opposite hemisphere. Participants' cognitive ability, brain activity and connectivity were assessed at baseline, midpoint (6 weeks), and post-test (12 weeks) using the N-Back and the dot pattern expectancy (DPX) task using stimuli that had not been trained. Group assignment remains blinded so far.

Results: 56 participants were randomized and received stimulation and 38 completed post-test assessments. Pre-registered analyses found significant improvements on N-back performance in all groups (main effect of time $p < .001$) without evidence for a group x time interaction ($p = .27$). Group x time effects for the DPX showed a trend ($p = .07$). Neither N-Back nor DPX showed significant group x time interactions in terms of long term brain activation changes.

Conclusions: We present evidence for near transfer as a functioning of training on working memory and executive control tasks. However, the robustness of these effects is unclear because current analyses have not found these behavioral changes similarly impacted at a neural level. Upon completing our main analyses, we will break the blind to interpret the impact of tDCS in facilitating the generalization of cognitive training.

Keywords: Cognitive Training, Transcranial Direct Current Stimulation (tDCS), Learning Generalization

Disclosure: Nothing to disclose.

P448. TMS Provokes Target-Dependent Intracranial Rhythms Across Human Cortical and Subcortical Sites

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Background: Transcranial magnetic stimulation (TMS) is increasingly deployed in the treatment of neuropsychiatric illness, under the presumption that stimulation of specific cortical targets can alter ongoing neural activity and cause circuit-level changes in brain function. While the electrophysiological effects of TMS have been extensively studied with scalp electroencephalography (EEG), this approach is most useful for evaluating low-frequency neural activity at the cortical surface. As such, little is known about how TMS perturbs rhythmic activity among deeper structures – such as the hippocampus and amygdala – and whether stimulation can alter higher-frequency oscillations. Understanding these effects is necessary to refine clinical stimulation protocols and better use TMS as a neuroscientific tool to investigate causal relationships in the brain. Recent work has established that TMS can be safely used in patients with intracranial electrodes (iEEG), making it possible to collect direct neural recordings at sufficient spatiotemporal resolution to examine oscillatory responses to stimulation.

Methods: We recruited 17 neurosurgical patients (male and female) with indwelling electrodes and recorded neural activity while patients underwent repeated trials of single-pulse TMS at two major cortical sites. The dorsolateral prefrontal cortex (DLPFC) was targeted on an anatomical basis, while the parietal cortex was targeted based on area of maximal functional magnetic resonance imaging (fMRI) connectivity to the hippocampus. Sham stimulation – wherein the TMS coil was directed away from the skull – was administered as a control. Subjects underwent at least 50 trials of active and sham stimulation at 100% or 120% of motor threshold. Pulses were delivered at 0.5 Hz, allowing for 2-second inter-stimulation analysis intervals. TMS-provoked brain signals were analyzed using spectral methods to assess for changes in oscillatory power and phase, and then statistically compared against sham trials using linear mixed-effects modeling. All experimental procedures were approved by the University of Iowa Institutional Review Board.

Results: TMS elicited widespread – but brief – changes in spectral power that markedly differed according to the stimulation target. Stimulation to the DLPFC drove widespread low-frequency (theta; 3-8 Hz) increases in frontolimbic cortices within the first 50-500ms following stimulation (Wald test, $z = 3.20$, $P = 0.001$), with particularly prominent responses in the

rostral anterior cingulate cortex. Parietal TMS provoked theta-band increases in the same interval, but only within the medial temporal lobe (MTL; $z = 3.75$, $P < 0.001$). DLPFC TMS was also associated with a 250-450ms frontotemporal suppression of power in the gamma (30-50 Hz) and high-frequency (HFA; 70-110 Hz) bands ($z = -3.81$, $P < 0.001$). These effects were replicated when examining hippocampal responses to TMS, with a notable suppression of gamma/HFA between 400ms and 600ms following a frontal stimulation pulse ($N = 9$ subjects; $z = -3.4$, $P < 0.001$). In both DLPFC and parietal stimulation, we found elevated inter-trial phase consistency at low frequencies in the early post-stimulation period, but these effects were greater following DLPFC TMS (frontal: $z = 4.7$, $P < 0.001$; temporal: $z = 3.13$, $P = 0.002$; limbic: $z = 4.94$, $P < 0.001$).

Conclusions: Taken together, we established that exogenous, non-invasive stimulation can be used to (1) provoke phase-locked theta increases and (2) briefly suppress high-frequency activity in a cortico-subcortical pattern that varies by stimulation target. Specifically, we demonstrated that TMS directed to cortical surface targets could yield changes in rhythmic activity in distant subcortical sites, including the hippocampus; parietal targeting resulted in specific spectral changes within the MTL, whereas DLPFC stimulation caused a broader frontolimbic response. These results demonstrate that combined TMS/iEEG can provide valuable electrophysiological insights into the complex spectral profile evoked by non-invasive brain stimulation.

Keywords: Transcranial Magnetic Stimulation, Gamma, Theta, Delta, EEG Electrophysiology, Intracranial EEG, Hippocampus

Disclosure: Nothing to disclose.

P449. Pre-Intervention Neuronal Response to Food Cues is Associated With Subsequent Weight Loss in Adults With Overweight/Obesity

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Background: Obesity rates are rapidly rising, giving rise to myriad health and quality-of-life concerns. Weight loss is associated with a reduction in comorbid conditions, such as cardiovascular disease, but can be difficult, with weight regain prevention even more challenging. As such, understanding the neuronal mechanisms underlying the regulation of energy balance could inform the development of improved strategies for successful weight-loss and maintenance. Towards this end, the current study used functional magnetic resonance imaging (fMRI) to examine the neuronal effects of two core lifestyle modification interventions for weight loss: exercise and diet. Specifically, the study aimed to determine how the neuronal response to visual food cues was associated with subsequent weight loss responsivity to a behavioral intervention.

Methods: Thirty-nine adults (7 M, 32 F) with overweight/obesity completed the study. Inclusion criteria included being 21-55 years old and sedentary (< 2 hours planned physical activity per week), with BMI between 27-40 kg/m2 and weight stability within 5% in the previous six months. After enrolling in the study, measures of body composition were taken, after which participants completed a 3-day, macronutrient-controlled, eucaloric run-in diet immediately prior to completing fMRI scanning while viewing visual stimuli (high-calorie foods, low-calorie foods, and non-food objects) in both fasted and fed states. The primary contrast of interest compared responses to high-calorie foods vs. non-food objects. After completing these baseline measures, participants were randomized to either a 12-week exercise intervention (treadmill walking, targeted intensity of 75% VO2max, 5 days per week) or a 12-week diet intervention (reduction in energy intake by ~2000 kcal/week to match the energy deficit produced by the exercise intervention). Baseline assessments were repeated post-intervention. Participants were categorized as "responders" if weight loss from pre- to post-intervention was > 3% and as "non-responders" if weight loss was < 3%. Imaging data were pre-processed using fMRIPrep, after which parameter estimates from first-level models were entered into second-level analyses in SPM12 and evaluated with directional contrasts. Neuronal response to food cues was compared between responders and non-responders.

Results: Data for one participant was excluded due to artifacts in fMRI data (final analysis $N = 38$, mean body mass index [BMI]: 30.85 +/- 3.21 mg/kg2; mean age 38.24 +/- 9.15 years; $N = 21$ exercise [3 M, 18 F]; $N = 17$ diet [4 M, 13 F]). Eighteen participants were determined to be "responders" based on >3% weight loss (4 M, 14 F; $N = 8$ diet, $N = 10$ exercise), with 20 "non-responders" (3 M, 17 F; $N = 9$ diet, $N = 11$ exercise). There were no significant differences between responders and non-responders in age, BMI, fat mass, or lean body mass pre-intervention ($p > 0.05$). Change from pre- to post-intervention for BMI, fat mass, and lean body mass significantly differed between responders and non-responders (BMI, fat mass: $p < 0.001$; lean mass: $p = 0.003$), with significant reductions in responders ($p < 0.001$), but not non-responders ($p > 0.05$). Greater pre-intervention response to high-calorie foods in the fasted compared to fed state was observed in inferior visual and parietal cortices in non-responders compared to responders, $p < 0.001$ (FDR-corrected for multiple comparisons). This effect was driven by greater response to high-calorie food cues in the fasted state in non-responders compared to responders.

Conclusions: Greater pre-intervention food-cue-related response in visual, visual association and attention-related brain networks in the fasted compared to fed state was observed in those who did not lose at least 3% body weight in a subsequent weight-loss intervention (non-responders), compared to intervention responders (i.e., lost > 3% body weight). This difference was driven by increased neuronal response to food cues in the fasted state in non-responders. This observation may suggest that those with heightened food cue responsivity are more resistant to weight loss from behavioral lifestyle interventions. As the current study did not include a sufficient number of men to allow for an investigation of potential sex-based differences, these effects should be examined in future work. Future studies can also further investigate if neuronal response to food cues can predict subsequent weight loss associated with other interventions (e.g., bariatric surgery, pharmaceutical weight-loss approaches) and if neurobiological signatures of weight-loss propensity could be used to help identify treatment targets for novel weight loss and maintenance strategies.

Keywords: Obesity, fMRI, Non Pharmacological Interventions, Weight Loss Treatment

Disclosure: Nothing to disclose.

P450. Electrophysiology Based Biomarkers as Outcome Measures Demonstrate Signal Detection and Reliability in a Simulated Clinical Trial at an Experienced Clinical Research Center Evaluating Study Drug (Ketamine) and Placebo

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Background: Event related potential (ERP) and resting state Pharmaco-Electroencephalogram - (QEEG), are increasingly incorporated into pharma sponsored studies to inform decision making (e.g., target engagement) and guide a drug's early development. EEG data have high translational value, typically with similar effects in animal and in human studies. However, results from study to study are variable, reducing confidence. Our study is designed to simulate a randomized placebo (Pbo) controlled clinical trial to detect differences in standardized ERP/QEEG measures between study drug (ketamine) and Pbo in healthy volunteers at an experienced early phase clinical research unit. The design includes two ketamine administration visits to evaluate ERP/QEEG reliability by estimating intraclass coefficients (ICCs). Low ICCs are a critical limiting factor for the use of ERP/QEEG as biomarkers. The usual convention for reliable study results are ICCs≥ 0.5 (moderate), with ICCs≥ 0.6 used in many NIMH and Pharma clinical trials. To our knowledge, no study has yet been performed that tested participants twice under ketamine administration vs placebo.

Methods: We conducted a randomized double blind, Pbo-controlled 3-arm, 3-period crossover study in healthy volunteers receiving ketamine x 2 (K1-K2) and Pbo on one visit. NCT04928703. Ketamine was administered as a 0.23 mg/kg bolus over 1 minute, followed by 0.58 mg/kg/hour for 30 minutes, followed by 0.29 mg/kg/hr for up to an additional 29 minutes. Pbo saline infusions emulated the same time frame. Estimation of ketamine effects vs placebo are denoted as K1-Pbo and K2-Pbo. [(K1-Pbo)+(K2-Pbo)]/2 averaged data was used to evaluate changes in ERP/QEEG and effect sizes (Cohen's d). As a measure of reproducibility K1 and K2 ICCs are reported. ERP/QEEG evaluations included: Passive, Duration-Deviant, Oddball task: Mismatch Negativity (MMN), N100; and P3a., Eyes closed Pharmaco-EEG parameters were estimated per IPEG guidelines (Jobert et al., Neuropsychobiology. 2012;66(4):201-20); Auditory Steady State (ASSR) 40 hz parameters and Active Auditory Oddball tasks included N100, P200, N200, P3b. ERP/QEEG data were recorded using the Cognision System, from active electrodes, positioned at Fz, Cz, Pz, F3, P3, F4, and P4 locations of the international 10-20 system. Site investigators were highly experienced in the conduct of electrophysiology studies as well as managing ketamine/K-analog compounds. For tests that met a priori quality control (QC), automated data cleaning, pre-processing, and feature extraction using pre-specified endpoints and statistical analysis plan (including ICCs, Cohen's d, and repeated measures ANOVA) were completed. This trial was conducted and data analyzed (ERP/QEEG) with the same design used in Early Drug Development. We acknowledge the contributions of the ERP Biomarker Qualification Consortium www.erpbiomarkers.org.

Results: Thirty-three subjects were enrolled with 31 randomized and 24 subjects completed all assessments (19 Male; 5 Female), with 7 subjects withdrawing consent due to ketamine related adverse events (AEs). All AEs were mild or moderate and consistent with ketamine's reported effects. Of the 300 electrophysiologic assessments (300 tests), 2% did not meet QC criteria. The QEEG showed good to excellent ICCs across most measures with medium to large effect sizes.

Illustrative results with statistically significant results ($p < 0.01$) include: Alpha1 Absolute power (ABS) 8.5-10.5hz ICC (K1-Pbo and K2-Pbo) of 0.907, Cohen's d 0.586 and ICC (K1-K2) of 0.760; Beta1 ABS 12.5-18.5 ICC (K1-Pbo and K2-Pbo) of 0.804, Cohen's d 0.66, and ICC K1-K2 of 0.712; and Gamma-ABS 30-40hz, ICC (K1-Pbo and K2-Pbo) of 0.495, Cohen's d 0.733, and ICC K1-K2 of 0.624. Active oddball task: P200 Amplitude (Amp)-CZ ICC (K1-Pbo and K2-Pbo) of 0.857, Cohen's d 0.814 and ICC K1-K2 of 0.792; P3b Amp-PZ ICC (K1-Pbo and K2-Pbo) of 0.544, Cohen's d 0.466 and K1-K2 0.631. ASSR 40hz-FZ Total Power ICC (K1-Pbo and K2-Pbo) of 0.768, Cohen's d 0.577 and ICC of K1-K2 of 0.493.

MMN demonstrated no group effect, with good to excellent ICCs: MMN Amp-CZ ICC (K1-Pbo and K2-Pbo) of 0.615, K-Pbo 0.760; MMN Latency-CZ ICC (K1-Pbo and K2-Pbo) 0.758 and K1-K2 of 0.642. Similar ICCs were observed for P3a and P200.

Conclusions: Our experience and these data demonstrate the feasibility of including ERP/EEG as translational/biomarker measures in Early Phase studies. High quality electrophysiologic data can be expected in a pharma study using an experienced clinical research site. Replicate K1-K2 infusions allowed the comparison of K1-Pbo and K2-Pbo with good to excellent ICCs and moderate to large treatment effect sizes. These data support greater confidence when designing target engagement studies including estimating sample size. The use of ICCs to 'qualify' a biomarker (a priori or gated design) is recommended.

Why some ERP/QEEG measures do not show a treatment effect deserves further study. K-Pbo ASSR 40hz ITC differences were not observed, possibly due to the timing at 1 hour post infusion. The absence of a significant effect on MMN Amp or Latency is still being explored. Preliminary data suggest a disordinal drug effect, where MMN moves in opposite directions AND the direction and magnitude of the effect can be predicted by the subject's baseline value (precision psychiatry?). This disordinal effect does not appear to be regression to the mean based on slope testing. Further study of low amplitude MMN (< 5uV) and pooling of additional data sets are underway.

Keywords: EEG Biomarkers, IV- Ketamine, Clinical Trial Design, CNS Clinical Trials, Translational Biomarker Approaches to Drug Development

Disclosures: Follow the Molecule: Owner (Self). CenExel Research: Consultant (Self). ProScience Research Group, Q-Metrx, Gilgamesh Pharmaceuticals, BioXcel Therapeutics, Neumora Therapeutics, Viage Therapeutics, Reviva Pharmaceuticals, Vandria Therapeutics: Consultant (Self). Johnson and Johnson, Amgen Pharmaceuticals, Intracellular Therapeutics: Stock / Equity (Self).

P451. Using Passive Smartphone Sleep Metrics to Detect Short-Term Changes in Mood and Suicidal Ideation in Adolescents

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Background: Over the past decade, suicide deaths in adolescents have significantly increased. Sleep behavior and patterns (e.g., onset, duration) undergo substantial change during adolescence, and approximately 70% of adolescents do not receive the recommended amount of daily sleep, which can impair psychological functioning and confer risk for suicidal thoughts and behaviors (STB). Given that sleep health is a common target of interventions, it is important to enhance our understanding of how sleep contributes to proximal risk for STB. Smartphone sensors (i.e., mobile accelerometry) provide an unobtrusive and scalable way to monitor daily sleep health in real-time over longer time periods. Accordingly, this provides an opportunity to test whether dynamic changes in sleep health contributes to the short-term escalation of STB. We hypothesized that diminished sleep health (i.e., late and more variable onset and chronotype, reduced and more variable duration, and increased social jetlag) assessed through smartphone sensors will associate with weekly clinically significant suicidal ideation.

Methods: Participants included adolescents (N = 99, 74 female, 13-18-years-old), oversampled for current suicidal ideation (n = 42)

or a history of suicide attempt in the past year (n = 26). At baseline, participants completed clinical assessments to determine their STB history and installed the Effortless Assessment Research System (EARS) application on their smartphones, allowing access to motion sensor data over 6 months. During the 6-month period, participants also received daily prompts regarding their past-day mood and weekly questions probing the severity of past-week suicidal ideation. Activity states were derived from continuous passive monitoring of motion data to quantify sleep periods. The start and end times of the longest phone stationary period within each 24-hour window was used to operationalize sleep onset (i.e., going to bed) and offset (i.e., wake up) times, respectively. Following data quality checks, sleep duration was quantified by the difference between sleep onset and offset. We also computed metrics of chronotype (i.e., the midpoint between sleep onset and sleep offset during weekends, when adolescents are relatively unrestricted by their school schedule) and social jetlag (i.e., the difference between the midpoint of sleep on weekends and weekdays). First, analyses examined whether self-report measures of sleep (i.e., circadian preference) at baseline associated with mobile sensor sleep data. Second, multilevel linear regressions examined within-person associations between mobile sensor sleep metrics and daily mood ratings. Last, multilevel logistic regressions examined whether the weekly average and variability (i.e., standard deviation) of mobile sensor sleep metrics (i.e., onset, chronotype, duration, and social jetlag) associated on a week-to-week basis with clinically significant suicidal ideation, the level at which licensed clinicians followed up with participants to conduct suicide safety risk assessments. Analyses of clinically significant suicidal ideation were limited to ideators and attempters to investigate associations between sleep health and suicidal ideation in those at highest risk for STB. Future analyses will test the temporal relationship among sleep health, mood, and suicidal behaviors.

Results: Self-reported circadian preference at baseline was associated with mobile-sensor chronotype, such that a greater preference for morning related to earlier bedtimes on weekends (b = -.04, SE = .02, p = .017). Additionally, greater daily within-person sleep duration related to higher past-day mood adjusting for between-person sleep duration, age, sex, and phone type (b = .35, SE = .13, p = 0.005). Among ideators and attempters, more variable sleep duration related to higher risk of clinically significant suicidal ideation on a given week, adjusting for weekly mean sleep duration, weekly mean mood, sex, and age (OR = 1.51, 95%CI [1.05, 2.16], SE = 0.28, p = .027). No other sleep health metrics (i.e., sleep onset, chronotype, or social jetlag) related to daily mood or weekly suicidal ideation (ps >.07).

Conclusions: Preliminary results reveal proximal associations among sleep duration, daily mood, and weekly suicidal ideation. These effects highlight the possibility of applying scalable tools (i.e., software installed on the personal smartphone) to identify short-term risk of STB among adolescents. In the future, these tools may be leveraged to develop just-in-time interventions, focusing on modifying specific sleep behaviors in the service of reducing STB risk.

Keywords: Suicidal Ideation, Sleep Disturbances, Ecological Momentary Assessment

Disclosure: Nothing to disclose.

P452. TDCS Augmentation of Cognitive Training in Healthy Adults

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Background: Cognitive impairment can cause debilitating effects for individuals in their daily functioning for important tasks such as maintaining attention during conversations, recalling new information, and multitasking. Transcranial Direct Current Stimulation (tDCS) has been shown to be a promising tool for cognitive improvement in psychiatric and neurological interventions. tDCS may offer a boost for stand-alone cognitive training in improving cognitive functioning.

Methods: This study utilizes triple-blinded protocol to assess the efficacy of tDCS concurrent with cognitive training to improve cognitive abilities over 12 weeks of regular training. Participants were assigned to one of three groups: 1) active 2mA left (AF3) anode - right (AF4) cathode, 2) active 2mA right (AF4) anode - left (AF3) cathode, or 3) sham stimulation concurrent with working memory training 3 times a week for a total of 12 weeks. At baseline, midpoint (6 weeks), and post-test (12 weeks), participants completed two cognitive paradigms, the N-Back and the DPX, and the MATRICS Consensus Cognitive Battery (MCCB). We applied a mixed ANOVA to assess the interaction of stimulation group and time.

Results: The study is not yet unblinded. A total of 40 participants (N = 10, 15, 15 across three groups) completed post-test assessments. MCCB scores performance improved over time across all participants (p < .001). The Attention and Vigilance subscale, however, showed a group x time interaction (p = .008), in which one group showed improvement over time, but the other groups did not.

Conclusions: Cognitive training is an effective tool for improving cognition in a group of healthy adults. Once we have completed our main analyses, we will break the blind to further assess the role of tDCS in cognitive improvement specifically.

Keywords: TDCS, Cognition, Learning and Memory, Cognitive Training

Disclosure: Nothing to disclose.

P453. The Opsin ChRmERa Offers Non-Invasive Expression Tracking With PET Imaging

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Background: Channelrhodopsins (ChRs) have revolutionized brain optogenetics and thus providing a powerful tool for precise control of neuronal activity. These light-sensitive ion channels allow us to manipulate specific neurons with high temporal and spatial resolution. However, the reliable and non-invasive tracking of ChR expression in vivo remains a significant challenge. Traditional methods, such as post-mortem immunohistochemistry lack real-time monitoring and cannot capture the changes in ChR expression over time. To overcome this limitation, we engineered ChRmERa, a novel fusion protein that combines the potent and red-shifted ChR (ChRmine) with the estrogen receptor ligand binding domain. This approach allows for non-invasive tracking of ChR expression using positron emission tomography (PET) with the radiopharmaceutical [18F]-fluoroestradiol (FES).

Methods: In this study, we first characterized the properties of ChRmERa through electrophysiological experiments in rodent brain slices. We injected AAV2/5-nEF DIO ChRmERa into the lateral hypothalamus of Vglut2-cre mice and performed whole-cell recordings from ChRmERa-expressing cells after 3 weeks. Next, we injected AAV2/5-hsyn1-ChRmERa into the rat and squirrel

monkey motor cortex and conducted PET imaging with the radiopharmaceutical [18F]-FES after the injection (rats: 5 weeks, squirrel monkey: 5 months). Additionally, we combined optogenetic stimulation and behavioral imaging with PET and [18F] fluorodeoxyglucose (FDG) to measure changes in regional brain glucose metabolism in awake mice injected with AAV2/5-hsyn1-ChRmERa in the motor cortex. Furthermore, we examined ChRmERa expression in two female rhesus macaques after AAV2/5-hsyn1-ChRmERa injection in the putamen. PET scans were conducted before and after the viral injection at multiple time points (6, 12, and 24 weeks), allowing for the longitudinal monitoring of ChRmERa expression in these macaques. In addition, we have investigated the functional activation of ChRmERa through single-unit recordings performed in awake macaques over time.

Results: Our electrophysiological results showed that ChRmERa retained its robust and efficient light-gated ion channel activity, comparable to ChRmine. Our PET imaging data showed that rats and the squirrel monkey injected with AAV-ChRmERa showed significantly higher binding of [18F]-FES in the motor cortex ($p < 0.05$) compared to the baseline scan. Immunohistochemistry further confirmed the post-mortem expression of ChRmERa in these animals, reinforcing its in vivo localization. We also found that optogenetic stimulation of the motor cortex in mice increases [18F]-FDG uptake in the motor cortex and the striatum ($p < 0.05$), as well as a decrease in [18F]-FDG uptake in the dorsal hippocampus ($p < 0.05$).

Our PET imaging studies showed that [18F]-FES binding in the putamen increased 9-fold in monkey #1 and 6-fold in monkey #2 at 6, 12 and 24 weeks. Finally, our functional studies of ChRmERa in awake monkeys revealed robust light-gated responses in 50% of putamen cells tested, and these responses remained stable to date (8 months after AAV injection).

Conclusions: Our findings provide evidence of ChRmERa's functional properties as an opsin and demonstrate its ability to be tracked longitudinally and non-invasively across rodents and nonhuman primates. The development of ChRmERa addresses the challenge of in vivo tracking of ChR expression and thus providing researchers with a valuable tool to advance the understanding of neuronal function and dysfunction. These striking results open up new possibilities for studying neuronal circuits in non-human primates.

Keywords: Optogenetics, PET Imaging, Mouse and Monkey Models

Disclosure: Nothing to disclose.

P454. Systematic Review of Psychostimulant Effects on Brain Activations and Functional Connectivity in Healthy Adults: Preliminary Results

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Background: Psychostimulant medications (methylphenidate [MPH], amphetamines [AMP]) have long been used therapeutically, but their pharmacodynamic effects on regional activations and brain functional connectivity remain unclear.

Methods: We conducted a systematic review on the use of psychostimulants in healthy adult participants, preregistered in PROSPERO (CRD42022365381). We searched PubMed, Web of Science, OVID (EMBASE, MEDLINE) and Scopus, from database inception to October 1st, 2022. Included were whole-brain neuroimaging studies which analyzed task-based activations and deactivations or resting-state indices after a single dose of MPH or AMP compared to its corresponding control condition.

Results: After deletion of duplicates and articles deemed irrelevant, 29 papers met inclusion criteria, comprising 937 subjects (39.3% female) with mean ± SD 30.2 ± 25.6 (median 18) subjects per study. Most studies ($n = 25$) were performed on a 3T MRI; one used 4T, and the remaining 1.5T. Multiple comparison corrections were generally reported, by contrast to measures of head motion, which were rarely provided. Among the 23 task-based studies, 7 were on cognitive control, 4 on reward learning, 2 assessed memory, 2 focused on perception, 2 on social communication, one on motor control and 4 were characterized as multi-domain. Here, we focus on the 7 cognitive control ($n = 327$; mean age: 24.4 ± 3.8) and 6 rest studies ($n = 152$; 21.1 ± 4.6). Nine studies used MPH (mean dose: 40.6 ± 11.0 mg) and four AMP (all at 20 mg).

For cognitive control tasks, significantly greater activations were reported after stimulant in medial, middle and inferior frontal gyrus, presupplementary motor area, supramarginal gyrus, superior parietal lobule, angular gyrus, inferior parietal gyrus, middle and superior temporal gyrus, paracingulate and anterior cingulate cortex, cerebellum, occipital gyri, caudate, dorsal thalamus, putamen, precentral gyrus, insula and parahippocampal gyrus. For the opposite contrast, control yielded stronger effects than stimulants in caudate. Two studies did not find significant differences between MPH and placebo on brain activity.

Half the resting-state studies measured perfusion, 2 utilizing pseudo-continuous arterial spin labelling, and one dynamic fast bolus tracking with ferucarbotran. The remaining studies reported regional homogeneity ($n = 1$), independent component analyses ($n = 1$) and global connectivity analyses ($n = 1$). Perfusion studies observed increases after stimulant administration in thalamus, medial dorsal nucleus, caudate nucleus, putamen, globus pallidus, amygdala, parahippocampal gyrus, insula, superior and medial frontal gyrus, paracentral lobule, cingulate cortex, postcentral gyrus, transverse temporal gyrus, parietal lobe, occipital cortex, cerebellum and brainstem/pons. Decreases in perfusion after stimulant administration were observed in anterior paracingulate cortex, insula and posterior cingulate cortex. Studies of functional connectivity highlighted increases after stimulant in thalamus, insula, precentral gyrus, middle and superior temporal gyrus and visual cortex. Control yielded stronger effects on frontal marginal gyrus, anterior cingulate gyrus, superior temporal sulcus, middle temporal gyrus, angular gyrus, inferior parietal gyrus, lingual gyrus and cerebellum.

Conclusions: An emerging albeit still preliminary literature suggests that acute psychostimulant effects in brain are widespread, but many questions remain. Sample sizes remain marginal for adequate statistical power, and the broad range of paradigms used hinders the ability to synthesize results to determine with precision the pharmacodynamic effects of psychostimulants on brain activity.

Keywords: Stimulants, Functional MRI (fMRI), Resting and Task fMRI, Acute Dose

Disclosure: Nothing to disclose.

P455. Altered Brain Histone Deacetylase Levels in Adults With Autism Spectrum Disorder

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Background: Epigenetic modifications, such as those that occur through histone deacetylases (HDACs), are recognized to play a role in the pathophysiology of autism spectrum disorder (ASD). Genome-wide acetylome analyses show altered histone acetylation in brain tissue of a group of individuals with idiopathic and syndromic ASD. Genetic disorders that are commonly associated with ASD such as 16p11.2 deletion/duplication syndrome and Rett syndrome show alterations in HDAC expression. Preclinical animal models of autism demonstrate alterations in brain HDAC levels and the restoration of social skills following HDAC inhibition. In humans, the HDAC family consists of several HDAC enzymes and a subset, namely HDACs 1, 2, and 3, can be imaged in vivo using [11C]Martinostat positron emission tomography (PET) imaging. In particular, HDAC1 and HDAC2 are highly relevant for cognition and neuroplasticity. The aim of this study was to use simultaneous [11C]Martinostat PET-magnetic resonance imaging (PET-MRI) to assess brain HDAC levels in adults with ASD.

Methods: Ten adults with ASD (7 males, 3 females, mean ± standard deviation (SD) age = 27.10 ± 6.61 years) and 18 neurotypical controls (CON) (8 males, 10 females, mean ± SD age = 27.22 ± 5.12 years) underwent a simultaneous PET-MRI scan with [11C]Martinostat. Individuals with ASD met the DSM-5 diagnostic criteria for ASD, corroborated by the Autism Diagnostic Observation Schedule, second edition (ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R) and had an intelligence quotient (IQ) above 85. Exclusion criteria included major physical illness, major surgery within the past six months, and PET-MRI contra-indications, including pregnancy and breastfeeding. Behavioral characteristics of individuals with ASD were obtained from their caretakers using the Social Responsiveness Scale, Second Edition (SRS-2), Aberrant Behavior Checklist, Second Edition (ABC-2), and Repetitive Behavior Scale, Revised (RBS-R). We focused on the Social Withdrawal subscale of the ABC-2 as a measure of social behavior. Participants with ASD were assessed with the Peabody Picture Vocabulary Test, 4th edition (PPVT-4) to measure receptive vocabulary. PET data were collected from 60 to 90 minutes post radiotracer injection. Whole brain voxelwise group comparisons of [11C]Martinostat uptake and correlations of behavioral and language measures with [11C]Martinostat uptake were conducted using a general linear model in FSL (FMRIB software library) FEAT with mixed effects and ordinary least squares, and a statistical threshold of $Z>2.3$, cluster-corrected $p < 0.05$. Age and sex were entered as covariates. Group comparison of age was conducted with a Mann-Whitney U test and group comparison of sex was conducted with a Fisher's exact test.

Results: Participants with ASD had an IQ of 100.30 ± 11.18 (range 91-127). This group of adults with ASD displayed variable levels of social difficulties based on the SRS-2 total T score (65.10 ± 7.56 (range 57-80)) and the ABC-2 Social Withdrawal subscale (11.30 ± 10.50 (range 0-31)), and repetitive behavior based on the RBS-R total score (15.70 ± 15.48 (range 2-55)). Higher scores on the SRS-2, ABC-2 Social Withdrawal subscale and RBS-R indicate more severe problems. The PPVT-4 standardized score was 101.4 ± 16.14 (range 65-125), displaying a range of receptive vocabulary skills from an extremely low score to a moderately high score.

ASD and CON groups did not show group differences in age ($U = 83.50$, $p = 0.77$) or sex ($p = 0.25$). Preliminary results showed higher HDAC levels in the left superior longitudinal fasciculus (SLF) and lower HDAC levels in the bilateral orbitofrontal cortex and right insula, Heschl's gyrus, superior temporal gyrus, and middle temporal gyrus in adults with ASD compared to CON ($Z > 2.3$, p cluster < 0.05). These brain regions have been implicated in ASD, with the orbitofrontal cortex and insula involved in emotion processing and the SLF and temporal lobe being key brain structures associated with language processing. With this sample size, no significant associations between HDAC levels and behavioral or language skills were observed in adults with ASD.

Conclusions: We identified altered HDAC levels in brain regions that have been implicated in ASD in adults with ASD. Given the involvement of HDACs in neuroplasticity, regional HDAC alterations may impact corresponding brain function. However, at this sample size, we did not detect associations between HDAC levels and caretaker-report behavioral measures or receptive vocabulary in adults with ASD. Ongoing and future work will be to expand the sample size to investigate sex differences in HDAC levels in ASD and associations between HDAC levels and symptom severity and language measures.

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Keywords: Autism Spectrum Disorder, Epigenetics, Human Neuroimaging, Histone Deacetylases

Disclosure: Nothing to disclose.

P456. MDMA Enhances Cortical Responses to Emotional Faces

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Background: MDMA is used recreationally and as an adjunct to psychotherapy, both of which may be related to its prosocial effects. Although the effects of MDMA are believed to be mediated by its action at serotonin receptors, little is known about how the drug affects neural reactivity to social or emotional stimuli. In the current study, we measured the effects of MDMA on cortical responses to a social-emotional oddball task in healthy individuals.

Methods: Twenty-four participants attended three sessions in which they received MDMA (100 mg), placebo, and methamphetamine (MA; 20 mg). Participants completed an emotional faces task consisting of images of human faces (angry, happy, neutral) and a cartoon face. The cartoon face was presented in 80% of trials, whereas the human faces (oddball stimuli) appeared in 20% of trials. Stimuli were presented in three blocks consisting of angry, happy, or neutral human faces along with cartoon faces. EEG signals included N170 peak, P3 peak, and MMN.

Results: MDMA, but not MA, increased N170 amplitude for both happy and angry faces compared to neutral and cartoon faces, relative to placebo. MDMA did not affect either the P3 peak or mismatch negativity.

Conclusions: The increase of N170 amplitude after MDMA is consistent with enhanced early processing of human emotional features, which may result in enhanced perception of emotional states in others. Enhanced perception of emotions in others may contribute to the effects of MDMA on social behavior and patient/therapist interactions.

Keywords: MDMA, Face Emotion Processing, EEG, Social Behavior

Disclosure: Nothing to disclose.

P457. Neural Effects of a Psychedelic Are Conserved in the Presence of a 5HT2A Antagonist and in the Absence of Corresponding Psychedelic Effects

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Background: Psychedelics have been used by humans for thousands of years and recent clinical studies suggest psychedelics are efficacious in treating depression. One of the key benefits of their therapeutic mechanism of action is broad symptom coverage along with rapid acting therapeutic effects, which is in contrast to traditional antidepressants which may take months to reach therapeutic effects. However, acute administration of psychedelics that have shown clinical benefit are associated with a psychedelic "trip" that includes psychedelic effects. It has also been shown that these perceptual effects occurs through activation of the serotonin 2A (5HT2A) receptor and pretreatment with a selective 5HT2A receptor antagonist blocks all of the acute changes in perception. There have been numerous preclinical studies showing that pretreatment with selective 5HT2A receptor antagonists blocks the behavioral effects of psychedelics associated with psychedelic effects in humans, while leaving the rapid acting antidepressant effects intact. However, it remains to be seen whether the perceptual effects of psychedelics in humans are necessary for their therapeutic effects. Here, we investigate the acute behavioral and neural effects of LSD, with both with pre-administration of the 5HT2A antagonist ketanserin and with placebo, in order to determine whether the behavioral and neural effects diverge at distinct time points.

Methods: We used a published dataset acquired in the course of a registered clinical trial (NCT02451072). 24 healthy subjects were included in this dataset. The study was designed as a fully double-blind, randomized, within-subject cross-over study. During a session, subjects were pretreated with either a placebo or the 5-HT2A antagonist ketanserin 60 minutes before being treated with either a placebo or LSD. Thus, each subject participated in 3 sessions in which they underwent each of the following pretreatment + treatment conditions in a randomized, balanced order: i) Placebo + placebo, ii) Placebo + LSD, and iii) Ketanserin + LSD. Two BOLD fMRI resting-state scans were performed, one 75 and the other 300 minutes after treatment. To assess participants' experience, a self-report questionnaire (5D-ASC) was administered 720 minutes after treatment, and a shorter version of the 5D-ASC 180, 250 and 360 minutes after treatment. From the BOLD fMRI time series we computed global brain connectivity (GBC) as the mean functional connectivity (FC) of a parcel with all other parcels. We then compared GBC maps within subjects between treatment conditions and at different time points.

Results: As previously reported, subjects pretreated with placebo and then LSD experienced changes in perception consistent with the psychedelic effects of LSD as measured by the 5D-ASC while both subjects pretreated with ketanserin and then LSD and subjects treated with placebo alone did not show notable effects on the 5D-ASC at any timepoint. In our new analysis reported here, we identified a more nuanced effect at the neural level. Ketanserin pretreatment revealed a functional brain pattern that was markedly different than the one observed in the placebo condition at the early timepoint. More specifically, the ketanserin + LSD neural effect did not correlate with the placebo + LSD neural effect. However, at the later time point (300 min after treatment administration), we observed a shift and the ketanserin + LSD effect exhibited a strong brain-wide correlation with the effect observed in the LSD + placebo condition. This effect was evident for both the GBC map ($r = 0.79$) and FC matrix ($r = 0.64$).

Conclusions: These analyses show that there are functional changes in brain connectivity induced by LSD that still occur after pretreatment with a 5HT2A antagonist and that persist in the absence of strong psychedelic effects. This indicates that even in the absence of strong psychedelic effects of LSD (i.e. in the ketanserin+LSD condition) at the later time point the evaluated neural changes strongly correlate with the neural effects visible during a psychedelic trip induced by LSD alone (i.e. in the placebo +LSD condition). These results in humans support the notion that LSD after pretreatment with ketanserin induces functional neural changes even in the absence of a strong psychedelic trip.

Keywords: Clinical Neurobiology, Psychedelic Effects, Functional Neuroimaging, fMRI, Psychedelic Therapy

Disclosure: Terran Biosciences Inc: Founder (Self)

P458. Behavioral Characterization of Zaleplon Effects in Rats: Further Evaluation and Influence on Glutamatergic Signalling in the Prefrontal Cortex

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Background: Zaleplon, a non-benzodiazepine sedative/hypnotic drug, exerts its pharmacological effects by selectively binding to the α1-subunit of the GABAA receptor. By increasing inhibitory neurotransmission, zaleplon may affect the balance between GABAergic and glutamatergic neurotransmission in various brain regions, including the prefrontal cortex. Our previous results have shown that following repeated zaleplon treatment, at a dose of 0.625mg/kg, GABA immunostaining of the prefrontal cortex remained unchanged while GABAAα1 levels were decreased. Hence, ongoing research was focused on components of glutamatergic neurotransmission. As subunits of NMDA receptor were partially affected, this study aimed to examine the effects of prolonged zaleplon treatment on vesicular glutamate transporter (vGluT1) expression in the prefrontal cortex of rats. Also, the behavioral effects of repeated administration of a low dose of zaleplon were further examined, as the selected dose previously acutely facilitated learning in rats.

Methods: Adult male Wistar rats, divided into two groups ($n = 6$ per group), were i.p. injected with a low dose of zaleplon (0.625 mg/kg) or saline, respectively, for five consecutive days. The active avoidance (AA) test was performed in automated two-way shuttle boxes, with 50 trials per day. During the first 5 s of each trial a sound signal was presented, allowing the animal to avoid shocks by moving to other compartment (avoidance response). If the animal did not respond within this period, a foot shock of 0.3 mA (7 s duration) was applied. The number of successful active avoidance responses was counted. Protein expression of vGluT1 was investigated in synaptosomes of the prefrontal cortex using the Western blot technique, and results were presented as a percentage of the control. For statistical analysis of data, Student's t-test was used, and $p < 0.05$ was considered statistically significant.

Results: In the AA test, the same dose of zaleplon (0.625 mg/kg), which acutely facilitated retrieval of avoidance memory, significantly ($p < 0.05$, Student's t-test) increased the acquisition rate in the group of rats treated with zaleplon during five days, compared to the saline group. Considering the vGluT1 protein expression, no statistically significant effect of zaleplon treatment was observed ($p > 0.05$, Student's t-test).

Conclusions: Our study demonstrated the memory-enhancing effects of repeatedly administrated zaleplon using an AA task in rats. To the best of our knowledge, our results are the first to show

that low doses of zaleplon can support retrieval-based learning without sedative effects. Furthermore, the repeated administration of zaleplon may induce potential changes in glutamate-mediated neurotransmission. Five-day intraperitoneal administration increased the level of the NR2A receptor subunit but not of vGluT1. Further research will elucidate the potential role of zaleplon in promoting synaptic plasticity, learning, and memory formation by provoking changes solely on the receptor subunits level.

Keywords: Zaleplon, Behavioral Pharmacology, Glutamate, Rats

Disclosure: Nothing to disclose.

P459. Identification of the 5-HT2A Signaling Pathways Responsible for Psychedelic Potential

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Background: Classical psychedelic drugs (serotonergic hallucinogens) show therapeutic potential in depression and other disorders. Although the serotonin 5-HT2A receptor (5-HT2AR) appears to be the primary target for psychedelics in the CNS, the subsequent downstream signaling events that mediate the effects of psychedelics have not been identified. Prototypical psychedelics activate both Gq/11 and β-arrestin2 (βArr2) signaling via 5-HT2AR, making their respective roles unclear. A further complication is that certain 5-HT2AR agonists such as lisuride do not induce psychedelic effects in humans despite activating Gq/11 and βArr2.

Methods: We developed a series of 5-HT2A-selective N-benzylphenethylamine (NBOMe) ligands with varying agonist efficacies (N = 16), including βArr2-biased ligands, and used them to evaluate the relationship between 5-HT2A Gq and βArr2 efficacy and psychedelic potential. 5-HT2AR Gq and βArr2 efficacy was assessed using bioluminescence resonance energy transfer (BRET). Psychedelic potential was assessed using the head-twitch response (HTR), a 5-HT2AR-mediated involuntary head movement in mice that is highly predictive of human psychedelic activity. HTR experiments were performed in in male C57BL/6J mice. Additional analyses compared the relationship between 5-HT2A Gq and βArr2 efficacy and psychedelic potential for phenethylamine psychedelics (N = 24), and for psychedelic and non-psychedelic 5-HT2AR agonists from the lysergamide and tryptamine structural classes (N = 8). Finally, we tested whether inhibition of the Gq-phospholipase C (PLC) signaling cascade can block the HTR.

Results: For the sixteen NBOMes, there was a robust correlation between HTR magnitude and 5-HT2A-Gq efficacy ($R_s = 0.8242$, $p = 0.0005$), whereas HTR magnitude was not correlated with βArr2 recruitment efficacy ($R_s = -0.01538$, $p = 0.9638$). None of the NBOMes with Gq Emax < 70% (relative to serotonin) induced the HTR, potentially indicating efficacy must exceed a threshold level to induce head twitches. For the 24 phenethylamine psychedelics, HTR magnitude was correlated with Gq efficacy ($R_s = 0.7339$, $p < 0.0001$) but not βArr2 recruitment ($R_s = 0.34$, $p = 0.104$) and all of the psychedelics had Gq efficacy > 70% Emax. For the eight tryptamines and lysergamides, HTR magnitude was correlated with Gq efficacy ($R = 0.8948$, $p = 0.0027$); the tryptamine and lysergamide psychedelics had Gq Emax > 70%, while their non-psychedelic analogs had Gq Emax < 70%. Confirming the role of Gq in the HTR, pretreatment with the selective Gq/11 inhibitor YM-254,890 ($F(3,12) = 8.69$, $p = 0.0025$) or the PLC inhibitor edelfosine ($F(2,16) = 11.34$, $p = 0.0009$) blocked the HTR induced by 1 mg/kg R-(-)-2,5-dimethoxy-4-iodoamphetamine (DOI), a psychedelic 5-HT2AR agonist.

Conclusions: These results indicate that 5-HT2A-Gq activation but not βArr2 recruitment serves a key role in mediating psychedelic-like behavioral effects. In addition, it appears that a threshold level of Gq efficacy is required to induce the HTR in mice and psychedelic effects in humans, potentially explaining why certain 5-HT2AR agonists such as lisuride are non-psychedelic. These results have implications for drug development because it may be possible to identify 5-HT2A-Gq partial agonists that do not induce the HTR and lack strong psychedelic effects in humans but retain sufficient efficacy to induce therapeutic neurophysiological effects such as neuroplasticity via 5-HT2AR.

Keywords: Psychedelics, 5-HT2A Receptor, Beta Arrestin 2, LSD, Psilocybin

Disclosures: Compass Pathways, Betterlife Pharma, Brightminds Bioscience, ATAI Life Sciences, Psilosterics, Alexander Shulgin Research Institute, Cognesy Therapeutics: Contracted Research (Self).

P460. Evidence to Show Nalfurafine is Aversive at Analgesic Doses Suggesting it is Not an Atypical Kappa Opioid Receptor Agonist

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Background: Kappa opioid receptor (KOPr) agonists have potent anti-inflammatory and analgesic properties but attempts to exploit them clinically have been thwarted by their dissociative, dysphoric, and psychotic adverse events. For example, these unacceptable side-effects led to the discontinuation of the CNS-acting KOPr drug, enadoline. Nalfurafine is a CNS-active, KOPr agonist marketed in Japan to treat uremic pruritus. It is atypical because it is a G-protein biased agonist which is believed to produce antinociception without inducing CNS adverse events typical of KOPr agonists. We tested the validity of this hypothesis by comparing the analgesic and aversive effects of nalfurafine and the typical, non-biased, KOPr agonist, U50,488, in tail withdrawal and conditioned place aversion (CPA) tests.

Methods: C57BL/6J mice (8-weeks old) were used. KOPr-induced spinal antinociception was assessed by 52°C warm water tail-withdrawal. Cut-off time was 15s to prevent tissue damage. After obtaining baseline tail-withdrawal time, mice received U50,488 (1.25; 5; or 20mg/kg, i.p.), nalfurafine (0.015; 0.06; or 0.24mg/kg, i.p.), or saline (i.p.) and were retested 30 min later. Drugs were administered blinded to the experimenter and counterbalanced over 4 to 5 consecutive days. KOPr-agonist induced changes in latency to withdraw the tail were converted to %max possible effect (%MPE): ((latency drug minus latency baseline)/(15s minus latency baseline))*100%, and plotted against log-dose values. Dose-responses were generated by least-squares linear regression analysis followed by calculation of 95% confidence interval (CI) after outliers identified by Grubbs test were removed (n = 1). The antinociceptive effect of U50,488 (5mg/kg) was compared to doses of nalfurafine by unpaired t-tests. Sex differences were investigated by extra sum-of-squares F test per KOPr agonist.

The aversiveness of U50,488 and nalfurafine was tested by CPA in a separate cohort of mice (8-weeks old; 24 males). Baseline preference scores between both compartments were obtained over 2 days in 15 min habituation sessions. Mice were counterbalanced based on preference into treatment groups and

conditioned in 4 single-day sessions. In 2 conditioning sessions they received a KOPr agonist (5mg/kg U50,488 or 0.06mg/kg nalfurafine, i.p.) in a blinded manner before 40 min of confinement to the paired compartment alternated by 2 sessions of saline (i.p.) before 40 min in the unpaired compartment. On the fifth day (CPA test), animals had 15 min access to both compartments, drug-free. CPA scores as discrimination index (DI) were calculated by: (time_paired minus time_unpaired)/total time, where a DI of 1 is perfect preference and -1 perfect aversion. DI at CPA test was compared to habituation by paired t-test. CPA DI scores between KOPr agonists were determined with unpaired t-tests. Significance level: $p < 0.05$ (two-tailed).

Results: 5mg/kg U50,488 decreased the latency to withdraw the tail by 26.6% [20.2-32.8%] (mean %MPE [95% CI]) ($n = 19$) which was statistically equi-effective to 0.06mg/kg nalfurafine, 36.5% [30.2-42.4%] (mean difference %MPE±SEM, p-value) (-9.9 ± 20.9%) ($p = 0.64$) ($n = 39$). A low dose of 1.25mg/kg U50,488 did not affect tail withdrawal (-1.0% [-10.9-9.1%]) ($n = 19$) nor did 0.015mg/kg nalfurafine (-3.3% [-13.7-7.0%]) ($n = 20$), and both low doses were equi-effective with each other (-2.3 ± 7.4%) ($p = 0.76$). A high dose of 20 mg/kg U50,488 decreased latency to tail withdrawal by 54.2% [44.1-64.3%] ($n = 20$) while 0.24mg/kg nalfurafine decreased it by 76.1% [65.1-87.2%] ($n = 20$). 20 mg/kg U50,488 produced 21.9 ± 7.4% less antinociception compared to 0.24mg/kg nalfurafine ($t(38) = 3.0$, $p = 0.005$). No sex-differences in tail withdrawal latencies were found for nalfurafine ($F(2,75) = 0.58$) ($p = 0.56$) ($n = 39$-40/sex) or U50,488 ($F(2,54) = 0.28$) ($p = 0.75$) ($n = 28$-30/sex).

U50,488 (5 mg/kg) induced significant CPA compared to baseline (mean difference in DI±SEM, 0.11 ± 0.05, $p < 0.05$) ($n = 12$), but so did 0.06mg/kg nalfurafine (-0.14 ± 0.02, $p<0.001$) ($n = 12$). There was no significant difference between U50,488- and nalfurafine-induced CPA at test (mean difference in DI±SEM, 0.03 ± 0.06, $p = 0.65$).

Conclusions: Nalfurafine, a putative atypical G-protein biased KOPr agonist, did not differ from U50,488, a typical non-biased KOPr agonist, in antinociceptive efficacy (tail withdrawal assay) and aversion (CPA). These results do not support the hypothesis that nalfurafine is atypical by virtue of producing analgesia without inducing dysphoria. In clinical trials, nalfurafine was generally well tolerated with few reports of psychiatric adverse events. The apparent divergence between the non clinical and clinical findings may be due to the indication, i.e., pruritis versus thermal algesia, the locus of therapeutic effect, species differences, and/or the respective doses required to produce efficacy. There is good evidence to show the antipruritic effect is substantially mediated by peripheral KOPrs because difelikefalin, a potent, selective, peripherally restricted, KOPr agonist, is also effective in treating uremic pruritis. An explanation for nalfurafine's lack of CNS side-effects when used clinically is because its anti-pruritic effect is peripherally mediated, and its concentration in the CNS is too low to produce dysphoria. In conclusion, the hypothesis that nalfurafine is an atypical, non-dysphoric KOPr agonist is probably incorrect.

Keywords: Kappa Agonist, Analgesia, Dysphoria, Nalfurafine

Disclosures: DevelRx Ltd: Board Member (Self). DevelRx Ltd: Stock / Equity (Self).

P461. The Enantiomer (S)-Tianeptine is Responsible for the Memory- and Cognition-Enhancing Effects of Racemic Tianeptine as Shown by the Novel Object Recognition Test in Vivo in Rats

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Background: Racemic tianeptine has been marketed for major depressive disorder (MDD) outside of the U.S. for more than 3 decades. Recent clinical studies also suggest that racemic tianeptine treatment improves memory and cognition in patients with Alzheimer's disease and depression, and in patients with bipolar disorder. Racemic tianeptine is composed of a 1:1 mixture of the enantiomers (S)- and (R)-tianeptine. It was previously reported that (R)-tianeptine is a weak agonist of the μ-opioid receptor. The aim of this study was to investigate the memory- and cognition-enhancing properties of racemic tianeptine and (S)- and (R)-tianeptine in the novel object recognition (NOR) test in rats.

Methods: In the NOR test, adult male Long-Evans rats (275-299 grams) were assessed for recognition memory in a test apparatus comprised of an open-field arena (40 x 40 cm) under dimmed lighting. All training and testing sessions were video recorded and scored by an observer blind to treatments. On Days 1 and 2, rats were allowed to freely explore the empty arena for a 10-minute habituation period. On Day 3, rats ($n = 16$/group) were given intraperitoneal (i.p.) injections of saline (vehicle), galantamine (1 mg/kg) serving as a positive control, racemic, and (S)- or (R)-tianeptine (3, 10, and 30 mg/kg). The (R)- and (S)-tianeptine enantiomers possessed a chiral purity of >99%. Test compounds were administered at the appropriate pretreatment time (30 min prior to testing for saline and galantamine; 60 min prior to testing for racemic tianeptine and both enantiomers). Rats were then placed into the test arena in the presence of two identical objects. Each rat was placed in the arena facing the same direction at the same position, and the time spent actively exploring the objects during a 3-minute training session (T1) was recorded. The rat was returned to its home cage following training. After 48 hours, the rats were administered test compounds again at the appropriate pretreatment time and placed into the test arena in the presence of one familiar object and one novel object. The time spent exploring each object was recorded for 5 minutes in the testing session (T2). The presentation order and position of the objects (left/right) in T2 was randomized between rats to prevent bias from order or place preference. The primary endpoint was the Recognition Index, defined as the ratio of the time spent exploring the novel object divided by the total time spent exploring both objects [(Novel / (Familiar + Novel)) × 100%] during the 5 min test session. A Recognition Index value of 50% suggests no memory of the familiar object from 48-hours prior. Data were analyzed using a one-way ANOVA followed by Dunnett's post hoc test. The study was approved by the Institutional Animal Care and Use Committee in accordance with the National Institute for the Care and Use of Laboratory Animals. The integrity of the data was ensured through a quality control process.

Results: Racemic tianeptine at 10 and 30 mg/kg significantly increased Recognition Index relative to vehicle during the 5-minute test as shown by Dunnett's post hoc test by 9.5% ($p < 0.05$) and 12.6% ($p < 0.001$), respectively. Racemic tianeptine at 3 mg/kg showed a 7.3% increase in Recognition Index, however, this was non-significant. (S)-tianeptine at 3 and 10 mg/kg significantly increased the Recognition Index by 10.5% and 9.3%, respectively (each $p < 0.05$), while 30 mg/kg showed a non-significant increase of 3.3%. (R)-tianeptine at 3 and 10 mg/kg showed no significant effects on Recognition Index. The high dose of 30 mg/kg (R)-tianeptine could not be evaluated since this dose caused overt sedation and catalepsy-like behavior in the rats, likely due to agonism at the m-opioid receptor. The reference compound galantamine at 1 mg/kg significantly enhanced recognition memory by 12% ($p < 0.01$), validating the test.

Conclusions: The current study demonstrated that racemic tianeptine and the (S)-enantiomer significantly improved recognition memory relative to vehicle, whereas the (R)-enantiomer did not significantly improve recognition memory. These results suggest that (S)-tianeptine can improve recognition memory

without the potential μ-opioid abuse liability of (R)-tianeptine and should be further explored for its potential memory and cognition-enhancing effects in conditions such as Alzheimer's disease, depression, and bipolar disorder.

Keywords: Memory Enhancing, Novel Object Recognition, Memory and Learning, Preclinical Models and Endpoints, In Vivo

Disclosure: Tonix Pharmaceuticals, Inc: Employee (Self).

P462. Prediction of Psychedelics and Non-Psychedelics Via Whole-Brain C-Fos Maps

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Background: Psychedelics are a class of compounds which have recently re-emerged as a source of potential therapies for treatment resistant mood disorders. Their function is poorly understood, though increasing neuroplasticity seems to be a key feature of their long-term influence. Although many compounds are called psychedelics, and others have overlapping properties, we lack a clear understanding of how these compounds differentially influence plasticity across the whole brain. Here, we examine this using whole-brain light sheet imaging to visualize the immediate early gene cFos, a marker of plasticity.

Methods: In this study, we examine the influence on cFos expression for 8 compounds, including psilocybin, 5-MeO-DMT, the SSRI fluoxetine (acute and chronic administration), the entactogen MDMA, the dissociative ketamine, and non-hallucinogenic serotonergic agonist 6-fluoro-DET. A total of 64 mice were assigned across 8 conditions (psilocybin at 1 mg/kg, 5-MeO-DMT at 20 mg/kg, acute fluoxetine at 10 mg/kg, chronic fluoxetine at 10 mg/kg daily for 14 days, MDMA at 7.8 mg/kg, ketamine at 10 mg/kg, 6-F-DET at 20 mg/kg, and saline). Groups had equal numbers of male and female mice. Mice were sacrificed 2 hours following drug administration, brains were cleared, stained for cFos, and imaged using whole-brain light sheet microscopy at spatial resolution of 1.5 um, 1.5 um, 4 um along the x, y, and z axis respectively. Images were co-registered with the Allen CCF, and cFos staining cells were counted using an automated algorithm in 316 summary structure regions. To compare between drugs, we developed a machine learning pipeline using sci-kit learn to identify regions most informative for classification. This pipeline involved preprocessing which transformed features from counts into percent per mouse, followed by transformation and scaling. Feature selection was carried out using the 'Boruta' technique, which relies on scrambled permutations to establish a feature importance threshold. A 4-fold cross-validation training and testing split was performed 100 times using a logistic regression model with ridge regularization, and results were averaged. These models were further interrogated using the Shapley Additive explanations (SHAP) package, to assign feature importance for each prediction made.

Results: We find distinct patterns of drug-evoked cFos expression across conditions, with many features distinguishing between the tested compounds. When training and testing a classifier on the full set of conditions, we find a mean AUC for the precision-recall curve of 0.71, with some compounds exhibiting near perfect classification (e.g., AUC = 0.99 for MDMA), while the same feature set yielded worse classification at chance level or below for other compounds (e.g., AUC = 0.5 for 6-F-DET or AUC = 0.39 for acute SSRI). A classifier trained on distinguishing psilocybin from ketamine achieved AUC of 0.87, with the dorsal agranular Insular cortex (AId), visceral area (VISC), xiphoid nucleus (Xi) and gustatory areas (GU) represented in a majority of models trained. We examined differences between 5-HT2A agonists (psilocybin, 5-MeO-DMT) and the entactogen MDMA. Perfect classification was achieved (AUC = 1.0), with a variety of thalamic nuclei (AM, AV, CL, LD, LGd, LP, VAL) and some cortical regions (SSp-ll, RSPd) being the most informative features and found in all models trained.

Conclusions: Despite some overlapping behavioral effects in humans, we found that psychedelics and related compounds produce distinct and distinguishable patterns when examining cFos expression in mice using whole-brain light sheet imaging. We identified both regions which are known to be influenced by these compounds, as well as new regions hitherto unexamined in these conditions. Our study showed that whole-brain cFos expression is a promising approach for screening compounds and producing new leads for further investigation, and classifiers like those trained here can reveal brain regions that may be driving the differential effects between therapeutic agents.

Keywords: Psychedelics, cFos, Neuroplasticity

Disclosure: Nothing to disclose.

P463. Blink Rate, Pupil Size, and Blink-Induced Pupil Changes Are Vigilance Dependent and Heritable

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Background: Eye-blink rate and pupil size are the two physiological measures relating to arousal networks, striatal and brainstem dopaminergic, norepinephrinergic and serotoninergic activity (Cazettes, 2021; Demiral, 2022; Murphy, 2014). While being considered as a pupillary artifact (Yoo, 2021), pupil size changes due to eye-blinks (named here as Blink Induced Pupil Dynamics, BIPD) are likely to be part of the general ascending arousal system as blinks are shown to initiate arousal nuclei activation (Demiral, 2023) and induce EEG changes related to conscious states (Bonfoglio, 2011) while the pupil size is linked to Locus Coeruleus (LC) activity (Murphy, 2014). By using HCP 7T fMRI dataset (Van Essen, 2013) which contain twins and multiple resting state fMRI runs together with eye-tracing, we investigated the reliability of the BIPD and a few other eye-related measures within and across subjects and examined the heritability of these measures with Mx models (Rijsdijk and Sham, 2002) via using mono and dizygotic intra-twin correlations. We classified resting state scans into two main levels of drowsiness (i.e., vigilant versus drowsy) via pupil size continuity, and conducted our analysis per each vigilance state.

Methods: HCP 7T fMRI dataset: Details can be found at https://www.humanconnectome.org. Eye-tracking preprocessing was conducted with Eye Link 1000 system with 1kHz sampling rate from the right eye. Time period between 40-400ms of pupil loss was marked as eye-blinks. Each resting scan was classified as one of the four states as follows: a) vigilant (where less than 10% time of the run pupil was not detected; b) drowsy (10%-40% pupil loss in a run); c) very drowsy (40%-70% pupil loss in a run); and d) discarded (any run with more than 70% pupil data loss). As a result of the above procedure, we classified a total of 560 runs as follows: 291 vigilant runs (across 111 subjects), 111 drowsy runs (across 75 subjects) and 85 very drowsy runs (across 59 subjects). 73 runs were discarded (across 41 subjects) leading to a total of 487 usable runs across 141 participants. We calculated blink rate, blink duration, average pupil size, and blink induced pupil dynamics (BIPD) measures for each run. We defined six BIPD measures: P1 (positive peak around 500ms) peak time and peak amplitude, N1

(negative peak around 1s) peak time and peak amplitude, N1 – P1 peak time difference, P1 -N1 peak-drop magnitude. To estimate the relative contribution of genetic and environmental sources to the total phenotypic variance, we fit linear structural equation models using the OpenMx package (Boker, 2023) in R software. ACE/ADE linear structural equation models were used. The best fitting models were chosen based on Akaike's Information Criterion (AIC).

Results: Within-subject reliability: Vigilant state; mean = 0.68 (std = 0.31, median = 0.83), and all drowsy states mean = 0.56 (std = 0.36, median = 0.69), indicating that BIPD and eye measures for a participant was highly reliable and stable within the vigilance state. Test-retest reliability per measure: For vigilant state; blink rate (.825), blink duration (.743), pupil size (.808), P1 peak time (.589), P1 peak amplitude (.374), N1 peak time (.876), N1 peak amplitude (.661), N1-P1 peak time difference (.766), P1-N1 peak magnitude drop (.385). For drowsy state; blink rate (.470), blink duration (.730), pupil size (.734), P1 peak time (.305), P1 peak amplitude (.755), N1 peak time (.387), N1 peak amplitude (.552), N1-P1 peak time difference (.397), P1-N1 peak magnitude drop (.715). Indicating that blink rate, blink duration, pupil size, N1 peak amplitude are highly reliable and stable across vigilance states, while P1 and N1 peak times and N1-P1 peak time difference were reliable for the vigilant state. Heritability analysis: Models with A (additive) and E (environmental) factors explained higher variance in Mx models: blink rate (a2 = .36 CI = .11-.56, e2 = .64 CI = .43-.88), blink duration (a2 = .40 CI = .16-.59, e2 = .59 CI = .40-.83), pupil size (a2 = .61 CI = .41-.74, e2 = .39 CI = .26-.58), P1 peak time (a2 = .35 CI = .03-.59, e2 = .64 CI = .40-.96), P1 peak amplitude (a2 = .19 CI = .28-1.9, e2 = .66 CI = .43-.96), N1 peak time (a2 = .27 CI = .01-.50, e2 = .72 CI = .49-.98), N1 peak amplitude (a2 = .46 CI = .17-.65, e2 = .54 CI = .34-.82), N1-P1 peak time difference (a2 = .25 CI = .01-.51, e2 = .75 CI = .48-.99), P1-N1 peak magnitude drop (a2 = .05 CI = -.25-.33, e2 = .95 CI = .66-1.24). Indicating that there was mild to strong additive/genetic factors in blink, pupil and BIPD measures.

Conclusions: Our study provides a mechanistic link between drowsiness, BIPD, blink and pupil dynamics, and shows that pupil and blink might share common neural sources simultaneously active during blink moment. Most of the BIPD measures have heritable component where significant additive genetic factors along with environmental factors dominate the structural equation models. In the future work, we are aiming to understand how addiction and substance use could influence BIPD, and whether it can be used as a simple behavioral biomarker for predicting abuse potential, withdrawal, and relapse risk.

Keywords: Eye-Blink, Pupil, Twin-Study, Heritability, Drowsiness

Disclosure: Nothing to disclose.

P464. Social Competition in Mice: The Role of Cortical-Subcortical Interactions

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Background: Social competition is essential for social living across species. Our recent work in mice demonstrates that medial prefrontal cortex (mPFC) neural activity is predictive of competitive success in a reward-based competition (Padilla-Coreano et al., 2022). Other recent studies across species support a role for mPFC in competitive success (Li et al., 2022; Ligneul et al. 2016). However, given that multiple subcortical regions play a role in reward seeking and dominance behavior, the mPFC is likely not working alone to coordinate social competition. The goal of this exploratory study was to identify cortical-subcortical functional networks underlying social competition behavior in mice. Given past studies implicating the mediodorsal thalamus, lateral hypothalamus and amygdala in dominance behavior (Zhou et al., 2017; Padilla-Coreano et al., 2022; Munuera et al., 2018) and the role of hippocampus in social memory (Phillips et al., 2019) we targeted our study to these subcortical regions.

Methods: Group housed male mice (n = 4) were implanted with nichrome multi-site chronic electrodes in the mPFC, basolateral amygdala (BLA), mediodorsal thalamus (MD), lateral hypothalamus (LH), and ventral hippocampus (vHPC). Mice were trained to associate a tone with a liquid reward. After reward learning, subject mice were wirelessly recorded during competition sessions with cagemates, such that two cagemates competed for rewards signaled by tones. As a control, mice were also individually recorded while receiving tones and rewards (reward only trials) and while rewards were randomly omitted (reward omission trials). These two types of trials matched the experience of hearing tones and receiving or not receiving rewards but lacked the social and competitive components, thus allowing us to isolate the responses that relate to social competition. Local field potentials from mPFC, BLA, MD, LH and vHPC and single cell activity from mPFC (n = 57) were analyzed during winning (n = 39), losing (n = 39), reward only (n = 62) and reward omission (n = 14) trials.

Results: All mice learned the association between tone and reward over 11 days with repeated trials (ANOVA $F = 9.68$, $p < 0.0001$). Our preliminary results suggest that the social competition task engages two brain rhythms, a slow 2-6 Hz and a 6-12 Hz rhythm. To address whether these brain rhythms were modulated by competitive success rather than receiving a reward, we compared power for these two frequency bands between winning vs reward only trials and losing vs omission trials. We found that power in all brain regions was modulated by winning. The vHPC and mPFC increased 2-6 Hz power during winning (rank sum winning vs reward vHPC $p = 0.003$; mPFC $p < 0.0001$), and winning modulated 6-12 Hz power in the MD, LH and BLA (rank sum winning vs reward MD $p = 0.003$; LH $p = 0.007$ and BLA $p = 0.01$). In the mPFC, mostly different neurons responded to reward and winning trials (16% encoded winning, 19% encoded reward and 8% encoded both). On the other hand, losing had a more selective effect, as only LH had significant power differences in response to losing for the 2-6 Hz rhythm (rank sum losing vs omission $p < 0.0001$). In the mPFC, 14% of the recorded neurons encoded losing while none had significant responses to reward omissions.

Conclusions: This preliminary study suggests that winning engages many mPFC subcortical connections. Particularly, the vHPC and mPFC engage the same slow rhythm, while losing evokes more local activity in mPFC that is not reflected in power changes in the local field potential. Interestingly, rhythms in the LH are modulated by both winning and losing but different frequencies were affected. Future studies will focus on analyzing directionality between these two rhythms across all cortical-subcortical connections to understand potential sources and causal roles.

Keywords: mPFC, Social Competence, Gamma, Theta, Delta

Disclosure: Nothing to disclose.

P465. A Markovian Neural Barcode Representing Mesoscale Cortical Spatiotemporal Dynamics

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Background: Cortical dynamics consist of stereotyped patterns of recurrent activity motifs. These are the underlying dynamical features that comprise large scale neural networks. Whether the temporal sequencing of these motifs is functionally or anatomically constrained, similar to a 'grammar' governing this dynamical system, is not known and disruptions to this structure may underlie pathological alterations seen in models for neuropsychiatric disease.

Methods: We use mesoscale cortical imaging to sample calcium dynamics in male and female transgenic Thy1-jRGECO1a mice. Animals are headfixed and cortical activity sampled at 50Hz from a large expanse of dorsal neocortex simultaneously in a state of quiet wakefulness, to align with human resting state imaging, or as they perform a task. We then quantify the sequencing of neocortical motifs using a first-order Continuous Time Markov Chain model that probabilistically describes the temporal sequences of activity motifs. Unwrapping transition probability matrices creates a 'Markovian Neural Barcode' to describe the 'grammar' constraining neocortical dynamics in models for neuropsychiatric disease, including stress, seizure, and psychopharmacological manipulations.

Results: The Markovian Neural Barcode describes a statistical structure, or an underlying grammar, governing large scale cortical dynamics. Projection of the Markovian Neural Barcode in principal component space reveals individualized signatures overlying this common structure ($n = 45$ mice, $n = 180$ recordings; Intra-Animal 0.06 ± 0.042; Inter-Animal 0.13 ± 0.069; Wilcoxon Rank Sum, $p = 1.14e\text{-}71$). The method is sensitive to models for neuropsychiatric disease, including seizure ($n = 8$; WRS, $p = 3.82e\text{-}7$) and explains sex differences in functional connectivity after chronic variable stress. Pharmacological manipulation of catecholamine, cholinergic, serotonergic, and glutamatergic systems reveal unique effects on the Markovian Neural Barcode (ex: $n = 6$ risperidone vs $n = 19$ vehicle: WRS $p = 1.1e\text{-}29$).

Conclusions: Neocortical activity motif sequencing is highly structured and perturbed in models for neuropsychiatric disease. The Markovian Neural Barcode provides a powerful lens from which to characterize normative and pathological neocortical dynamics.

Keywords: Functional Data Analysis, Mouse Brain, Electroconvulsive Therapy, Neuropsychopharmacology

Disclosure: Nothing to disclose.

P466. Human In Vivo Striatal Dopamine Synthesis Capacity and MEG Measured Cortical Network Connectivity

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Background: Molecular neuroimaging studies using L-DOPA related radiotracers have shown abnormally increased striatal dopamine synthesis capacity in some patients with schizophrenia, and it has been suggested that this phenotype may be an important biomarker in psychosis, possibly characterizing treatment responsiveness. Furthermore, in parallel, corticostriatal connectivity metrics during resting state fMRI paradigms have been found in some cohorts to predict response to antipsychotic medication. This is in keeping with longstanding 'dysconnectivity' hypotheses about illness pathophysiology and accumulating evidence for abnormal resting state network dynamics across the cortex in schizophrenia. However, despite important dopaminergic synapses throughout the cerebral cortical landscape and preclinical models suggestive of widespread modulatory effects of dopamine, it remains unclear how tethered striatal dopamine synthesis capacity and cortical connectivity metrics might be. To answer this question, we studied a cohort of healthy individuals in whom we measured both striatal dopamine synthesis capacity with [18F]-FDOPA PET and interregional functional coupling with magnetoencephalography (MEG).

Methods: Fifty-five healthy individuals without psychiatric illness (mean age 36 ± 11 years, 29 women) underwent both [18F]-FDOPA PET and MEG in separate sessions at the NIH Clinical Center in Bethesda, Maryland. Abstinence from caffeine and nicotine for four hours pre-scanning was required for all scans. For [18F]-FDOPA only, a six-hour fast was employed to prevent competitive slowing of radiotracer transport across the blood brain barrier; additionally, an oral dose of carbidopa was administered one hour before [18F]-FDOPA injection to prevent peripheral tracer decarboxylation. After reconstruction and canonical corrections, PET data were rigid-body adjusted for interframe motion, spatially warped to a PET-specific template, and smoothed to improve signal-to-noise ratios. The time-activity curve from a cerebellar reference region served as the input function for standard graphical linear modeling using PMOD software to estimate the specific uptake parameter, Ki. MEG data were recorded in an upright position with eyes-closed during a four-minute acquisition with a 275-sensor whole-head CTF MEG system at 600 Hz. Standard preprocessing used MNE-Python and included censoring bad channels and epochs, bandpass and notch filtering, and dSPM assisted source localization. Data were aligned to a separately collected T1 weighted MRI anatomical image using three fiducial markers and spatially warped to an MNI space structural target. FreeSurfer software was used to parcellate the cortex, and pair-wise phase lag indices were calculated as a measure of interregional coupling. Associations of these indices with overall whole-striatum Ki were tested with R software using linear modeling that controlled for age and sex. Results meeting a threshold of $p < 0.0001$ were examined further with post-hoc testing for each of three bilateral subdivisions of the striatum (associative, sensorimotor, ventral).

Results: A positive association between striatal tracer-specific uptake and MEG interregional coupling was found in specific frontotemporal and fronto-occipitoparietal circuitry (all $p's < 8 \times 10\text{-}5$). Post-hoc analyses revealed that these findings were largely attributable to dorsal striatal subregions, with both the associative and sensorimotor subregions showing connections between regions of the frontal and temporal cortices as well as frontal and parietal cortices, whereas the ventral striatum did not show this pattern.

Conclusions: Normative variability in trait presynaptic dopamine synthesis capacity may have implications for long-range functional connectivity in the human brain. To the extent that both frontotemporal and frontoparietal communication abnormalities have been identified in dopamine-related neuropsychiatric conditions such as schizophrenia these data support future examination of dopamine-driven connectivity phenomena in people living with these conditions. If replicated, these preliminary results would suggest greater involvement of dorsal (associative and sensorimotor) than of ventral striatum in cortico-cortical connectivity, consistent with anatomical models. Despite widespread dopamine system footprints throughout the cortex, striatal presynaptic dopamine synthesis capacity variance, at least in the healthy state and within the confines of our sample size, may have select interregional effects.

Keywords: Dopamine, MEG, PET

Disclosure: Nothing to disclose.

P467. Unbiased Phenotyping and Systematic Analysis of Social Attachment Behaviors in Prairie Voles

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Background: Throughout the animal kingdom, organisms build short- and long-lasting bonds that enable social cooperation to facilitate reproduction and survival. In humans, impairments in forming or maintaining long-lasting social relationships play a key role in many neuropsychiatric conditions. The challenge of understanding the biology behind deficits in social attachment, such as those seen in autism, schizophrenia, or trauma, stems from the lack of common model organisms that demonstrate meaningful attachment behaviors. Prairie voles are socially monogamous and form robust, life-long attachments, thus providing an invaluable opportunity to study how the brain orchestrates social attachment behavior.

Understanding the relationship between the brain and behavior requires an integration of neurobiology and ethology in the study of naturalistic behaviors. To comprehend the behavioral strategies that underlie social attachment, we need novel tools and analytical frameworks capable of measuring animal pose and describing pose dynamics. Recent advances in computational neuroethology have enabled high-fidelity, high-throughput tracking of animal pose as well as detection of recurrent behavior modules. However, existing methods are geared toward the study of individual, rather than social, behaviors, and no known platform exists to investigate the social attachment behaviors unique to prairie voles.

Methods: Our computational goals for unbiased behavior phenotyping are three-fold. First, we have accelerated the detection of well-known behaviors using consistent and reliable algorithms. Second, we have generated fingerprints of recurring behavior patterns that distinguish male from female voles, pair-bonded from not pair-bonded voles, wild-type from mutant voles, and socially monogamous from socially non-monogamous vole species. Third, using machine learning and dynamical modeling, we are gaining biological insight into the salient features (e.g., body parts, movement patterns) and timescales (e.g., short-acting sensory cues, longer-lasting internal states) that govern social behavior.

Results: We developed novel methods to track and quantify both contours and keypoints of interacting animals. With these tracking data, we have built both supervised and unsupervised methods for behavior identification. We are now constructing novel frameworks to analyze reciprocal, dynamically coupled social behavior.

Conclusions: Using the methods we are developing, we will soon be able to compare, for the first time, reciprocal behavioral patterns mediating social attachment as well as their disruption in the context of mutations linked to neuropsychiatric illness such as autism spectrum disorder and schizophrenia. Likewise, we will be able to rigorously assess the impact of environmental disruptions on distinct components of social attachment behaviors. Our high-throughput behavior phenotyping platform may facilitate the screening of social behavior modulators and nominate treatments that reverse pathological behavior patterns. In the future, we also plan to pursue the joint analysis of behavior syllables and neural recording data, yielding hypotheses about the neural mechanisms that underlie social behavior.

Keywords: Social Attachment, Social and Behavioral Deficits, Unbiased Effect Size Estimation

Disclosure: Nothing to disclose.

P468. Neuronal Ensembles in the Rodent Amygdala Allow Social Information to Motivate Later Decisions

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Background: Social experiences carry tremendous weight in our decision making, even decision making lacking explicit social content. However, mechanisms by which the brain translates social information into action selection strategies are unclear.

Methods: We conducted Social Incentivization of Future Choice (SIFC), in which mice are trained to respond for two equally-preferred food reinforcers. Then, one food is paired with a novel conspecific. Mice later prefer the conspecific-associated food, even in the absence of the conspecific. Chemogenetic strategies were then employed to silence projections from the prelimbic subregion (PL) of the medial prefrontal cortex to the basolateral amygdala (BLA). Structural analyses of dendritic micro-architecture following SIFC utilized 3D-reconstructions of BLA neurons in Thy1-YFP mice. We used Fos2A-iCreER (TRAP2) transgenic mice to capture neuronal ensembles active during social interaction for later manipulation.

Results: Inactivating PL-to-BLA projections obstructed social preference in SIFC while leaving social memory intact, indicating that these projections are necessary for socially-driven choice. Mice that performed SIFC had greater densities of mature dendritic spines – those likely to contain synapses – on excitatory BLA neurons relative to mice that did not. BLA neurons were activated by socially novel vs. familiar animals, and those stimulated by social experience were necessary for mice to later favor rewards associated with social conspecifics, but not make other choices. Meanwhile, PL neurons stimulated by social experience were necessary for choice behavior in social and non-social contexts alike.

Conclusions: We demonstrate that BLA neuronal ensembles may serve as engrams for social memory, facilitating SIFC, given 1) they are stimulated by social novelty, a constituent component of SIFC 2) they undergo structural plasticity during SIFC, and 3) that cells stimulated by social experience are necessary for memory retrieval in the SIFC task, but not other tasks.

Keywords: mPFC, Basolateral Amygdala, Social Cognition, Decision Making, Operant Behavior

Disclosure: Nothing to disclose.

P469. Kappa Opioid Receptor Availability and Risk for Disordered Eating and Self-Injury: Preliminary Results From an [11C]EKAP PET Study in Borderline Personality Disorder

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Background: Borderline personality disorder (BPD) is a serious psychiatric condition associated with high morbidity and mortality and elevated risk for suicide. Of particular concern, BPD is characterized by self-destructive and impulsive problem behaviors that contribute to risk, such as self-injurious behaviors (SIB), prescription misuse (PM), aggression, and binge eating (BE). Despite this, treatments capable of affecting overall symptom severity and reducing risk in BPD are limited. It has been

hypothesized that deficits exist in the endogenous opioid system in BPD, leading to sensation-seeking behaviors to stimulate opioid release. Promisingly, recent evidence has implicated the kappa opioid receptor (KOR) in BPD and associated features. Pilot data revealed lower frontolimbic KOR availability of individuals with BPD relative to healthy adults (HA). Negative correlations were observed between KOR availability and impulsivity and emotion regulation. Increased impulsivity and emotion dysregulation have direct relevance to self-destructive, impulsive, behaviors. To date, however, relationships between KOR and such behaviors has not been directly investigated. This study examined relationships between KOR availability, BPD, and problem behaviors in vivo using [11C]EKAP PET.

Methods: Individuals with BPD (N = 13; problem behavior engagement ranged from 25-41%), and healthy adults (HA; N = 13) matched for age, sex, and smoking history were recruited from the community. All Participants completed 1 MRI scan and 1 PET scan with [11C]EKAP, as well as a battery of psychiatric and cognitive assessments. The radiotracer was injected as bolus and subjects were scanned for 120 minutes. Volume of distribution (VT: the ratio of activity in tissue relative to that in blood, corrected for metabolites) was computed using arterial input function. Primary analyses focused on a circuit of 6 frontal and limbic brain regions relevant to the pathophysiology of BPD and the noted problem behaviors: dorsolateral prefrontal cortex (dlPFC); orbitofrontal cortex (OFC); ventromedial prefrontal cortex (vmPFC); anterior cingulate cortex (ACC); amygdala; hippocampus. Problem behaviors, specifically, BE, SIB, risk-taking, aggression, and PM, were measured by the Borderline Symptom List – Supplement (BSLS), completed by participants on scan day.

Results: ANOVA analyses revealed significant group differences in KOR availability as a function of a number of problem behaviors during the week of the scan. Specifically, significant differences were observed in individuals reporting BE ($F(2,21) = 7.07$, $p = .005$, $d = 1.85$; BPD BE 39% ($d = 2.23$) lower than HA, 17.2% ($d = 1.03$) lower than BPD non binging). Similarly robust differences were observed in BPD individuals who reported uncontrolled anger ($F(2,21) = 7.6$, $p = .003$, $d = 1.85$; BPD anger 30.4% ($d = 2.07$) lower than HA, 16.7% ($d = 0.99$) lower than BPD without), and PM ($F(2,21) = 4.7$, $p = .02$; BPD PM 28.2% ($d = 1.97$) lower than HA, 13.0% ($d = 0.86$) lower than BPD no-misuse). No differences were observed in risky driving, risky sexual behaviors, or threats for suicide. Only one individual reported self-harm on the week of the scan, making analyses focused on SIB unfeasible in the current sample. Significantly, presence, and severity of the noted behaviors (BE, anger, PM) in BPD was positively correlated with other meaningful predictors of risk and functional impairment in BPD, including difficulties in emotion regulation, impulsivity, and pain tolerance ($r's = .41$-$.72$).

Conclusions: Preliminary results support a relationship between KOR, problem behaviors, and clinical predictors of risk and functional impairment in BPD. Individuals with BPD who reported binging, uncontrolled anger, and PM had lower frontolimbic KOR availability relative to matched HA. Of clinical significance, the presence and severity of BE, PM, and uncontrolled anger correlated with predictors of risk and impairment in BPD including difficulties in emotion regulation, impulsivity, and depressed mood, variables which have been shown to predict both future SA and suicide mortality. In light of emerging dimensional conceptualizations of personality disorders, identifying transdiagnostic factors that contribute to risk and impairment could provide crucial insights across conceptualizations of psychiatric disorders. Taken together, these results provide the first direct evidence for a possible role for KOR in the pathophysiology of risk and problem behaviors, both generally and in BPD specifically. Further evaluation of KOR targets for the treatment of suicidal behavior in BPD is warranted.

Keywords: Borderline Personality Disorder, Binge Eating, Emotional Dysregulation

Disclosure: Nothing to disclose.

P470. Zuranolone Safety and Tolerability in Adults With Postpartum Depression: Analyses From SKYLARK, a 50 Mg Placebo-Controlled Study

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Background: Zuranolone is an investigational positive allosteric modulator of synaptic and extrasynaptic GABAA receptors and a neuroactive steroid in clinical development as a once-daily, oral, 14-day treatment course for adults with major depressive disorder or postpartum depression (PPD). The randomized, double-blind, placebo-controlled SKYLARK Study (NCT04442503) demonstrated that zuranolone 50 mg significantly improved depressive symptoms (as assessed by 17-item Hamilton Rating Scale for Depression total score) at Day 15 (primary endpoint; $p < 0.001$) and was generally well tolerated in adults with PPD.

Methods: In the SKYLARK Study, patients were randomized 1:1 to receive zuranolone 50 mg or placebo for 14 days. Safety and tolerability were assessed by the incidence and severity of treatment-emergent adverse events (TEAEs), rates of dose reduction and treatment discontinuation, as well as weight gain and sexual dysfunction.

Results: The SKYLARK Study assessed safety data from 98 patients treated with zuranolone 50 mg and 98 patients treated with placebo. TEAEs were reported in 66.3% of zuranolone-treated patients and 53.1% of placebo-treated patients. In patients that experienced TEAEs, most reported mild (zuranolone, 50.8%; placebo, 75%) or moderate (zuranolone, 44.6%; placebo, 23.1%) events. The most common (≥5%) TEAEs were somnolence (26.5%), dizziness (13.3%), sedation (11.2%), headache (9.2%), diarrhea (6.1%), nausea (5.1%), urinary tract infection (5.1%), and COVID-19 (5.1%) with zuranolone, and headache (13.3%), dizziness (10.2%), nausea (6.1%), and somnolence (5.1%) with placebo. Dose reduction due to TEAEs was 16.3% in patients receiving zuranolone vs 1.0% in patients receiving placebo; the most common TEAEs (>1 patient) leading to zuranolone dose reduction were somnolence (7.1%), dizziness (6.1%), and sedation (3.1%). Treatment discontinuation due to TEAEs was 4.1% in patients receiving zuranolone vs 2.0% in patients receiving placebo; TEAEs leading to zuranolone discontinuation in >1 patient included somnolence (2.0%). Serious TEAEs were reported in 2.0% of zuranolone-treated and 0% of placebo-treated patients; these included upper abdominal pain (1.0%, [1/98]), peripheral edema (1.0%, [1/98]), perinatal depression (1.0%, [1/98]), and hypertension (1.0%, [1/98]). Per investigators, serious TEAEs were not related to zuranolone. No signals for weight gain or sexual dysfunction were identified.

Conclusions: In adults with PPD, zuranolone 50 mg was generally well tolerated. Most TEAEs were mild or moderate in severity. Dose reduction due to TEAEs mainly resulted from somnolence, dizziness, and sedation, while treatment discontinuation due to TEAEs was low. No signals for weight gain or sexual dysfunction were identified.

Keywords: Postpartum Depression, Zuranolone, Safety/Tolerability, Clinical Efficacy

Disclosure: Sage Therapeutics: Grant (Self).

P471. Preliminary Examination of Postpartum Mental Health in Relation to SARS-CoV-2 Infection and Gene Expression in the Placenta

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Background: Untreated and under-treated perinatal mental health conditions are associated with negative consequences for pregnant and postpartum people. Following the COVID 19 pandemic there was a dramatic rise in the incidence of peripartum depression and anxiety [1]. The immune system plays an important role in infections and has been implicated as a potential mechanism in the development of maternal psychiatric disorders. The placenta orchestrates immune changes during pregnancy, modulating maternal immune response to perinatal infections. Further, circulating placental factors impact maternal innate immunity and inflammatory cascade [2]. Herein, we investigate associations amongst gestational SARS-CoV-2 infection, postpartum depression, and expression of immune and inflammation-related genes in the placenta.

Methods: We leveraged data and placental villi samples collected prospectively from 141 female pregnant participants enrolled in Generation C, a prospective cohort study (April 2020-February 2022) at the Mount Sinai Health System in New York City. Gestational SARS-CoV-2 infection was assessed through SARS-CoV-2 antibodies, PCR test results during pregnancy, and electronic medical record (EMR) review. Edinburgh Postnatal Depression Scale scores (EPDS) at 6-weeks postpartum were abstracted from EMR, we report the number of participants with a score of 11 or higher, a previously established threshold for postpartum depression diagnoses [3]. Placental expression of 347 immune/inflammation related genes from the Molecular Signatures Database (MSigDB) [4] was profiled with RNA-sequencing. First, we conducted differential gene expression analysis by gestational SARS-CoV-2 status using the Limma R package to fit linear regression models adjusted for maternal age, gestational age at delivery, and infant sex. Next, we interrogated the relationship between the differentially-expressed genes from the previous analysis (predictor variable) and EPDS scores around 6 weeks postpartum (continuous outcome variable) with linear regression analysis adjusted for gestational age, Distressed Communities Index scores (a measure of economic wellbeing of communities) based on participant zip code, lifetime history of anxiety/depression, pre-pregnancy BMI, and timing of EPDS assessment.

Results: 10 (7%) participants had an EPDS score of 11 or higher. 24 (17%) participants had SARS-CoV-2 infection during pregnancy and the median gestational age at delivery was 39 weeks (Interquartile Range = 1.0). Antenatal SARS-CoV-2 infection was found to be associated with downregulation of PTGER2 expression in the placenta, (logFC = -0.50, adjusted p-value = 0.022) and 37 additional genes at nominal p-value < 0.05. Linear regression analysis of these 38 genes to examine the effect of placental immune gene expression on maternal EPDS scores at 6-weeks postpartum revealed 4 genes (FZD5, CXCR6, BANK1, and MET) negatively associated at p-values < 0.05.

Conclusions: These results suggest that antenatal SARS-CoV-2 infection may impact placental function, such as expression of PTGER2, the gene encoding the receptor for prostaglandin E2. Moreover, gestational SARS-CoV-2 infection was linked to placental down regulation of four genes (FZD5, CXCR6, BANK1, and MET), whose increased expression in the subsequent analysis was associated with lower EPDS scores ie less postpartum depression. Thus, our findings suggest that lower expression may predispose patients to perinatal mood disorders. In previous studies, SARS-CoV-2 infection has been associated with lower expression of CXCR6 in lung tissue from infected patients [5], and lower expression of MET has been linked to depression [6]. While this study was limited by sample size, these results suggest the need for further exploration of these immune-related genes and the role they play in postpartum depression.

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Keywords: Placenta, Immune System, Postpartum Depression, Novel Coronavirus (SARS-CoV-2), Gene Expression

Disclosure: Nothing to disclose.

P472. Clinical Subtypes of Perinatal Depression Demonstrate Distinct Psychological Profiles

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Background: Perinatal depression (PPD) is a common disorder with potential for debilitating consequences in both mothers and their developing infants. Similar to depression across the lifespan, patients with PPD show variable response to psychotherapeutic and pharmacological interventions. PPD presents with differential onset timing and symptom profiles, raising the possibility of clinical subtypes (Putnam et al., 2017). It is unclear how such potential subgroups differ in terms of basic psychological constructs or indices that may be relevant to treatment responsiveness. Here, we match a previously published method (Putnam et al., 2017) for identifying clinical PPD subtypes. We then examine and compare the psychological profiles of these symptom-defined PPD subtypes.

Methods: We performed clinical subtyping using existing data from a multi-site cohort study, the Nulliparous Pregnancy Outcomes Study (NuMom2b). We performed a factor analysis on the Edinburgh Postnatal Depression Scale (EPDS) and subsequently grouped patients by applying k-means clustering to their factor scores. We limited analysis to patients with EPDS total scores of >9 ($n = 2466$). To maintain subsequent independence, we performed the factor analysis and calculated clusters on a training subsample within 70% of the NuMom2b dataset ($n = 1724$). We performed factor analysis on the polychoric correlation matrix of EPDS item scores and used an oblique rotation method (oblimin). We compared clusters on the Perceived Stress Scale (PSS), Pregnancy Experiences Scale (PES), Connor-Davidson Resilience Scale (CDRS), and the Multidimensional Scale of Perceived Social Support (MSPSS) utilizing ANOVA and post-hoc, pairwise t-tests. We then assigned subjects in a held-out test subsample of the NuMom2b dataset ($n = 742$) to these pre-calculated clusters and matched the above comparisons. Finally, we utilized a completely independent dataset ($n = 77$) for external replication of our PSS findings.

Results: We selected a 3-factor solution (by parallel analysis) in our factor analysis of EPDS item scores. We term these factors "depressed mood", "anxiety", and "anhedonia" based on their EPDS item weightings, with "depressed mood" showing the largest range between clusters. K-means clustering on individual patients along these factor dimensions determined an optimal 3-cluster solution (by maximum silhouette score). Each cluster differed significantly across the three factors ($p < 0.001$). We found significant differences between PPD clusters on the PSS in training, test, and external replication datasets ($p < 0.001$, $p < 0.001$, $p < 0.02$, respectively). We found significant differences across clusters in the PES, CDRS, and MSPSS in both training and test datasets ($p < 0.001$ in all comparisons). Post-hoc testing revealed that cluster 1 demonstrated higher PSS ($p < 0.001$) and PES scores ($p < 0.001$), while also showing lower CDRS ($p < 0.001$) and MSPSS scores ($p < 0.05$) than clusters 2 or 3. Cluster 3 also demonstrated higher MSPSS scores than cluster 2 ($p < 0.01$).

Conclusions: We identified 3 clinical symptom-based subgroups of PPD patients using the EPDS. These subgroups demonstrated distinct stress, social support, and resilience characteristics. We found one subgroup with higher scores on all EPDS-based symptom dimensions. This subgroup also demonstrated increased general and pregnancy-related stress with worse social support and resilience. Clinical subgrouping in this manner revealed a particular subset of patients who may benefit most from targeted social support and coping skills training. In continued work, we are examining demographic, social, and physiological profiles of PPD subgroups.

Keywords: Postpartum Depression, Clinical Subtypes, Perinatal Mental Health, Perinatal Stress, Social Support

Disclosure: Nothing to disclose.

P473. The Influence of Prenatal SSRI Exposure and Maternal Depression on Social Attention in Toddlers: A Pilot Eye-Tracking Study in the MYRNA Cohort

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Background: The use of selective serotonin reuptake inhibitor (SSRI) antidepressants has escalated over recent decades across the globe. All SSRIs have the ability to cross the placental barrier, entering fetal circulation. Observational studies and rodent studies have consistently reported the association between prenatal SSRIs exposure and social behavior deficits. The impacts of prenatal SSRI and maternal depression exposures on toddlers' social attention are however, relatively understudied areas.

Methods: To bridge this research gap, our study employed an eye-tracking experiment aimed at gauging toddlers' social preferences. This study was conducted as part of the ongoing Mother and Youth: Research on Neurodevelopment and Behavior (MYRNA) study in Sherbrooke, Canada. During the experiment, toddlers were presented with a film that included both geometric and social imagery. Key metrics including fixation duration and the number of saccades within each area of Interest (social vs. geometric) were measured and calculated. The design of the experiment facilitated the comparison of the impact of prenatal exposure to SSRIs (SSRI group), pregnancies affected by maternal depression without the use of psychotropic medication (PMD group), and pregnancies occurring under regular health conditions (HC group). The diagnostic status was confirmed via a Structured Clinical Interview for DSM-5 (SCID-5) conducted during the third trimester of pregnancy, while medication exposure was ascertained through self-reported and pharmacy data. Eye-tracking data were collected and analyzed in a pilot subsample of toddlers (age 24 months, 31 females, 41 males) born to: 53 moms in the HC group, 11 in the PMD group, and 8 in the SSRI group.

Results: The overall impact of the participant group on fixation durations for social objects was borderline significant ($F = 2.73$, $p = 0.072$, partial eta squared $= 0.074$), indicating some degree of variation across the three study groups. When comparing the PMD and HC groups specifically, a two-sample t-test revealed that toddlers in the PMD group had a shorter fixation duration on social objects compared to those in the HC group ($t = 2.33$, $p = 0.01$). Upon controlling for maternal postnatal depressive symptoms, income, and education in a multiple linear regression analysis, we observed lower fixation duration for social objects in the PMD group (trend only, $\beta = -0.78$, $t = -1.78$, $p = 0.08$). A similar non-significant trend was observed for the SSRI vs HC comparison ($\beta = -0.67$, $t = -1.04$, $p = 0.30$). This model accounts for roughly 42% of the variation in how long toddlers focus on social objects, indicating that our chosen predictors may influence the fixation duration for social objects. We found no significant differences between groups regarding the number of rapid eye movements or "saccades".

Conclusions: This study suggests that prenatal SSRI exposure and maternal depression may influence toddlers' social attention. The trend towards reduced fixation duration on social objects in the PMD group, as well as the SSRI group, prompts further exploration into the nuanced effects of these factors on early social attention development. Importantly, these findings underscore the complexity of developmental trajectories and the need for an integrative approach to better comprehend how prenatal and postnatal environments interact to shape child development. Despite the exploratory nature of our study and the limitations posed by the relatively small sample size, our findings suggest the utility and potential of eye-tracking technologies in probing and quantifying social attention in toddlers, thereby contributing to early detection and intervention strategies for populations at risk. Once we have amassed a more robust dataset, we can further verify and investigate these intriguing trends. Future research should build on these initial findings with larger, longitudinal studies to fully understand the long-term implications of prenatal SSRI exposure and maternal depression on child development.

Keywords: Maternal Depression, Prenatal SSRI Exposure, Social Attention, Eye Tracking

Disclosure: Nothing to disclose.

P474. Allopregnanolone and Anxiety-Potentiated Startle in SSRI-Responsive Premenstrual Dysphoric Disorder (PMDD)

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Background: Premenstrual dysphoric disorder (PMDD) is an affective disorder that affects roughly 5% of menstruating individuals. PMDD symptoms, including irritability, anxiety, low mood, and emotional lability, switch on in the luteal (premenstrual) phase of the menstrual cycle and switch off in the follicular phase. PMDD is likely due to aberrant sensitivity to normal fluctuations of ovarian steroid hormones and their metabolites across the menstrual cycle. Progesterone, an ovarian steroid hormone, is converted to allopregnanolone (ALLO), a neuroactive steroid that acts at the GABA-A receptor (GABA-A-R) to produce anxiolytic and sedative effects. There is evidence of decreased sensitivity to ALLO's effects in PMDD, including saccadic eye velocity, a measure of GABA-A-R-mediated sedation. Similarly, anxiety-potentiated startle (APS) is mediated by the ALLO-sensitive and GABA-A-R rich bed nucleus of the stria terminalis (BNST). Prior work from our laboratory found no significant differences in APS between controls and PMDD participants in either menstrual cycle phase, contrary to our hypotheses. However, those analyses did not account for ALLO levels, which may influence APS. In the present analyses, we accounted for ALLO, assessing whether ALLO level influenced APS among PMDD and controls in the follicular and luteal phases of the menstrual cycle. We also assessed luteal phase sertraline treatment impact on these outcomes.

Methods: Biological females with regular menstrual cycles (24-39 days; confirmed ovulation) who were not using psychotropic or hormonal medications were recruited. Each participant completed two months of prospective ratings with the Daily Rating of Severity of Problems (DRSP), as well as a structured clinical interview (SCID), to confirm PMDD diagnosis (PMDD group) or absence of symptoms (control group), prior to laboratory testing. Participants completed three laboratory sessions; one in the follicular phase (5-11 days post-menses onset) and two in the luteal phase (8-12 days post ovulation). During the second luteal phase, PMDD participants were treated with open-label sertraline (50mg/d) from ovulation to menses. The PMDD group was divided into sertraline Treatment Responders (PMDD-R) and Treatment Non-Responders (PMDD-NR), with treatment response defined as at least 30% improvement in luteal phase DRSP score compared to the untreated luteal phase. APS was assessed via eyeblink electromyography (EMG) using Grillon's threat of shock protocol, and allopregnanolone was measured by gas chromatography/mass spectroscopy in serum; outcomes were assessed in each of the menstrual cycle phases. Multilevel linear models predicted APS from phase (follicular, untreated-luteal, treated-luteal), group (PMDD-R, PMDD-NR, Control), log-transformed ALLO, and the phase*group*ALLO interaction. Models controlled for DRSP score and day of cycle.

Results: The sample included $n = 52$ participants (27 controls, 25 PMDD). There were no main effects of phase, group, or ALLO level on APS (all p's>0.05). However, there was a significant interaction between phase*group*ALLO predicting APS, showing a different ALLO effect on APS between PMDD-R and PMDD-NR in the treated luteal phase ($E = -12.21$, $CI = -21.77$ – -2.65, $p = 0.013$). Specifically, in the follicular and untreated luteal phase there was a negative relationship between ALLO and APS among PMDD-R, and the directionality switched in the treated luteal phase so that ALLO and APS were positively correlated among PMDD-R.

Conclusions: The present analyses sought to build on prior work from our laboratory that found no significant differences in APS between controls and PMDD, but did not account for ALLO levels. The present analyses assessed ALLO's impact on APS. We found that ALLO level did not significantly affect APS. However, among individuals with PMDD who responded to sertraline treatment (PMDD-R), ALLO and APS were negatively correlated in both the follicular and luteal phases, i.e., higher ALLO levels predicted lower APS. With sertraline treatment, this directionality switched, so that higher ALLO levels predicted higher APS. These results are surprising, as we hypothesized that ALLO would be negatively correlated with APS, reflecting ALLO's sedative effects on this measure of psychophysiological arousal. The findings are similar to our previous work in which PMDD-R participants showed a different pattern from PMDD-NR; specifically, among PMDD-R participants APS was elevated in the untreated luteal phase and lower in the treated luteal phase, which was different from PMDD-NR participants. Thus, individuals with PMDD who respond to SSRIs may have distinct characteristics in ALLO and/or GABA-A-R function from those who do not respond.

Keywords: Premenstrual Dysphoric Disorder, Acoustic Startle Response, Neuroactive Steroids, GABA, Menstrual Cycle

Disclosure: Nothing to disclose.

P475. Bidirectional Associations Between Peripartum Allopregnanolone and Depression Severity With Postpartum Gray Matter Volume in Adult Women

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Background: Peripartum depression (PND) is one of the most common complications of pregnancy and childbirth, with untreated PND associated with short- and long-term harmful consequences for mother and child. Peripartum neuroplasticity is well characterized in rodents though understanding of these processes in humans remains comparatively limited. Recent evidence indicates that human pregnancy induces structural and functional neuroplasticity in areas of the default mode network (DMN), salience network (SN), and reward network. Moreover, alterations in functional connectivity of these brain networks are found in PND. Notably, DMN connectivity has been found to be correlated with plasma allopregnanolone (ALLO) in PND. The relationship between PND severity, ALLO concentrations, and gray matter volume in PND is unknown. We examined longitudinal peripartum bidirectional associations between ALLO and depression severity and their association with postpartum gray matter volume, using random intercept cross-lagged panel models (RI-CLPMs). RI-CLPMs account for the fact that perinatal women may enter the study with different initial levels of ALLO and depression severity and have unique trajectories. We hypothesized that higher depression severity would predict greater plasma ALLO concentrations at subsequent peripartum time points, indicating a bidirectional relationship. Furthermore, we expected that both depression severity and ALLO concentration would be predict altered postpartum gray matter volume within the DMN, the SN, and reward network.

Methods: Data were analyzed from two similarly designed prospective studies in unmedicated, peripartum women at-risk

for PND (AR-PND) and healthy control peripartum women (HCW). The final dataset included 48 HCW and 77 AR-PND enrolled. We analyzed data from the 45/48 HCW who maintained euthymia and completed the postpartum MRI and the 40/77 AR-PND who developed a major or minor depressive episode at the time of MRI. Participants were evaluated at two antepartum and two postpartum visits. All visits included the Edinburgh Postnatal Depression Scale (EPDS) and blood draw for ALLO quantification. Visit 1 also included a demographic questionnaire and structured research diagnostic interview. Visit 4 also included the same structured research diagnostic interview completed at visit 1 and structural MRI acquisition. MRI data was acquired with one research-dedicated 3.0 T Philips Achieva whole-body MR system using phased-array receiver SENSE head coil. T1-weighted anatomical MRI images and T2-weighted TSE scans were collected to serve as intermediate registration targets. Each participant's MPRAGE image was processed using the recon-all pipeline for cortical reconstruction and volumetric segmentation from FreeSurfer version 7.3.2. The FreeSurfer Regions of Interest (ROIs) were defined using the Destrieux Atlas cortical parcellation of sulco-gyral boundaries using an inflated cortical surface reconstruction and the FreeSurfer segmentation of deep gray matter volumetric structures. We examined a set of a priori ROIs within the DMN, the SN, and reward network. For each ROI, primary analyses were conducted using the FreeSurfer volume metrics. Peripartum plasma concentrations of ALLO were determined by liquid chromatography-tandem mass spectrometry. Group comparisons of volume (i.e., PND versus HCW) were conducted across all ROIs. The False Discovery Rate correction was employed at two different nominal levels ($q = .05$ and .10) and measures of volume that survived the FDR were included in further analyses. RI-CLPMs were then estimated in MPlus 8.1 using full information maximum likelihood to examine the bidirectional associations between ALLO plasma concentration and depression severity, as measured by the EPDS, across visits 1-3, and their relation to MRI outcomes at visit 4. Maximum likelihood parameter estimates with robust standard errors were used to account for non-normality.

Results: We identified a unidirectional association between PND severity and ALLO concentration, suggesting greater depression severity early in the peripartum period contribute to subsequent changes in ALLO concentration ($\beta = .26$, $p = .009$), while variations in ALLO levels during the peripartum period influences the severity of depressive symptoms postpartum ($\beta = .38$, $p = .007$). Antepartum depression severity (visit 2, $\beta = .35$, $p = .004$), ALLO concentration (visit 2, $\beta = .37$, $p = .001$), and postpartum depression severity (visit 3, $\beta = .39$, $p = .031$), predicted right anterior cingulate volume. Antepartum ALLO concentration (visit 2, $\beta = .29$, $p = .001$) predicted left suborbital sulcus volume. Antepartum depression severity (visit 1, $\beta = .39$, $p = .006$ and visit 2, $\beta = .48$, $p < .001$) predicted right straight gyrus volume. Postpartum depression severity (visit 3, $\beta = .36$, $p = .001$) predicted left middle-posterior cingulate volume.

Conclusions: This study provides the first evidence of bidirectional associations between peripartum ALLO and depression severity with postpartum gray matter volume and highlight the importance of the DMN and reward network in PND. Results across the four examined brain regions contribute to our understanding of the complex interplay between PND severity, ALLO and postpartum structural volume. The distinct patterns of association suggest the involvement of different neural circuits and mechanisms underlying PND.

Keywords: Neurosteroid, Voxel-Based Morphometry (VBM), Perinatal Depression

Disclosures: Sage Therapeutics, Premier Healthcare, Woebot Health: Contracted Research (Self). Sage Therapeutics, Brii Biosciences, Gerbera Therapeutics, Neuroscience Software, Reunion Neuroscience: Consultant (Self).

P476. Effects of Hormonal Contraception on Reward Processing: Preliminary Data From a Placebo-Controlled fMRI Study

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Background: Up to 30% of women who start hormonal contraception discontinue it within 6 months, with adverse changes in mood and decreases in libido being two of the most frequently cited reasons for discontinuation. Despite this, little is known about how hormonal contraception influences basic affective processes. The present project is a placebo-controlled trial of an oral contraceptive pill using both neural and behavioral measures to assess its effects on reward processing.

Methods: 144 healthy women (aged 18 and above) will be recruited to undergo assessment of reward function using self-report measures and a novel fMRI task during the mid-late follicular phase (between days 9-14 of cycle), when reward sensitivity is highest. Participants will be randomized to start an oral contraceptive pill containing ethinyl estradiol and levonorgestrel ($n = 72$) or placebo ($n = 72$) on the first day of the following menstrual cycle. Follow-up behavioral and fMRI assessment occur after 21 days of the oral contraceptive pill or placebo when the placebo group is in the luteal phase. Luteal phase follow-up will allow for comparison of endogenous estradiol and progesterone with their corresponding synthetic analogues. Change-scores from baseline to follow-up assessments will be compared between treatment groups for self-reports of interest in sexual and non-sexual activities as measured by the Sexual Desire Inventory and Dimensional Anhedonia Rating Scale. In addition, participants undergo an fMRI task designed to evaluate neural reward processing during anticipation and receipt of pleasurable images (both erotic and non-erotic). Here we present data showing task feasibility in this population. We carried out preliminary analyses that examined activation in the nucleus accumbens and ventromedial prefrontal cortex regions of interest in baseline data from 22 women and in 9 completers (placebo $n = 4$; oral contraceptive $n = 5$).

Results: At baseline, women showed increased response to erotic relative to neutral images in the nucleus accumbens ($p = 0.004$) and ventromedial prefrontal cortex ($p = 0.002$). Preliminary data from 9 completers was analyzed to evaluate potential group differences in reward responsivity. Although not statistically significant, the change in neural activation in the nucleus accumbens and ventromedial prefrontal cortex from baseline was lower in the oral contraceptive group compared to the placebo group during viewing of erotic images (nucleus accumbens $d = 0.729$; ventromedial prefrontal cortex $d = 0.306$).

Conclusions: The present project will allow for rigorous psychoneuroendrocrine assessment of an oral contraceptive pill and establish a protocol to test the neural effects of other current and future contraceptive formulations. Preliminary results suggest that the oral contraceptive pill, ethinyl estradiol with levonorgestrel, may decrease reward responsiveness to erotic stimuli.

Keywords: Hormonal Contraceptive Use, Neuroendocrinology, Reward, Placebo-Controlled trial

Disclosure: Nothing to disclose.

P477. Maternal Toll-Like Receptor 7 Activation in Combination With Early Postnatal Resource Deprivation Stress Induce Sex-Biased Behavioral and Proteomic Alterations in Mice

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Background: Maternal infection during pregnancy increases the risk of neuropsychiatric disease in exposed offspring. Rodent models of maternal immune activation (MIA) typically involve in utero immune activation using infectious agents such as bacteria or double-stranded RNA. Two of the most common models stimulate toll-like receptor 4 (TLR4) using the bacterial endotoxin lipopolysaccharide or TLR3 using the mimetic poly(I:C). However, some of the prenatal infectious agents that are most strongly linked to risk for neurodevelopmental disorders are single-stranded viruses such as rubella or influenza. Single-stranded mimetics that stimulate TLR7 are relatively underutilized in rodent MIA models.

Despite the risk, the majority of maternal infections do not result in offspring neurodevelopmental disorders. MIA appears to act as a 'priming event', increasing susceptibility to other risk factors. In humans, early-life adversity increases the risk for stress-related emotional and cognitive disorders later in life and many neuropsychiatric disorders are exacerbated by stressful perinatal experiences such as early-life maltreatment or neglect. Here, we studied the impact of a two-hit model of MIA activation in combination with early-life stress on offspring neurodevelopment.

Methods: Here, we studied the impact on offspring neurodevelopment of MIA by TLR7 stimulation. To model resource deprivation stress, we used a limited bedding and nesting (LBN) paradigm to induce neural and behavioral alterations. We assessed maternal care behavior towards offspring on postnatal days 6 and 9. We assessed communicative, social, perseverative, and anxiety-like behaviors in both male and female offspring. Total and phospho-proteomic analyses of midbrains were performed following cessation of behavioral testing. In a second cohort, placentas and fetal brain were collected on embryonic day 18 for gene expression analyses of inflammatory factors. All experimental protocols in animal studies 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. Three-way ANOVAs (prenatal treatment x postnatal caging x offspring sex) were performed for postnatal measures, whereas two-way ANOVA (prenatal treatment x offspring sex) were performed for prenatal measures to determine significance.

Results: Regardless of prenatal treatment, we find that LBN exposure results in fragmented maternal care, with LBN-exposed mothers spending more time off-nest, and less time nursing/grooming than do Ctrl housing-exposed mothers (main effect of postnatal caging, $p < 0.05$). We demonstrate that male pups exposed to maternal TLR7 activation emit significantly fewer ultrasonic vocalizations than do vehicle-exposed males (prenatal treatment x offspring sex interaction, $p < 0.05$). We found that the combination of maternal TLR7 activation in combination with early postnatal resource deprivation stress decreased sociability behavior only in males (prenatal treatment x postnatal caging x offspring sex interaction, $p < 0.05$). Finally, we observed an increase in self-grooming perseverative behaviors, again only in male mice (prenatal treatment x offspring sex interaction, $p < 0.05$).

Total proteome analyses revealed a greater proportion of differentially expressed proteins in female brains following dual-hit of prenatal TLR7 activation and postnatal LBN stress than in male brains, whereas there were more alterations to the male phospho-proteome following two hits. GO analyses suggest that proteins with phosphorylation changes in male brains are involved in regulation of behavioral pathways. We are currently finalizing analyses of placental and fetal brain inflammatory gene expression following exposure to maternal TLR7 activation.

Conclusions: A two-hit mouse model of maternal TLR7 activation in combination with early life resource deprivation stress induces sex-biased alterations in communicative, perseverative, and social behaviors. This dual hit differentially alters brain proteome and phospho-proteome regulation in female and male offspring. We are currently assessing fetal brain and placental inflammatory profile following maternal TLR7 activation.

Keywords: Maternal Immune Activation, Fetal Brain Development, Cytokines, Placenta, Toll-Like Receptors (TLRs)

Disclosure: Nothing to disclose.

P478. Components of Mental Distress During Pregnancy in Relation to the Microbiome: Data From US and Swedish Cohorts

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Background: Mental distress in pregnancy is associated with negative long-term outcomes for mother and child. Yet, we have lacked biomarkers that could reflect the numerous physiologic and environmental changes happening across pregnancy that may indicate mental distress is putting parent and child at higher risk of negative outcomes. The gut microbiome may represent a proxy for environment, health behaviors, and host immune system functioning to better understand when distress requires intervention.

Methods: Second and third trimester pregnant individuals from the United States ($n = 83$) and Sweden ($n = 429$), completed the Edinburgh Postnatal Depression Scale (EPDS) and provided fecal samples analyzed with whole genome metagenomics. Measures of microbial community diversity (e.g., alpha-diversity which characterizes each person's microbial community in relation to numbers of and how evenly distributed are different bacteria types), the relative abundance of specific types of bacteria, and potential metabolomic functioning as assessed by Gut Brain Modules were analyzed in relation to different components of mental distress as assessed by the EPDS. In addition to the EPDS, individuals were characterized by past psychiatric history and diagnoses (e.g., Mini-international Neuropsychiatric Interview and the Structured Clinical Interview for DSM Disorders-V). Venn diagrams were used to assess which individuals were shared between clusters and timepoints.

Results: Individuals from both cohorts with lower mental distress, assessed by the EPDS, had a significant change in alpha-diversity, as assessed by three different methods, from 2nd to 3rd trimester; while individuals with higher distress did not. Of note, distress of the US cohort differed significantly between 2nd and 3rd trimesters ($p = 0.016$), while the Swedish cohort did not ($p = 0.65$). Microbial communities of Swedish individuals differed based on higher or lower distress ($p = 0.015$); only 3rd trimester US microbial communities trended toward being

different ($p = 0.076$). Differential abundance for individuals with higher distress included lower Alistipes finegoldii and Clostridium aspargiforme. Bacteroides uniformis was higher in individuals from the US who reported more past episodes of depression. Four distinct potential function groups were identified; varying in relation to higher anxiety, anhedonia, depression, or self-harm and by cortisol degradation, short chain fatty acid synthesis and degradation functioning. Cortisol degradation was lower in the Swedish cohort in clusters 2 and 3 in the 2nd trimester; cluster 2 associated with higher anxiety and cluster 3 with higher anhedonia. Lower cortisol degradation was associated with clusters 1 and 3 in the 3rd trimester; cluster 1 associated higher anhedonia and self-harm. In the US, cortisol degradation was lower in clusters 1 and 2 in the 2nd trimester and 3rd trimester; cluster 1 associated with self-harm in the 2nd trimester and higher anxiety in 3rd trimester. In Sweden, Cluster 2 in the 2nd trimester and Cluster 3 in the 3rd trimester had the highest number of shared individuals ($n = 71$). In the US, Cluster 2 in both 2nd and 3rd trimester shared the most individuals ($n = 19$).

Conclusions: There were some differences between the US and Swedish cohorts in distress across two timepoints in pregnancy that indicate the importance of assessing multiple timepoints and consideration that there may be differences in trajectories of distress between different geographic cohorts. It is also important to consider subtypes of symptoms, especially as anxiety, anhedonia, depression and self-harm help better group individuals in relation to microbiome compositions and potential functioning. Pregnant individuals with greater mental distress, particularly anhedonia, anxiety and self-harm, may have a less adaptable microbiome; and as reflected by potential functioning of the microbiome, less able to adapt to necessary changes in cortisol degradation, tryptophan metabolism, SCFA production, and choline availability. It has generally been thought that the 2nd trimester is a period of lower mental distress both due to more stability of both physiologic and psychologic changes; and yet this research indicates there are subsets of individuals with higher distress in the 2nd trimester reflected by microbial functioning. This study also supported prior studies implicating bacteria related to dietary fiber, particularly for individuals with a longer lifetime history of mental distress. Larger samples sizes are required to further subtype individuals based on past history of depression and anxiety and the microbiome's ability to adapt in pregnancy. It is a complex picture that is emerging between symptom subtypes, timing, and microbiome potential functioning; but also, a picture that indicates there is the potential to combine these three considerations in assessing dyads to identify biologic contributors that increase risk of negative outcomes of mental distress and identify when and what intervention may be possible.

Keywords: Pregnancy, Gut Microbiome, Anhedonia, Anxiety, Self-Harm

Disclosures: Sage Therapeutics: Contracted Research (Self). Abbvie Laboratories: Stock / Equity (Spouse/Partner).

P479. The Immune Phenotype of Perinatal Anxiety in the Happy Mother, Healthy Baby (HMHB) Study

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Background: The perinatal period involves immune changes crucial for fetal development. At the same time, given the bidirectional communication of the immune system and the brain, immune alterations might contribute to perinatal mood and anxiety disorders. Our previous research has identified an immune fingerprint to perinatal anxiety. In this study, we sought to evaluate distinct immune characteristics linked to prenatal anxiety within the context of a randomized controlled trial designed to reduce anxiety symptoms (the Happy Mother, Healthy Baby (HMHB) study.

Methods: We enrolled 117 pregnant women (56 with anxiety indicated by a score ≥8 on the anxiety subscale of the Hospital Anxiety and Depression Scale - HADS, 61 healthy controls) from the public Holy Family Hospital in Rawalpindi, Pakistan. In addition to repeat measurement of the HADS, plasma samples were collected at four timepoints the first (T1), second (T2), and third (T3) trimesters of pregnancy and at 6 weeks postpartum (PP). Using highly sensitive multiplex kits from Meso-Scale Discovery, we assessed at each time point immune indicators that had shown significance in our previous research (CCL3, CCL11, CCL13, CCL17, IFN-γ, IL-6, CXCL-8, IL-10, IL-12p70, TNF-α, IL-17A). The statistical approach relied on a K-means cluster analysis of joint-trajectories to identify distinct data-driven anxiety subgroups of women based on repeated measures HADS data across antenatal measurements (T1, T2, T3), given the expected change in anxiety from baseline with intervention. Principal components analysis was used to examine clustering of the 11 plasma-derived immune indicators. Then, a factor-based composite Z-score was computed for each immune cluster to compare K-means anxiety groups in longitudinal mixed effect models across pregnancy and postpartum.

Results: K-means cluster analysis unveiled three groups: Group A: Non-Anxiety ($n = 51$, 52.6%), Group B: displaying high and consistent anxiety ($n = 26$, 26.8%), Group C: characterized by initial high anxiety that decreased considerably over time ($n = 20$, 20.6%). We used generalized linear models to compare immune marker concentrations among these three groups in an exploratory analysis with no correction for multiple comparisons. Group B (high and consistent anxiety) had significantly higher concentrations of CCL11 (Eotaxin) at T1 ($p = 0.011$) and at T2 ($p = 0.004$) compared to group A (non-anxiety group) and higher concentrations of TNF-α ($p = 0.037$), IL-12p70 ($p = 0.012$), and CXCL-8 (IL-8) ($p = 0.037$) at T2 compared to group C (decreasing anxiety over time). To reduce multiple comparisons, and following an approach we have used previously, we then used principal component analysis to identify two distinct functional clusters of immune markers at the second trimester of pregnancy: Cluster 1 consisted of CCL3, CCL11, CCL13, CCL17 (chemokines) and explained 22.54% of the variation with factor loadings ranging from 0.071 to 0.445. Cluster 2, including CXCL8, IFN-γ, TNF-α, IL-6, IL-8, IL-12p70 (innate immune cytokines), accounted for 18.86% of the variation with factor loadings ranging from 0.284 to 0.448. Collectively, these two clusters accounted for 41.40 % of the total variance. Of note, IL-10 and IL-17A were independent, and did not distinctly load onto either Cluster A or B. Preliminary analysis examining showed that women within the high anxiety group (B) had sustained elevated Cluster 1 (chemokine) activity compared to the other anxiety groups. The decreasing anxiety group (C), by contrast, showed a decrease in both Cluster 1 (chemokine) and Cluster 2 (innate immune) activity from T1 to T2 and a rebound in T3. Next steps for analysis will include a mixed effects model that incorporates an adjustment for relevant covariates such as the use of psychiatric medications, maternal BMI, and gestational timing of measurement.

Conclusions: In this study, preliminary results suggest a unique immune fingerprint to high perinatal anxiety (B) compared to our non-anxiety and decreasing anxiety groups.

Keywords: Pregnancy, Anxiety, Pro-Inflammatory Cytokines, Chemokines

Disclosure: Nothing to disclose.

P480. Gene Expression Profiling in the Dentate Gyrus of Individual Patients With Schizophrenia by Immaturity-, Neural Hyperexcitation-, and Decreased pH-Related Changes

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Background: The biological heterogeneity of patients with schizophrenia is one of the obstacles that makes elucidation of the mechanisms of schizophrenia difficult. To understand the pathophysiology of schizophrenia, it is necessary to assess the biological features of each individual patient. Several hypotheses, such as neurodevelopmental abnormalities, neural hyperexcitation, and decreased brain pH, have been proposed to explain the pathophysiology of schizophrenia. However, it is unknown whether and to what extent expression changes related to these hypotheses are represented in individual patients are unknown.

Methods: Using publicly available transcriptome data, we calculated the differentially expressed genes (DEGs) in the hippocampus of individual patients and evaluated their overlap with DEGs associated with developmental changes (human hippocampal development), neural hyperexcitation (hippocampus of a rodent model of epilepsy), and changes in pH (genes whose expression levels are correlated with pH in the human cortex).

Results: Gene expression patterns in the hippocampus of individual patients showed varying degrees of immaturity-like, neural hyperexcitation-like, and decreased pH-like changes, with significant group differences in the three conditions.

Conclusions: These results suggest that pathophysiological changes associated with immaturity, hyperexcitation, and decreased pH may be involved to varying degrees in individual patients with schizophrenia. Further studies are needed to reveal a full picture of inter-individual variation in gene expression, which may help develop more efficient individualized treatments based on biological features.

Keywords: RNA Sequencing, Postmortem Brain Tissue Gene Expression, Schizophrenia (SCZ)

Disclosure: Nothing to disclose.

P481. βIV Spectrin Abundancy, Cellular Distribution, and Sensitivity to AKT Regulation are Associated With Schizophrenia

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Background: Spectrins, a crucial class of cytoskeletal proteins, play a pivotal role in regulating the cellular architecture. Emerging evidence suggests that pathogenic variants or differential expression of spectrins may contribute to the pathogenesis of several neurodevelopmental disorders, including schizophrenia (SCZ). Transcriptional analyses of post-mortem brain tissue have demonstrated that a subset of transcripts belonging to the spectrin protein family is severely disrupted in individuals with SCZ and may be linked to disease progression. Additionally, spectrins have been found to be differentially regulated in the temporal cortex and in the subgenual anterior cingulate cortex of SCZ patients. β spectrins are the master structural elements of the axon initial segment (AIS), a specialized subcellular compartment crucial for neuronal firing. Specifically, βIV spectrin directly interacts with voltage-gated $Na+$ (Nav) channels, controlling their precise localization at the AIS and modulation of neuronal firing. Previous research has demonstrated that the AKT/GSK3 signaling pathway regulates the distribution of βIV spectrin in primary hippocampal neurons. Given the extensive literature on the involvement of the AKT/GSK3 pathway in SCZ, these findings provided the basis for investigating whether: (i) there are alterations in βIV spectrin transcript, protein distribution, and relative abundance in SCZ; (ii) the sensitivity of βIV spectrin to the AKT/GSK3 pathway is altered in SCZ; and (iii) βIV spectrin is a target of the AKT/GSK3 pathway.

Methods: βIV spectrin in post-mortem human dorsolateral prefrontal cortex tissue was determined via a previously published RNA-seq dataset in PsychEncode and immunohistochemistry and confocal image analysis of samples from the NIMH Human Brain Collection Core. Perturbations of the AKT/GSK3 pathway were performed via kinase inhibition in neurons derived from induced pluripotent stem (iPS) cells from patients and healthy controls, followed by immunocytochemistry and confocal imaging. Additional analysis of imaging data from both tissue and cell culture were further analyzed by Random Forest Classifier. Finally, potential phosphorylation sites on βIV spectrin by AKT and GSK3 were identified.

Normality was first assessed using QQ plots for each dataset and log transformed if necessary. Average fluorescent intensity of neurites and soma for each condition were analyzed using a Two-Way mixed model ANOVA with subject as the random effect to account for within-subjects variability followed by Dunnett's (within groups) or Sidak's (between groups) multiple comparisons test was used for neuronal cultures to determine differences in βIV spectrin in neurites and soma. A nested t-test was used to determine differences between healthy controls and SCZ patient in post-mortem brain tissue. These analyses were performed using GraphPad Prism 9. Transcriptome analysis was conducted in R, and p-values were adjusted for multiple testing using the Benjamini-Hochberg method.

Results: RNAseq analysis revealed that βIV spectrin is significantly increased in the dlPFC at both the transcriptomic and protein level, as analyzed by RNAseq analysis and confocal imaging. Further analysis of transcriptomic data showed that AKT transcripts are differentially expressed in SCZ patients compared to controls, with AKT3 significantly decreased and AKT2 significantly increased. Interestingly, the level of AKT2 and βIV spectrin correlate together, while no such correlation occurred for βIV spectrin and AKT3. Random Forest classification was also able to correctly distinguish between AIS originating from SCZ patients with 94% accuracy.

Analysis of neurons derived from iPS cells showed that βIV spectrin was decreased at the AIS of SCZ neurons at all tested conditions. Further, βIV spectrin in healthy control neurons showed a preserved reactivity to inhibition of AKT, a finding previously published in primary hippocampal neurons. Inhibition of AKT also increased immunofluorescence of βIV spectrin in the soma of healthy controls, a response not seen in SCZ neurons. Random Forest classification was able to correctly distinguish treatment groups with >90% accuracy in all cases, with the highest accuracy achieved in the SCZ + AKT inhibitor group (97.1%). Finally, examination of the amino acid sequence of βIV spectrin showed several sites that may be phosphorylated by AKT, supporting that βIV spectrin may be directly phosphorylated by AKT.

Conclusions: Several converging lines of evidence from human samples, including both post-mortem tissue and neurons from iPS cells support that regulation of βIV spectrin by kinases such as AKT may be an important molecular phenotype of SCZ. Specifically, the

regulation of AKT may be blunted in SCZ. Restoring this regulation may provide new pharmacological treatments for the treatment of SCZ.

Keywords: Axon Initial Segment (AIS), Schizophrenia (SCZ), Akt

Disclosure: IonTx: Founder (Self).

P482. Risk Genes for Psychosis Regulate Cellular Circadian Rhythms and Genome-Wide Effects on Rhythmic Gene Expression

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Background: Patients with psychotic disorders such as bipolar disorder and schizophrenia show disrupted circadian rhythms. It is known that a substantial portion of the genome is temporally regulated, and expressed in a rhythmic manner under the control of the circadian clock. Moreover, temporal coordination of gene expression is essential for the proper function of many neuronal processes. Risk associated genes for psychosis and mood disorders contain variants that also determine chronotype, but their role in molecular clock pathways and gene expression rhythms remains unknown.

Methods: To understand how psychosis risk genes contribute to rhythmic transcription across the genome, we used human neuronal precursor cells (NPCs) grown from healthy donors. Using siRNA, we knocked down expression of the psychosis risk genes CACNA1C, TCF4, ANK3, or ARNTL in NPCs. Gene expression was examined at five times over 24 h using whole-transcriptome RNA sequencing. Rhythm and pathway analyses were performed to identify sets of rhythmic genes impacted by knockdown of the different risk genes.

Results: All knockdowns altered cellular circadian rhythms and the number of rhythmic genes across the genome. CACNA1C knockdown increased the number of rhythmic transcripts, whereas the other interventions, especially ARNTL resulted in loss of rhythms. The phase and amplitude of rhythmic transcripts was distinctly altered by each intervention. Pathway analysis revealed that reduced risk-gene expression led to rhythm changes in transcripts related to synaptic transmission, cellular stress response, and gated ion channels, pathways previously implicated in psychosis.

Conclusions: Our findings indicate that CACNA1C, ANK3, TCF4, and ARNTL contribute to rhythmic expression throughout the genome. The alteration of many pathways implicated in BD may be related to a change in the rhythmicity of transcripts resulting from genetic variations. By exploring the mechanism of the circadian influence of these BD-associated risk genes, we may better understand the connection between BD and circadian rhythms.

Keywords: Gene Co-Expression Networks, Circadian Rhythm, Psychosis-Risk, Bipolar Disorder (BD), Chronotype

Disclosure: Alkermes: Consultant (Self).

P483. Vulnerable Pyramidal Neurons in Primate Dorsolateral Prefrontal Cortex Express an Enriched Calcium Interactome: Critical Role of Calbindin and Cav1.2 in Higher-Order Cognition

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Background: The recently evolved dorsolateral prefrontal cortex (dlPFC) is essential to higher cognition, working memory and abstract thought, with pyramidal cell microcircuits in layer III that are able to excite each other to keep information "in mind" without sensory stimulation. However, these pyramidal cells are remarkably susceptible in neuropsychiatric disorders, where layer III is the focus of synapse dendritic atrophy in schizophrenia and neurodegenerative disorders such as Alzheimer's disease (AD), where it highly correlates with degree of cognitive impairment. In particular, the layer III pyramidal cells that express the calcium-buffering protein, calbindin, when healthy are the subset preferentially lost in AD. However, it is unknown why these cells are so susceptible to pathology, while nearby neurons are more resilient. The current study identified the calbindin (CALB1) expressing pyramidal cells in human and macaque dlPFC, examining their transcriptomic signatures, as well as additional studies of their connections and molecular regulation in macaque dlPFC, and found that they express magnified calcium signaling needed to sustain mental representations. However, higher levels, during chronic stress, caused a loss of firing and impaired cognition.

Previous research has shown that layer III dlPFC is the site of microcircuits with extensive recurrent excitation needed for "Delay cells" to maintain spatially tuned neuronal firing during spatial working memory, where the open state of HCN channels on dendritic spines provides dynamic changes in network connectivity. Delay cell firing depends on NMDA-GluN2B neurotransmission (encoded by GRIN2B), the subtype that closes most slowly and fluxes high levels of calcium. Calcium may be needed to support persistent firing, but it is well established that excessive levels can drive dendritic atrophy and tau hyperphosphorylation, and genomic studies have consistently found links between mutations in the L-type voltage-gated calcium channel (LTCC), CACNA1C (Cav1.2) and cognitive impairment, including increased risk for schizophrenia and other neuropsychiatric disorders, including AD. Cav1.2 is a key component of the stress response in heart, where noradrenergic stimulation of β1-adrenoceptors (β1-AR) activates Cav1.2 to drive internal calcium release from the sarcoplasmic reticulum, increasing muscle contraction. However, Cav1.2 actions in primate dlPFC are unknown and how they may relate to the calbindin-expressing pyramidal cells that are the focus of degeneration.

Methods: The current study integrated single nucleus RNA-sequencing in human and rhesus macaque dlPFC, multi-label immunofluorescence (MLIF), super resolution immunoelectron microscopy (immunoEM), in vivo physiology coupled with iontophoresis of pharmacological compounds and behavior in rhesus macaque dlPFC to evaluate the calcium interactome (CACNA1C, GRIN2B, KCNN3).

Results: We showed that, in both human and macaque dlPFC, these cells have especially high expression of GRIN2B, CACNA1C and KCNN3, encoding the NMDAR-GluN2B and LTCC Cav1.2 channels that flux high levels of calcium into the neuron, and the SK3 potassium channel that whose open state is increased by calcium. A series of further studies in macaques showed that the CALB1-enriched pyramidal cells preferentially connect to the contralateral dlPFC, suggesting that increased calcium may be needed to maintain firing across the corpus callosum. ImmunoEM demonstrated that Cav1.2, SK3 channels and β1-AR are all concentrated on layer III dendritic spines, similar to NMDAR-

GluN2B, with Cav1.2 on the plasma membrane near the calcium-storing spine apparatus, positioned to further increase calcium actions via internal release. Physiological recordings from cognitively engaged macaques showed that either inadequate or excessive LTCC actions, the latter driven by β1-AR stimulation, markedly reduced Delay cell firing needed for working memory via opening of SK potassium channels. Comparable effects were seen at the behavioral level, with stress-induced working memory impairment rescued by LTCC or β1-AR blockade.

Conclusions: These data reveal a mechanism by which stress impairs dlPFC cognitive function, and also suggest that either loss-of-function or gain-of-function mutations in CACNA1C would be harmful to dlPFC function and increase risk of neuropsychiatric disorders. As elevated calcium signaling is known to drive AD pathology, the data also explain why this subset of pyramidal cells with an enriched calcium interactome is especially susceptible to tau pathology and degeneration. The current findings are a rare example where transcriptomic and genomic data can be related to the dysfunction of a higher cortical circuit, illuminating how molecular insults give rise to symptoms of cognitive impairment.

Keywords: Voltage-Gated Calcium Channel, Acute and Chronic Stress, Noradrenergic Signaling, SK3 Calcium-Activated Potassium Channels, Calbindin

Disclosure: Nothing to disclose.

P484. Induced Pluripotent Stem Cell Modeling of Rare Variants Casual in Psychosis

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Background: Schizophrenia is a genetically heterogenous disease with developmental origins and a pathogenesis that involves abnormal synapse formation and maintenance. Although the most recent genome wide association studies implicate ~270 sites, each variant only makes a marginal contribution to relative risk. In total, common variants explain ~24% of the variation in schizophrenia, a disease which is approximately 80% heritable. This suggests that other elements in the genome may confer larger amounts of risk. New statistical genomics techniques focusing on rare variants have implicated a small number of genes that increase the odds of schizophrenia by a factor of greater than 20. Among these variants is a protein-truncating variant in the GRIA3 gene. GRIA3 encodes for a subunit of the AMPA receptor which plays key roles in synaptic transmission and therefore, learning, memory and psychiatric disease. To study the role of GRIA3, we used the Mount Sinai BioME (a biobank with whole exome sequencing on over 50,000 people with diverse ancestries from across NYC) to identify a family carrying protein-truncating variants in GRIA3. Supporting the importance of GRIA3 in psychiatric disease, several members of the identified family suffer from psychosis and intellectual disability. Our team has recruited several members of this family and have collected blood. Using stem cell reprogramming and directed differentiation techniques, we will generate patient-specific induced pluripotent stem cell (iPSC) lines and direct them towards 2D cortical neuron cultures and 3D neural organoids. Using CRISPR/Cas9 technology, we will gene-edit the variant into iPSC lines from family members without disease as well as non-family members, to understand the role of the variant in various genetic backgrounds.

Methods: We have collected whole blood from one affected male, one female carrier, and one unaffected female. We plan to isolate peripheral blood mononuclear cells (PBMCs) from whole blood and reprogram to pluripotency using the CytoTune 2.0 Sendai Reprogramming Kit. In addition to these controls, we have iPSCs from an unaffected male and female from outside the family for genetic diversity. Finally, we will use CRISPR/Cas9 to generate isogenic controls to control for variant dosage, sex differences, and genetic background.

Aim 1: Determining neurodevelopmental consequences of GRIA3 variant. Using 3D differentiations to cerebral organoids, we will model defects in progenitor cell proliferation and migration, differences in cerebral organoids size, and differences in cell fate trajectory between our conditions.

Aim 2: To interrogate the whole cell and network-level electrophysiological derangements in GRIA3 mutant brain tissue. To determine the effect of this GRIA3 variant on the AMPA receptor, we will perform whole-cell patch clamp on differentiated neurons from cases and controls within the family as well as our gene-edited controls. We will use whole-cell patch clamp to examine calcium permeability and total current flow during evoked potentials including mean inward and outward glutamatergic currents. Moreover, we will implement high frequency stimulation protocols for inducing long term potentiation differentiated neurons in 2D as previously described. Firing frequency and action potential voltage before and after LTP induction protocol will reveal the extent of induction. We hypothesize that protein truncating variants in GRIA3 will cause abnormal neuronal firing, synaptic transmission, and network activity.

Results: In order to validate our 2D cortical neuron differentiations, we use the neural stem cell marker Nestin, the neurodevelopmental marker Pax6, the mature neuron markers Tuj1 and MAP2A, along with the AMPA-R subunits GRIA1-3. With the exception of Nestin, which peaks at D14 during our neural progenitor phase, our markers increase over time and exhibit maximum expression at our last time point. GRIA3 is expressed by our model and is a first step towards showing our system is sufficiently mature to manifest our disease state.

Conclusions: The iPSC model system differentiated to excitatory, glutamatergic neurons reveals a cell fate and receptor profile that is sufficient for modeling our AMPA-R variant. Advancing the aims of this project, introducing more members of the family to improve our background and get subtler changes in genetic backgrounds, and possibly introducing more families with new ultra-rare variants from our BioME represents a unique opportunity for revealing the causal mechanisms of disease. By introducing secondary mutations, we may begin to understand the polygenic contributions to variants with interaction effects.

Keywords: Induced Pluripotent Stem Cells (iPSCs), Schizophrenia, Organoids

Disclosure: Nothing to disclose.

P485. Precise Therapeutic Targeting of Distinct NRXN1+/- Mutations

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Background: As genetic studies continue to identify risk loci that are significantly associated with risk for neuropsychiatric disease, a critical unanswered question is the extent to which diverse mutations --sometimes impacting the same gene-- will require common or individually tailored therapeutic strategies. Here we consider this in the context of rare, heterozygous, and

nonrecurrent copy number variants (2p16.3) linked to a variety of neuropsychiatric disorders that impact NRXN1, a pre-synaptic cell adhesion protein that serves as a critical synaptic organizer in the brain. Complex patterns of NRXN1 alternative splicing are fundamental to establishing diverse neurocircuitry, vary between the cell types of the brain, and are differentially impacted by unique patient-specific (non-recurrent) deletions. Progress towards precision medicine may require restoring each person's NRXN1 isoform repertoires in a cell-type-specific manner.

Methods: Towards this, here we contrast the cell-type-specific impact of unique patient-specific mutations in NRXN1 using human induced pluripotent stem cells, employing an array of RNA-sequencing and electrophysiological methodologies.

Results: Perturbations in NRXN1 splicing causally lead to divergent cell-type-specific synaptic outcomes: whereas NRXN1+/- deletions result in a decrease in synaptic activity throughout glutamatergic neuron maturation, there is an unexpected increase in synaptic activity in immature GABAergic neurons. Both glutamatergic and GABAergic synaptic deficits reflect independent loss-of-function (LOF) and gain-of-function (GOF) splicing defects. Towards clinical relevance, we show that treatment with b-estradiol increases NRXN1 expression in glutamatergic neurons, while antisense oligonucleotides knock-down mutant isoform expression across both glutamatergic and GABAergic neurons.

Conclusions: Our results suggest that aberrant NRXN1 splicing is causally related to synaptic dysfunction, therefore, direct or indirect manipulation of NRXN1 splicing isoforms provides a promising therapeutic strategy for treating humans with NRXN1 deletions.

Keywords: Neurogenetics, Induced Pluripotent Stem Cells, Electrophysiology, Gene Therapy

Disclosure: Nothing to disclose.

P486. Differential Gene Expression Between Layers 3 and 5 in the Subgenual Anterior Cingulate Cortex Within Unaffected Comparison Subjects and Across Psychiatric Disorders

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Background: Dysfunction within the subgenual anterior cingulate cortex (sgACC) has been implicated across psychiatric illnesses. Differences in gene expression have been uncovered within this brain region in psychosis as well as mood disorders. Interestingly, the sgACC is comprised of multiple subregions, or Brodmann areas (BAs), including BA 24, 25, 32 and 33, which each have unique laminar patterns and cytology. Furthermore, cells within specific lamina from this region project to distinct targets. For example, neurons within layer 3 primarily form cortico-cortical connections while layer 5 contains subcortical projection neurons. Previous transcriptomic studies of psychiatric disease have been conducted in homogenate brain tissue and have not discriminated between subregions or lamina. Thus, to better interpret studies of psychiatric illness, we first sought to understand how this region differs in nonpsychiatric comparison subjects. These preliminary studies have informed collection strategies within a larger cohort of subjects, encompassing transdiagnostic psychiatric disorders.

Methods: We performed laser capture microdissection, RNA sequencing, and differential expression (DE) analysis to investigate changes in gene expression across cortical subregions (BA 24a, 24b, and 32), layers (L3 and L5), and sub-lamina (5a and 5b) within postmortem human tissue collected from the sgACC of nonpsychiatric comparison subjects ($n = 6$, balanced for sex). Transcripts were considered DE if adjusted $p < 0.05$. Similar analyses are currently underway within our larger psychiatric cohort ($n = 120$) and, in addition to DE, will include a "time of death" (TOD) analysis, enabling us to examine diurnal rhythms of gene expression by organizing subjects across a 24-hour clock based on their TOD.

Results: Across subregions, we found no significant differences in transcript expression within individual cortical layers. For instance, the transcriptional profile of L3 did not differ across sgACC subregions. However, between-layer comparisons revealed striking differences between L3 and L5 (1,056 transcripts). Bioinformatic analyses were used to compare biological process enrichment between lamina (Metascape) and were also visualized as weighted gene co-expression network analysis (Cytoscape), suggesting distinct functions between L3 and L5 Further, L5a and L5b were transcriptionally similar across subregions and, when collapsed to increase statistical power, showed fewer DE patterns between one another (145 transcripts). Although the current study was underpowered to uncover sex-differences, exploratory analysis suggests that male subjects may largely be driving DE between L3 and L5 (1,102 transcripts in males vs. 171 transcripts in females).

Conclusions: Our results demonstrate that individual cortical layers are similar within subregions of the sgACC, but transcriptional signatures between across L3 and L5 are very different, particularly in pathways involving brain development, presynaptic function, cell-cell junction signaling and dendritic spines. Given evidence for the role of specific cortical layers within individual features of psychiatric illness and distinct neuronal projections amongst laminae, identifying how gene expression in distinct cortical layers differ may improve our understanding of disease-related mechanisms in the brain and aid in the development of novel informed treatments.

Keywords: Postmortem Brain Tissue, RNA-Sequencing, Laser Capture Microdissection, Schizophrenia (SCZ), Mood Disorders

Disclosure: Nothing to disclose.

P487. Abnormal Neuronal Excitability and Glutamate Transmission in a Human iPSC Model of 22q11.2 Deletion Syndrome

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Background: The 22q11.2 deletion syndrome (22q11DS) is the most common human chromosomal interstitial-deletion disorder, occurring in approximately 1/4000 live births. The syndrome is associated with neuropsychiatric disorders such as schizophrenia (SCZ) and autism spectrum disorder. Significantly, 20-30% of 22q11DS individuals develop SCZ by early adulthood, such that 22q11DS is among the most robust genetic predictors of SCZ. Studying this syndrome affords a unique opportunity to unravel the pathophysiology of SCZ and other associated disorders. However, to date the molecular consequences of the 22q11.2 deletion and how these lead to neuronal dysfunction is poorly understood. In this study, we investigated the functional significance of this deletion by evaluating the electrophysiological properties of human induced pluripotent stem cell (HiPSC)-derived neurons from subjects with 22q11DS.

Methods: HiPSCs were generated from blood samples collected from 8 subjects, including four 22q11DS patients and four sex- and age-matched healthy controls (HC), by using the non-

integrating sendai-virus approach. Using the forced expression of Neurogenin 2 approach, human iPSCs were converted into a homogeneous population of excitatory induced neurons (iNs). Whole cell patch clamp recordings were performed on these neurons at 2, 4, 6 and 8 weeks after differentiation. Membrane properties were examined in current clamp mode by measuring membrane potential changes in response to membrane current injections. Single action potentials were induced through a ramp current injection protocol to examine action potential kinetics. Data analysis was performed using MATLAB, MiniAnalysis, and customized scripts. Synaptic transmission and homeostatic plasticity were examined in voltage-clamp mode with a holding potential of -60 mV. Spontaneous excitatory postsynaptic currents (sEPSCs) were recorded using potassium gluconate-based patch solution, and miniature EPSCs (mEPSCs) were recorded using a Cesium Methyl sulfonate-based patch solution and with the presence of tetrodotoxin (TTX) and the GABAA receptor antagonist GABAzine in the perfusate. To induce homeostatic plasticity, neuron cultures were treated for 24 hours with TTX (1 μM) and the non-NMDA glutamate-receptor antagonist DNQX (20 μM). We analyzed all EPSC recordings using MiniAnalysis software.

Results: We first examined membrane properties of neurons at several developmental stages. While the resting membrane potential remains stable from two to eight weeks post-differentiation, the input resistance and time constant decreased gradually throughout development. At two and four weeks, 22q11DS and HC neurons showed similar membrane properties: resting membrane potential, input resistance, time constant, and action potential kinetics were not significantly different. However, at both 6 weeks and 8 weeks post-differentiation, 22q11DS neurons exhibited significantly lower action potential thresholds ($p < 0.01$) and smaller amplitudes of fast after-hyperpolarization potentials (fAHP) compared to HCs ($p < 0.05$), indicating the 22q11DS neurons exhibited hyperexcitability in a developmental-stage-dependent manner.

We next examined glutamatergic transmission and homeostatic plasticity. Compared to HC neurons, 22q11DS neurons had lower frequencies of spontaneous EPSCs but the EPSCs had similar amplitudes. TTX/DNQX treatment for 24 hours increased the amplitude of mEPSCs in HC neurons, but not in 22q11DS neurons. This result suggests that the 22q11 deletion disrupts homeostatic plasticity in 22q11DS neurons.

Conclusions: In a human iPSC model of 22q11DS, we found neurons from 22q11DS patients had lower action potential thresholds and smaller fAHP amplitudes at 6 and 8 weeks post-differentiation, but not at 2 and 4 weeks. The results suggest that cortical-like excitatory iNs derived from 22q11DS subjects become hyper-excitable as they develop. We also observed decreased glutamate-mediated transmission and disruption of homeostatic plasticity in 22q11DS neurons. If similar differences in cortical neuronal properties occur in the developing brains of patients with 22q11DS, such differences might account for some 22q11DS-related altered behavioral outcomes. The human iPSC model provides a unique tool for understanding the pathophysiological mechanisms of 22q11DS and, possibly, schizophrenia.

Keywords: 22q11.2 Deletion Syndrome, Schizophrenia (SCZ), Human Pluripotent Stem Cells, Electrophysiology

Disclosure: Nothing to disclose.

P488. The Role of Nucleus Accumbens D3 Dopamine Receptors in Antipsychotic Efficacy

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Background: Second generation antipsychotics (SGAs) are widely used treatments for people with serious mental illnesses and other neurological conditions. Research into antipsychotic mechanisms of action have predominantly focused on their actions at D2 dopamine receptors given our more involved understanding of these G-protein coupled receptors (GPCRs). Many of these SGAs also bind D3 dopamine (D3R), a subset of the Gi-coupled D2R family, with some binding at higher affinity compared to D2Rs. Given recent advances in structural biology and pharmacology, we now have the tools to dissect out the function of D3R independent of D2R using selective agonists/antagonists and genetic deletion. A convergent area of interest lies in the nucleus accumbens where D3Rs are enriched in contrast to areas in the dorsal striatum where D2Rs dominate. Our understanding of the role of the nucleus accumbens in reward learning and motivation makes it an attractive target for the treatment of many neuropsychiatric disorders.

Methods: For slice electrophysiology, whole-cell current- and voltage-clamp recordings will be made from nucleus accumbens medium spiny neurons in 250 μm-thick acute coronal slices prepared from male mice. D3R-expressing neurons will be targeted by crossing D3-Cre mice with Ai14 reporter mice, which carry a floxed td-Tomato fluorophore that can be visualized with 880nm 2-photon excitation. These cells will be compared to Cre lines that report expression of D1 or D2. To assess D3R function, we will measure intrinsic excitability properties, evoked EPSCs/IPSCs as well as miniEPSCS/IPSCs in conditions with perfusion of D3R selective agonists/antagonists (PD128907, GR103691) and SGAs (cariprazine, aripiprazole, quetiapine, clozapine). Additionally, selective AMPAR and NMDAR antagonists (NBQX, R-CPP) can be used to analyze AMPAR/NMDAR current ratio and kinetics and investigate the effects of D3R on the synaptic plasticity of medium spiny neurons in the nucleus accumbens. For behavioral testing, we will use the novelty-suppressed feeding paradigm to induce stress and assess motivation and anxiety-like behavior. D3R-cKO mice will undergo stereotaxic injection into the nucleus accumbens to create selective knock-out of D3Rs in the nucleus accumbens with AAV-Cre-GFP.

Results: Data from ex vivo slice electrophysiological experiments analyzing spontaneous mini events in D3R-expressing medium spiny neurons of the nucleus accumbens show a decrease in mIPSC amplitude after the addition of a selective D3R agonist ($p0.05$) in a paired t-test. There is also no significant change in mEPSC amplitude or frequency after addition of the D3R agonist. These results suggest that activation of D3R in the nucleus accumbens modulates inhibitory activity, likely through downstream regulation of GABAA receptors. The consistent mIPSC frequency with a significant change only in amplitude is also suggestive of a postsynaptic effect rather than the influence of presynaptic D3Rs. This is further confirmed by evoked experiments in which a similar reduction in IPSC amplitudes are observed after local electrical stimulation with a conservation of the paired pulse ratio after addition of D3R agonist drug.

Conclusions: By examining the specific function of D3R in the nucleus accumbens in mice we are able to better understand the action of currently prescribed SGAs and promote development of more efficacious treatments with less significant side effect burdens. Combining pharmacology and electrophysiological tools to study the local circuitry of the nucleus accumbens with site-specific loss-of function mouse behavioral assays, we can begin to tease apart the physiological function of D3Rs in the ventral striatum and identify potential new targets for future therapeutics. Our current results show that D3R agonism results in decreased inhibitory activity in medium spiny neurons in the mouse nucleus accumbens. This suggests that the D3R-associated activity of currently prescribed SGAs such as cariprazine leads to modulation of downstream inhibitory tone.

Keywords: Synaptic Function, Dopamine (D2, D3) Receptors, Antipsychotic Drugs

Disclosure: Nothing to disclose.

P489. Probing the Impact of Antipsychotics on Dynamic Microtubules and Calcium Signaling in Dopaminergic Neurons

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Background: Neuronal form and function rely on microtubules, critical cytoskeletal components that convert between stable and dynamic forms. Dynamic instability, characterized by the rapid growth and shrinkage of the dynamic pool, has recently been found to play key roles in synaptic plasticity, affecting both presynaptic and postsynaptic sites. Numerous studies implicate microtubules and microtubule-associated proteins in psychiatric diseases, including schizophrenia, attention deficit hyperactivity disorder, depression, bipolar disorder, and autism spectrum disorder. Particularly, recent human studies have suggested that a loss of microtubule dynamicity could be contributing to the disruptions in plasticity observed in schizophrenia and major depressive disorder. Despite these findings, there is little investigation into whether dynamic microtubules might be affected in psychiatric diseases and their treatment. Here, we introduce tools for viral and image analysis to explore microtubule dynamics in living neurons and synapses. We investigate how dopaminergic neuron activity influences microtubule dynamics and assess the effects of antipsychotics (clozapine and haloperidol) on these dynamics.

Methods: To label only the dynamic pool of microtubules while observing cytoskeletal architecture or monitoring neuronal activity, we generated two adeno-associated virus (AAV) constructs that express a fluorescently-tagged microtubule cap protein, EB3, to provide real-time tracking of growing microtubule tips: 1) a construct that utilized a bicistronic element to provide visualization of cellular architecture and dynamic microtubule activity, used in primary cortical neuron cultures from neonatal mice; 2) a construct that utilized a DIO (Double-Floxed Inverted Open reading frame) element to allow for cell-type specific expression in midbrain cultures derived from mixed-sex pooled DAT-ires-cre;Ai38 neonatal mice, to provide dynamic microtubule tracking and simultaneous calcium imaging in dopaminergic neuron axons and dendrites.

The neuronal cultures were infected and imaged after 7 days. We measured baseline dynamic microtubule activity and then responses after bath application of clinically relevant concentrations of haloperidol (0.1 μM), clozapine (1 μM), or vehicle control (0.1% DMSO). Neuronal processes were imaged at 10-minute intervals after, for up to one hour, and analyzed using custom ImageJ scripts ($n \geq 3$ cultures per treatment group). Statistical analysis used one-way ANOVA, Two-way ANOVA with repeated measures, and a student's t-test (GraphPad Prism 9, San Diego, USA).

Results: We have validated this viral strategy for imaging dynamic microtubules in a cell-type specific manner. The results provide the initial characterization of dynamic microtubules in dopaminergic neurons, including their regulation by calcium signaling. Our preliminary evidence indicates that pharmacologically relevant levels of clozapine rapidly and powerfully increase microtubule dynamic instability in dopaminergic axons via enhanced depolymerization and decreased velocity. These changes are expected to alter the trafficking of synaptic vesicles, mitochondria, and other organelle trafficking that control axon form and synaptic activity.

Conclusions: We introduce a novel, neuron-type-specific viral approach and a computational pathway for investigating microtubule dynamics at neurites and synapses. Preliminary findings highlight the effect of clozapine on dynamic microtubules, which may underlie its regulation of synaptic activity. These findings may reveal a novel role for clozapine in the treatment of schizophrenia, potentially contributing to its superior efficacy clinically, especially in cases of treatment-refractory schizophrenia and negative symptoms. Future work will adapt this approach to probe microtubule dynamics in models of schizophrenia, autism spectrum disorder, and early life stress.

Keywords: Antipsychotic, Cytoskeleton, Calcium Imaging, Dopaminergic Neurons

Disclosure: Nothing to disclose.

P490. Sulforaphane for the Treatment of Negative Symptoms in Schizophrenia

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Background: Negative symptoms persist in many patients with schizophrenia after positive symptoms are reduced by antipsychotic medication and are associated with persistent problems in social functioning and other functional outcomes in schizophrenia. There are few established treatments for negative symptoms in schizophrenia. Oxidative stress, inflammation and epigenetic modifications involving HDAC have been implicated in the pathophysiology of schizophrenia. Sulforaphane has antioxidant properties and is an HDAC inhibitor. The object of the current study was to determine the efficacy of sulforaphane in treatment negative symptoms in patients with schizophrenia who were stabilized on antipsychotics and had predominant negative symptoms.

Methods: This was a randomized double-blind placebo controlled study of patients (male and female) with schizophrenia who were stabilized on antipsychotic medication and had predominant negative symptoms (PANSS negative symptoms higher than positive symptoms) in Hunan China. Patients received daily doses of either 2 (1700 mg) tablets daily of Extra Strength Avmacol (Nutramax sulforaphane tablets glucoraphanin content 30 mg/tablet) or placebo tablets for 24 weeks. All other medication was stable thought the trial. Psychiatric symptoms were measured with PANSS scale and CGI. Side effects were assessed with TESS scale. Analysis used intent to treat mixed model analysis for symptom scores and Mann Whiney U Test for each side effect item scores.

Results: 53 patients treated with sulforaphane and 24 patients treated with placebo who had a least one post intervention outcome evaluations were analyzed. Sulforaphane treated patients showed a significantly greater decrease in PANSS negative symptom total score ($P = .01$) and PANSS Negative factor score ($P = .02$) than placebo treated patients with the most prominent difference occurring at 24 weeks ($P \leq .001$) with large effect size at this time point ($d = 0.8$). Sulforaphane's effect on decreasing negative symptoms was not mediated by change in scores of depression or cognitive factors on the PANSS. There were no significant differences between sulforaphane and placebo on change in the CGI scale. Sulforaphane was well

tolerated and there were few differences between sulforaphane and placebo on items in the TESS side effect scale.

Conclusions: The results of this study suggest that add-on high dose sulforaphane may significantly reduce negative symptoms in stabilized schizophrenic patients on antipsychotic medications who have predominant negative symptoms. The pronounced effect may only be seen after several months of treatment. The clinical meaningfulness of this reduction in negative symptoms needs further evaluation.

Keywords: Negative Symptoms, Sulforaphane, Schizophrenia

Disclosure: Nothing to disclose.

P491. Meta-Regression of Adjunctive Treatment Trials for Negative and Other Residual Symptoms in Schizophrenia: A Differential Relationship of Treatment and Placebo Response With Sample Size

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Background: Negative and other residual symptoms of schizophrenia typically persist despite treatment with best available medications for schizophrenia. Clinical studies have evaluated the effects of multiple potential non-dopamine type 2 receptor (D2-antagonists) compounds for adjunctive use, but no approved compounds are yet available. Moreover, interpretation of adjunctive studies may be affected by placebo responses, which have recently been shown to correlate with sample size and site number in monotherapy trials of D2-antagonist antipsychotics in schizophrenia. Here, we performed a meta-analysis and meta-regression of adjunctive treatment studies for negative and other residual symptoms of schizophrenia across several mechanism of action (MoA), operationalized as MoA's with 5 or more studies, including at least one multi-center study.

Methods: We conducted a literature search of adjunctive treatment studies for which both single- and multi-center studies were available. We identified 161 treated vs. placebo comparisons across 127 individual studies across 8 MOA. Meta-analysis and meta-regression analyses were conducted with sample size as a covariate.

Results: Significant effects were observed for 5-HT3R antagonists ($d = 1.03$. $p = .01$); estrogen modulators ($d = .42$, $p < .001$); anti-inflammatories ($d = .40$, $p = .01$); NMDAR modulators ($d = .34$, $p < .001$); anti-depressants ($d = .33$, $p < .001$); and alpha-7 nicotinic agonists ($d = .10$, $p = .02$), whereas non-significant results were obtained for DA modulators ($d = .14$, $p = .1$) and AChE inhibitors ($d = .17$, $p = .38$).

Across MOA, the magnitude of the placebo response scaled with sample size to a greater extent than treatment response, leading to a significant reduction in trial effect size with sample size ($p < .0001$).

The negative symptom effect size for those treated with active drug did significantly change with greater sample size (Beta = 2.07, $p = 0.37$). In contrast, the negative symptom effect size for those receiving placebo significantly increases with sample size (Beta = -5.2, $p = 0.03$). Drug/Placebo difference in negative symptoms effect size diminishes with larger total sample sizes and becomes non-significant for $N = 400$. Similar results were seen for other residual symptoms, along with differential responses between single and multi-center studies. Significant results were obtained preferentially with sample sizes in the range of 30 to 150 individuals.

Conclusions: These results highlight the potential efficacy of specific add-on mechanisms and encourages further clinical development. In addition, the results highlight the importance of considering the differential sample size effects on the placebo vs. treatment response when designing adjunctive clinical trials in schizophrenia.

Keywords: CNS Clinical Trials, Clinical Development, Negative Symptoms

Disclosures: MedinCell, Merck, Leal, Karuna: Advisory Board (Self).Otsuka: Consultant (Self). NIMH, Sunovion, Click, Neurocrine, Taisho, Boehringer Ingelheim: Contracted Research (Self),

P492. KarXT (Xanomeline–Trospium) Demonstrates Broad Efficacy in People With Schizophrenia Across a Wide Range of Demographic Subgroups: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled Emergent Trials

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Background: Currently available antipsychotics, all of which share some D2 dopamine receptor blocking activity, are associated with well-known efficacy and tolerability limitations. A significant unmet need exists for new antipsychotic medications with different mechanisms, broader efficacy, and better tolerability. Drugs with novel mechanisms, including muscarinic receptor agonism, have recently shown promise in the treatment of people with schizophrenia. In the three 5-week, randomized, double-blind, placebo-controlled EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT04738123) trials, KarXT (xanomeline–trospium chloride) was associated with a significant reduction in symptoms vs placebo and was generally well tolerated in people with schizophrenia experiencing acute psychosis. In these trials, KarXT was not associated with many of the common side effects of D2 dopamine receptor antagonists. In this analysis, we pooled results from all the short-term EMERGENT trials to further characterize the efficacy of KarXT across a range of demographic subgroups.

Methods: The EMERGENT trials were 5-week, randomized, double-blind, placebo-controlled, inpatient trials conducted in people with schizophrenia experiencing acute psychosis. EMERGENT-1 and EMERGENT-2 were conducted in the United States, and EMERGENT-3 was conducted in the United States and Ukraine. Key inclusion criteria were a recent worsening of positive symptoms warranting hospitalization, Positive and Negative Syndrome Scale (PANSS) total score >80, and Clinical Global Impression–Severity score 4 or higher. Participants were randomized 1:1 to KarXT or placebo. KarXT dosing (xanomeline/trospium) started at 50 mg/20 mg twice daily (BID) and increased to a maximum of 125 mg/30 mg BID. In each trial, the primary efficacy endpoint was change from baseline to week 5 in PANSS total score. Data from the 3 EMERGENT trials were pooled, and efficacy analyses were conducted in the modified intent-to-treat population, defined as all randomized participants who received 1 or more trial drug dose and had a baseline and 1 or more postbaseline PANSS assessment. The efficacy of KarXT and placebo were compared across participant subgroups based on key baseline demographic parameters: age, sex, race, ethnicity, country, PANSS total score, and body mass index (BMI).

Results: A total of 640 participants (KarXT, $n = 314$; placebo, $n = 326$) were included in the pooled efficacy analyses. For the overall population, KarXT was associated with a significantly greater reduction in PANSS total score at week 5 compared with placebo (KarXT, -19.4; placebo, -9.6 [least squares mean (LSM) difference, -9.9; 95% CI, -12.4, -7.3; $P < 0.0001$; Cohen's d, 0.65]). In

the subgroup analyses, KarXT was associated with a greater reduction in PANSS total score at week 5 compared with placebo across evaluated baseline demographic parameters. The KarXT-placebo LSM difference (95% CI) in PANSS total score change from baseline to week 5 for key baseline demographic parameters was -9.1 (-12.9, -5.2) for age < 45 years and -10.3 (-13.7, -6.9) for age 45 years or older; -9.1 (-14.2, -3.9) for women and -10.1 (-13.1, -7.1) for men; -11.0 (-14.0, -8.0) for Black/African American and -6.7 (-11.9, -1.5) for White participants; -6.6 (-14.6, 1.4) for Hispanic/Latino participants and -10.5 (-13.2, -7.7) for other ethnicities; -9.5 (-12.2, -6.8) for participants from the United States and -15.9 (-23.3, -8.6) for participants from the Ukraine; -7.5 (-11.2, -3.8) for baseline PANSS total score < 95 and -11.4 (-14.9, -7.8) for baseline PANSS total score 95 or higher; and -9.5 (-12.9, -6.1) for baseline BMI < 30 kg/m2 and -10.1 (-14.0, -6.2) for baseline BMI 30 kg/m2 or higher.

Conclusions: In these pooled analyses from the 3 EMERGENT trials, KarXT demonstrated a greater reduction in PANSS total score compared with placebo across all evaluated participant subgroups. These findings suggest that the strong, consistent efficacy that KarXT showed in each of the 3 pivotal trials has broad efficacy across a wide range of people with schizophrenia and further support the potential of KarXT to be first in a new class of antipsychotic medications based on muscarinic receptor agonism and without direct D2 dopamine receptor blocking activity. The ongoing EMERGENT-4 and EMERGENT-5 trials are evaluating the longer-term safety and efficacy of KarXT.

Keywords: Schizophrenia (SCZ), Psychosis, KarXT, Xanomeline, Muscarinic Receptor Agonist

Disclosure: Karuna Therapeutics: Employee (Self).

P493. Karxt (Xanomeline–Trospium) for the Treatment of Agitation in Schizophrenia: PANSS–EC Results From Three Randomized, Double-Blind, Placebo-Controlled Trials

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Background: Acute agitation is common in people with schizophrenia, and the Positive and Negative Syndrome Scale – Excited Component (PANSS–EC composed of excitement, tension, hostility, uncooperativeness, and poor impulse control items) has been used to assess the efficacy of agitation treatments. KarXT combines the dual M1/M4 preferring muscarinic receptor agonist xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride.

Methods: Three 5-week, randomized, double-blind, placebo-controlled studies EMERGENT-1 (NCT03697252), EMERGENT-2 (NCT04659161), and EMERGENT-3 (NCT-04738123) met the primary endpoint of a significant reduction in Positive and Negative Syndrome Scale (PANSS) total score through week 5 versus placebo, improved other key efficacy measures and was generally safe and well-tolerated. Post hoc analysis of the change from baseline of PANSS–EC score was conducted using methods similar to that for the primary endpoint.

Results: PANSS–EC scores were significantly reduced with KarXT as compared with placebo at Week 5 across all three EMERGENT studies. In EMERGENT-1, KarXT ($n = 90$) was statistically significantly superior ($p = 0.0002$) to placebo ($n = 92$) in decrease (improvement) of PANSS–EC score at Week 5. In EMERGENT-2, KarXT ($n = 126$) was statistically significantly superior ($p = 0.0026$) to placebo ($n = 126$) at Week 5. In EMERGENT-3, KarXT ($n = 125$) was statistically significantly superior ($p < 0.0001$) to placebo ($n = 131$) at Week 5.

Conclusions: KarXT has potential to be the first in a new class of treatments for people with schizophrenia based on muscarinic receptor agonism. Post hoc analyses showed improvement in agitation as measured by the PANSS–EC.

Keywords: Schizophrenia (SCZ), M1 and M4 Muscarinic Receptors, Xanomeline, KarXT

Disclosures: Karuna Therapeutics: Employee (Self). Karuna Therapeutics: Stock / Equity (Self).

P494. Modulation of Hippocampal Hyperactivity in Schizophrenia With Levetiracetam: a Randomized, Double-Blind, Cross-Over, Placebo-Controlled Trial

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Background: Previous neuroimaging studies of the fractional amplitude of low frequency fluctuations (fALFF) have demonstrated hippocampal hyperactivity in patients with schizophrenia. We hypothesized that levetiracetam (LEV), an anti-epileptic drug binding to the synaptic vesicle glycoprotein 2A, normalizes the hippocampal excitation/inhibition imbalance in persons with schizophrenia and can be measured using fALFF.

Methods: Thirty healthy control participants and 30 patients with schizophrenia were randomly assigned to a double-blind, cross-over trial (NCT04559529) to receive a single administration of 500 mg oral LEV or placebo during two study visits. Both male and female participants were recruited. At each visit, we assessed resting state normalized fALFF. We used linear mixed models to test for group and treatment effects and a group-by-treatment interaction. We conducted a follow-up intermediary analysis to test whether hippocampal activity is normalized in patients treated with LEV (i.e., activity of patients treated with placebo > patients treated with LEV > control participants treated with placebo). All models were adjusted for age and median framewise displacement to account for differences in motion.

Results: Hippocampal fALFF was significantly elevated in patients with schizophrenia ($p = 0.004$). Hippocampal fALFF decreased in schizophrenia patients relative to healthy controls after LEV treatment, but the effect did not reach statistical significance ($p = 0.089$). We found a linear relationship of LEV treatment on hippocampal fALFF signal ($p = 0.003$), in which hippocampal fALFF was highest in patients after placebo treatment, lowest in control participants after placebo treatment, and intermediary in patients after LEV treatment. Post-hoc tests revealed differences between healthy control participants treated with placebo and patients with schizophrenia treated with placebo ($p = 0.014$). In contrast, we found only a trend-level difference between patients treated with placebo and patients treated with LEV ($p = 0.052$) and no difference between healthy control participants treated with placebo and patients with schizophrenia treated with LEV ($p = 0.173$).

Conclusions: We found evidence for hippocampal excitation/inhibition imbalance and a normalizing effect of LEV in schizophrenia using fALFF. Notably, we replicated the previous finding of higher hippocampal fALFF in schizophrenia. We found preliminary evidence that LEV decreases hippocampal fALFF, more in schizophrenia than in healthy control participants, although the effect was small and did not reach statistical significance. Additional studies, in early stage psychosis cohorts and with longer duration of LEV treatment, are needed to establish levetiracetam as a treatment for schizophrenia.

Keywords: Hippocampus, Schizophrenia (SCZ), Functional Neuroimaging, Clinical Trial, Levetiracetam

Disclosure: Nothing to disclose.

P495. Efficacy and Safety of Ulotaront in the Treatment of Schizophrenia: Results of Two 6-Week, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials

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Background: Ulotaront is a trace amine-associated receptor 1 (TAAR1) agonist with 5-HT1A agonist activity in clinical development for the treatment of schizophrenia. Ulotaront was discovered through a target-agnostic approach optimized to identify drug candidates lacking direct D2 and 5-HT2A receptor antagonism, while demonstrating an antipsychotic-like phenotypic profile in vivo. Ulotaront has demonstrated efficacy in a 4-week, randomized, double-blind, placebo-controlled, flexible-dose (50 mg/d, 75 mg/d) Phase 2 trial [1] in patients with an acute exacerbation of schizophrenia, with effect sizes (vs. placebo) of 0.45 (Positive and Negative Syndrome Scale [PANSS] total score), 0.52 (Clinical Global Impression-Severity [CGI-S] score), and 0.48 (Brief Negative Symptom Scale [BNSS] score) at Week 4. Continued improvement was observed in a 26-week, open-label extension study [2] with responder rates (≥30% reduction in PANSS total score) of 93% (Week 26 data) and 74% (LOCF-endpoint); and with a 6-month completion rate of 67%. We summarize here the results of two Phase 3 fixed-dose studies designed to further evaluate the efficacy and safety of ulotaront in acutely psychotic adults with a diagnosis of schizophrenia (DIAMOND 1, NCT04072354; and DIAMOND 2, NCT04092686).

Methods: Both studies were multicenter (DIAMOND 1, 43 total sites; DIAMOND 2, 57 total sites), randomized (1:1:1), double-blind, placebo-controlled, parallel-group, 6-week fixed-dose trials evaluating the efficacy and safety of two doses of ulotaront (50 mg/d and 75 mg/d; 75 mg/d and 100 mg/d) in adult patients with a DSM-5 diagnosis of schizophrenia who were acutely psychotic (PANSS total score ≥ 80). In DIAMOND 1 and 2, enrollment was limited to patients with no more than 2 or 3 prior hospitalizations for acute psychotic episodes, respectively. Patients were hospitalized during double-blind treatment. Study medication was taken once-daily at bedtime, with or without food. The primary endpoint was Baseline-to-Week-6 change in PANSS total score. In each study, the sample size provided 90% power to reject the null hypothesis of no drug vs. placebo difference in the primary endpoint in at least one dose group, with a global 2-sided alpha of 0.05, while accounting for early dropouts. The primary efficacy endpoint was evaluated using a mixed model for repeated measures (MMRM) analysis under the missing-at-random assumption. Subgroup analyses were performed to examine the potential impact of the COVID-19 pandemic.

Results: DIAMOND 1 (50 mg/d and 75 mg/d): A total of 432 patients were randomized (modified intent-to-treat [mITT]) to ulotaront 50 mg/d (n = 142; Baseline mean PANSS total score, 102), ulotaront 75 mg/d (n = 145; mean PANSS total score, 102), and placebo (n = 145; mean PANSS total score, 102). Six-week completion rates were 76.4%, 81.4%, and 81.5%, respectively. The least-squares (LS) mean (SE) change from Baseline in PANSS total score at Week 6 was −16.9 (1.6) for ulotaront 50 mg/d (not significant [n.s.]), −19.6 (1.6) for ulotaront 75 mg/d (n.s.), and −19.3 (1.5) for placebo. DIAMOND 2 (75 mg/d and 100 mg/d): A total of 460 patients (mITT) were randomized to ulotaront 75 mg/d (n = 153; Baseline mean PANSS total score, 101), ulotaront 100 mg/d (n = 152; mean PANSS total score, 100), and placebo (n = 155; mean PANSS total score, 100). Six-week completion rates were 78.1%, 75.3%, and 82.6%, respectively. LS mean (SE) change from Baseline in PANSS total score at Week 6 was −16.4 (1.5) for ulotaront 75 mg/d [n.s.], −18.1 (1.5) for ulotaront 100 mg/d [n.s.], and −14.3 (1.5) for placebo. In a pooled analysis of DIAMOND 1 and DIAMOND 2 subjects enrolled prior to the COVID-19 pandemic (March 13, 2020) ulotaront showed similar efficacy findings as in the previously reported Phase 2 study [1]. DIAMOND 1 and 2 (50 mg/d, 75 mg/d, 100 mg/d): The most common adverse events for all doses of ulotaront were schizophrenia, headache, insomnia, and anxiety; no dose-related increase in incidence of adverse events was observed, and all number needed to harm (NNH) values versus placebo were ≥10. The incidence of extrapyramidal events was low in the ulotaront dose groups and similar to placebo.

Conclusions: Ulotaront did not achieve significance on its primary efficacy endpoint (change from Baseline in PANSS total score at Week 6) for the 50 mg/d or 75 mg/d dose groups in the DIAMOND 1 study, or the 75 mg/d or 100 mg/d dose groups in the DIAMOND 2 study. A major contributor to the lack of significant difference in ulotaront vs. placebo change scores appears to be an unusually high placebo response, particularly in the DIAMOND 1 study. Pre- vs. post-COVID-19 pandemic efficacy analyses suggest an impact of the COVID-19 pandemic on the placebo response in these studies.

Keywords: Schizophrenia (SCZ), TAAR1, Phase III Trial, Clinical Trial, Ulotaront

Disclosure: Sumitomo Pharma America: Employee (Self).

P496. Pharmacologic Augmentation of Computerized Targeted Cognitive Training in Individuals With Schizophrenia: Interim Analyses of Clinical Effects

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Background: Antipsychotic medications can mitigate certain clinical symptoms of schizophrenia (SZ), but do not fully ameliorate those symptoms or address impairments in cognitive and psychosocial functioning. Computerized targeted cognitive training (TCT) has been shown to improve clinical, cognitive, and daily functioning in SZ, but these benefits of TCT are modest in magnitude and evident in only about half of TCT users, even after 40 or more hours of training. This study tests whether either d-amphetamine (AMPH: 5 mg po 1-h prior to TCT) or memantine (MEM: 10 mg bid) can amplify and/or accelerate the clinical gains from a 30-hour course of TCT.

Methods: To date, 61 individuals with SZ or schizoaffective disorder (mean age 44.76, range 21-65; M:F = 36:25) have enrolled. Of these, n = 39, 31 and 28 have completed 10h, 20h and 30h of TCT, respectively. Carefully screened subjects were tested on two days separated by one week: comprehensive measures of clinical symptoms and function were obtained, together with potential predictive behavioral, electroencephalographic and auditory fidelity measures after either placebo (PBO: Test 1) or test drug (Test 2: PBO, AMPH (5 mg po) or MEM (20 mg po)). Training began either 1-week later (for subjects receiving AMPH) or after a 3-week titration to MEM 10 mg bid (for subjects receiving MEM). Over the next 10-12 weeks, participants completed 30 training sessions of a complete TCT suite (1-1.5h/

session; 2-3 sessions/week). For the present analyses, subjects were divided into 3 groups: AMPH Group received 5 mg of AMPH po, 1-h prior to each TCT session. MEM Group were titrated to 10 mg MEM bid prior to TCT onset and remained at that dose throughout the course of TCT training. PBO Group received placebo, either 1-h prior to each TCT session, or as daily pills titrated and dosed identically to MEM. Outcome measures (clinical symptoms, function scales, and MCCB) as well as EEG and auditory fidelity measures were acquired after 10, 20 and 30 sessions of TCT training, and 12 weeks post-training. Pill identity (active or placebo) was blind to both study subject and staff. Cohen's d effect sizes relative to PBO are reported here.

Results: Overall subject attrition was low and did not differ across groups. Compared to PBO Group, both AMPH and MEM Groups showed medium-to-large effect size gains across clinical and functional measures relative to baseline. Gains in both active drug groups were evident at the earliest time point (after 10 TCT sessions) and largely maintained across the full treatment time course (30 sessions) as well as 12w following TCT cessation. Significant improvements were observed across psychosis, mood, and function domains (PANSS positive: AMPH: d = -0.93; MEM: d = -1.20; PANSS negative: AMPH: d = -0.85; MEM: d = -1.05; PANSS general: AMPH: d = -0.28; MEM: d = -0.71; PANSS total: AMPH: d = -0.74; MEM: d = -1.04), mood (YMRS: AMPH: d = -1.38; MEM: d = -0.64; PHQ-9: AMPH: d = -1.20; MEM: d = -0.67) and function (WHODAS: AMPH: d = -1.23; MEM: d = -0.35). Importantly, no measures detected worsening of symptoms in any group; consistent with this, no subjects experienced a study-related serious adverse event.

Conclusions: These interim results suggest that either AMPH (5 mg 1h prior to TCT) or MEM (10 mg bid throughout training) can significantly augment the therapeutic response to TCT among SZ patients. Improvements were found in psychosis, mania, depression, and function domains, with no detected adverse effects. This evidence supports pharmacologic augmentation of TCT as a promising and novel therapeutic approach, warranting further exploration in larger samples.

Keywords: Schizophrenia, Cognition, Targeted Cognitive Training

Disclosure: Nothing to disclose.

P497. Salience Network Segregation in Youth and Young Adults With Prodromal Psychosis Symptoms

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Background: Understanding neurobiological similarities between individuals who exhibit prodromal symptoms may help improve early identification and inform intervention strategies. In this study, we aimed to (1) identify neurobiologically similar subject groups by integrating resting state functional connectivity and psychosis prodromal symptom data and (2) identify discriminating symptom profiles and resting state brain activation patterns in the identified subject groups.

Methods: Our sample (N = 1158) for the study was extracted from the Philadelphia Neurodevelopmental Cohort (PNC) and included individuals of ages 12-21 years with fMRI and self-reported psychopathology data. Data was obtained from dbGaP after data access and IRB approvals. Prodromal positive symptoms were measured by the Structured Interview for Psychosis-Risk Syndromes (SIPS) scale. After preprocessing and stringent quality control of fMRI data, 792 subjects (594 youth subjects between ages 12-17 and 198 early adult subjects between ages 18-21) were included in the final analysis. Analysis was conducted separately for both the youth and young adult samples. We first constructed a two-layer multiplex network based on pair-wise similarity distances between subjects. The two possible connections between subjects are their similarity in resting-state functional connectivity (neuroimaging layer) and their responses to SIPS items (symptom layer). We then fit a community detection algorithm, a stochastic block model (SBM) to identify subject clusters in the multiplex network. The parameters were estimated using a variational expectation-maximization algorithm, and the clustering was initialized by fitting separate simple SBMs to each layer. We selected the optimal number of blocks for our models using the integrated completed likelihood (ICL) and selected models that converged with the highest ICL. Analyses were performed on communities of subjects obtained from the block assignment procedure. For each community, we evaluated the mean segregation for salience, default mode, frontoparietal, and dorsal attention networks.

Results: The multiplex network for youth resulted in 4 communities or blocks (n = 82,171, 191 and 150) whereas for young adults there were only 2 blocks (n = 137 and 61). The mean and variance of the neuroimaging layer edge weights were nearly identical across all blocks for both youth and the young adult groups whereas there was considerably more variation in the mean and variance of the symptom layer edge weights between blocks for both groups. One block (youth, n = 82 and young adult, n = 137) had the highest segregation values for salience network but not default mode network, frontoparietal network, or the dorsal attentional network; this block also had the highest mean values of SIPS and the highest mean scores across all psychopathology domains.

Conclusions: Using a data driven approach integrating global similarities in resting state brain activation and psychosis prodromal symptoms, we identified distinct subgroups with differences in symptom profiles and network segregation. Salience network segregation was associated with higher prodromal symptoms. Our findings add to the growing body of evidence for the cardinal role of salience network in psychosis.

Keywords: Prodromal Psychosis, Resting State Functional Connectivity, Youth

Disclosure: Nothing to disclose.

P498. Resilience and Protective Factors in Clinical High Risk Youth Offer Targets for Intervention to Improve Outcome

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Background: The study of the putative prodrome of psychosis provides an opportunity to examine risk factors as well as protective factors that enhance resilience and predict clinical and functional outcome of individuals at Clinical High Risk (CHR) for psychosis. Protective factors and resilience are described as modifiers that reduce odds of developing a disease from a known risk factor. The North American Prodrome Longitudinal Studies (NAPLS) Consortium, as well as other research groups, have identified protective factors associated with better outcomes, symptom remission and failure to convert to psychosis. In the present study we explore potential protective factors in CHR participants at highest risk for psychotic conversion based on high scores on the NAPLS Psychosis Risk Calculator.

Methods: N = 647 male and female CHR participants from the NAPLS 3 study were assessed on the Psychosis Risk Calculator previously developed and validated in the NAPLS 2 sample. A

median split was performed and those 324 individuals who scored highest on the calculator were divided into those who were known to have converted to psychosis within a 2 year period (CHR-C, N = 47) and those who did not (CHR-NC, N = 277). CHR-C vs CHR-NC participants were compared using nonparametric, univariate and multivariate tests across a range of demographic, historical and biomarker variables available in the NAPLS 3 database that were not part of the calculator and are candidate protective/resiliency markers: household income, premorbid functioning, positive life events, prosocial involvement, sleep, neurocognitive, startle and metabolic measures.

Results: CHR participants scoring in the top half of the Psychosis Risk Calculator were more likely to convert to psychosis compared to the lower half ($p < 0.001$). Within the top half, the CHR-NC sample was more likely to have older parents ($p < 0.02$) and to be of Hispanic background ($p < 0.03$). Better premorbid adjustment also characterized CHR-NC vs CHR-C that was primarily driven by more prosocial involvement ($p < 0.04$) and peer support ($p < 0.05$). In terms of biomarkers, CHR-NC participants had greater sleep duration compared to CHR-C ($p < 0.03$) as well as higher IQ per the WASI ($p < 0.04$) and better working memory assessed with the Auditory Working Memory CPT ($p < 0.001$). There were significant sex X conversion effects in startle reactivity, with male CHR-NC having less startle reactivity compared to CHR-C ($p < 0.007$).

Conclusions: The primary focus of CHR research has been risk factors and prediction of psychosis, while less is known about protective factors that might have improved outcome or prevented psychosis. Protective factors including better premorbid functioning, prosocial behavior, better sleep, neurocognitive functioning and less reactivity to stress may contribute to greater resiliency in individuals at greatest risk for developing psychosis. Clearly, therapies focused on psychological resilience, social skills training and family therapy are warranted in the CHR population along with lifestyle counseling. In addition, cognitive training and supported education may bolster resilience in this vulnerable population. Future CHR research should focus on improving assessment of psychological resilience as well as biological resilience, as a means of enhancing both psychotherapies and biological interventions. Areas of future interest might include lifestyle factors (diet, exercise, health), polygenic resilience measures, brain structure and function, as well as treatments received that might moderate better outcomes in the CHR population.

Keywords: Risk and Resilience, Clinical High Risk, Psychosis, Prodrome, Protective Factors

Disclosure: Nothing to disclose.

P499. Connectome-Based Prediction of Cognitive Functioning in Early Psychosis: Determinants of Prediction Success and Failure

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Background: Cognitive impairment is a debilitating and treatment-resistant aspect of psychotic disorders and a strong predictor of functional outcomes. The early phase of psychotic illness represents a crucial therapeutic window mainly due to greater neural plasticity. To develop effective, individually tailored interventions, it is important to establish reliable neural predictors linking measures of brain function to individual differences in cognitive outcomes in this early stage of the disease. Connectome-based predictive models (CPMs) have shown promise in identifying brain patterns that predict cognitive outcomes, however, the accuracy of individual-level predictions show substantial variability, which limits the clinical utility of these models.

Methods: Here, leveraging the publicly available, multi-site imaging data from the Human Connectome Project for Early Psychosis, we used CPMs to identify brain network patterns underlying broad cognitive functioning in patients with early phase psychosis. We determined the accuracy of these models in predicting fluid, crystallized and total cognition scores in novel individuals with early psychosis using 100 unique train-test splits created in the HCP-EP cohort (N = 92). We utilized permutation testing to determine the significance of the predictions ($p < 0.05$). Moreover, we examined the effect of individual sociodemographic and clinical factors on how accurately a patient's cognitive outcome could be predicted. To do so, we related covariates including age, sex, education, parental socioeconomic status (SES), clinical symptom score (PANSS total), and antipsychotic medication exposure to misclassification index (MI), a metric derived from a support vector machine (SVM) algorithm generating binary predictions of cognitive scores (e.g., low, high). Spearman rank correlation between the continuous covariates and MI were computed ($p < 0.05$), whereas for binary covariates, group median values between different subgroups were compared via Wilcoxon rank sum test ($p < 0.05$).

Results: CPM predictions of the cognitive scores were significant ($p < 0.05$, FDR corrected for the three outcome measures). Median prediction accuracies (measured as the correlation between predicted and observed scores) were $r = 0.31$, 0.29, and 0.22 for total, fluid, and crystallized cognition respectively. Functional connectivity among the default mode, dorsal attention and frontoparietal networks, as well as multisensory networks were consistently selected during cross-validation iterations, and thus, largely accounted for individual differences in cognitive functioning. We also found that CPMs failed to predict cognitive outcome accurately for a significant number of patients (mean MI = 0.32). A detailed analysis of model failure has identified parental SES ($r = -0.3$), race (mean MI: 0.60 for White, 0.28 for non-White groups) and antipsychotic medication exposure ($r = -0.26$) as the factors that are most strongly associated with misprediction.

Conclusions: We demonstrate that cognitive outcomes can be predicted using functional connectome-based markers in early psychosis. Nevertheless, the models failed to accurately predict outcomes in a significant portion of the study sample. Our findings reject the one-size-fits-all approach in predictive modeling in early psychosis, and highlight the importance of considering both sociodemographic and disease-related factors when building predictive models.

Keywords: Cognitive Functioning, Early Psychosis, Brain-Based Predictive Modeling

Disclosure: Nothing to disclose.

P500. Social Isolation Rearing Impairs Probabilistic Reversal Learning and Social Behavior in Rats

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Background: In schizophrenia, social withdrawal occurs early in the course of illness, prior to symptoms of psychosis, and predicts conversion to psychosis. Based on the course of illness it is likely that the severity of social withdrawal/isolation contributes to the neuropathology in schizophrenia; however, the mechanism

through which this progression occurs is not known. Preclinical studies will provide a better understanding of the impact of social isolation on neural circuitry and cognitive behavior and identify potential therapeutic targets for schizophrenia. The current studies examined the effects of social isolation rearing (SIR) on several behaviors relevant to schizophrenia, e.g. prepulse inhibition of startle, social behavior, and cognitive flexibility. Behavioral deficits in schizophrenia are heavily influenced by glutamate signaling in the frontal cortex and hippocampus. Because astrocytes regulate glutamate transmission and are altered in schizophrenia, we examined astrocyte levels in SIR and socially housed rats.

Methods: Male and female rats were weaned on postnatal day 24 and housed either in isolation (1/cage) or socially in groups of 2/cage. In the first experiment, rats (n = 19-22/sex/housing) were tested for acoustic startle and prepulse inhibition 8 weeks post-weaning. A subset of rats (n = 12/sex/housing) were then tested in a social approach task to measure preference for a stranger rat vs. an inanimate object. Stranger rats were age and sex-matched. A second study tested SIR and Social rats in a probabilistic reversal learning task (n = 6-7/sex/housing), which measures feedback-driven decision-making. Using feedback history, subjects discriminate between target and non-target stimuli. In the PRL task, a target response is normally rewarded (80%) but occasionally punished (20%), whereas a non-target response is normally punished (80%) but occasionally rewarded (20%). When the target stimulus has been identified (indicated by 8 consecutive target responses) the reward contingencies reverse. Performance was assessed by the number of completed reversals/session. Further, Win-Stay and Lose-Shift strategies were analyzed to provide information about reward and punishment sensitivity, respectively. In a third set of rats, a subset of Isolates (n = 4) and Socials (n = 5) were used to evaluate astrocytes using immunohistochemistry for glial fibrillary acidic protein (GFAP).

Results: Similar to our previously published data, SIR rats exhibited decreased PPI [$F(1,76) = 7.82$, $p < 0.01$]. In a startle threshold test, increasing acoustic pulse intensities produced increased startle response in all groups. There was a main effect of sex with males showing greater startle than females [$F(1,76) = 14.19$, $p < 0.001$] and a trend toward increased startle in SIR rats [$F(1,76) = 2.74$, $p = 0.10$]. SIR rats spent more time exploring the stranger rat compared to the Object ($p < 0.05$); whereas SIR rats did not prefer the stranger rat over the object, i.e. less social approach behavior. All rats learned the task as evidenced by increased reversals over test days [main effect of Day; $F(11,286) = 16.36$, $p < 0.001$]. SIR rats showed an overall decreased number of reversals across the 12-day training period [Housing, $F(1,26) = 34.43$, $p < 0.001$; Housing x Day, [$F(11,286) = 2.23$, $p < 0.05$). SIR rats completed fewer overall trials compared to social rats [$F(1,26) = 21.44$, $p < 0.001$]. When controlling for number of trials completed, SIR rats still showed decreased reversals per 100 trials, although the effect was less pronounced, [$F(1,26) = 4.44$, $p < 0.05$]. Target Win-Stay and Target Lose-Shift did not differ between housing conditions. Preliminary studies in a subset of rats (n = 3-5/group) indicate a trend toward increased GFAP in the dentate gyrus ($p = 0.12$).

Conclusions: Similar to our previous findings, SIR rats show deficits in PPI and increased startle magnitude. Novel findings include demonstration of social approach deficits in SIR and a more extensive test of probabilistic reversal learning and extending these tests to another strain. Decreased number of trials completed, consistent with our previously published studies, accompanied deficits in reversals in the PRL in SIR rats. Computational modeling of learning strategies are underway. Preliminary data indicate alterations in astrocytes in SIR rats. Because of the important role astrocytes play in glutamate signaling and neurodevelopment, future studies will assess the potential of targeting astrocyte function pharmacologically in the SIR model.

Keywords: Social Isolation, Cognitive / Behavioral Flexibility, Astrocyte

Disclosure: Nothing to disclose.