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P1. Accelerated Brain Aging is Associated With Increased Likelihood of All-Cause Mortality: Findings From the Second Wave of Dallas Heart Study (DHS-2)

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Background: Accelerated brain aging has been linked to increased mortality. A recent report from the Lothian Birth Cohort found that higher structural magnetic resonance imaging (MRI)-predicted brain age as compared to chronological age was associated with higher likelihood of all-cause mortality. Similarly, the Sleep Heart Health Study found that higher sleep electroencephalogram (EEG)-predicted brain age as compared to chronological age was associated with reduced life expectancy. Therefore, in this report, we used data from the second wave of Dallas Heart Study (DHS-2) to evaluate the association between neuroimaging-predicted brain age and all-cause mortality.

Methods: Brain age ($n = 1949$) was estimated using T1-weighted structural MRI scans from DHS-2 (obtained between September 2007 and December 2009) and a previously-published Gaussian Processes Regression model (https://doi.org/10.5281/zenodo.3476365). Accelerated brain aging (Δ brain age) was computed as follows: (brain age) minus (chronological age). Mortality data until December 2016 was collected from the National Death Index. Participants were grouped as low [< (mean) minus 1 standard deviation (SD)], medium (mean ± 1 SD), and high (>mean+1SD) Δ brain age. Kaplan Meier survival curves were used to estimate the association between Δ brain age groups and all-cause mortality. Cox proportional hazards regression were used to account for other features that may be associated with all-cause mortality.

Results: Features associated with higher Δ brain age included presence of diabetes (estimate = 1.42 years, 95% CI: 0.49 years, 2.35 years), amount of alcohol consumed ($r = 0.10$, $p < 0.0001$), and waist-to-hip ratio ($r = 0.09$, $p < 0.0001$). Among diabetics, higher glycated hemoglobin (HbA1c) levels were associated with higher Δ brain age ($r = 0.27$, $p < 0.0001$). Over a median follow-up of 97.5 months, 13/284 (4.6%) in low, 45/1369 (3.3%) in medium, and 29/295 (9.8%) in high Δ brain age groups died. Participants of DHS-2 in high Δ brain age group had 2.3 (95% CI: 1.2, 4.5) and 2.6 (95% CI: 1.6, 4.2) times higher likelihood of all-cause mortality than those in low or medium Δ brain age group, respectively even after controlling for Framingham 10-year risk score (based on age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, and smoking), race, ethnicity, income, education, waist to hip ratio, presence of diabetes, presence of hypertension, and history of myocardial infarction.

Conclusions: Accelerated brain aging was associated with higher likelihood of all-cause mortality. Future studies are needed to replicate these associations in a prospective fashion and to understand the pathophysiological mechanisms that link accelerated brain aging to all-cause mortality.

Keywords: Brain Age, Mortality, Dallas Heart Study, Hemoglobin A1C, Kaplan-Meier Survival Curve

Disclosure: Nothing to disclose.

P2. Female Selective Impairment of Glucose Metabolism in an Alzheimer's Disease Model

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Background: Alzheimer's disease (AD) is the sixth leading cause of death in the United States, affecting 1 in 10 people over the age of 65. Age and sex are the two most important factors determining AD incidence, with women's lifetime risk double that of men. As women live longer, the total number of women with AD substantially outnumbers men, making the discovery of the molecular links between sex, age, and AD of the greatest significance. There is growing evidence linking metabolic dysfunction with AD. We hypothesize that impairment in glucose metabolism is greater in females and related to worse AD-like pathogenesis.

Methods: Glucose and insulin tolerance were measured in male and female triple transgenic (APPSW/PS1M146V/TauP301L; 3xTg-AD) AD mice at 10 and 12-months of age. All experiments were approved by the University of Miami Miller School of Medicine Institutional Animal Care and Use Committee and conducted according to specifications of the NIH as outlined in the Guide for the Care and Use of Laboratory Animals. RT-qPCR and ELISA were performed to analyze inflammatory cytokine expression, enzyme activity and mitochondrial biogenesis. Unpaired Student's t test was used for comparisons of two means. Pearson's correlation was used for correlation analysis. A P value < 0.05 was deemed to be of statistical significance.

Results: Female 3xTg-AD mice had decreased glucose tolerance at 10 months of age ($P < 0.01$) and decreased insulin tolerance at 12 months ($P < 0.05$) compared to males. Gene expression of insulin like growth factor 1 (Igf1) in the prefrontal cortex (PFC) was lower in females compared to males ($P < 0.05$). Levels of amyloid beta (Aβ) -40 and -42 were significantly greater in the PFC of

female 3xTg-AD mice ($P < 0.0001$ and $P < 0.05$, respectively). There was a correlation between PFC Aβ42/40 ratio and glucose tolerance in females (R squared = 0.13), possibly linking impaired glucose tolerance to amyloid beta deposition and disease progression.

Conclusions: Our data suggest that targeting impairments in glucose metabolism in females may benefit AD. We plan on further investigating the link of sex hormones and sex-specific epigenetic changes on glucose metabolism in the brain and its connection to AD.

Keywords: Sexual Dimorphism, Glucose Metabolism, Alzheimer's Disease

Disclosure: Nothing to disclose.

P3. Exercise Opens a 'Molecular Memory Window' to Facilitate Changes in Gene Expression, Synaptic Plasticity and Memory

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Background: We have previously demonstrated that exercise enables hippocampal-dependent learning in conditions that are normally subthreshold for encoding and memory formation and depends on hippocampal induction of brain-derived neurotrophic factor (BDNF) as a key mechanism. In male mice with prior exercise experience, only a brief exercise period is required to reactivate the increase of BDNF in the hippocampus, suggesting that there exists a 'molecular memory' for the prior exercise experience that facilitates subsequent learning. We hypothesize that an epigenetic molecular memory of exercise as a previous experience primes specific genes for subsequent activation upon new learning, resulting in facilitated memory formation.

Methods: In this study, we used RNA-sequencing to begin to define the molecular and epigenetic signature underlying exercise-enhanced learning in the hippocampus. Adult male mice underwent different periods of initial exercise (0-3 weeks), a sedentary delay period (0-2 weeks), and a brief 2-day period of reactivating exercise, followed by 3 min subthreshold training in an object location memory task. This allowed us to identify exercise parameters that enable the formation of robust long-term memory for object location in conditions that are normally subthreshold for encoding. Those parameters were then used to examine hippocampal long-term potentiation (LTP). Using the same parameters, we also examined gene expression using RNA sequencing during the memory consolidation period, one hour after training. To examine the role of identified gene targets in hippocampus-dependent learning and synaptic plasticity, we used intra-hippocampal delivery of AAV1-ACVR1C point mutant constructs that either enhance or disrupt function and allowed it to express for two weeks before onset of behavior. Next, sedentary mice were trained using either a subthreshold (3 min) or standard (10 min) object location memory task and memory was tested by examining exploration of the new object location the following day. The same mice from were used to assess the impact of Acvr1c manipulation on hippocampal long-term potentiation using theta burst stimulation in the schaffer collateral pathway.

Results: We find that brief 2-day re-introduction to exercise following a sedentary delay was sufficient to re-gain cognitive benefits in object location memory and enhance hippocampal LTP (similar to effects of initial exercise) relative to controls. RNA-Sequencing data from dorsal hippocampus tissue taken from male mice during the memory consolidation window, post-exercise, demonstrates that different exercise parameters led to distinct transcriptional profiles. Data point to a novel plasticity protein, ACVR1C as being up-regulated in conditions in which exercise facilitates learning and maintained throughout the 'molecular memory window' for exercise. Using intra-hippocampal delivery of AAV1-ACVR1C point mutant constructs, we find that ACVR1C bi-directionally modulates hippocampus-dependent learning and memory as observed by either disrupted or facilitated performance in object location memory. Using slices from the same mice, we also find bi-directional modulation of hippocampal LTP.

Conclusions: Together, these data point to ACVR1C as critical in learning and memory and as a potential key contributor in the maintenance of the 'molecular memory window' for exercise.

Keywords: Epigenetics, Memory, Hippocampus, Synaptic Plasticity, Exercise

Disclosure: Nothing to disclose.

P4. Cell-type Diversity in Cholinergic Circuits: Determining Factors That Confer Vulnerability With Age

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Background: Acetylcholine plays a primary role in coordinating many cognitive behaviors. One way this is accomplished is via extensive, highly branched axonal arbors that provide input to many cortical and subcortical domains. These arbors have precise functional and topographical organization which allow acetylcholine to coordinate cortical/subcortical activity and modulate behavior.

It is well established that age-related loss of cholinergic neurons and fragmentation of cholinergic projections is related to lower cognitive performance. But closer examination reveals that not all cholinergic projections are created equal. We and others have found regional heterogeneity across cholinergic terminal fields in aging and early in cognitive impairment. Specifically, some cholinergic projections are affected far sooner and to a much greater degree than others. This heterogeneity, including the cholinergic circuits that are vulnerable, is, remarkably, conserved across species. Here we sought to investigate what confers resilience or vulnerability of cholinergic circuits with age.

Methods: To assess vulnerability of cholinergic neurons and projections in aging we focused on two cholinergic terminal fields that are vulnerable with age: the entorhinal cortex (EC) and the basolateral amygdala (BLA). These regions receive cholinergic input from distinct cholinergic nuclei and have different timescales of deterioration with age. We used two behavioral assays that uniquely engage each circuit as a readout of function: displaced object recognition (EC) and cued fear conditioning (BLA).

Using young, male and female wild-type (C57/BL6J) mice, we first assessed behavioral performance on each assay. Using Fos immunohistochemistry as a marker of activated neurons, we next determined degree of engagement of the EC or BLA and its relationship with behavior. To determine the involvement of cholinergic neurons in these behavioral assays, we used Fos immunohistochemistry along with a marker for cholinergic neurons (Chat). The colocalization of both markers defined activated cholinergic neurons. To determine whether activated cholinergic neurons preferentially projected to specific terminal fields, we layered retrograde labeling strategies onto our behavioral assays. These experiments were then repeated in aged mice to assess the consequence of age on behavioral response, cholinergic neuron recruitment, and activation of EC or BLA.

It has been found that forebrain cholinergic neurons can also express proteins that synthesize or help store other neurotransmitters.

This complicated [and ever-changing] definition of cell-identity may in fact become a crucial determinant for subpopulations of cholinergic neurons. In the context of aging, here we ask: first, in young animals, what proportion of cholinergic neurons co-express mRNA markers for glutamate or GABA, and second, if this proportion changes with age. When coupled with behavioral assays, we can also ask whether activated cholinergic neurons preferentially subscribe to a cell-identity.

Results: We found that young animals consistently spend more time exploring the displaced object during the DOR task. Interestingly, this difference is no longer observed with age. While DOR performance in young animals leads to an increase in activated neurons within the EC, aged animals have fewer activated neurons within the EC. We also found that DOR performance in young animals activated cholinergic neurons of the medial septum/diagonal band, whereas the number of activated cholinergic neurons was lower with age and lower in animals with poor performance.

Using a cued fear conditioning task we have previously found that normal performance in this task (i.e. elevated freezing in response to the tone) requires activation of cholinergic neurons within the nucleus basalis of meynert (NBM), cholinergic signaling within the BLA, and BLA activation. With age, we find less freezing behavior across the recall session coupled with fewer activated neurons in the BLA, and fewer activated cholinergic neurons within the NBM.

Finally, using the RNAscope assay, we have identified subsets of cholinergic neurons across the basal forebrain that express mRNA for glutamatergic or GABAergic markers. Ongoing studies investigate whether these activated cholinergic neurons cluster with a common cell-identity, and whether the proportion of these co-expressing subtypes changes with age.

Conclusions: These studies provide valuable insights into the involvement of cholinergic neurons in cognitive behaviors and the consequence of age on cholinergic circuits. Importantly, they underscore a growing body of literature that shows incredible diversity and functional organization within the cholinergic system. This diversity may be key in understanding which factors lead to vulnerability of cholinergic circuits across species and may provide insight into important factors within circuits that remain resilient with age.

Keywords: Cholinergic System, Aging, Cell-Type Diversity

Disclosure: Nothing to disclose.

P5. HDAC6 Inhibition Reverses Chemobrain: Role of Glutamatergic Signaling

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Background: There are no FDA-approved drugs to treat chemotherapy-induced cognitive impairment, or chemobrain, one of the most debilitating sequalae of cancer treatment preventing patients from returning to their pre-cancer lives. Treatment with the HDAC6 inhibitor ACY-1083 reverses chemobrain in mice. Here, we provide data suggesting that ACY-1083 restores cognitive function in mice treated with doxorubicin by reversing glutamate excitotoxicity in the hippocampus.

Breast cancer patients experience chemobrain more than any other category of patients, and doxorubicin is the most utilized chemotherapy to treat breast cancer and known to induce chemobrain. Doxorubicin increases inflammatory cytokines that link neuroinflammation and excitotoxicity, an increase of glutamatergic signaling associated with cognitive decline. HDAC6 inhibition or genetic deletion have been shown to block glutamatergic signaling in acute stress and Parkinson's models.

We hypothesize that treatment with the HDAC6 inhibitor ACY-1083 reverses doxorubicin-induced cognitive impairment by normalizing glutamatergic signaling.

Methods: To test this hypothesis, we investigated changes in neural activity and glutamatergic synaptic markers in the hippocampus of female mice treated with doxorubicin and ACY-1083. We (1) measured cognitive function in the puzzle box test and novel object recognition test and used (2) snRNA sequencing to examine transcriptional changes in subsets of neurons, (3) immunofluorescence to detect changes in neural activity markers (dFosB), synaptic markers (synaptophysin and PSD95), and glutamate transporter expression levels (EAAT2), and (4) Western blot to measure changes in hippocampal glutamate receptors (AMPAR subunits mGluR1 and mGluR2).

Results: Doxorubicin induced cognitive disfunction in the puzzle box test ($p = 0.017$) and novel object recognition test ($p = 0.002$), upregulated transcripts related to neurodegenerative disease in glutamatergic DG neurons ($p < 0.05$), increased dFosB neural activity signal in the DG ($p = 0.028$), decreased PSD95 in the CA3 region of the hippocampus ($p = 0.011$).Treatment with ACY-1083 restored cognitive function in the puzzle box test ($p = 0.001$) and novel object recognition test ($p = 0.006$), normalized the transcriptomic changes in glutamatergic DG neurons ($p < 0.05$) and upregulated pathways involved in glutamatergic ($p < 0.04$) and GABA ($p < 0.05$) neurotransmission, tended to normalize dFosB in the DG ($p > 0.05$), and increased total mGluR1 ($p = 0.004$) and mGluR2 ($p = 0.042$) expression.

Conclusions: Results from this study indicate that cognitive deficits resulting from doxorubicin treatment are associated with increased neural activity in glutamatergic neurons and increased mGluR1 surface expression in the hippocampus. The results also indicate that ACY-1083 may reverse chemobrain and the increased neural activity in mice with doxorubicin-induced cognitive deficits. ACY-1083 may exert these effects by increasing EAAT2, responsible for 80-95% of glutamate uptake and predicted to have neuroprotective properties when upregulated, and promoting surface expression of PSD95, improving synaptic integrity and function. The asymmetrical changes in synaptophysin and PSD95 expression provides additional indication that these synapses are glutamatergic. Doxorubcin and ACY-083 induced changes in AMPAR surface expression may be responsible for regulating glutamate signaling, rather than total AMPAR expression.

We aim to further characterize neural activity, including activity markers, synaptic markers, receptor surface expression, and dendritic density. Additional studies will measure number of neural spikes and neural synchrony in vitro and in vivo, and characterize active neurons using pharmacological probes. Though novel in the context of chemobrain, the results of this study support the application of HDAC6 inhibitors as possible therapeutics across disease states and conditions driven by glutamate excitotoxicity.

Keywords: Neurodegenerative Disease, TBI, Cognition, HDAC Inhibitors, Chemobrain

Disclosure: Nothing to disclose.

P6. The FAB Rodent Model of Alzheimer's Disease Displays Aberrant Hippocampal Activity and Dopamine System Dysfunction

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Background: Individuals affected by Alzheimer's disease (AD) often experience comorbid psychosis, which severely diminishes

the quality of life for the patient and their family. Because of the potential risk antipsychotic medications present to the elderly, there is an immediate need to establish novel alternative therapies. Psychosis (including hallucinations and delusions) has been demonstrated to be associated with a dysregulation of the dopamine system. We have previously demonstrated that psychosis observed in schizophrenia, may be attributed to aberrant regulation of dopamine neuron activity by the hippocampus. Because the hippocampus has been identified as a site of pathology in AD, we posit that it may also be a key region contributing to comorbid psychosis in AD.

Methods: We used the ferrous amyloid buthionine (FAB) rodent model of AD to model a sporadic form of the disease, as well as, in vivo electrophysiology to examine alterations in hippocampal activity and dopamine system function. As a behavioral correlate of dopamine dependent behaviors, we measured the locomotor inducing effects of MK-801. Only male rats were used in this study.

Results: FAB rats display both structural and functional alterations in the hippocampus, which is accompanied by a decrease in spontaneous low frequency oscillatory activity and an increase in the firing rates of putative pyramidal neurons. Additionally, FAB rats exhibit robust increases in dopamine neuron population activity and an augmented response to the locomotor-inducing effects of MK-801, consistent with what is observed in other models of psychosis.

Conclusions: These data suggest that aberrant hippocampal activity in AD may contribute to dopamine dependent psychosis. We believe that understanding the pathophysiology leading to comorbid psychosis in AD, will lead to novel targets for the treatment of this disease.

Keywords: Alzheimer's Disease, Psychosis, Dopamine, Hippocampus

Disclosure: Nothing to disclose.

P7. Anxiety Impacts Cognitive Decline in Female Alzheimer's Disease Mice and Predicts Dementia Transition in the ADNI Human Dataset

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Background: Neuropsychiatric disturbances, such as depression and anxiety, are observed in 90% of Alzheimer's disease (AD) patients and are frequent in those at risk for AD. However, until recently, much of the research targeted co-morbid depression. Similarly, epidemiological studies show that neurodegeneration and clinical symptoms occur more rapidly in females once diagnosed. Although most AD studies have been performed using male mice, females represent two-thirds of the AD population and are more susceptible to depression and anxiety. Here, we aimed to determine the impact of sex and anxiety throughout AD progression on cognitive and psychiatric endophenotypes.

Methods: Male and female control (Ctrl) and APP/PS1 (AD) mice at 2, 4, and 6 months of age were tested in a battery of behavioral paradigms to assay anxiety-like behavior as well as in a contextual fear conditioning (CFC) task to assay learning and memory ($n = 4$-17). Memory trace activation throughout the brain ($n = 4$-6) was measured using our activity-dependent tagging system, the ArcCreERT2 x enhanced yellow fluorescent protein (EYFP) x AD (APP/PS1) mice, which allow for brain-wide indelible labeling of neurons activated during learning. Cross-correlations between all pairs of brain regions were calculated in *R*, using the rcorr function in the Hmisc package. As a translational component, The Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset was used to examine anxiety and dementia transition in an AD human cohort ($n = 1{,}650$). For up-to-date information, see www.adni-info.org. The dataset used was downloaded on October 28th, 2018. All statistical tests were adjusted controlling for age, years of education, and sex. All rodent data were analyzed using JMP© software (SAS Institute, Cary, NC). Data were analyzed using ANOVA, with repeated measures when appropriate. Student t-tests were used for post-hoc comparisons. Cell counts were normalized by volume. Alpha was set to 0.05 for all analyses. Data are expressed as means+/− SEM.

Results: We found that female AD mice exhibited decreased rearing behavior in the open field (OF) at 2 months of age ($p < 0.05$), increased marble burying (MB) at 4 months of age ($p < 0.01$) and, decreased activity in the light side of the light dark test (LDT) at 2 months of age ($p < 0.05$) when compared to female Ctrl mice. Male AD mice did not exhibit increased anxiety-like behavior in these tasks relative to male Ctrl mice. These data suggest that female AD mice exhibit increased anxiety-like behavior at an earlier age.

Next, CFC was used to assay memory. AD female mice displayed memory deficits as early as 2 months of age ($p < 0.05$) and this deficit continued across ages ($p < 0.01$). However, male AD mice did not exhibit memory deficits until 4 months of age ($p < 0.01$). Interestingly, increased marble burying behavior was correlated with memory decline in AD female mice at 6 months of age ($p < 0.05$). After CFC, mice were euthanized, and brain tissue was stained at 6 months of age. Memory trace activation was measured throughout the hippocampus. EYFP, a measure of encoding activation, was similar among the groups. c-Fos, a measure of retrieval activation, was increased in the dorsal DG (dDG), dorsal CA1, and dorsal CA3 (dCA3) in female mice compared to males ($p < 0.0001$). Memory trace activation was decreased in the dDG of AD male mice when compared to female Ctrl mice ($p < 0.05$), while memory trace activation was decreased in dCA3 of female AD mice when compared to female Ctrl mice ($p < 0.05$). These data represent a sex-specific circuit change in AD progression. To understand how the functional connectivity between brain regions is implicated in AD, we computed whole-brain c-Fos activation and found differences in network organization, changes in correlated regions, and sex-specific effects in different amygdala regions.

Using the ADNI dataset, we found increased anxiety in AD patients in both men and women compared to cognitively normal (CN) patients (Male, MCI OR = 8.29, 95% CI: 3.57-10.29, $p < 0.0001$; Male, AD OR = 24.85, 95% CI: 10.49-58.87, $p < 0.0001$; Female, MCI OR = 3.03, 95% CI: 1.69-5.42, $p = 0.0005$; Female, AD OR = 7.35, 95% CI: 4.00-13.56, $p < 0.0001$). We next examined anxiety and amyloid (Aβ) positivity from cerebral spinal fluid (CSF). Women with anxiety and CSF Aβ transitioned to dementia more quickly than males ($z = 2.15$, $p = 0.032$) (in Male: HR = 3.84, 95% CI 2.10-7.00, $p < 0.0001$; Female: HR = 20.95, 95% CI 5.04-87.18, $p < 0.0001$). We next tested whether brain volumes differed by anxiety group. Interestingly, females with anxiety showed smaller hippocampal and amygdala volumes while males tended to have larger right amygdala and right hippocampus volumes. Using Elasticnet, we evaluated whether anxiety and brain atrophy could predict the transition to dementia. Based on repeated 5-fold cross validation in 10 random initializations of cross-validation, there were 23 ROIs that were selected at least once in the model, and their average importance scores and average coefficients were reported. Anxiety was the most important variable to predict dementia transition above brain atrophy and age.

Conclusions: These results shed light on the sex-specific behavioral and brain-wide network changes that occur throughout AD progression in males and females. In line with numerous recent studies, we hypothesize that neuropsychiatric symptoms can be used as potential biomarkers in AD and can facilitate development of personalized therapeutics for male and female AD patients.

Keywords: Alzheimer's Disease, Anxiety, Sex Differences, Engram, Hippocampus

Disclosure: Nothing to disclose.

P8. Influence of Sex on Memory Across the Lifespan of Normally Aging Rats

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Background: Women typically live to older ages than men and are more likely to be afflicted by Alzheimer's disease (AD), an age-associated brain disorder characterized by multi-dimensional cognitive decline. However, few studies have robustly evaluated how biological sex influences trajectory of cognitive changes in preclinical models of aging. Further, a preponderance of such studies has focused exclusively on age-related decline of hippocampus-dependent forms of memory. Critically, this means that concurrent, and potentially complicating, effects of aging on neuroanatomically dissociable forms of memory, including prefrontal cortex-dependent working memory, remain comparatively understudied. Consequently, fundamental studies of memory, spanning multiple cognitive domains, in normally aging male and female rats could reveal the basis for sex-related susceptibility to AD or worse cognitive symptoms in advanced age.

Methods: Male and female Fisher 344 rats were obtained from the National Institute of Aging (NIA) at 4 ($n = 32$; 16M/16F), 12 ($n = 28$; 14M/14F) and 22 ($n = 31$; 14M/17F) months of age. Rats were characterized in the Morris water maze (MWM) using an 8-day place-learning (spatial reference memory) procedure that depends on the hippocampus. Performance on probe trials interpolated throughout testing were used to calculate individualized spatial learning index scores. After the conclusion of hidden-platform place-learning, we evaluated rats in the MWM using a visible-platform, cue-learning protocol that requires integrity of the striatum. Finally, rats were characterized on an operant delayed match to sample (DMTS) test of working memory, a behavioral probe for the integrity of the prefrontal cortex.

Results: In the MWM task, analysis of probe trials distributed across days of testing determined that training interacted with age and sex. To examine this interaction, we calculated the weighted sum of probe trial performance, and found that, overall, males exhibited better spatial learning than females and that middle-aged and aged rats were impaired relative to young adults. In the DMTS task, we observed a significant effect of age on working memory choice accuracy but no reliable differences between males and females or interaction between sex and age. Post hoc tests determined that aged rats were less accurate than young adults or middle-aged rats while these latter two age groups were not reliably different from each other. In contrast to these effects of age on hippocampus- and prefrontal cortex-dependent forms of cognition, no effects of age were observed on striatum-dependent cue learning. Correlational analyses comparing performance on place-learning and delayed-matching revealed no significant inter-relationships between these two tasks, nor were any correlations deemed significant when subdividing rats according to sex or age.

Conclusions: We conclude that spatial reference memory is more sensitive to early decline with age than working memory and that spatial reference memory of females is less accurate than in males over the full lifespan. These differences suggest that focused study of the sex-specific neurobiological underpinnings of the aging hippocampus could lead to a better understanding of the fundamental mechanisms that contribute to increased severity of memory problems in older women. Also important to the broader consequences of aging on the brain is the observation that decline of prefrontal cortex-dependent memory reliably emerges at advanced age. This profile suggests that more pervasive forms of memory loss are contemporaneously situated to exacerbate cognitive symptoms in subsets of highly susceptible, aged individuals. However, screening for complex memory loss may require detailed neuropsychological assessments as decline across domains was not correlated among aged individuals, indicative of independent effects of aging across neuroanatomically dissociable forms of cognition.

Keywords: Sex Differences, Alzheimer's Disease, Declarative Memory, Executive Function

Disclosure: Nothing to disclose.

P9. Neuromelanin-Sensitive Imaging Links Locus Coeruleus Anatomy to Cognitive Performance in Individuals With Late-Life Depression and Age-Matched Healthy Controls

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Background: Late-life depression (LLD) is a risk factor for subsequent age-dependent cognitive deterioration and dementia. Post-mortem cellular and molecular pathology studies suggest neurodegenerative changes in norepinephrine projections originating in the locus coeruleus (LC) may represent a shared biological mechanism underlying major depressive disorder (MDD) and age-dependent cognitive deterioration. Neuromelanin (NM) is a dark pigment that builds up in norepinephrine neurons in the LC as a by-product of oxidative norepinephrine metabolism and can be visualized in vivo using NM-sensitive magnetic resonance imaging (MRI). Its levels follow an inverted U-shaped trajectory as a function of normal aging, peaking around mid-life and steadily decreasing in individuals >60 years old, with higher levels considered to be neuroprotective and associated with better memory in healthy older adults. Here, we set out to evaluate the multivariate relationships between MRI-assessed NM signal along the entire rostro-caudal extent of the LC and performance across multiple neurocognitive domains in individuals with LLD and age-matched never-depressed healthy controls (HC).

Methods: Participants ($N = 48$, including 25 LLD (18 women, age 68.08 ± 5.41), and 23 HC ($n = 12$ women, age 70 ± 8.02)) underwent neuroimaging and neurocognitive testing. NM-sensitive MRI data was collected using a gradient echo sequence with a magnetization transfer pulse. We defined the LC bilaterally as the brightest cluster of 6 adjacent voxels within an anatomically pre-defined search space, which we then hierarchically divided into 3 segments along a rostral-middle-caudal dimension in each hemisphere. LC-NM signal was quantified as the average contrast-to-noise ratio within the derived segments relative to a reference region in the central pons, containing minimal NM. We analyzed neurocognitive performance via the 5 index scores of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; attention, immediate memory, delayed memory, language, and visuospatial ability), and a total of 9 scores from the Delis-Kaplan Executive Function System (D-KEFS; time-to-completion on the 4 CWIT and 2 TMT tasks, and total scores on the 3 Verbal Fluency tasks), for a total of 14 independent measurements. Canonical correlation analysis (CCA) was used to quantify the multivariate relationship between the age- and sex-corrected 6 LC-NM ('predictor' set) and 14 neurocognitive performance ('criterion' set) features, across the combined LLD and HC groups.

Results: The CCA analysis derived 6 synthetic predictor and criterion variable pairs, with a combined canonical correlation (Rc) of .808, and an effect size (r2) of 96.8%. The full CCA model was significant, as evaluated by parametric testing, Wilks' $\lambda = 0.032$, $F(84, 162.44) = 1.658$, $p = 0.003$, and confirmed by permutation testing, $p(\text{perm},1999) = <.001$. Subsequent hierarchical testing revealed the

first variate (CV1, capturing variates 1:6) to explain 65.3% of variance (Rc2), and the second variate (CV2, capturing variates 2:6) to also be significant, $p = .04$, with a canonical correlation of .769, explaining 59.08% of variance. We evaluated feature importance via standardized structure coefficients (rs > .4), which were stable under jackknife resampling. CV1 showed high contributions from the left and right rostral LC, and RBANS delayed memory, where lower memory performance was associated with lower NM signal in the right but higher NM signal in the left rostral LC. CV2 showed high contributions from the left and right middle, and right caudal LC, and RBANS immediate memory and attention, where lower cognitive performance was associated with lower NM in all segments. Importantly, we found similar results when excluding $n = 9$ participants (7 LLD, 2 HC) taking noradrenergic-acting medication, which may affect LC-NM signal. We also found that LLD and HC participants did not show differential multivariate relationships between LC-NM and neurocognitive performance, $p = .895$, endorsing our joint analysis. Furthermore, LLD and HC participants did not differ in overall neurocognitive performance or LC-NM signal (all $p > 0.1$)

Conclusions: We identified novel spatially specific multivariate relationships between neuromelanin signal in the LC and cognitive performance in late life across the HC-to-LLD spectrum. These results implicate the rostral LC in delayed memory performance, and suggest middle and caudal regions of the LC may selectively support immediate memory and attention. Ongoing studies will evaluate NM signal in the LC as a marker of subsequent vulnerability to cognitive decline and dementia risk, particularly in individuals with LLD.

Keywords: Neuromelanin-sensitive MRI, Late-life Depression, Cognition, Locus coeruleus (LC)

Disclosure: Nothing to disclose.

P10. Association of a Novel MRI-Based Measure of Locus Coeruleus-Norepinephrine System Integrity With Braak Stage and Neuropsychiatric Symptom Severity in Alzheimer's Disease

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Background: The clinical and pathophysiological correlates of degeneration of the locus coeruleus (LC)-norepinephrine system in Alzheimer's disease (AD) are imperfectly understood. Prior work investigating the norepinephrine system in aging using assays of cerebrospinal fluid or postmortem tissue have found dysregulation of this system is associated with neuropsychiatric symptoms of AD (NPS), a common and debilitating aspect of the illness. This study assessed integrity of the LC-norepinephrine system using a novel and non-invasive in-vivo method, neuromelanin-sensitive MRI (NM-MRI), to determine if LC integrity is associated with severity of AD and with NPS, independent of aspects of cortical pathophysiology (amyloid-β and tau burden).

Methods: Cognitively normal older adults ($n = 118$), and individuals with mild cognitive impairment (MCI, $n = 44$), and AD ($n = 28$) underwent MR imaging and tau and amyloid-β positron emission tomography (with [18F]MK6240 and [18F] AZD4694, respectively). Integrity of the LC-norepinephrine system was assessed based on contrast-to-noise ratio of the LC on unprocessed NM-MRI images relative to a central pons reference region. The LC was segmented on these images and divided into 5 rostrocaudal sections using a novel semi-automated algorithm that searched for hyperintense LC voxels within an over-inclusive LC mask registered from standardized space to native space. Manual LC segmentation was also performed to compare against the semi-automated segmentation method. Braak stage of AD was derived from regional binding of [18F]MK6240. NPS were assessed with the Mild Behavioral Impairment Checklist (MBI-C), cognitive impairment with the Mini-Mental State Exam, and dementia severity with the Clinical Dementia Rating Scale. Statistical analyses related clinical measures to LC signal and other neuroimaging measures using Spearman partial correlation and linear regression analysis.

Results: Signal contrast was decreased in tau-positive participants in all LC sections except for those on the rostral and caudal ends. This decrease in signal contrast was most pronounced in mid-caudal LC ($t186 = -3.93$, $p = 0.0001$). Therefore, this portion of the LC was examined in subsequent analyses. LC signal contrast here was negatively correlated to Braak stage (Spearman $\rho = -0.31$, $p = 0.00007$), cognitive impairment ($\rho = -0.15$, $p = 0.048$), and dementia severity ($\rho = -0.28$, $p = 0.0001$).

In tau-positive participants ($n = 51$), higher LC signal predicted worse NPS severity ($\rho = 0.35$, $p = 0.018$) independently of tau burden, amyloid-β burden, and cortical gray matter volume. This relationship appeared to be driven by the impulse dyscontrol domain of NPS, which was highly correlated to LC signal ($\rho = 0.45$, $p = 0.0023$).

Semi-automated LC segmentation performed slightly better than manual LC segmentation in identifying AD-related LC signal loss (Spearman ρ of LC signal derived from manual segmentation. to Braak stage, cognitive impairment, and dementia severity = -0.31, -0.12, -0.20, respectively).

Conclusions: NM-MRI reveals loss of LC integrity that correlates to severity of AD. However, LC preservation in AD may also have negative consequences by conferring risk for impulse control symptoms, independent of other aspects of AD pathophysiology. These results demonstrate the utility of NM-MRI to interrogate the role of the norepinephrine system in human studies of the mechanisms of AD pathophysiology. They also provide early evidence in favor of NM-MRI as a practical and non-invasive biomarker that has potential to indicate NPS risk or likelihood of response to specific treatments.

Keywords: Alzheimer's Disease, Norepinephrine, Neuromelanin-Sensitive MRI, Locus coeruelus, PET Imaging

Disclosure: Patent on neuroimaging analysis method presented in abstract; Patent (Self)

P11. Temporal Relations Among Emotional and Behavioral Factors in Late-Life Depression During the COVID-19 Pandemic

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Background: Late-life depression is associated with social isolation and poor quality of life. The COVID-19 pandemic created unique psychological stressors and disrupted social support systems, which may have uniquely impacted older adults' depressive symptomatology. We aimed to study the relationship between emotional (depression, anxiety, stress) and behavioral (sleep and physical activity) factors over time in older adults with a history of depression.

Methods: We conducted weekly assessments over 12 weeks with 20 participants aged 60 years and older with a previous diagnosis of Major Depressive Disorder. Assessments consisted of telephone/zoom interviews and included the following five standardized questionnaires: Montgomery –Åsberg Depression Rating Scale, Hamilton Anxiety Rating Scale, Perceived Stress

Scale, Insomnia Severity Index, and Physical Activity Scale for the Elderly. We employed a depression-focused cross-lagged panel model (CLPM) to examine within-week correlations among the five measures.

Results: The depression-focused CLPM identified statistically significant week-to-week self-predictive effects for each of the measures: depression ($\beta = 0.964$, $P < .001$); anxiety ($\beta = 0.728$, $P < .001$); stress ($\beta = 0.650$, $P < .001$); sleep ($\beta = 0.647$, $P < .001$); and physical activity ($\beta = 328$, $P < .001$). Depression was also found to be a strong predictor of stress ($\beta = 0.254$, $P < .01$), insomnia ($\beta = 0.224$, $P < .05$), and physical activity ($\beta = -0.212$, $P < .05$) the following week. No other cross-measure predictions were statistically significant.

Conclusions: Our study highlights the protracted negative effects of depression on the emotional and behavioral wellbeing of older adults and supports the need for longitudinal assessments and targeted interventions for late-life depression.

Keywords: Late-Life Depression, COVID-19, Anxiety and Stress, Depression, Sleep

Disclosure: Nothing to disclose.

P12. Vortioxetine Reverses the Cognitive Impairment Induced by Degarelix in a Middle-Aged Rodent Model of Androgen Deprivation Therapy

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Background: Androgen deprivation therapy (ADT) is a mainstay treatment for prostate cancer, but over half of patients will experience cognitive impairments that increase with duration of treatment. Unfortunately, there is little relief for patients that experience cognitive decline associated with ADT, thus greatly diminishing their quality of life. Deficits observed in ADT patients occur in cognitive domains mediated by the medial prefrontal cortex (mPFC) and hippocampus (Hipp). As the average age of prostate cancer patients is around 65 years old, and age is also accompanied by cognitive decline, it is likely that age can exacerbate these impairments. Vortioxetine is a multimodal antidepressant that improves cognitive impairment in depression. Therefore, vortioxetine may also improve cognition in patients that experience cognitive decline due to ADT. Previously, our lab has established a middle-aged surgical castration model of ADT, in which vortioxetine reversed cognitive impairments induced by castration. But chemical castration is more widely used in the clinic to treat prostate cancer. Thus, in the current study, middle-aged rats were treated with the gonadotropin-hormone releasing antagonist, degarelix. We hypothesize that ADT will induce similar cognitive impairments when compared to surgical castration in middle aged rats, and that vortioxetine will reverse these deficits.

Methods: 12-13 month old Sprague Dawley rats were used, as this is the age in which mild cognitive impairments begin to emerge. Rat were injected with the gonadotropin releasing hormone antagonist degarelix (3 mg/kg in 5% mannitol, s.c.). Surgical castration was also used in a comparator group. Controls received either a sham surgery or a vehicle injection of 5% mannitol. Following the injection or surgical procedure, rats were singly housed. Beginning 10 days after surgery or degarelix, rats were administered vortioxetine in the diet (28 mg/kg/day) or control chow for 21 days. Seven days prior to behavioral testing, animals were food restricted to 12g/day. For behavioral testing, all animals underwent the novel object location (NOL) test and the attentional set-shifting test (AST) as readouts of hippocampal and mPFC function, respectively. Upon completion of behavior, tail vein blood samples were taken to measure levels of testosterone. Two-way ANOVA, followed by Tukey's multiple comparison test, was used to analyze all behavioral results (GraphPad Prism 8, San Diego, USA). All procedures were approved by the University of Texas Health San Antonio Institutional Animal Care and Use Committee and complied with National Institutes of Health guidelines.

Results: Results: On the NOL test, both surgical and chemical castration induced impairments in spatial memory (surgical: $p < 0.05$, $d = 0.610$; degarelix $p < 0.05$, $d = 1.456$) in comparison to control rats, indicating an impairment in hippocampal-mediated cognition. Vortioxetine reversed these deficits back to baselines comparable to controls in surgically castrated ($p < 0.05$, $d = 0.514$) and trends towards rescuing deficits in degarelix treated rats ($p < 0.09$, $d = 1.497$). On the AST, surgically and chemically castrated rats displayed deficits on the extra-dimensional set shifting task, which is mediated by the mPFC (surgical: $p < 0.05$, $d = 0.381$; degarelix: $p = 0.08$, $d = 0.937$). Results further indicate that vortioxetine is effective in reversing deficits (surgical: $p < 0.05$, $d = 0.677$; degarelix: $p = 0.11$, $d = 0.817$), an mPFC mediated task, in ADT-treated rats.

Conclusions: Both surgical castration and degarelix induced cognitive impairments in the NOL test and on the extra-dimensional shift of the AST, indicating impairments mediated by the Hipp and mPFC, respectively. Vortioxetine rescued these deficits in both behavioral paradigms and in each treatment group. These results indicate that vortioxetine may be an effective treatment option for older prostate cancer patients that undergo ADT and experience cognitive decline. Future experiments will investigate the role of cancer, which promotes inflammatory processes and may exacerbate insults to cognition due to ADT.

Keywords: Antidepressant, Androgen, Medial Prefrontal Cortex, Hippocampus, Cognitive Decline

Disclosure: Nothing to disclose.

P13. Prefrontal Cortical Development Across Adolescence in Mouse and Marmoset

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Background: Adolescence, the transition from juvenile to adult, is a developmental period marked by a prolonged structural change in brain circuits that coincides with increased cognitive capacity and sensory- and risk-seeking behaviors. From humans to monkeys to rodents, evidence suggests that developmental changes are most prolonged and pronounced in brain regions such as the prefrontal cortex (PFC) that are functionally linked to these behaviors. Furthermore, both the brain structures and the behaviors are linked to psychiatric disorders such as schizophrenia that are most commonly diagnosed in adolescents and young adults. While inroads have been made to understand the mechanisms that drive PFC maturation and the contributions of PFC to an array of cognitive tasks, the connections between the PFC's developmental changes, its functional circuit dynamics, and its impacts on behavior remain unclear. To understand how genetic and environmental risk for psychiatric disease shape this developmental trajectory (and vice versa), we must first better establish neurotypical adolescent PFC development.

Methods: Here, we employ a range of anatomical, electrophysiological and behavioral techniques to map changes in PFC structure and function across development and species. In mice, we used ex vivo slice electrophysiology to track changes in the

excitatory postsynaptic activity, excitatory/inhibitory inputs, and intrinsic properties of layer II/III pyramidal neurons (Pyr) and parvalbumin (PV)-positive interneurons across development. To link changes in PFC structure to function, we have trained both mice and marmosets to perform a multi-armed bandit task which probes features of action switching and risk-taking behaviors.

Results: In mice, we found that the frequency and amplitude of miniature excitatory postsynaptic events in PFC layer II/III neurons decreased steadily throughout a prolonged period of adolescent development, stabilizing to adult levels around four months of age. Utilizing electrical stimulation of synaptic inputs to the layer II/III Pyr, we found a systematic shift in the balance of excitation and inhibition whereas the predominant source of input was excitation in young mice and feedforward inhibition in adult mice. Moreover, we found that PV cells, the major source of inhibition in this circuit, underwent a maturation of their synaptic inputs that was opposite and delayed relative to Pyr. These data were supported by optogenetics-assisted mapping of two major PFC inputs, cortico-cortical and thalamocortical afferents showing the shift from excitation to inhibition in Pyr neurons and the opposite in PV/ . In addition, we found changes in intrinsic excitability that paralleled the changes in local and long-range circuitry. In addition to these structural and physiological changes over adolescence, we are currently exploring behavioral changes in the multi-armed bandit task in both mice and marmosets at various stages of development. We have found that both species are capable of learning the task, will perform large numbers of trials, and will adapt their behavior to changing reward contingencies. Marmosets will provide a unique opportunity to bridge the gap between rodent and primate behavior by probing action switching with an identical task across development.

Conclusions: These results revealed a systematic shift in the organization of the mouse PFC that far extends the traditional window of adolescence and provides the baseline for perturbations to genes and environment. Armed with a deeper understanding of the circuit architecture developed in mice, we are well positioned to investigate what and how these features are changing in other species. Our focus on PFC-dependent behavior provides the first common bridge between species where the marmoset provides incredible access into a primate brain. The behavioral data provides quantifiable measures that can be used to directly compare the performance across developmental stages and species.

Keywords: Adolescence, Prefrontal Circuit Maturation, Mouse, Marmoset, Cognition

Disclosure: Nothing to disclose.

P15. Uncovering RNA-Binding Protein Regulators of Associative Memory and Cognitive Healthspan

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Background: Cognitive decline is a major deficit that arises with age in humans, the cause of which is poorly understood. A major distinction between normal aging and neurodegenerative disease is that normal age-related memory defects occur in the absence of major neuronal loss, suggesting that loss of learning and memory is instead due to dysfunction in the circuits and molecules necessary for normal memory formation. Thus, by identifying components necessary for normal cognitive performance in healthy, young animals, we will gain insight into processes that are necessary to maintain cognitive performance with age.

A key class of molecules regulating learning and memory are RNA binding proteins (RNABPs), which can bind to specific sequences or secondary structures on target mRNAs and then regulate the translation, splicing, transport, and stability of the mRNA. As regulators of protein synthesis in response to diverse stimuli, RNABPs are also necessary for neuronal proteostasis, and their dysfunction is linked to several neurological disorders. More recently, analysis of aged human and macaque brains found an age-dependent decoupling of mRNA transcript and protein expression. Thus, it is likely that loss of normal RNABP function is one of the molecular mechanisms underlying age-related cognitive deficits.

One class of RNABPs linked to both neuronal function and to aging are the Pumilios (PUMs). Levels of PUM2 increase in multiple organisms in an age dependent manner, including mice and the nematode worm C. elegans. PUM2 is considered as a "pro-aging" factor as knockdown of its ortholog in worms extends lifespan PUM2 mRNA levels negatively correlate with lifespan in mice. Recently, our transcriptomic profiling of adult C. elegans neurons and neuronal subcompartments found that several PUM orthologs (PUFs) are abundantly expressed in the adult nervous system. Here we set out to uncover the role of these PUFs in associative memory and neuronal aging, using our C. elegans model system.

Methods: C. elegans maintenance: Animals were maintained under standard laboratory conditions and fed the E. Coli strain OP50 ad libitum. Synchronized populations for behavior and lifespan assays were generated by standard hypochlorite treatment.

RNAi Treatment: Standard RNAi by feeding was performed to achieve gene knockdown. Briefly, HT115 E. Coli expressing RNAi was fed to C. elegans. 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 (LC108 [punc-119::sid-1]) that overexpresses a double stranded RNA transporter in all 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.

Lifespan Assays: Standard C. elegans lifespan assays were performed in the context of RNAi treatment. For each condition, three biological replicates of ~100 worms were used. Data was analyzed by log-rank (Mantel-Cox) method in Kaplan-Meier survival analysis.

Results: We find that various PUF family members specifically regulate translation-dependent associative memory specifically in adult neurons. Interestingly, knockdown of PUF family members PUF-5 (ortholog of mammalian Pum1 and 2) and PUF-8 (ortholog of mammalian Pum2), have differential effects on memory in young adults – knockdown of PUF-5 causes deficits specifically in translation-dependent ITAM ($p < 0.0001$), while PUF-8 knockdown improves memory performance as evidenced by maintaining memory for a positive olfactory association two-hours post training, a timepoint where forgetting has normally occurred ($p < 0.001$).

We established a role for PUF/PUM family members in age-related cognitive decline. We find that adult-only, neuron-specific RNAi knockdown of PUF-5 results in an accelerated cognitive aging phenotype ($p < 0.01$), while knockdown of PUF-8 resulted in improved associative memory performance in aged adult animals when compared to age-matched empty vector control treated animals ($p < 0.05$). We find that neuron-specific knock down of both PUF-5 and PUF-8 has no detectable effect on lifespan ($p >$

0.05), suggesting that the behavioral phenotypes we observed are tissue-specific aging phenotypes, and not due to altered longevity.

Conclusions: Here we have identified the PUF/PUM RNABP family as key regulators of age-related cognitive decline in an invertebrate model system. These effects on age-related memory loss were dissociated from overall organismal aging, suggesting that PUF/PUMS are important for proper maintenance of optimal neuronal function with age.

In ongoing work, we are determining which mRNA targets of PUF/PUM family members are necessary for their effects on memory and cognitive aging, and are performing mechanistic studies to understand how PUF/PUM RNABPS regulate the maintenance of memory ability with age.

Keywords: Memory and Learning, RNA Binding Protein, Ageing

Disclosure: Nothing to disclose.

P16. Preventing and Reversing Opiate-Induced Persistent Postoperative Cognitive Dysfunction in Aged Male Rats With Selective TLR4 Antagonist

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Background: Postoperative cognitive dysfunction (POCD) is a constellation of debilitating cognitive symptoms that disproportionately afflict older individuals immediately after surgery. These symptoms, lasting days to months, range from mild confusion to an inability to form long-term memories, to dementia. Importantly, persistent symptoms are associated with greater risk of patients developing Alzheimer's disease. It is well known that opioids can bind and activate the mu opioid receptor to elicit analgesia, and the toll-like receptor 4 (TLR4) to evoke a neuroinflammatory response. Our rodent model of POCD has previously demonstrated that the opiate morphine administered for a week following laparotomy, an exploratory abdominal surgery, caused long-lasting neuroinflammation and hippocampal-dependent memory impairments lasting at least 8 weeks post-surgery in aged, but not young adult rats. We further showed that these impairments were independent of the mu-opioid receptor and dependent on neuroinflammation. Here, we extend these studies by examining the role of the TLR4 in this impairment by administering the selective TLR4 antagonist, LPS-RS, either 1 week postsurgery and morphine or immediately preoperatively and measuring memory function.

Methods: Aged (24 mos) male F344xBN rats ($n = 6$-9/group) underwent laparotomy under isoflurane anesthesia, and were treated with saline or morphine (2 mg/kg, i.p.) twice a day for 7 days after surgery. In exp. 1, they then received repeated central injections (via cisterna magna) of either saline or one of 3 doses of LPS-RS (500 ng, 5 ug, or 50 ug) once a day for the next 7 days. In exp. 2, rats received a single injection of LPS-RS (50 ug) immediately prior to surgery. Four weeks later, rats were trained in a contextual fear conditioning paradigm and memory for what was learned was tested 4 days later.

Results: In exp 1, not surprisingly, long-term memory was impaired in rats that received morphine postoperatively and saline thereafter, as this replicated what we have shown previously. Low (500 ng) and medium (5 ug) doses of LPS-RS were ineffective at reversing the memory deficits as their memory performance was significantly impaired compared to saline-treated controls (all $p <$ 0.05). However, the 50 ug dose completely rescued the memory deficit caused by surgery and morphine as these rats performed no differently than post-op saline-treated controls ($p > 0.05$). Furthermore, in exp 2, a single dose of LPS-RS (50 ug) immediately prior to surgery was effective at preventing the persistent memory deficit caused by morphine ($p < 0.05$.

Conclusions: Together, these findings suggest that TLR4 plays a critical role in the development of morphine-mediated persistent POCD in aged rats as blocking central TLR4 activation either prior to surgery or one week after surgery was effective at mitigating precipitous memory impairments.

Keywords: Postoperative Cognitive Dysfunction, Alzheimer's Disease, Toll-Like Receptors (TLRs), Opioids, Opioid Antagonist Treatment

Disclosure: Nothing to disclose.

P17. Demographic and Clinical Characteristics of Antipsychotic Drug- Treated Older Adults With Bipolar Disorder From the Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE –BD) Project

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Background: Antipsychotic drugs (APS) are widely used to treat patients with bipolar disorder, but there is limited information on how they might best be used in older-age bipolar disorder (OABD). This is a first-ever analysis of the Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) project which investigated demographic and clinical characteristics of OABD patients with (versus without) current APS treatment. We hypothesized that OABD on APS would have more severe manic symptoms (higher YMRS scores), greater number of previous psychiatric hospitalizations and higher somatic comorbidity burden, especially with respect to renal and cardiovascular disease vs. OABD not on APS.

Methods: The analysis used baseline, cross-sectional data from 16 international contributing studies. The dependent variable for this analysis was exposure to APS (vs. non-APS group) in adults ≥ age 50 years with BD. Predictors included demographic and clinical variables (age, gender, age of onset, symptom severity of BD [mania/depression], number of hospitalizations, rapid cycling, psychiatric and medical comorbidities); random effects of study were included in generalized mixed models. In the sample on APS, type of drug (1st vs. 2nd generation APS), number of drugs, relative dosage with respect to age and use of concurrent lithium treatment was also evaluated.

Results: The sample with APS data was comprised of 1,020 individuals, mean age 63.2 (SD 9.02), including 434 (42.5 %) women, 684 (67.1%) with Type 1 BD, and age of onset mean 31.64 (SD 10.02) years. There were 468 (45.9%) individuals on APS. Comparing sub-samples by APS treatment status, individuals on APS were younger ($p = .001$), had more past psychiatric hospitalizations ($p = .003$) and more likely to have musculoskeletal comorbidities ($p = .011$). There were no significant differences for gender, age of onset, BD symptom severity, rapid cycling status or psychiatric comorbidity.

Conclusions: Close to half of this OABD sample are prescribed APS and some significant clinical differences exist between OABD prescribed vs. not prescribed APS. Aligned with our preliminary hypotheses, individuals prescribed APS have a greater number of past psychiatric hospitalizations and selective somatic comorbidity vs. those not on APS. In contrast to our initial hypotheses, musculoskeletal comorbidity was more common in those on APS, while there were no differences in cardiovascular or renal disease

burden. It is possible that musculoskeletal effects are related to extrapyramidal symptoms and/or tardive dyskinesia, which are potential side effects of APS. Also in contrast to our original hypothesis, manic symptom severity did not differ between APS and non-APS groups, possibly reflective of the cross-sectional methods used in this analysis. Future studies need to examine longitudinal outcomes among OABD prescribed APS in order to help tease out causal effects vs. prescriber/patients preference vs selective cohort effects.

Keywords: Bipolar Disorder, Geriatric, Antipsychotic Treatment, Big Data

Disclosures: Nuromate, Otsuka, Alkermes, International Society for Bipolar Disorders (ISBD), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Patient-Centered Outcomes Research Institute (PCORI): Contracted Research (Self)

Alkermes, Otsuka, Janssen, Myriad, Health Analytics, Frontline Medical Communications, Consultant, Self, Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate: Royalties (Self)

American Physician's Institute, MCM Education, CMEology, Potomac Center for Medical Education, Global Medical Education, Creative Educational Concepts, Psychopharmacology Institute: Other Financial or Material Support (Self)

P18. The Menopause Transition is Associated With Differences in PTSD and Depression Symptoms in Trauma-Exposed Black Women

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Background: Posttraumatic stress disorder (PTSD) and depression, two common psychiatric outcomes following trauma exposure, are more than twice as prevalent in women than men. Although evidence from studies indicate that gonadal steroid hormones play an important role in conferring risk for negative outcomes following trauma exposure in females, less is known regarding brain and behavioral health in women during the menopausal transition, who have received minimal focus in trauma research to date. Thus, in the current study we assessed the relationship between stages of the menopause transition (pre, peri and post) on symptoms of PTSD and depression in trauma-exposed Black women from an urban community sample. We hypothesized that stages of the menopause transition associated with hypogonadism (perimenopause and menopause) would be associated with greater symptoms of PTSD and depression.

Methods: Participants were approached randomly in the waiting rooms of medical clinics at a public hospital in Atlanta, Georgia from 2005 to 2017. Inclusion criteria included being a Black female between 18 and 65 years old, not actively psychotic, and able to give informed consent. Study procedures were approved by the Emory Institutional Review Board and the Grady Research Oversight Committee. Initial interviews were conducted in the clinic waiting rooms by trained interviewers, and included questionnaires regarding demographics, trauma history, and psychiatric symptoms ($n = 5302$). The Modified PTSD Symptom Scale (PSS) and Beck Depression Inventory (BDI) were used to capture PTSD symptom severity (and sub-scales) and depressed mood, respectively. Reproductive status was determined using aged cutoffs, with women <40 years of age categorized as premenopausal ($n = 2741$), women between 40 and 55 years of age as perimenopausal ($n = 1830$), and women >55 years old as postmenopausal ($n = 731$). ANOVAs adjusting for income, education, and lifetime trauma exposure (childhood and adult) were used to assess the effects of reproductive stage on total PTSD and depression symptom severity, as well as PTSD subscale scores for hyperarousal, avoidance/numbing, and intrusive symptoms (based on the Diagnostic and Statistical Manual of Mental Disorders IV).

Results: There was a main effect of reproductive stage on depression ($F = 11.334$, $p < 0.001$) and PTSD ($F = 8.587$, $p < 0.001$) symptom severity, as well as for PTSD subscale scores for hyperarousal ($F = 11.637$, $p < 0.001$), avoidance/numbing ($F = 5.950$, $p = 0.003$), and intrusive symptoms ($F = 11.637$, $p < 0.001$). Symptoms of depression were greater in perimenopausal women compared to premenopausal women ($p < 0.001$). Total PTSD symptom severity was greater in perimenopausal women compared to premenopausal ($p = 0.016$) and postmenopausal women ($p < 0.001$). Furthermore, postmenopausal women had significantly lower PTSD symptoms than premenopausal women ($p = 0.012$). Hyperarousal symptoms of PTSD were significantly greater in perimenopausal women compared to premenopausal ($p = 0.002$) and postmenopausal ($p = 0.001$) women. Avoidance/numbing symptoms of PTSD were greater in perimenopausal women compared to premenopausal ($p = 0.061$) and postmenopausal ($p = 0.001$) women. Finally, intrusive symptoms of PTSD were greater in perimenopausal women compared to postmenopausal ($p < 0.001$), but not premenopausal women ($p = 0.164$). Postmenopausal women had significantly lower intrusive symptoms than both premenopausal ($p = 0.008$) and perimenopausal ($p < 0.001$) women.

Conclusions: Taken together, the current data show that symptoms of PTSD and depression in women are impacted by reproductive stage, such that perimenopausal women show higher symptom severity than premenopausal and postmenopausal women. This main effect of perimenopause on PTSD symptom severity was driven by hyperarousal and intrusive symptoms. Interestingly, postmenopausal women showed lower symptoms of PTSD compared to premenopausal women, suggesting that fluctuations rather than absolute levels of gonadal hormones may exacerbate risk for PTSD symptoms in trauma-exposed women. The current study is limited by its cross-sectional design, the use of self-report measures of PTSD and depressive symptoms, and the use of age as a surrogate marker of reproductive status as opposed to physiological and biological markers of the menopause transition. Longitudinal studies are necessary to better understand how changes in gonadal hormones over the course of the menopause transition impact the symptoms, neurobiology and psychophysiology of PTSD. These future studies have critical implications for the treatment of trauma-related behavioral health outcomes in aging Black women.

Keywords: Women's Mental Health, PTSD Depression, Menopause

Disclosure: Nothing to disclose.

P19. In Vivo Imaging of LC-NE Integrity: Mechanism for Racial/Ethnic Disparity in Preclinical AD

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Background: Despite studies suggesting that blacks may be at greater risk of developing AD, there have been few studies investigating health disparities, and blacks have been underrepresented in many prominent AD biomarker studies and clinical trials. The current ATN biomarker classification system may not fully account for health disparities and can't explain the increased prevalence among blacks for both AD and AD vascular risks of diabetes and hypertension when compared to whites. Research on cognitive aging has traditionally focused on how decline in various cortical and hippocampal (Hip) regions influences cognition. However, tau pathology emerges decades before amyloid pathology, appearing first in the brainstem (BS); particularly in the

locus coeruleus (LC), the source of brain's norepinephrine (NE). Our decade-long studies in humans using a norepinephrine transporter (NET)-selective radiotracer ([11C]MRB) have demonstrated a special vulnerability of LC to aging and stress.

Methods: Co-registration of PET (dynamic [11C]MRB), MRI and the FreeSurfer (FS) atlas images of each individual was used to generate regional time-activity curves using Firevoxel. Binding potential (BPND) values were determined using MRTM2 with occipital as the reference region. Annual percent change (APC) of BPND was calculated based on linear regression ($APC = 100 \times (em - 1)$, m: slope) and effects of age, gender and ethnicity on tracer binding were evaluated.

Results: For all HC ($N = 31$), with both genders and all races included, age-sensitive decline of NET availability was observed; e.g., 0.3-0.5%/yr for Hip, BS and olfactory. However, our data reveals that the decline rate of NET is much faster among blacks starting in the mid-30s, particularly in black males; e.g., 2-3%/yr vs. 0.14-0.23%/yr in thalamus and brainstem for black males vs. white males ($p < 0.00001$).

Conclusions: In addition to our previously determined age effect on MRB-NET binding, this report further reveals the role of ethnicity effects on NET availability. Our study showed that a faster decline of LC-NE function occurs in blacks, possibly caused by cumulative stress to socioeconomic disadvantage and racial discrimination and may be responsible for the different disease expression among blacks. Thus, NET availability imaging represents a novel biomarker approach to racial-dependent strategies for diagnosis and assessment of therapeutic interventions.

Keywords: Health Disparity, LC-NE, PET Imaging, Alzheimer's Disease, Biomarker

Disclosure: Nothing to disclose.

P20. Linking Gut Microbiome Dysbiosis to Accelerated Brain Aging: Findings From the Texas Resilience Against Depression (T-RAD) Study

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Background: Neuroimaging-predicted brain age has gained recent attention for its role as a biomarker of accelerated aging of the brain. Work from our group and others has linked accelerated brain aging to cardiovascular disorders, diabetes, obesity, and reduced life expectancy. However, pathophysiological mechanisms underpinning accelerated brain aging have remained unknown. In this preliminary analysis of our ongoing Texas Resilience Against Depression Study, we evaluated the associations between gut microbiome dysbiosis and accelerated brain aging in individuals with depression across the lifespan.

Methods: Participants of T-RAD study with structural magnetic resonance imaging (MRI) and stool samples available were included (Total $N = 103$; Female $N = 71$; Male $N = 32$). Neuroimaging-predicted brain age was estimated using T1-weighted structural MRI scans and a previously-published Gaussian Processes Regression model (https://doi.org/10.5281/zenodo.3476365). Accelerated brain aging (Δ brain age) was computed as follows: (brain age) minus (chronological age). 16S rRNA gene sequencing was used to characterize the gut microbiome. Covariates for all analyses included age, sex, race, ethnicity, and body mass index. As number of predictor features [amplicon sequence variant (ASV), $N = 10184$] far exceeded the number of subjects ($N = 103$), an elastic net model with repeated 10-fold cross was used to identify those that were associated with accelerated brain aging. Subsequently, a canonical correlation analysis was used to evaluate the variance in accelerated brain aging that was associated with the identified ASVs.

Results: The mean chronological age of participants was 46.82 years [standard deviation (SD) = 14.98; range: 14 years, 82 years]. The neuroimaging-predicted brain age was highly correlated with chronological age (Pearson's $r = 0.91$, $p < 0.0001$), and the mean Δ brain age was 3.08 years (SD = 6.25). The elastic net model retained sever ASVs that were associated with accelerated brain aging. The spearman's correlation of these with Δ brain age was 0.61. Five of the seven were from the Firmicutes phyla whereas two were from the Bacteroidetes phyla. Within the Firmicutes phyla, all five belonged to the family Lachaniospiraceae which are anaerobic spore forming bacteria that ferment polysaccharides to short chain fatty acids and alcohol, have been linked to diabetes and were reported to differentiate individuals with major depressive disorder (MDD) from healthy controls in a recent systematic review. Within the Bacteroidetes phyla, both identified ASVs belonged to genus Bacteroides and have been linked to obesity previously. Abundance of these seven ASVs accounted for 37.7% of the variance in Δ brain age ($p < 0.0001$).

Conclusions: We have preliminarily identified evidence that links gut microbiome dysbiosis to accelerated brain aging in individuals across the lifespan. Future studies are needed to replicate these findings in larger samples and to identify specific mediators (immune cells or their secreted proteins) that link the gut microbiome dysbiosis to accelerated brain aging.

Keywords: Brain Age, Gut Microbiome, T-RAD Study, Depression

Disclosure: Nothing to disclose.

P22. Brain Imaging Correlates of Metabolic Function in Adults Who are Overweight/Obese

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Background: Metabolic dysregulation is currently considered a major risk factor for hippocampal pathology, which can lead to cognitive dysfunction. The aim of the present study was to characterize the influence of key metabolic drivers on functional connectivity of the hippocampus in overweight/obese adults.

Methods: Insulin resistance (IR) was directly quantified by measuring steady-state plasma glucose (SSPG) concentration during the insulin suppression test and fasting levels of insulin, glucose, leptin, and cortisol, and measurements of body mass index and waist circumference were obtained in a sample of healthy cognitively intact adults ($n = 104$). Resting-state neuroimaging data were also acquired for the quantification of hippocampal functional cohesiveness and integration with the major resting-state networks (i.e. default mode network, central executive, salience networks). Data-driven analysis using unsupervised machine learning (k-means clustering) was then employed to identify clusters of individuals based on their metabolic and functional connectivity profiles.

Results: K-means clustering identified two clusters with metabolically distinct profiles, which differed primarily by the plasma levels of leptin [40.36 (29.97) versus 27.59 (25.58) μg/L] and the degree of IR (SSPG concentration: 161.63 (65.27) versus 125.72 (66.81) mg/dL]. Despite no difference in the performance of selective cognitive tasks (i.e. episodic memory) between individuals in clusters, those in the cluster with higher leptin and IR showed lower functional cohesiveness within each hippocampus and lower integration of posterior and anterior components of the left and right hippocampus with the major resting-state networks.

Conclusions: In overweight and obese adults, lower resting-state hippocampal connectivity is associated with peripheral

insulin resistance independent of measures of adiposity, a relationship that may be regulated by leptin. In future work, a longitudinal analysis of follow-up data in this cohort could shed further light on the implications of these findings.

Keywords: Hippocampus, Insulin Resistance, Leptin, Connectivity

Disclosure: Nothing to disclose.

P23. Age-Dependent Modulation of Synaptic Mitochondrial Respiration in the Hippocampus and Prefrontal Cortex Varies as a Function of Sex

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Background: Mitochondrial dysfunction may precipitate age-related alterations in memory and cognition leading to the onset of dementia-related disease. Synaptic mitochondrial function tightly regulates effective learning and memory behaviors – both of which are compromised with age-related decline. However, the pattern of changes in synaptic mitochondrial function as a product of natural aging remains unknown. Sex differences in mitochondrial function and dementia-related diseases are prominent, yet a mechanism explaining the increased prevalence in women when compared to men remains unknown. Here, male and female Wistar rats were used to determine the influence of sex and age on synaptic mitochondrial function in regions susceptible to age-related changes in neurometabolic function and relevant for cognitive function: the hippocampus (HPC) and prefrontal cortex (PFC).

Methods: The HPC and PFC were dissected from the brains of 18 male and 18 female Wistar rats in either young (75 days), middle-aged (6 months), or aged (12 months) groups. Both the HPC and PFC were processed for the isolation of functional synaptosomes via an isotonic Percoll gradient. Oxygen Consumption Rate (OCR) of these synaptic mitochondria were plated in triplicate at 40μg/100μL in phenol red free DMEM plus 1.0M glucose, 100mM pyruvate, and 200mM L-glutamine. Mitochondrial respiration was assessed using Agilent's Seahorse XFe24 and the Cellular Mitochondrial Stress assay using the concentrations of 2μM oligomycin, 1μM FCCP, and 0.5μMrotenone/antimycin A per well. Synaptosomes derived from the same isolation were examined separately for relative density of mitochondria within the synaptosomes using a ratio of Hexokinase I to SNAP25 through Western blot protein densitometry.

Results: In males, age altered overall OCR within synaptic mitochondria from the PFC ($F(2,180) = 32.96$, $p < 0.0001$) and HPC ($F(2,180) = 60.31$, $p < 0.0001$). Within the PFC ($F(22,180) = 1.59$; $p = 0.05$) and HPC ($F(22,180) = 2.719$, $p = 0.0001$) middle-aged males had significantly lower overall OCR than both the young ($p < 0.0001$) and aged ($p < 0.0001$) males. OCR between young males and aged males did not differ ($p > 0.05$). Changes in mitochondrial dynamics reflected the patterns seen in middle-aged males. Compared to young and aged males, middle-aged males had reduced basal respiration ($F(2,30) = 13.02$; $p < 0.0001$), maximal respiration ($F(2,30) = 9.52$; $p = 0.0006$), proton leak ($F(2,30) = 10.54$; $p = 0.0003$), ATP production ($F(2,30) = 26.63$; $p < 0.0001$), and spare capacity ($F(2,30) = 6.44$; $p = 0.005$). Young and aged males did not show any differences in mitochondrial dynamics ($p > 0.05$). Western blot densitometry indicated that young and middle-aged males had similar densities of synaptic mitochondria ($p > 0.05$) but aged males showed a considerably higher density ($F(2,12) = 6.85$; $p = 0.01$) than both young and middle-aged males ($p < 0.0001$).

In females, OCR of synaptic mitochondria derived from the PFC ($F(2,180) = 48.20$; $p < 0.0001$) and HPC ($F(2,180) = 208.5$, $p < 0.0001$) were altered by age. PFC synaptic mitochondrial OCR was elevated in middle-aged females compared to young ($p = 0.03$) and aged females ($p < 0.0001$). OCR in young females was higher than aged females ($p < 0.0001$). Similarly, middle-aged females had increased HPC OCR compared to young ($p < 0.0001$) and aged ($p < 0.0001$) females and young females had increased OCR compared to aged females ($p < 0.0001$). Mitochondrial dynamics in females showed that middle-aged females had higher basal respiration ($F(2,30) = 21.63$; $p < 0.0001$), maximal respiration ($F(2,30) = 26.17$; $p < 0.0001$), ATP production ($F(2,30) = 20.59$; $p < 0.0001$), and spare capacity ($F(2,30) = 29.88$; $p < 0.0001$) in both the HPC and PFC than the young and aged females. Proton leak between young and middle-aged females was not altered ($p > 0.05$). Young females had elevated maximal respiration and proton leak ($F(2,30) = 20.61$; $p < 0.0001$) compared to aged females. ATP production and spare capacity were not altered with age between young and aged females ($p > 0.05$ for all comparisons). Densitometric analysis indicated young and middle-aged females had a similar density of mitochondria within each synaptosomal sample ($p > 0.05$), but density of synaptic mitochondria in aged females was reduced ($p = 0.004$).

Conclusions: These data support growing evidence of mitochondrial function as a mechanism driving sex-specific differences in cognitive decline as a product of natural aging. These considerable changes in mitochondrial dynamics and function suggest an age-dependent vulnerability in mitochondria at the synapse, where mitochondrial decline may contribute to the neuronal compromise and cognitive impairment with aging. The sex differences evident in these data provide insight into a mechanism by which males and females diverge in synaptic mitochondrial function possibly contributing to sex disparities in age-related decline.

Keywords: Mitochondrial Respiration, Ageing, Sex Differences, Synapses, Mitochondria

Disclosure: Nothing to disclose.

P24. Role of Microglia and Aging-Associated Changes in the Thalamus for Cognitive Impairment After Brain Injury

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Background: Microglia are resident immune cells and maintain homeostasis in the brain. Recent preclinical rodent studies have also highlighted the functional heterogeneity in microglia, but little is known about the impact of regional heterogeneity in microglia on cognitive function. I will present our recent research using cortical brain injuries in mice as a model to address the role of thalamic microglia activation in cognitive impairment.

Methods: Young adult and aging mice (6 and 12 months) received unilateral cortical injuries or sham operations. Novel object recognition (NOR) tests and immunohistochemistry were performed three weeks or later after the injuries when the inflammation in primary injury sites was attenuated. Local depletion of microglia and blockade of their signaling were conducted by injecting monoclonal antibodies through cannulas. Chemogenetic manipulation of neurons and microglia was conducted to determine the causal role of thalamic neurons and microglia in cognitive dysfunction.

Results: Microglia in the thalamus showed a delayed activation after cortical brain injuries, starting around day 7 and reaching its peak around day 21. Their activation was more prominent than those in the hippocampus and inversely correlated with the NOR deficits ($n = 4$-7 per group; $p < 0.05$, t-test). Local depletion of microglia in the thalamus, but not in the hippocampus, between days 5 and 15 post-injury attenuated the NOR deficits of injured mice at day 21 ($n = 6$-8 mice per group; $p < 0.01$, t-test). Microglia depletion also normalized neuronal c-Fos expression and microglia activation in the thalamus, hippocampus (CA1 and CA3), perirhinal

cortex (Prh), and the medial prefrontal cortex (mPFC) of the injured mice ($n = 6$-8 mice per group; $p < 0.01$, t-test). In contrast, local microglia activation in the thalamus by an LPS injection and a DREADD activation (Tmem119CreERT2; hM3D (Gq)-mCitrinefl/fl mice) impaired NOR in the non-injured mice ($n = 4$-6 mice per group; $p < 0.05$, t-test). Thus, the thalamic microglia activation is sufficient to impair recognition memory. In aging mice, the thalamic microglia activation was further enhanced and accompanied by accumulation of phosphorylated tau proteins (phosphor-tau) and aging-associated increase in the expression of interleukin-33 (IL-33) ($n = 7$-8 mice per group; $p < 0.05$, t-test). Blockade of IL-33 signaling in the thalamus attenuated aging-associated worsening of NOR deficits, microglia activation, and phosphor-tau accumulation ($n = 7$-8 mice per group; $p < 0.05$, t-test).

Conclusions: Our findings demonstrated the critical role of microglia and aging-associated changes in the thalamus in cognitive impairment after cortical injuries in mice. Further studies on the mechanisms of aging-associated changes in the thalamic microenvironment and microglia may lead to the identification of potential therapeutic targets to intervene cognitive impairment.

Keywords: Thalamus, Microglia, Ageing, Traumatic Brain Injury, Cytokines

Disclosure: Nothing to disclose.

P25. Memantine Enhances Prepulse Effects on Startle Magnitude and Latency in Patients With Alzheimer's Disease

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Background: The uncompetitive NMDA receptor antagonist, memantine (MEM), enhances measures of early auditory processing, including prepulse inhibition of acoustic startle (PPI), in both rodents and humans; in humans, MEM effects on PPI were detected in both healthy subjects (HS) and patients with schizophrenia (SZ), and particularly among older subjects in both groups. MEM has positive and protective effects within early auditory processing circuitry, and we reported that MEM enhanced auditory discrimination in both HS and SZ patients. MEM is used to treat moderate-to-severe Alzheimer's Disease (AD); while it slows progression of cognitive and behavioral disturbances in AD, this effect is modest, short-lived and heterogeneous. We are determining if acute effects of MEM challenge, including changes in early auditory processing, can predict clinical sensitivity to MEM in AD patients. As part of a planned interim analysis, we now report on the effects of MEM on PPI and related measures in 10 patients with AD.

Methods: Subjects to date are 10 carefully screened individuals with diagnoses of AD (mean (range): age = 72.8 (68-80y); MoCA = 16.4 (6-23); education = 16.6 (14-18y); M:F = 5:5). Baseline neurocognitive measures included the MoCA and ADAS-cog. Subjects completed a double-blind order-balanced study of MEM (placebo (PBO) vs. 20 mg; 2 test days separated by 1 week) on subjective, autonomic, cognitive and electrophysiological measures. At 210 min post-pill, acoustic startle and PPI were measured per published methods, using 42 trials, with 6 conditions: a 115-dB(A) 40-ms noise burst (pulse alone (PA)) over a 70 dB(A) noise background, and the same burst preceded 10, 20, 30, 60 and 120 ms by a 20 ms noise prepulse 15 dB above background. This session previously detected acute PPI-enhancing effects of 20 mg MEM at 60 ms prepulse intervals in HS and across all prepulse intervals in SZ patients. To measure startle habituation, 3 PA trials were presented at the session start and end. %PPI was assessed across all intervals, with an a priori prediction of MEM-enhanced PPI at 60 ms intervals. Two subjects were startle "non-responders" (mean startle on PA trials < 5 startle units) and were omitted from analyses of prepulse effects. Time (ms) to peak startle response was recorded for all trial types, and latency facilitation was the difference between peak latency on PA vs. prepulse+pulse trials. At 275 min post-pill, neurocognition was assessed via the RBANS. At 345 min post-pill, electroencephalographic (EEG) measures were used to assess mismatch negativity and the Auditory Steady State Response (40 Hz coherence and power). Comparisons are reported as effect size (Cohen's d).

Results: Compared to PBO, MEM (20 mg po) had minimal effects on autonomic or subjective measures and had no significant effect on RBANS performance. There were no effects of MEM on startle magnitude on PA trials ($d = 0.03$). Subjects exhibited robust startle habituation ($d = 0.67$) that was unaffected by MEM. Prepulses produced interval-dependent potentiation vs. inhibition of startle magnitude; across all prepulse conditions, subjects averaged 10.98% PPI after PBO vs. 29.48% after MEM ($d = 0.52$). For the 60 ms interval, where maximal MEM effects on PPI were previously detected, subjects averaged -14.11% PPI after PBO vs. 21.32% after MEM ($d = 0.75$). Prepulses facilitated peak startle latency ("latency facilitation"); for 60 ms intervals, latency facilitation was significantly enhanced after MEM (mean (SD) = 11.01 (6.35) ms) vs. PBO (2.12 (5.05) ms) ($d = 1.56$). MEM effects on EEG measures will also be reported.

Conclusions: These findings have several implications. First, they extend evidence that MEM enhances auditory sensorimotor gating independent of diagnosis (HS vs. SZ vs. AD); this suggests that MEM enhances sensorimotor gating not by targeting a source of pathology per se, but instead by acting on healthy circuitry, perhaps relatively early in the auditory system. This explanation might account for the ability of MEM to enhance latency facilitation in the present study, and to enhance auditory discrimination in both HS and SZ subjects; more broadly, such a mechanism might account for reported benefits of MEM on clinical state and neurocognition in both patients with AD and schizophrenia, despite obvious differences in the "higher" CNS pathophysiology of these disorders. Second, the acute changes in PPI and latency facilitation after MEM ingestion confirm that these measures can be used to detect an AD patient's sensitivity to acute MEM challenge, and potentially help predict their sensitivity to MEM's therapeutic effects. Other acute MEM effects on EEG measures might have similar utility. We are testing this hypothesis, as study subjects follow the laboratory testing described herein with a 24-week open-label trial of MEM (10 mg bid). Lastly, consistent with our past findings, the present findings confirm that acute MEM-induced changes in early auditory information processing are not accompanied by acute gains in neurocognition, at least as assessed by the RBANS. This pattern previously led us to propose that changes in early auditory processing must be sustained over time in order to effect gains in neurocognition; alternative explanations, including the possibility that specific patient subgroups might show more rapid neurocognitive gains from acute MEM, will be examined when the full study sample has been acquired.

Keywords: Alzheimer's Disease, Memantine, Prepulse Inhibition

Disclosure: Nothing to disclose.

P26. Beta-Carbophylline, a CB2-Selective Phytocannabinoid, Differentially Modulates Attention and Inhibitory Control in Young and Aged Mice

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Background: Although cannabis use in adolescents and adults is known to exert detrimental effects on cognition, limited evidence indicates that its use in old age may not cause poor cognitive performance. In fact, recent studies show beneficial cognitive effects of low doses of THC (a principle psychoactive component

of cannabis) on learning and memory in aged rodents. From a therapeutic standpoint, the use of THC to combat age-related cognitive decline may have a limited utility in clinics due to its addictive potential. Accumulating evidence has linked inflammation and immune dysregulation to Alzheimer's disease and other forms of age-related dementia. Moreover, the activation of cannabinoid 2 (CB2) receptor signaling is associated with anti-inflammatory properties. We have previously shown that beta-caryophyllene (BCP), a non-psychoactive sesquiterpene abundant in cannabis and known to activate CB2 receptors, attenuates inflammation in mouse models of neuropathic pain and stroke. Here we assessed the effects of BCP, on cognitive performance in young and aged mice.

Methods: Young (2 months) and aged (15 months) male and female C57BL/6J mice were trained in an operant go/no-go (GNG) visual discrimination task that assess attentional capacities and inhibitory control under conditions of response conflict. This task requires animals to discriminate between go cues (stationary panel light) and withholding (no-go) cues (blinking panel light) to earn rewards. Each GNG behavioral session consisted of 45 trials with pseudorandomized presentation of 50% go and 50% no-go cues. Animals trained to criterion (75% total correct responses for 3 consecutive days) were injected with different doses of BCP (0mg/Kg, 25 mg/Kg, 50 mg/Kg, and 100 mg/Kg; i.p.) to assess performance using a within-subjects design.

Results: Aged mice required more training sessions to attain criterion as compared to the young mice (aged: 44.31 ± 3.39; young: 32.06 ± 2.09; $p < 0.002$). A significant main effect of BCP dose was observed on the go trial performance with a decline in % hits ($F3,72 = 5.13$, $p = 0.005$) and higher % omission errors ($F3,72 = 6.23$, $p = 0.004$) with increasing doses. Although the hit rate remained comparable between the two age groups following the vehicle injection ($p = 0.14$), it trended higher in aged mice with 25mg dose ($F1,26 = 3.49$, $p = 0.07$). The analyses of no-go trial performance revealed the interaction between dose x age x sex approached significance ($p = 0.06$). Interestingly, % false alarms declined in aged females at the lower BCP dose ($17.53 \pm 3.13\%$ vs $27.44 \pm 3.13\%$ with vehicle); however this effect was not observed in males.

Conclusions: Our data illustrate that acute administration of a CB2 receptor agonist differentially impact cognitive performance in young and aged mice. Specifically, administration of lower doses of BCP improves attention control to visual cues in aged mice while higher doses impair attention regardless of age. Moreover, this phytocannabinoid was marginally more effective in improving response inhibition in aged female mice indicating that sex differences in cognitive trajectories might be an important determinant for the efficacy of CB2 agonists. Future studies are warranted to determine whether the effect of BCP on cognitive functioning in aging is causally linked to its immunomodulatory effects.

Keywords: Aging, Cannabinoids, Attention, Inhibitory Control
Disclosure: Nothing to disclose.

P27. Amygdalostriatal Transition Zone Neurons Encode Sustained Valence to Direct Conditioned Behaviors

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Background: The ability to respond appropriately to stimuli that predict rewards or punishments lies at the core of evolutionary fitness, and is disrupted in a number of neuropsychiatric disease states. Despite the overwhelming consensus that the amygdala is important for mediating associative learning, bilateral loss-of-function manipulations of the lateral amygdala (LA), basolateral amygdala (BLA) and central nucleus (CeA) still result in substantial residual behavioral responses to conditioned stimuli which are currently unexplained by any existing conceptual framework. Although relatively unexplored, the amygdalostriatal transition zone (ASt) is anatomically poised to provide a shortcut between corticolimbic and basal ganglia circuitry, and, in parallel with the amygdala, mediate associative learning and behavioral responses to salient stimuli. Like the amygdala, the ASt receives converging sensory input from the thalamic and cortical pathways. However, the downstream projections of the ASt are distinct from the canonical outputs of the amygdala complex, and are integrated with striatal circuits involved in action selection. Despite this intriguing circuit connectivity the function of the ASt is almost completely unknown, resulting in a major gap in our knowledge of circuits underlying motivated behaviors. Here, we characterized the transcriptomic profile of the ASt in comparison to neighboring amygdalar or striatal nuclei, and collect cellular resolution recordings of genetically-defined neurons during a valence discrimination task to interrogate the functional role of ASt circuitry.

Methods: To investigate the role of the ASt in associative learning and motivated behaviors, we first used single-nucleus RNA sequencing to generate a comprehensive profile of gene expression in ASt neurons and adjacent GABAergic brain regions ($n = 18$-25 mice, >15000 cells per brain region, >50k unique molecular identifiers per cell). We then quantified the genetic identity of neurons in the ASt, dorsal striatum (DS) and tail of striatum (TS) using RNAscope labelling targeted to dopamine receptor 1 (drd1a, 'D1 + ') and dopamine receptor (drd2, 'D2 + ') ($N = 8$ mice, 16 sections ASt, 8 mice, 12 sections DS, 8 mice, 12 sections TS). We used in vivo electrophysiology to examine changes in ASt neuron responses to conditioned stimuli predicting aversive foot shocks in a pavlovian fear conditioning paradigm ($n = 8$ mice, 30 neurons Paired group, $n = 5$ mice, 27 neurons Unpaired group), as well as responses to distinct conditioned cues predicting aversive and rewarding stimuli ($N = 9$ mice, 41 neurons). ¬To examine neural activity in D2 + ASt neurons, we used in vivo miniscope imaging to record changes in GCaMP7f fluorescence in response to cues predicting aversive and rewarding stimuli (Preliminary data, $n = 39$ neurons). Finally, to determine if D2 + ASt neuron activity was necessary for behavioral responses to conditioned stimuli, we targeted D2 + neurons with the inhibitory opsin NpHR, and examined the effects of reversibly inhibiting these neurons on responses to aversive and rewarding stimuli during a two-tone discrimination task ($N = 8$ mice NpHR, 9 mice eYFP).

Results: Our RNA sequencing data showed that the ASt neurons formed a distinct cluster from neurons in the Tail of Striatum (TS), dorsal striatum (DS) and central nucleus of the amygdala (CeA). We found that the ASt has a significantly greater proportion of D2 + ASt neurons than both the dorsal striatum and tail of striatum (Chi-square test, $p = 0.0010$ ASt v. DS, $p = 0.0081$ ASt v. TS). Our in vivo electrophysiological recording data demonstrated that following pavlovian fear conditioning, ASt neuron responses to a shock-predicting cue were significantly greater in 'paired group' mice compared with 'unpaired group' controls where cues and shocks were explicitly unpaired (RM ANOVA, Effect of Group $p = 0.028$). Additionally, our preliminary calcium imaging data suggest that D2 + ASt neurons also show increased in conditioned cue responses following fear conditioning. Finally, in loss-of-function experiments we found that optogenetic inhibition of D2 + ASt neurons caused a striking reduction in conditioned fear responses to a shock-predicting cue (43% decrease in freezing, $p = 0.0145$, paired t-test).

Conclusions: Our study provides the first demonstration that ASt neurons are sufficient to drive robust freezing and avoidance

behaviors, and undergo conditioned changes in responsiveness to cues which predict aversive stimuli. Additionally, we show that the ASt contains a higher proportion of D2 + neurons than other regions of the striatum, and that inhibition of these D2 + neurons results in a significant reduction in fear response (conditioned freezing) to cues predicting aversive stimuli. Consequently, we believe that the ASt may be an overlooked and critical structure of the amygdala complex that contributes to behavioral responses to conditioned stimuli.

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

Disclosure: Nothing to disclose.

P28. Attention Training in Anxiety Disorders Alters Cingulo-Opercular Network Signal

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Background: Altered attention may be a core cognitive feature of anxiety disorders. Extensive research has shown that anxiety disorders in children and adults are linked with biases in threat-related attention. Recent work implicates additional aspects of attention and its underlying neural networks in pediatric anxiety disorders. Our laboratory found that increased anxiety positively correlated with increased stimulus-driven attention and brain activity within the ventral attention network. We designed a novel treatment to see if targeting these processes could reduce clinical anxiety, completing a small clinical trial in pediatric anxiety disorders. At ACNP 2020, we presented the initial results of this clinical trial. Cognitive training successfully lowered anxiety and decreases in anxiety correlated with changes in goal-directed attention. Here, we analyze how cognitive training affected the cingulo-opercular network (CON) and the relationship of network changes to anxiety improvements.

Methods: In a small ($n = 18$, 12 female, ages 8-12) clinical trial (Clinicaltrials.gov, ID # NCT03790696), we recruited children with generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder. Subjects were initially screened using validated measures (SCARED and Mood and Feelings Questionnaire) and then diagnosed using a semi-structured interview (K-SADS-PL). We excluded subjects with diagnoses of attention deficit hyperactivity disorder, developmental disorders, or schizophrenia. Participants underwent twice weekly cognitive attention training for eight (8), forty-five (45) minute sessions. In the training task, participants received cues indicating the side of the screen on which the target would appear after a variable cue-target interval. We measured anxiety before, during, and after training using the SCARED-parent report as our primary measure. Participants completed pre- and post-training neuroimaging including fMRI of an attention task. We analyzed BOLD signal within inferior frontal gyrus (IFG) regions of interest, segmented by their involvement in specific attention-related cognitive networks. We modeled the effects of training and anxiety on BOLD signal. We examined the relationship of CON signals to anxiety changes by correlating task-related signals in an IFG CON node to anxiety at baseline and after training.

Results: Participants' anxiety decreased significantly after training as measured by the SCARED – parent report (mean change [95% CI]: -22.44 [-16.96 – -27.92], $p < 0.001$). BOLD signals in a CON node showed a significant main effect of training, decreasing after training ($p < 0.02$). We also found a significant interactive effect of training and anxiety on this CON node ($p < 0.01$). Prior to training, there is no significant correlation between CON node signal and anxiety ($r = -0.45$, $p = 0.14$). After training, there is a significant positive correlation between the CON node and anxiety ($r = 0.68$, $p < 0.015$).

Conclusions: We completed a small clinical trial using cognitive attention training to treat pediatric anxiety disorders. After training, we observed reduced anxiety, altered attention, and signal changes within neural attention networks. We specifically focused on how training affected a node of the cingulo-opercular network. This network is involved in executive function including stable task-level control. We found that attention training lowered signals in a CON node. Further, there was a shift in the relationship between this node's activity and anxiety after attention training. While there was no relationship between anxiety and signal in this CON node at baseline, signal within this node after training was positively related to anxiety. Participants whose signal remained elevated showed higher levels of residual anxiety. Taken together, these findings implicate successful reduction in CON signal as a key aspect of successful treatment via attention training. This work highlights the fundamental role of attention and its related networks in anxiety disorders. We plan to expand on this work by characterizing individual attention profiles in the search for personalized intervention targets.

Keywords: Anxiety Disorders, Functional MRI (fMRI), Cingulo-Opercular Network, Ventral Attention, Clinical trial

Disclosure: Nothing to disclose.

P29. Prevalence Correlates, and Potential Pro-Inflammatory Biomarker Predictors CRP, SAA, sICAM-1, sVCAM-1 for Post-Traumatic Stress in Older Adults With Hypertension During the Early Phase of the COVID-19 Pandemic

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Background: Post-traumatic stress disorder (PTSD) and symptoms (PTSS) include intrusion phenomena, avoidance, hypervigilance, and negative alterations in mood and cognition and are associated with increased risk for cardiometabolic and neurodegenerative disorders (Celano, 2016), especially in the aged. Immune dysregulation may underlie these associations (Quinones, 2020), as higher proinflammatory marker levels such as C-reactive protein (CRP) are shown in PTSD (Kim, 2020). Elevated CRP and intercellular adhesion molecule 1 (ICAM-1) also predict future PTSD (Sumner, 2018). Cytokine dysregulation could underlie onset of neuropsychiatric symptoms in COVID-19 survivors (Troyer, 2020), but findings of inflammation underlying pandemic-related PTSS in the general population is limited. We aimed to examine prevalence, correlates, and predictors of pandemic-related PTSS in a cohort of older adults with hypertension. We hypothesize that (a) the prevalence of PTSS in the elderly will be greater than pre-pandemic prevalence in the general population; (b) older adults who endorse PTSS will report poorer health-related outcomes during the pandemic when compared to participants who do not endorse PTSS; and (c) pre-pandemic baseline clinical characteristics and inflammatory and endothelial markers (CRP, serum amyloid A (SAA), soluble ICAM-1, soluble vascular cell adhesion molecule 1 (sVCAM-1) will predict increased risk of pandemic-related PTSS.

Methods: Adults aged 60-90 years with stage 1 hypertension (SBP > 130mmHg) in San Diego, CA, who had previously

participated in a 12-week behavioral intervention for hypertension between 2016-2020, and had completed psychological and cognitive assessments, hemodynamic testing, and aforementioned plasma biomarker measurements. The pandemic data were collected between May and September 2020 via an online or mailed survey. Measures of the pandemic impact included the Coronavirus Health Impact Survey (CRISIS) and the Primary Care PTSD Screen (PC-PTSD). Other clinical characteristics were measured by respective rating scales, including Beck Depression Inventory-II (BDI-II), UCLA Loneliness Scale (ULS-8), Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Anxiety 8a and Sleep Disturbance 8a, Connor-Davidson Resilience Scale (CD-RISC-10), Neff Self Compassion Scale (SCS), 20-Item Short Form Health Survey (SF-20), and Functional Activities Questionnaire (FAQ). Prevalence of PTSS was determined based on PC-PTSD cut-off scores (Freedy et al., 2010). Group comparisons were conducted using Wilcoxon rank sum or Chi-squared tests, for non-normally distributed continuous and categorical variables, respectively. Binary and ordinal logistic regression analyses were used to test whether pre-pandemic measures predicted PTSS group status and PC-PTSD scores, respectively, during the COVID-19 pandemic.

Results: Ninety-five subjects completed the study, and 40 (42.1%) participants endorsed at least one item on the PC-PTSD, while 7 (7.4%) participants endorsed three or more symptoms on the PC-PTSD. PTSS + ($n = 40$) and PTSS- ($n = 55$) groups, based on PC-PTSD cut-off scores of one, did not differ in demographic variables: age, race, ethnicity, marital status, first language, or education. No participants reported having tested positive for COVID-19 infection. PTSS + group reported significantly greater depressive symptoms (W = 450), loneliness (W = 605), anxiety (W = 392), and sleep disturbance (W = 527), along with significantly lower resilience (W = 1405), compassion (W = 1514), health perception (W = 1434), physical functioning (W = 1513), and adaptive functioning (W = 781) (all p's =< 0.01) compared to PTSS- group. Logistic regression models demonstrated that female biologic sex (OR = 2.67, 95% CI 1.44-4.96, $p = 0.002$) and pre-pandemic anxiety scores (OR = 4.02, 95% CI, 1.56-10.35, $p = 0.004$) significantly predicted PTSS during the pandemic, but pre-pandemic biomarker levels (CRP, SAA, sICAM-1, sVCAM-1) did not.

Conclusions: Prevalence of PTSS in this cohort of older adults with hypertension during the COVID-19 pandemic was 7.4%, which is greater than the pre-pandemic prevalence of PTSD in the general population of 4.7% (Goldstein et al., 2016) but lower than 15-23% reported in other adult samples during the pandemic (e.g., Cenat et al., 2021). Participants who endorsed at least one PTSS also reported poorer mental health and health-related outcomes, including lower health perception, physical functioning, and more impairment in instrumental activities of daily living. Our findings suggest that older adults might experience the pandemic as traumatic at relatively lower rates, but in those individuals who do, it is associated with known risk factors for cognitive decline, which warrants further validation in larger studies. Female sex and baseline pre-pandemic anxiety levels predicted PTSS during the pandemic, which is consistent with studies of pandemic-related PTSS in other adult samples. However, baseline acute-phase and vascular inflammatory markers did not predict PTSS during the pandemic; biologic risk factors of pandemic PTSS in older adults with hypertension therefore remain to be elucidated. Understanding pandemic PTSS in aging adults with chronic conditions that increase risk for COVID severity will aid in developing targeted prevention and mitigation strategies to decrease the psychological and physiological burden of the pandemic for vulnerable aging populations.

Keywords: Neuroinflammation, Posttraumatic Stress, Biomarkers, Older Adults, Cardiovascular

Disclosure: Nothing to disclose.

P30. BDNF Bioavailability Differentially Impacts Adolescent and Adult Safety Learning

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Background: A prevailing molecular framework thought to underlie mood and anxiety disorders is the neurotrophic hypothesis, which postulates that reductions in neurotrophic support can alter neural plasticity in key regions implicated in anxiety and fear responses. In line with this, to examine how the neurotrophin BDNF contributes to the pathophysiology of anxiety disorders our lab has utilized a knock-in mouse line carrying the human Val66Met polymorphism, which leads to decreased BDNF bioavailability. Adult mice expressing the Met allele recapitulate the phenotypic hallmarks of humans with this polymorphism, especially with regard to altered anxiety- and fear-related behaviors. In contrast, substantially less is known about the impact of BDNF signaling on the development of fear-related circuits, despite a peak in anxiety disorder diagnoses in early adolescence. The present study investigated the impact of BDNF bioavailability on the acquisition and application of safety cue learning, a form of fear inhibition with high clinical relevance.

Methods: Adolescent (postnatal day, P29) and adult (P70) Val66Met mice and littermate controls underwent discriminative conditioning during which they were repeatedly presented with fear cues (a tone paired with a footshock) and safety cues (a second tone, no footshock). To test the ability of the learned safety cues to modulate fear, a subset of mice (adolescent: $n = 12$ control, 11 Val66Met; adult: $n = 13$ control, 13 Val66Met) were subsequently exposed to a simultaneous compound presentation of the fear and safety cue together in a novel context (i.e., summation test for conditioned inhibition). Separate cohorts of mice underwent standard extinction (adolescent: $n = 12$ control, 10 Val66Met; adult: $n = 12$ control, 11 Val66Met) or extinction with a safety cue intermixed (adolescent: $n = 11$ control, 13 Val66Met; adult: $n = 14$ control, 12 Val66Met). Freezing behavior was quantified as a measure of fear.

Results: Following discriminative conditioning, all mice froze more during fear than safety cues ($p < 0.001$), but the magnitude of discrimination was significantly decreased for Val66Met adult mice ($p < 0.01$). In contrast, during presentations of the fear/safety compound, freezing was reduced relative to a fear cue presented alone (i.e., conditioned inhibition) in adult mice of both genotypes, and wild-type adolescent mice (p's < 0.05), while Val66Met adolescent mice showed an inability to inhibit fear during the compound, indicating impaired conditioned inhibition. Within-session rates of extinction were faster for standard extinction than intermixed safety extinction in all mice ($p < 0.02$). However, during a retention test two weeks after extinction adult mice of both genotypes and wild-type adolescent mice that underwent intermixed safety extinction exhibited reduced freezing relative to standard extinction (p's < 0.05), indicating an extinction memory benefit associated with safety cue presence. Val66Met adolescent mice exhibited comparable freezing regardless of extinction training condition.

Conclusions: Our data suggest dissociable impacts of BDNF bioavailability on the neural circuitry underlying threat discrimination, conditioned inhibition, and extinction memory formation. Despite previously reported limitations in fear regulation in adult Val66Met mice, we show that these mice can successfully utilize safety cues to inhibit fear. However, reduced levels of BDNF across adolescent development limit the efficacy of safety cues. In sum, this line of research informs both age- and genotype-specific patterns of fear responding which may have translational value for

the personalized treatment of anxiety disorders. Ongoing studies are investigating how the relative distribution of BDNF throughout fear regulation circuitry across development (focusing on the ventral hippocampus and medial prefrontal cortex) impacts fear responding.

Keywords: Adolescence, BDNF Val66Met, Fear Learning

Disclosure: Nothing to disclose.

P31. Associative Fear Learning in PTSD May Depend Upon Non-Associative Fear

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Background: Posttraumatic stress disorder (PTSD) is a severe fear-related disorder. Fear and extinction learning are the most studied associative fear learning mechanisms in PTSD and are central to its development and recovery. However, other fear mechanisms that have been studied less may be important as well.

Evidence suggests a distinct role of UCR in fear learning and risk of developing PTSD. Studies in rodents and healthy humans have found that UCR during fear acquisition is related to distinct neural mechanisms that may interact with neural mechanisms involved in associative fear learning. Furthermore, physiological UCR following trauma exposure prospectively predicts the development of PTSD. In adults with fear- and anxiety-related disorders, patients with high UCR have shown elevated fear acquisition compared with healthy controls. Similarly, in a sample of trauma-exposed individuals without PTSD, participants with high UCR had elevated fear acquisition. However, there was no correlation between UCR and PTSD symptom severity.

To our knowledge, the relationship of UCR with fear acquisition, fear extinction, and PTSD severity is not established. Thus, we directly tested these associations in a sample of PTSD patients. We hypothesized that elevated UCR would be associated with elevated fear acquisition and with impaired fear extinction. We did not hypothesize an association with PTSD symptom severity.

Methods: Participants included 43 DSM-5 PTSD patients (37 female) and 14 individuals with sub-threshold PTSD (8 female). Skin Conductance Response (SCR) was recorded during Habituation, Acquisition, and Extinction. The unconditioned stimulus (US) was an airblast to the larynx. Conditioned stimuli were two colored shapes: one was paired with the US during Acquisition (CS +) and one was never paired with the US (CS-). Habituation was four trials of each CS. Acquisition consisted of 12 trials of each CS, with the US following each CS + trial. Extinction consisted of 16 trials of each CS type. Mean UCR was calculated using all 12 US presentations during Acquisition and participants were sorted into a High UCR Group or Low UCR Group by median split. Mean SCRs for CS + and CS- during Acquisition and Extinction were calculated after omitting the first trial of each CS type for each phase. Difference scores for Acquisition and Extinction were calculated as mean CS- SCR minus mean CS + SCR for each phase. PTSD severity was total score on the Clinician Administered PTSD Scale (CAPS) for DSM-5.

Conditioned SCR responses during Acquisition and Extinction were evaluated using 2x2 ANOVA with a within-subjects factor of stimulus (CS + , CS-) and a between-subjects factor of UCR group (High UCR, Low UCR). Post hoc t-tests followed statistically significant ANOVA results. Continuous associations of UCR with conditioned SCR and with PTSD severity were assessed using linear regression models. To assess robustness of findings, all analyses were performed both with and without biological sex and baseline SCR variables. Baseline SCR was the average SCR during Habituation.

Results: In Acquisition, ANOVA revealed main effects of UCR group ($F(1,55) = 23.67$, $p < .0001$) and stimulus ($F(1,55) = 13.28$, $p = 0.0006$), and a significant interaction of UCR group and stimulus ($F(1,55) = 8.98$, $p = 0.0041$). Post hoc t-tests found greater SCR to both CSs in the High versus Low UCR Group (CS + : $t(42.61) = 5.2$, $p < .0001$; CS-: $t(48.01) = 3.5$, $p = 0.0012$). Stimulus *t*-tests (CS + versus CS-) within UCR groups revealed differential SCR (CS + > CS-) in the High UCR group ($t(28) = 3.67$, $p = 0.0010$), but not the Low UCR group ($t(27) = 0.81$, $p = 0.42$). Regression analyses identified positive correlations of mean UCR with difference score ($R2 = 0.22$; $p = 0.0002$), CS + SCR ($R2 = 0.40$; $p < .0001$) and CS- SCR ($R2 = 0.17$; $p = 0.0010$). When controlling for sex and baseline SCR, the correlation of mean UCR with CS- SCR was not significant. Female sex was negatively associated with SCR to CS-.

In Extinction, ANOVA revealed a main effect of UCR group ($F(1,55) = 8.44$, $p = .0053$), but no main effect of stimulus, and no interaction of stimulus and UCR group. Post hoc *t*-tests found greater SCR to both CSs in the High versus Low UCR Group (CS + : $t(34.89) = 2.9$, $p = .0059$; CS-: $t(51.35) = 2.32$, $p = 0.0243$). Stimulus comparison *t*-tests (CS + versus CS-) within UCR groups found no difference in either group. Regression analyses revealed a positive correlation of mean UCR with CS + SCR ($R2 = 0.10$; $p = 0.0188$), but not with CS-SCR or difference score. When controlling for sex and baseline SCR, no UCR effects were found. Female sex was negatively associated with SCR to CS + and CS-.

Regression analysis predicting PTSD symptom severity found no association of UCR with total CAPS.

Conclusions: High UCR was associated with significantly elevated associative fear learning but not extinction learning in this PTSD sample. The finding of elevated fear acquisition in PTSD patients with high UCR is consistent with studies in other fear- and anxiety-related disorders. Thus, high UCR may be a transdiagnostic risk factor for elevated conditioned fear acquisition. Importantly, high UCR indicates a larger sympathetic nervous system response to a putatively fear eliciting stimulus, which may impact the participant's experience of the US. Thus, the UCR could affect what is learned, in addition whether an association is learned. Although high UCR was not associated with impaired extinction learning, it may be relevant to individual differences in extinction memory and this is an important future direction.

Keywords: Post Traumatic Stress Disorder, Skin conductance responses, Fear conditioning and extinction, Unconditioned responses

Disclosure: Nothing to disclose.

P32. The Toxic Effect of Worry on Hippocampal Volume – a Subfields Analysis

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Background: Anxiety disorders have the highest lifetime prevalence of any psychiatric disorder. Late-life anxiety is associated with higher rates of Alzheimer's disease and related dementias. Recent reports have indicated that late-life anxiety is associated with lower hippocampal volumes and with higher rates of cognitive decline in amyloid-positive individuals. In this study of cognitively intact older adults, we investigated the association between hippocampal subfield volumes and worry – a primary symptom of generalized anxiety disorder.

Methods: We recruited 84 older individuals (males and females, >50years) with varying worry with and without anxiety (generalized anxiety disorder, panic disorder, social phobia, etc.) and/or mood disorders (e.g., major depressive disorder, persistent depressive disorder, or unspecified depressive disorder). All participants undergo MRI and assessments measuring worry with the PSWQ, Penn State Worry Questionnaire. A sagittal, whole-brain T2-weighted Sampling Perfection with Application optimized Contrasts using different flip angle Evolution (SPACE) was collected with TR = 3200 ms, TE = 563 ms, FA = 120 deg, FOV = 320 × 300 with 208 slices, 0.8 mm3 isotropic resolution, no slice gap, and GRAPPA with acceleration factor of 2 (total time 5.95 min). We segmented hippocampal subfields with Freesurfer v. 7.2 and conducted manual quality checks. After conducting multiple imputations using random forest method in 'mice' package in *R*, we conducted linear regression for each subfield (and total volume) investigating the association with worry adjusting for age, sex, race, education, and cumulative illness severity.

Results: We found that greater total volume of the subiculum was associated with greater worry severity [ß = -1.7, $p < 0.05$] while adjusting for age, sex, race, education, and cumulative illness severity. We did not find that worry was associated with total hippocampal volume or other subfields.

Conclusions: Worry had a toxic effect on the subiculum and is a part of a transdiagnostic model of repetitive negative thoughts, which are a risk factor for Alzheimer's disease. Worry did not correlate with total hippocampal volume as has been identified in previous studies, but our results indicate that its effects may be more specific to particular areas like the subiculum.

Keywords: Anxiety, Hippocampal Subfields, Generalized Anxiety Disorder, Cortical Atrophy

Disclosure: Nothing to disclose.

P33. Behavioral Differences and Neural Correlates of Emotional Trauma on Social Interactions in Rats

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Background: Individuals with PTSD and other anxiety disorders show excessive fear and persistent avoidance of activities, places, or people associated with their emotional trauma. Consequently, such individuals have difficulty assessing danger, which can lead to deficits in social interactions. Preclinical studies in rats can reveal the behavioral and neural mechanisms of fear and avoidance and how social interactions are altered by emotional trauma. Here, we combined two established aversive learning paradigms to examine the effects of differential emotional trauma on social interactions. We assessed behavioral and neural correlates of fear or avoidance behaviors followed by social exploration and dominance tests.

Methods: Rats underwent 8 days of platform-mediated avoidance or fear conditioning or were naïve controls ($n = 30$-34 per group, both sexes) exposed to the same chamber, platform, and tone. Conditioning procedures were matched, such that Fear rats received a similar # of shocks as Avoidance rats, but Avoidance rats could avoid shock by moving to the platform, unlike Fear rats. Single unit recordings in anterior cingulate cortex (ACC) were performed in 2 male Avoidance rats ($n = 147$ units). Firing rate during tone and platform entry was compared against ACC baseline firing.

Following conditioning, rats underwent social exploration: 1 conditioned rat was placed in an open field with an empty cage (3 min), followed by the introduction of a same-sex unfamiliar rat in the cage (3 min). Time spent near cage during both periods was measured. Rats also underwent social dominance: 2 rats with differing emotional traumas (fear/avoidance/naïve), were placed on either ends of a plexiglass tube. Dominance was assessed by # of wins across 3 trials (when 1 rat pushed other rat out of tube).

Results: We validated a new rat model of emotional trauma using fear and avoidance tasks that control for # of shocks and a naïve group that controls for the presence of tone, platform, and other contextual information. On Day 8 of conditioning, Avoidance and Naïve rats showed similar freezing levels, which was significantly lower compared to Fear rats ($p < 0.05$). Preliminary unit recordings in avoidance rats show that 17% (24/139) of ACC cells were excitatory tone-responsive, whereas 15% (21/139) of cells were inhibitory tone-responsive. Moreover, 13% (11/93) were excitatory platform-responsive, whereas 9% (8/93) were inhibitory platform-responsive.

During social exploration, Avoidance and Naïve rats spent similar time investigating the unfamiliar rat. Both of their time spent was significantly greater in both time periods compared to Fear rats (empty cage, $p < 0.05$; with rat, $p < 0.05$). This effect was driven by males, as there were no differences in social exploration in females across all trauma types. We also found a sex-dependent effect of trauma type on social dominance: Male Fear rats were more dominant over male Avoidance rats ($p < 0.05$) but not over male Naïve rats.

Conclusions: Despite Avoidance and Fear rats receiving a similar number of shocks (~16, across 8 days), Avoidance rats behaved like Naïve rats during social exploration, suggesting that an adaptive strategy such as active avoidance can model coping, but this effect was only observed in males. Our unexpected finding that male Fear rats were more dominant over male Avoidance rats suggests that Avoidance rats were avoiding a potential threat (stressed individual). Finally, ongoing experiments aim to determine how ACC correlates differ during social interactions among rats with different traumatic experiences.

Keywords: Auditory Fear Conditioning, Active Avoidance, Prelimbic Cortex, Anterior Cingulate Cortex (ACC), Social Behavior

Disclosure: Nothing to disclose.

P34. Trauma Symptoms and Orbitofrontal Cortex Volume in Veterans With Suicidal Behavior

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Background: Recent estimates from the Department of Veterans Affairs suggest that an average of 17.6 Veterans die by suicide per day (Office of Mental Health and Suicide Prevention, 2021). A range of clinical and neurobiological measures have been related to suicide behaviors, including trauma, mood disorder symptoms, and alterations of the orbitofrontal cortex (OFC). To date, few studies have focused on specific behavioral experiences and responses to trauma in relation to the neurobiological correlates of trauma in Veterans. The current study therefore examined associations between psychological impacts of trauma and OFC brain volume in a sample of Veterans with and without suicidal behavior.

Methods: Fifty-two veterans (43 males, 9 females) between the ages of 18 and 55 completed a structured interview assessing history of suicidal behavior, specifically suicide ideation and attempts (Columbia Suicide Severity Rating Scales (CSSRS)). Participants also completed the clinician-administered Trauma Symptom Inventory (TSI), which yields ten clinical subscale scores: Anxious Arousal, Depression, Anger/Irritability, Intrusive Experiences, Defensive Avoidance, Dissociation, Sexual Concerns, Dysfunctional Sexual Behavior, Impaired Self-Reference, and

Tension-Reduction Behavior. The Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Inventory (HAM-A) were given to assess symptoms of anxiety and depression.

Veteran participants also completed magnetic resonance imaging (MRI) on a 3.0 Tesla Siemens Magnetom Verio scanner using a standard 12-channel head coil. Using a T1-weighted 3D MPRAGE GRAPPA sequence, the axial plane T1-weighted images were acquired with the following parameters: Echo Time (TE) = 3.42 ms, Repetition Time (TR) = 2000 ms, Inversion Time (TI) = 1100 ms, Flip Angle = 8°, 256 × 256 acquisition matrix, 160 slices, and 1.0 mm slice thickness. ANOVAs and correlations were completed in SPSS.

Results: Thirty Veterans reported a history of suicide ideation only (+SI) and 22 veterans reported a history of suicide attempt and ideation (+SA). Veterans in the +SA group reported increased depressive and anxious symptoms compared to Veterans in the +SI group (Veterans+SA HAM-A = 16.0, SD = 8.59, HAM-D = 14.95, SD = 6.54; Veterans+SI HAM-A = 7.0, SD = 5.45, HAM-D = 7.33, SD = 6.29; *p*'s < .001). After controlling for HAM-A, HAM-D, and sex, Veterans in the +SI group showed correlations between the left hemisphere medial orbitofrontal cortex (lhmOFC) volume and the TSI Anger/Irritability ($r = -.54$, $p = .005$) and TSI Tension Reduction Behavior ($r = -.43$, $p = .03$) subscales. Veterans in the +SA group showed correlations between the lhmOFC and the TSI Sexual Concerns ($r = -.57$, $p = .01$) and Dysfunctional Sexual Behavior ($r = -.47$, $p = .04$) subscales in addition to the TSI Anger/Irritability ($r = -.59$, $p = .007$) and TSI Tension Reduction Behavior ($r = -.58$, $p = .009$) subscales. Other TSI subscale scores did not show a significant relationship with lhmOFC volume by suicide behavior group.

Conclusions: Results from this study suggest that OFC volume and post-trauma symptoms have unique association patterns in Veterans with SI only compared to Veterans with SA. Specifically, irritable affect and engaging in external efforts to reduce stress (e.g., angry outbursts, self-harm) were negatively related to mOFC volume in both Veterans with SI and in Veterans with SA. However, sexual dysfunction, sexual dissatisfaction, and unwanted sexual thoughts or feelings were additionally negatively related to mOFC volume in Veterans with SA. Due to the cross-sectional nature of these data, it is unclear whether correlations between post-trauma symptoms and OFC volume were a cause or effect of suicidal behavior. Nonetheless, these findings have significant clinical implications, as they suggest that individuals with SI versus SA may differ in appraisal of reward value and behavioral outcomes in relation to anger, irritability, and sexual dissatisfaction.

Keywords: Magnetic Resonance Imaging, Suicide, Trauma Exposure, Veterans

Disclosure: Nothing to disclose.

P35. Differential Effects of the Stress Peptides PACAP and CRF on Sleep and Body Temperature in Male and Female Mice

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Background: Sleep and stress have a reciprocal relationship, whereby stress often causes changes in sleep, and abnormal sleep cycles can exacerbate symptoms of stress. Problems with sleep are part of the diagnostic criteria for many stress-related psychiatric disorders, including major depressive disorder (MDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD). Our lab has previously demonstrated that chronic social defeat stress (CSDS) in mice produces effects on sleep that resemble those seen in depression, including increases in rapid eye movement (REM) sleep and reductions in the amplitude of daily body temperature rhythms. Stress is known to alter sleep patterns, but the specific contributions of stress-related peptides pituitary adenylate cyclase-activating polypeptide (PACAP) and corticotropin-releasing factor (CRF) on sleep have not been directly described and compared. In behavioral tests, both PACAP and CRF can produce stress-like effects (e.g., enhanced acoustic startle, reduced social interaction and motivation, disrupted attention) although there is some evidence that the effects of PACAP are often more persistent than those of CRF. There are also known sex differences in PACAP and CRF systems, as well as sex differences in the prevalence of stress-related psychiatric disorders in clinical populations. Here, we examined the effects of PACAP and CRF on sleep architecture, body temperature, and locomotor activity in male and female mice using a wireless telemetry system that enables sustained periods of continuous data collection in untethered, freely moving mice.

Methods: C57BL/6J mice underwent surgeries to implant intracerebroventricular (ICV) cannula and wireless telemetry transmitters (DSI) that enable continuous, untethered recordings of EEG, EMG, as well as core body temperature and locomotor activity. ICV administration of PACAP (0.25 µg; $n = 10$ males, 9 females), CRF (1.0 µg; $n = 9$ males, 8 females) or vehicle (aCSF; $n = 9$ males, 8 females) occurred at 9am, 2 hours after lights on in a 12 hour light/dark cycle. PACAP and CRF doses were selected based on behavioral effects in elevated plus maze. Baseline data was collected for 4 days prior to treatment and for a week after infusion. Vigilance states—active/wake, slow wave sleep (SWS), REM sleep—were analyzed as percent of Baseline at 24 hr and 1 week after infusion. In females, estrous phase was determined using body temperature. Changes in vigilance state by Condition (Vehicle, PACAP or CRF) and Timepoint (Baseline, 24 Hours, and 1 Week) were compared with 2-way ANOVAs or mixed effects analyses where necessary. Significant effects were further examined with Tukey's post-hoc comparisons.

Results: In the 24 hours after peptide administration, PACAP-treated mice display increased SWS duration compared to Vehicle and CRF-treated animals (*P*'s < 0.001), increased time in REM sleep compared to Vehicles ($P < 0.05$), and decreased time active/wake compared to Vehicle and CRF-treated animals (*P*'s < 0.01). Compared to Baseline vigilance states, PACAP animals display increased REM sleep at 24 hours ($P < 0.0001$) and 1 week ($P < 0.05$) after PACAP administration. Further examination of sleep changes in PACAP-treated mice in the 24 hours after treatment revealed no changes in bouts of SWS or Wake, but increased bouts of REM sleep compared to Baseline, and Vehicle and CRF-treated mice (*P*'s < 0.001). In mice administered PACAP, most alterations in sleep patterns occur during the dark phase, with increased REM sleep and SWS, and decreased wake (*P*'s < 0.01) hours after PACAP administration and when mice are typically awake and active. Corresponding with changes in vigilance states, PACAP-treated animals display decreased core body temperature during the dark (active) phase in the 24 hours after PACAP administration compared to baseline. In CRF-treated animals, there were no significant changes in durations or bouts of vigilance states compared to baseline or compared with Vehicle animals. No sex differences were observed in any treatment condition.

Conclusions: PACAP causes alterations in sleep architecture that are broadly similar to those caused by CSDS. In particular, PACAP-treated animals display increased REM sleep which did not completely return to baseline levels 1 week after treatment. PACAP administration also caused disruptions to the daily patterns of core body temperature, which were observed after CSDS and are frequently seen in individuals with depression. In contrast, CRF did not disrupt sleep patterns when administered in doses that produce stress-like effects on behaviors and elevated plasma corticosterone (CORT) levels. No sex differences were observed in the impact of either these stress-related peptides on vigilance

states. Understanding similarities and differences in the contributions of PACAP and CRF in stress-related sleep alterations may enable improvements in the diagnosis and treatment of stress-related psychiatric disorders.

Keywords: REM Sleep, PACAP, CRF, Slow Wave Sleep

Disclosure: Nothing to disclose.

P36. Prdm2 Modulates Fear Memory Consolidation Through Neurons Projecting From Prelimbic Cortex to the Basolateral Amygdala

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Background: Identifying the neural circuits and molecular level mechanisms of excessive fear memory may enable the discovery of molecular pathways that can be targeted to treat fear-related disorders. Substantial evidence indicates a role of the epigenetic mechanisms in memory formation and consolidation. We recently found that downregulation of the epigenetic enzyme PR containing domain 2 (PRDM2) in the prelimbic cortex (PL) potentiated stress-induced relapse to alcohol seeking. Given the role of PRDM2 in stress response as well as the high prevalence and overlapping neuronal substrates of comorbid alcohol use- and anxiety disorders, we hypothesized that Prdm2 deficiency in the PL may be one of the shared mechanisms between these disorders and may therefore participate in the development of pathological fear.

Methods: We used a viral shRNA approach to knock down prelimbic Prdm2 in rats, and assessed the effects of this manipulation on acquisition, expression, and extinction of cued conditioned fear ($N = 18$-20). Given the critical role of the PL projections to the BLA in cued conditioned fear, we determined whether Prdm2 KD regulates fear through this neuronal pathway, using a projection-specific strategy that utilized a Cre-dependent KD vector in combination with a retrogradely transported Cre-vector ($N = 18$-20). We then conducted patch clamp experiments to determine the functional role of Prdm2 KD on PL-BLA neuronal activity. Finally, we used viral translating ribosomal affinity purification (vTRAP) with high throughput RNA sequencing to determine the downstream molecular mechanisms through which PRDM2 regulates this neuronal pathway ($N = 18$).

Results: We found that Prdm2 KD in the PL increases fear expression (One way ANOVA: $F(1,36) = 7.0$; $p = 0.012$) without affecting fear acquisition or extinction. Downregulation of Prdm2 after allowing fear memory to become consolidated did not affect subsequent expression of fear. This suggests that Prdm2 KD exacerbates fear expression by strengthening fear memory consolidation. Our dual viral approach demonstrated that Prdm2 KD specifically in the PL-BLA projecting neurons was sufficient to increase fear expression (one-way ANOVA: $F(1,37) = 4.6$; $p = 0.038$), indicating that Prdm2 KD may modulate fear memory consolidation through the regulation of the PL-BLA neuronal pathway. In line with this hypothesis, we found that Prdm2 KD increased the expression of genes involved in neuronal morphogenesis, synaptic cell-adhesion, and exocytosis. Moreover, patch clamp recordings suggested that Prdm2 KD increased release probability in the PL-BLA projecting neurons.

Conclusions: Together our results suggest a role of the epigenetic enzyme PRDM2 in fear memory consolidation by increasing synaptogenesis in the PL-BLA projecting neurons.

Keywords: Epigenetic, Conditioned Fear Memory, Brain Circuitry, Prelimbic Cortex, Basolateral Amygdala

Disclosure: Nothing to disclose.

P37. Access to Neighborhood Opportunity as a Moderator of Anxiety and Irritability Symptom Severity and Impairment in a Large Transdiagnostic Sample of Youth

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Background: Anxiety and irritability represent two commonly occurring and severe childhood psychiatric symptoms present across a wide range of disorders. While a substantial amount of work focuses on internal factors that underly the emergence and expression of anxiety and irritability, little is known regarding the impact of external factors on anxiety and irritability symptom severity and resulting impairment. Access to quality neighborhood resources is a critical external feature that has known effects on childhood development. However, it remains unknown whether lack of neighborhood opportunity and access to quality resources may exacerbate the symptoms of anxiety and irritability and make them more impairing. In which case, a one size fits all treatment approach may not adequately help all children. In order to better understand how external factors impact childhood anxiety and irritability, the current study presents preliminary analyses of the moderating effect of access to neighborhood resources on the relationship between anxiety and irritability severity laying the groundwork for analyses examining structural neural correlates.

Methods: 582 community referred children (Age $M(SD) = 13.35$ (9.37) years, 49.5% male) with a wide range of childhood psychiatric disorders including anxiety disorders ($n = 245$), attention deficit hyperactivity disorder ($n = 78$), disruptive mood dysregulation disorder (including subthreshold symptoms, $n = 171$), or no psychiatric is disorder ($n = 76$) were recruited to participate in a larger research protocol at the National Institute of Mental Health. For each participant we measured access to neighborhood opportunity using the Childhood Opportunity Index (COI). The COI is a composite score that captures a range of neighborhood level features that impact childhood development including education, health and environment, and social and economic features. Scores represent the nationally normed percentile The COI values used in the current study were nationally normed with values representing the percentile for each census tract, $M(SD) = 83.130(20.051)$. The parent-report affective reaction index was used to measure irritability, $M(SD) = 4.360(3.885)$, with scores ranging from 0 to 64. The parent-report screen for child anxiety relation emotional disorders was used to measure anxiety, $M(SD) = 20.646(14.460)$ with scores ranging from 0 to 12. Higher scores represent higher levels of symptom severity. Lastly the clinical global assessment scale was used to measure impairment, $M(SD) = 59.56(16.459)$, with lower scores representing higher levels of impairment. Scores range from 0 to 100.

Results: To investigate whether the relationship between symptom severity (i.e. anxiety/ irritability) and impairment were moderated by COI we conducted two independent multiple regression models predicting impairment with SES, Race, and Ethnicity entered as covariates. For this model, the size of our sample is adequately powered to detect effects of Cohen's $D \geq 0.275$ (power = 0.80, alpha = 0.05). In our first model, we included irritability, COI, and the interaction between the two as predictors. Results revealed no significant interaction effect, b = -0.0003 CI95 [-0.0012-0.0006], $t(575) = -0.655$, $p = 0.513$, and thus no evidence for a moderation effect of COI on the relationship between irritability and impairment such that higher levels of irritability were associated with higher levels of impairment, b = 0.121 CI95[0.045-0.197], $t(575)$

$= 3.115$, $p = 0.002$, regardless of level of access to opportunity. For our second model, we included anxiety, COI, and the interaction between the two as predictors. Results revealed a moderation effect of COI on the relationship between anxiety and impairment, b $=$ -0.005 CI95[-0.010-0], $t(575) = -1.985$, $p = 0.048$, such that while anxiety symptoms were associated with greater impairment all levels of COI greater, this effect was largest at higher COI percentiles. Additional analyses will be conducted examining structural neural correlates of the interaction effect between anxiety symptom severity and COI. We will specifically examine neural circuits mediating stress with region of interest analyses targeting amygdala and hippocampal gray matter volume.

Conclusions: This is the first study to examine the influence of neighborhood level access to opportunity as a moderator of the relationship between symptom severity and impairment in a large sample of transdiagnostic youth. Our results indicate that the relationship between anxiety but not irritability symptom severity and impairment was moderated by neighborhood access to opportunity. Anxiety levels were more strongly associated with impairment for children living in neighborhoods with high access to opportunity and children with low access to opportunity exhibited relatively more impairment when levels of anxiety were low. This suggests that for children living in neighborhoods with relatively low access to opportunity, treatment of anxiety alone may be insufficient to address underlying impairment. Future work in this area is essential for creating more effective treatments for children from all neighborhoods.

Keywords: Anxiety, Environmental Risk Factors, Pediatric Irritability

Disclosure: Nothing to disclose.

P38. Association of Astrocyte Derived Exosome Cytokines and PTSD Symptoms in Veterans

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Background: Growing evidence suggests inflammation plays a role in trauma-related psychiatric disorders. Studies suggest PTSD is associated with altered immune protein levels. Little is known, however, about the relationship between central and peripheral inflammation in driving PTSD.

Methods: To specifically probe the relationship between the central nervous system (CNS) and peripheral inflammation, we isolated astrocyte-derived exosomes (ADEs) from peripheral blood plasma, in samples from subjects with and without PTSD ($N = 32$). After exosomal lysis, cargo protein cytokines, in addition to plasma cytokine levels, were quantified using multiplex enzyme-linked immunosorbent array plates. These cytokines were compared to clinical measures of PTSD using the PCL-5 and PHQ9.

Results: We found modest detection of some but not all cytokines as exosome cargo in ADEs, including IL-2, IL-6, IL-1β TNFα, and IFNγ. Most cytokines from ADEs did not correlate significantly with plasma cytokine levels (ρ ranging from 0.059 - 0.570), except for IL-2 measured from both plasma and ADEs (ρ$=$ 0.498, $R\text{^}2 = 0.170$, $p = .004$). We detected a significant relationship between anhedonia and IL-1β and IL-2 levels in ADEs (ρ$=$0.493, $p < 0.01$; ρ$=$0.489, $p < 0.01$, β corrected for 5 cytokines). Moreover, subjects endorsing the highest level of anhedonia exhibited significantly greater cytokine cargo compared to groups that did not endorse anhedonia (~50x IL-1β increase: $F(1,31)>3.60$, $p = 0.005$, and ~6x IL-2 increase, $F(1,31)>3.20$, $p = 0.009$; $p < 0.01$, Dunnet's post hoc test comparison to a 0 anhedonia score).

Conclusions: Our findings that few plasma cytokines appear to correlate with cytokines isolated from ADEs, suggests that ADE cytokines may represent a tissue-specific signature of CNS immune dysregulation. These exploratory findings highlighting the association between ADE cytokine levels and anhedonia underscore that ADE's may hold promise to identify immune dysfunction in neuropsychiatric disorders.

Keywords: PTSD, Immune Biomarkers, Brain-Enriched Exosomes, Cytokines

Disclosure: Nothing to disclose.

P39. Prepronociceptin-Expressing Neurons in the Extended Amygdala Track Relative Location of Aversive Odors

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Background: Motivational states consist of behavioral and physiological components controlled by multiple brain regions. An integral component of this neural circuitry is the bed nucleus of the stria terminalis (BNST), a part of the extended amygdala. Recently we found prepronociceptin-expressing neurons in the BNST (BNST-Pnoc neurons) modulate rapid changes in physiological arousal upon presentation of motivationally salient stimuli (Rodriguez-Romaguera et al., 2020). Pupillometric assessment combined with two-photon calcium imaging in head-fixed animals demonstrated that BNST-Pnoc neuronal responses directly correspond with rapid increases in pupillary size when mice are exposed to both aversive (TMT predator odor) and rewarding (peanut oil) odors. However, the response dynamics of BNST-Pnoc neurons involved in encoding behavioral response to the same motivationally salient stimuli remains unknown. Here, we sought to understand the encoding properties of BNST-Pnoc neurons when freely moving mice are exposed to salient odors.

Methods: In the present study, we used cell-type-specific viral constructs combined with calcium imaging approaches to assess response dynamics of BNST-Pnoc neurons. To visualize activity of individual BNST-Pnoc neurons, head mountable miniature microscopes were implanted in freely moving mice exposed to either TMT or peanut oil in their homecage ($n = 4$-6/group, 2 groups). To test if BNST-Pnoc neuronal activity is necessary to modulate approach or *m* avoidance behavior to salient odors, we optically inhibited BNST-Pnoc neurons when mice were presented TMT and peanut oil in their homecage ($n = 8$-10/group, 2 groups). Lastly, we performed optical stimulation to drive activity of BNST-Pnoc neurons to determine if this was sufficient to increase time spent near TMT and peanut oil ($n = 6$-8/group, 2 groups).

Results: Calcium-imaging analysis showed that population activity of BNST-Pnoc neurons increased in mice exposed to TMT, as compared to peanut oil ($p = 0.04$). Furthermore, the activity of individual BNST-Pnoc neurons correlated significantly more with proximity to odor source when mice were exposed to TMT, as compared to peanut oil ($p = 0.01$). This suggest that BNST-Pnoc neurons preferentially encode relative location of aversive odors. Photoinhibition of BNST-Pnoc neurons decreased the amount of time spent in the odor zone when mice were exposed to TMT($p = 0.02$), but not peanut oil ($p = 0.89$). In contrast, photoactivation of BNST-Pnoc neurons did not alter time in the odor zone for TMT ($p = 0.71$) or peanut oil ($p = 0.87$). Taken together, our data suggest that BNST-Pnoc neuronal activity is necessary, but not sufficient, for mice to explore the relative location of aversive odors.

Conclusions: We previously showed that BNST-Pnoc neurons encode for arousal responses to motivationally salient odors. Here,

this study demonstrates that activity of BNST-Pnoc neurons correspond with the proximity to the source of an aversive odor. Additionally, photoinactivation results suggest that BNST-Pnoc neurons are necessary for mice to engage with aversive odors. Taken together, our new data further suggests that manipulating BNST-Pnoc neurons might be a promising target for disorders defined by hyperarousal and excessive avoidance behavior.

Keywords: Anxiety and Stress, Hyperarousal, Extended Amygdala, in vivo Calcium Imaging, Optogenetics

Disclosure: Nothing to disclose.

P40. The Endocannabinoid 2-Arachidonoylglycerol Mediates the Specificity of Fear Memories

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Background: Post-traumatic stress disorder (PTSD) is a psychiatric disorder that develops following exposure to a traumatic event. Its lifetime prevalence is estimated to be 6.8%. Fear responses to stimuli that were previously present during a traumatic experience enables survival. However, in PTSD, patients may experience generalization of their fear responses even to otherwise safe stimuli. The endocannabinoid (eCB) system is a retrograde neurotransmitter system that has been implicated in regulating fear and anxiety. 2-arachidonoylglycerol (2-AG), one of the major centrally active eCB lipids, is thought to mediate resiliency to traumatic experiences. We aimed to determine if and how 2-AG signaling may be involved in mitigating generalization of fear.

Methods: We used a mice model of fear-conditioning in combination with systemic injections of a drug (DO34) that blocks synthesis of 2-AG. For fear-conditioning, mice were exposed to 8 tone presentations (CS+), each co-terminating with a brief electric foot-shock. The following day (Day2), a memory recall test was conducted by exposing mice to alternating presentations of 2 novel tones (NT) and 2 CS+ tones. Mice were injected with DO34 (50 mg/kg) intraperitoneally either 2 hours prior to Day1 or Day2. Fear responses were measured by quantifying the percentage of time during tone presentations that the mice exhibit freezing (immobility except movement required for breathing). For contextual fear conditioning, mice were exposed to the conditioning context (CtxA) and 2 unsignaled shocks were delivered. This was repeated on Day 2. On day 3, mice were injected with DO34 or vehicle and exposed to CtxA or a novel context; freezing was quantified for the duration of the session. For our in vivo recording experiments, mice were injected with a viral vector expressing the calcium indicator GCaMP7f in the prelimbic cortex (PL) and a miniature GRIN lens above PL. Mice were allowed to recover and were habituated to having a miniaturized microscope attached to a baseplate sitting over the lens. Following habituation, mice were conditioned to tones as described above while simultaneously recording calcium activity using the minituarized microscope. The following day, mice were injected with either vehicle or DO34 and were exposed to NT and CS+ tones as described above. Individual calcium traces were extracted and peritone histograms were generated from the Z-scored data. This Z-scored data was further analyzed by classifying tone evoked activity changes (exceeding +/- 3 Z-scores).

Results: To address if 2-AG is involved in regulating fear generalization, mice were injected with DO34 either prior to fear conditioning ($n = 10$ per group) or fear recall ($n = 19$ and 16, vehicle and DO34 respectively). Mice injected with DO34 showed a significant increase in freezing only to novel tone presentations (all p's < 0.0338), but not to the CS+, suggesting that blocking 2-AG signaling enhances fear generalization to novel tones. To address whether 2-AG is involved in the regulation of other fear modalities, we conducted a similar experiment but this time using contextual fear conditioning. Injecting DO34 prior to contextual fear conditioning ($n = 14$ CtxA-vehicle, $n = 17$ novel context-vehicle, $n = 15$ CtxA-DO34, $n = 15$ CtxA-DO34) or recall ($n = 9$ CtxA-vehicle, $n = 9$ novel context-vehicle, $n = 9$ CtxA-DO34, $n = 10$ CtxA-DO34) led to increased freezing to the novel context only (all p's < 0.0269).

To address how fear generalization is represented at the neural level and how this representation is modified by reductions in 2-AG, we repeated our fear conditioning experiment while recording changes in single cell calcium activity. Our imaging data shows no difference in the average novel tone-evoked response between vehicle and DO34 groups ($n = 624$ and 617 neurons, vehicle and DO34 respectively). Focusing on neurons that significantly change their activity to the tone did not reveal any differences in magnitude between groups for either (+) responsive ($n = 103$ and 93 neurons, vehicle and DO34 respectively) or (-) responsive neurons ($n = 89$ and 58 neurons, vehicle and DO34 respectively). Interestingly, the proportion of neurons that respond to both CS+ and novel tones was significantly larger for the DO34 group (8.82% vs 16.39 %; chi square statistic = 7.7732, $p = 0.00530$) while the proportion of neurons that respond to the CS+ was smaller (32.35 % vs 20.56%; chi square statistic = 11.3122, $p = 0.00077$. Thus reducing 2-AG signaling leads to increased generalization and this in turn is associated with an increased proportion of PL neurons that signal equally to both CS+ and novel tones.

Conclusions: Our present data suggests that 2-AG signaling may be required for maintaining the specificity of fear memories. Conversely, 2-AG deficient states may increase the likelihood of developing pathological fear following a traumatic experience. Furthermore, reducing 2-AG leads to a larger proportion of PL neurons that fail to discriminate between CS+ and novel tones. Thus, discrimination between conditioned stimuli and novel stimuli is embedded in the PL and disrupting 2-AG signaling leads to overgeneralization, which in turn is reflected in a non-specific representation of the CS+ in PL.

Keywords: Fear Generalization, Endocannabinoid, In Vivo Calcium Imaging, Prelimbic Cortex, 2-AG

Disclosure: Nothing to disclose.

P41. The Learning of Spatial Locations Associated With Thermal Threat and Safety Requires Processing in Medial Prefrontal Cortical Regions and is Profoundly Affected by Social Isolation Stress

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Background: The ability of animals to learn and differentiate spatial locations associated with threat and safety is imperative for adaptive behavioral control to minimize potential aversive consequences. Growing evidence implicates distinct subregions of the medial prefrontal cortex (mPFC), such as the prelimbic (PL) and infralimbic (IL) divisions, in threat and safety learning and the regulation of behaviors associated to these functions. However, most studies have evaluated the role of PL and IL in threat and safety using Pavlovian paradigms involving discrete cues predicting either the delivery or omission of electric shocks, or instrumental paradigms requiring the initiation or suppression of actions to avoid electric shocks. Thus, the neural mechanisms underlying threat and safety learning during more naturalistic

paradigms and how they are affected during stress-induced disease-like states remain poorly understood.

Methods: In this study, we first describe a novel learning paradigm in mice in which we used thermal stimuli to simulate threat-like (~5°C) and safety-like (~30°C) zones within an acrylic apparatus. We then used a social isolation stress paradigm (2-week isolation period) to describe how a history of stress alters the ability of mice to learn about threat and safety locations. In addition, we used an optogenetic-mediated silencing strategy to examine the functional role of PL and IL during the novel task, and to evaluate their contribution during stress-related deficits.

Results: After a single 10-min training session in the task involving the threat (cold) and safety (warm) zones, mice kept exhibiting avoidance and seeking behaviors for these zones, respectively, during a 24-hr long-term memory (LTM) session in which the entire apparatus had a homogenous temperature (experimental group trained with the different temperatures vs. control group trained without the different temperatures; n's = 7-9; 71% vs. 14% time spent seeking the previously warm zone; $p < 0.001$). In an initial social isolation stress experiment, while this stressor did not affect behavioral performance during training (i.e., mice optimally distinguished the cold and warm zones), it produced a significant impairment in subsequent LTM (no-stress group vs. stress group, n's = 8; 76% vs. 50% time spent seeking the previously warm zone; $p = 0.039$). Interestingly, this stress effect was fully prevented with optogenetic silencing of the PL-mPFC during training (No-Stress YFP = 85%, Stress YFP = 31%, No-Stress ArchT = 83%, Stress ArchT = 76%; n's = 12-13; $p = 0.0005$). In contrast, preliminary findings indicate that the stress effect can be mimicked in no-stress controls receiving optogenetic silencing of the IL-mPFC during training (No-Stress YFP = 76%, Stress YFP = 48%, No-Stress ArchT = 33%, Stress ArchT = 38%; n's = 6; $p = 0.055$).

Conclusions: Collectively, these findings demonstrate that mice can optimally distinguish, learn, and remember spatial locations associated with naturalistic thermal threat and safety, and that the ability to form lasting memories for threat and safety locations is significantly affected by psychological stressors such as prolonged social isolation. Finally, our findings also demonstrate that the PL and IL divisions of the mPFC play major contributions for the learning of threat and safety locations and to mediate stress-related deficits.

Keywords: Fear, Anxiety and Stress, Avoidance and Escape, Amygdala, Hippocampus

Disclosure: Nothing to disclose.

P42. Ventromedial and Insular Cortical Volume Moderates the Relationship Between BDNF Val66Met and Threat Sensitivity

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Background: While the BDNF Val66Met polymorphism has been linked to various trauma and anxiety – related psychiatric disorders, limited focus has been on the neural structures that might modulate its relationship with objective measures of threat sensitivity. Therefore, we assessed whether there was an interaction of Val66Met polymorphism with brain area volumes previously associated with anxiety and PTSD, such as the ventromedial prefrontal cortex (vmPFC), insular cortex (IC), and dorsal and ventral anterior cingulate cortices (dACC and vACC), in predicting fear-potentiated psychophysiological response in a clinical sample of Veterans.

Methods: 110 participants engaged in a fear-potentiated acoustic startle paradigm and provided genetic and imaging data. Fear conditions included no, ambiguous, and high threat conditions (shock). Psychophysiological response measures included electromyogram (EMG), skin conductance response (SCR), and heart rate (HR).

Results: PTSD status, trauma history, and demographics were also assessed. There was an interaction of Met allele carrier status with vmPFC, IC, dACC, and vACC volumes for predicting SCR ($p <$ 0.001 for all regions). However, only vmPFC and IC significantly moderated the relationship between Val66Met and psychophysiological response (SCR).

Conclusions: The Val66met polymorphism may increase susceptibility to PTSD and anxiety disorders via an interaction with reduced vmPFC and IC volume. Future research should examine whether these relationships might be associated with a differential course of illness longitudinally or response to treatments.

Keywords: Anxiety and PTSD, BDNF Val66Met, Psychophysiology, Structural MRI

Disclosure: Nothing to disclose.

P43. Threat Imminence Reveals Distinct Links Among Anxiety, Anticipatory Physiological Response, and Cortical-Subcortical Intrinsic Functional Connectivity

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Background: Clinical observations and research emphasize excessive fear responding to anticipated threat as hallmark symptoms of anxiety disorders, leading to disruptive, maladaptive defensive behaviors.

The psychobiological mechanisms mediating these aberrant responses are incompletely specified, limiting mechanistic understanding and treatment development. Research in animals indicates that fear responses manifest as a function of threat imminence through conserved neural circuitry. Elucidating the temporal dynamics of fear responses could clarify the psychobiological mechanisms mediating excessive fears in anxiety, and identify potential biomarkers. Here, we examine whether pathological pediatric anxiety is associated with distinct patterns of threat-anticipatory psychophysiological response, and link these patterns to intrinsic functional connectivity as a potential biomarker for anxiety.

Methods: Participants were 50 youths (ages 8-17 years), including 25 youth with anxiety disorders and 25 healthy youth, who completed a paradigm in which skin-conductance (SC) data were recorded while noxious heat-pain anticipation was induced. SC data were averaged in successive bins separating anticipation of instructed highly-painful (threat) and non-painful (safety) heat cues and heat delivery. We tested the CueXImminenceXGroup interaction to examine differential patterns of threat-anticipatory responding. For a subset ($N = 36$), resting-state functional connectivity imaging data were available (10-minute scan, 3T scanner). Network-based analyses then identified functional networks in which connectivity correlated with magnitude of increasing response in anticipation of threat, and moderation of these associations by anxiety.

Results: A significant Cue X Imminence X Group interaction emerged, $F(3,144) = 7.55$, $p < 0.001$, $\eta\_p\text{^}2 = 0.14$. Follow-up analyses indicated greater increase in patients in physiological response in threat vs safety trials with outcome imminence, indicating distinct, aberrant dynamics of threat-anticipatory response. The magnitude

of threat-anticipatory response correlated significantly, $p = 0.035$ (network mass, FDR-corrected), with function in a network comprised of positive connectivity between ventromedial prefrontal cortex (vmPFC) with bilateral ventral hippocampus, basolateral amygdala, and central amygdala. Anxiety was found to moderate these associations, pFDR = 0.005, with stronger association in anxiety between vmPFC-hippocampus connectivity and physiological response. No sex effects were found.

Conclusions: These findings show, for the first time, that anxiety disorders are associated with aberrant temporal dynamics of anticipatory physiological responding. Further, anticipatory response magnitude was associated with intrinsic functional connectivity within a specific cortical-subcortical network implicated in animal research on fear, with moderation by anxiety of a subnetwork within this circuit. These findings reveal aberrant evolving of fear processes in anxiety, and identify a potential biomarker for such processes which could guide circuit-specific treatment development.

Keywords: Anxiety, Brain, Developmental Psychopathology

Disclosure: Nothing to disclose.

P44. Associations of Leptin, Ghrelin, Psychiatric Disorders and Childhood Adversity in Healthy Young Adults

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Background: Childhood adversity is a major risk factor for a range of health problems, including psychiatric conditions, diabetes, and cardiovascular disease. Stress-related changes in health behaviors, such as diet, suggest a role for endocrine factors that influence intake. Leptin and ghrelin are hormones responsible for appetite regulation and may contribute to the relationship of early adversity, psychiatric function, and cardiometabolic health. This study examined levels of leptin and ghrelin, adversity, and psychiatric disorders in a sample of healthy young adults with and without parental loss and childhood maltreatment.

Methods: Young adults ages 18-40 ($N = 227$; 67% female) were recruited via community advertisements and assessed for eligibility via phone screen. Participants with early life stress ($N = 129$) experienced childhood maltreatment, and a subset ($n = 97$) also had parental loss. Among early life stress participants $n = 67$ had a current psychiatric disorder. Control participants ($N = 98$) had no maltreatment or parental loss or psychiatric disorders. Standardized interviews and self-reports assessed demographics, adversity, medical/psychiatric history, health behaviors, and anthropometrics including body mass index (BMI) were measured. Participants had no acute or chronic medical conditions, current medications, bipolar or psychotic disorders. Fasting blood samples were assessed for leptin and total ghrelin using the Bio-Plex Pro Human Diabetes Panel (Bio-Rad Laboratories, Hercules, CA, USA).

Results: Point biserial correlations revealed that leptin had significant positive associations with adversity ($r = .16$, $p = .016$) and psychiatric disorders ($r = .24$, $p < .001$) and ghrelin had significant negative associations with adversity ($r = -.18$, $p = .01$) and psychiatric disorders ($r = -.27$, $p < .001$). In a linear model including covariates age and sex, adversity ($F(223,3) = 6.16$, $p = .01$, adj. $R2 = .30$) and sex ($p < .001$) were significant predictors of leptin. When added to the model, current psychiatric disorders ($F(221,4) = 4.32$, $p = .04$, adj. $R2 = .31$) and sex ($p < .001$) were significant and the relationship of adversity ($p = .31$) with leptin was abolished. When BMI was added, neither adversity ($p = .96$) nor psychiatric disorders ($p = .27$) were significant, and BMI ($F(220,5) = 143.87$, $p < .001$, adj. $R2 = .58$) and sex ($p < .001$) each significantly predicted leptin. In a model controlling for age and sex, adversity ($F(223,3) = 8.53$, $p = .004$, adj. $R2 = .06$) and sex ($p = .01$) were significant predictors of ghrelin. When added to the model, current psychiatric disorders ($F(221,3) = 12.09$, $p = .001$, adj. $R2 = .11$) and sex ($p < .001$) were significant, and adversity ($p = .51$) no longer predicted ghrelin. After BMI was added, BMI ($F(222,4) = 43.30$, $p < .001$, adj. $R2 = .21$), sex ($p < .001$), age ($p = .01$) and psychiatric disorders ($p = .004$) were each significant, and adversity ($p = .93$) was not significant.

Conclusions: These findings demonstrate that early adversity is positively associated with leptin and negatively associated with ghrelin in healthy young adults. This relationship remained significant when controlling for age and sex and was abolished when controlling for psychiatric disorders and BMI. The relationship of psychiatric disorders and ghrelin remained significant when controlling for BMI. Associations with early life adversity appeared to be due to effects of current psychiatric disorders. These findings are not confounded by medical comorbidities or medications, as participants are healthy young adults. Relationships between early adversity, psychiatric functioning, leptin, and ghrelin will be further examined and discussed. Future longitudinal studies will be needed to investigate the temporal and possibly causal relationships between these factors.

Keywords: Leptin, Ghrelin, Early Life Stress, Childhood Adversity, Cardiometabolic Risk

Disclosure: Nothing to disclose.

P45. Fkbp5 Expression Increases in Mouse Serotonin Neurons Following Repetitive Mild TBI

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Background: Serotonin is a key mediator of stress-related disorders and novel therapeutic targets within serotonin neurons are needed to combat these disorders. We previously identified numerous sex- and stress-regulated genes in serotonin neurons, including Fkbp5, which codes for the glucocorticoid receptor co-chaperone protein FKBP51, in a forced swim model of acute stress. Fkbp5 polymorphisms are associated with risk of psychiatric problems including depression, post-traumatic stress disorder (PTSD), and suicide. Repetitive mild traumatic brain injury (mTBI), which is common in civilians and highly prevalent among military service members, is also associated with the above psychiatric sequelae. Given the high comorbidity between repetitive mild traumatic brain injury and these psychiatric sequelae and the clinical relevance of this blast injury model, we sought to investigate the expression of Fkbp5 in a mouse model of blast.

Methods: We examined how a history of repetitive (3×) blast exposure (blast-mTBI) affects Fkbp5 expression using an established mouse model of blast-mTBI. Fkbp5 mRNA expression in the dorsal raphe serotonin neurons was examined by colocalization of Fkbp5 and Tph2 signals at both acute (4 hours) and chronic (6 months) post-blast using RNAscope.

Results: Following blast injury, both the number and percentage of serotonin neurons expressing Fkbp5 increased, with greatest increases seen in absolute number of Tph2 + /Fkbp5+ coexpressing cells at chronic timepoints across all levels of dorsal raphe (~1.5 fold), as well as proportion of serotonin neurons expressing Fkbp5 in caudal dorsal raphe at acute time points (more than two-fold). Levels of Fbkp5 gene mRNA expression in serotonin neurons appear to increase as well, with largest increases seen in caudal dorsal raphe at acute time points and rostral dorsal raphe at chronic timepoints. Interestingly, the number of Tph2-expressing neurons following mTBI appears to decrease transiently (by about half), then increase back to baseline

levels at chronic time points. This unexpected change in Tph2 mRNA expression partially mediates the change in proportion of serotonin neurons that coexpress Fkbp5.

Conclusions: Our results support the growing body of evidence linking Fkbp5 to stress-related disorders, provide an important follow up to our previous findings linking Fkbp5 to serotonin, and to our knowledge represent the first evidence linking Fkbp5 to mTBI. We are now examining potential associated between Fkbp5 and adverse physiological and behavioral outcomes. These findings support the potential for a novel therapeutic target for stress-related disorders which are currently treated with drugs that target the serotonin system.

Keywords: Serotonin, FKBP5, TBI, RNAscope fluorescence in situ hybridization, glucocorticoid

Disclosure: Employee: Consultant (Spouse)

P47. Electronic Multiplexed Neurochemical Monitoring

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Background: While multiplexed tools for monitoring in vivo electrophysiology have been extensively developed, technologies for recording multiple neurotransmitters simultaneously are more limited. Nevertheless, chemical communication via a large variety of neurotransmitters plays a central role in brain information processing

Methods: We developed implantable aptamer field-effect transistor (FET) neuroprobes for monitoring neurotransmitters. Silicon-based neuroprobes were fabricated using high-throughput micro-electro-mechanical-system (MEMS) technologies, where probes with shanks of either 150 μm or 50 μm widths and thicknesses were fabricated on each 4 inch Si wafer. Nanoscale FETs with ultrathin (~3 nm) In2O3 semiconductor films were prepared using a scalable sol-gel process. The In2O3 surfaces were coupled with synthetic oligonucleotide receptors (aptamers) to recognize and detect the neurotransmitter serotonin.

Results: Aptamer-FET neuroprobes enabled femtomolar serotonin detection limits in the brain and spinal cord with minimal biofouling. Stimulated serotonin release was detected in vivo. We monitored serotonin, dopamine, pH, and temperature on the multiplexed devices.

Conclusions: Our devices open opportunities to integrate aptamer-FET sensors with other types of Si-based implantable probe measurements for integrated neural activity recordings at high spatiotemporal resolution and to advance our understanding of brain function.

Keywords: Serotonin, Dopamine, In Vivo, Multi-electrode Arrays

Disclosure: Nothing to disclose.

P48. Peripheral Nuclear Factor-Kappa B Pathway Activity in Women With Type 2 Diabetes Mellitus is Associated With Posttraumatic Stress Disorder and Depressive Symptom Severity, and Exposure to Early Life Stress

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Background: Inflammatory mediators as well as molecular signaling pathways that regulate inflammation, in particular nuclear factor-kappa B (NF-κB), have been implicated in the pathophysiology of stress-related psychiatric disorders, including major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Considerable evidence also suggests that inflammatory mediators and NF-κB are dysregulated in those with exposure to adverse childhood experiences (ACEs). However, the majority of research to date has been conducted in medically healthy research participants or participants with mixed comorbid physical illnesses. Accordingly, the goal of the present study was to determine the relationship between acute psychosocial stress-induced NF-κB pathway activation in peripheral blood mononuclear cells (PBMCs) and stress-related psychiatric illness (i.e., PTSD and MDD) symptom severity in trauma-exposed women with type II diabetes mellitus (T2DM).

Methods: PBMCs were collected from $N = 70$ women (ages 28-65, mean age 50.9, $SD = 8.9$) before, during, and after challenge with the Trier Social Stress Test (TSST). PTSD symptom severity was assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), MDD symptom severity with the Beck Depression Inventory (BDI), and childhood trauma with the Childhood Trauma Questionnaire (CTQ). We quantified nuclear factor-κB (NF-κB) pathway activity in PBMCs using DNA-binding enzyme-linked immunosorbent assay (Active Motif). NF-κB responsiveness to acute psychosocial stress was aggregated as area under the curve from ground (AUCg) using the trapezoidal method. Associations between NF-κB AUCg and phenotypic variables in $N = 70$ participants were examined using Spearman's rank correlation coefficients, because outcomes were not normally distributed (Shapiro-Wilk).

Results: NF-κB responsiveness to the TSST (i.e., NF-κB AUCg) was positively associated with PTSD symptom severity (CAPS-5 criterion B: intrusive symptoms [$r = .34$, $p = .014$], C: avoidance symptoms [$r = .30$, $p = .035$], and D: negative alterations in cognitions and mood [$r = .29$, $p = .035$] symptoms, but not criterion E: arousal symptoms) as well as MDD severity ($r = .25$, $p = .039$). NF-κB AUCg was also positively correlated with ACE exposure (i.e., CTQ total score) ($r = .25$, $p = .039$), as well as CTQ subscales of emotional abuse ($r = .33$, $p = .005$) and emotional neglect ($r = .27$, $p = .025$). We also noted associations between hemoglobin A1c and ACE exposure ($r = .29$, $p = .014$) and MDD severity ($r = .39$, $p = .001$).

Conclusions: These findings suggest that NF-κB responsiveness to acute psychosocial stress may be involved in the severity of symptoms of MDD and PTSD for women with T2DM, and that the same inflammation responsiveness may be exacerbated by exposure to early life stress. Early life stress exposure and stress-related psychiatric disorder severity may also drive dysregulation of blood glucose control in women with T2DM.

Keywords: Post Traumatic Stress Disorder, Depression, Early-Life Stress, Nuclear Factor Kappa B, Women

Disclosure: Nothing to disclose.

P49. Disruption of Memory Allocation by Stress: A Role for Parvalbumin Interneurons and Endocannabinoid Signaling

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Background: The ability to remember which cues in a particular environment predict threat, and which do not, is imperative for survival. Overgeneralisation of threatening cues, such that also neutral cues are perceived as threatening, may result in excessive anxiety-like behaviour, and is a core symptom in many anxiety-related disorders and PTSD. Stress may promote such over-generalisation of memory, and hence may instigate or amplify anxiety-disorders. The overarching objective of these studies is to decipher the key pathways that underlie stress-induced memory

generalisation at the level of behaviour, network dynamics and the cellular level, with a focus on inhibitory interneuron signalling.

Methods: Mice were exposed to corticosterone injections or acute restraint stress, and the specificity of memory during fear conditioning and reward learning was assessed. Using in vivo fibre photometry, opto- and chemogenetics and iDISCO we establish the underlying cell types and networks mediating these effects.

Results: After stress, mice show stronger memory generalization, both for memory with a positive and negative valence. In parallel, the lateral amygdala ensembles encoding for these memories are enlarged, and these enlarged ensembles were responsible for the generalized expression of the memories. Stress suppresses the activity of parvalbumin (PV) + -interneurons, and indeed the effects of stress on memory generalization and ensemble size could be prevented by activation of PV + -interneurons, while inhibition of PV + -interneurons mimicked the effects of stress. We next show that endocannabinoid signalling within the lateral amygdala, which is directly modulated by stress, underlies the stress effects on interneurons and memory generalization.

Conclusions: Stress results in generalized memory expression, and disrupted memory allocation, which is prevented by modulating PV + -interneuron activity. We propose that endocannabinoid signalling mediates these effects. Understanding these neurobiological mechanisms of stress-induced memory generalisation may be a first step towards the development of novel treatment strategies for anxiety-related pathologies.

Keywords: Acute Stress, Glucocorticoids, Memory, Endocannabinoids, PTSD

Disclosure: Nothing to disclose.

P50. Ventral Hippocampal Neural Ensemble Activity Modulates (R,S)-Ketamine's Prophylactic Fear Buffering Effects

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Background: Stress can lead to a wide variety of psychiatric illnesses such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, some individuals are more susceptible to developing psychopathology in response to stress, while others exhibit stress resilience, but the research into the underlying neurobiology of this phenomenon is still in its infancy. We have previously shown that (R,S)-ketamine can act as a prophylactic against stress-induced behavioral despair when administered 1 week prior to various stress models and can buffer fear expression in mice. We have also demonstrated that this prophylaxis is partially mediated by activity in ventral CA3 (vCA3) region of the hippocampus. Furthermore, dysregulated neural activity, specifically in regions such as the ventral hippocampus, is a hallmark of MDD and PTSD pathology. However, previous studies have only assessed (R,S)-ketamine's prophylactic effects at single timepoints. No studies have demonstrated how neural activity changes during prophylactic (R,S)-ketamine treatment, during the encoding of a stressor, or during the expression of fear.

Methods: Here, we used Inscopix nVoke's in vivo calcium imaging system in freely moving mice to determine the neural dynamics in vCA3 and vCA1 that may be underlying prophylactic (R,S)-ketamine efficacy. A GCaMP6f virus was injected into vCA3 or ventral CA1 (vCA1) of male 129S6/SvEv mice at 7 weeks of age, and subsequently a GRIN lens was implanted over the injection site. Four to 6 weeks later, a baseplate was installed to visualize calcium transients, and 1 week later, calcium activity was recorded during and immediately following saline or (R,S)-ketamine (30 mg/kg) administration ($n = 4$-5 mice per group). One week following drug administration, mice underwent contextual fear conditioning (CFC). Five days later, mice were re-exposed to the CFC training context to assay memory retrieval and were then tested in assays to measure avoidance behavior and behavioral despair. Calcium activity was recorded during each of the behavior sessions. Imaging was motion corrected using the Inscopix Data Processing software, and transient data was obtained using the enhanced constrained non-negative matrix factorization (CNMF-E) algorithm for one-photon data. All data were analyzed in Python using nonparametric statistical tests such as the Mann-Whitney U test and the Friedman ANOVA.

Results: As we have shown previously, (R,S)-ketamine buffered fear expression following CFC ($p = 0.0376$), but did not alter avoidance behavior ($p = 0.3220$). Immediately after (R,S)-ketamine administration, calcium transient rates were decreased in vCA3 ($p < 0.0001$), but increased in vCA1 ($p < 0.0002$). During CFC encoding and context re-exposure, (R,S)-ketamine administration resulted in decreased calcium transient rates in vCA3 and increased calcium transient rates in vCA1 ($p < 0.0001$). During CFC encoding, there was also a significantly reduced percentage of shock-selective cells only in vCA3 of (R,S)-ketamine-treated mice ($p < 0.0001$). Graph theory network analysis revealed that ventral hippocampal correlated activity (measured by clustering coefficient and degree centrality was decreased in both vCA3 and vCA1 of (R,S)-ketamine-treated mice both during CFC encoding and context re-exposure ($p < 0.0001$). Correlated activity was also decreased in both vCA3 and vCA1 during behavioral despair and avoidance behavior assays ($p < 0.0001$).

Conclusions: Here, we report that (R,S)-ketamine differentially modulates vCA3 and vCA1 during fear memory expression, blunts the stress response in vCA3, and decreases overall correlated activity in the ventral hippocampus. These data suggest that (R,S)-ketamine's resilience-enhancing fear buffering effects may depend on differential activity changes in the ventral hippocampus throughout treatment and behavioral expression. In particular, prophylactic (R,S)-ketamine may be reversing deleterious hyperactivity and hyper-connectivity in vCA3 induced by stress. These results also propose a potential node in the brain to target in order to increase stress resilience in susceptible populations.

Keywords: (R,S)-Ketamine, In Vivo Calcium Imaging, Ventral Hippocampus, Contextual Fear, Prophylactic

Disclosure: Nothing to disclose.

P51. mGluR5 and Cognitive Functioning: In Vivo Examination in Posttraumatic Stress Disorder and Major Depression

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Background: A robust literature supports the role of the metabotropic glutamate receptor type 5 (mGluR5) in cognitive functioning. mGluR5 is also implicated in the pathophysiology of posttraumatic stress disorder (PTSD) and major depressive disorder (MDD), which are characterized by cognitive impairment. However, the relationship between mGluR5 and cognition in MDD and PTSD has not yet been directly investigated. To address this gap, we examined the relationship between in vivo mGluR5 availability and cognition in individuals with PTSD, MDD, and matched healthy adults (HA).

Methods: Individuals with PTSD ($N = 28$ MAge = 36.7), MDD ($N = 21$, MAge = 38.7), HA ($N = 28$, MAge = 39.5) were recruited from the community and matched for age, gender, and smoking status. Participants completed an MRI and 18F-FPEB PET scan, psychiatric and cognitive assessments.

Results: Multivariate analyses of variance were performed with mGluR5 availability (VT) in five fronto-limbic regions as dependent variables, and diagnosis, cognitive domain score performance, and diagnosis*cognitive domain score as independent variables. Only the interaction of diagnosis* attention was significant ($F4,64 = 3.011$, $p = .024$). More specifically, higher mGluR5 availability was associated with poorer performance on tests of attention in the PTSD group (r's = -.41 to-.44, p's = .016-.028), while the opposite was true in MDD (r's = .59 to .65, p's = .002-.006, no significant effect in the hippocampus). mGluR5 availability was unrelated to cognitive domain score performance in the HA group.

Conclusions: We observed a significant relationship between fronto-limbic mGluR5 availability and performance on tests of attention in individuals with MDD and PTSD. This finding aligns with animal work showing dysregulation in mGluR5 in cognitive functioning. The nature of this relationship differed as a function of diagnosis. These results suggest that interventions targeting this receptor may help bolster cognitive difficulties, but highlight the potential importance of employing different mGluR5 directed treatment strategies in MDD and PTSD.

Keywords: PET Imaging Study, mgluR5, PTSD, MDD, Cognition

Disclosure: Nothing to disclose.

P52. Neuropeptide Plasticity Underlying Cue-Dependent Aversive Learning

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Background: Animals need to respond to future threats and salient information for survival. Integration of excitatory and modulatory information on motivational brain circuits, such as the Nucleus Accumbens (NAc), prepares an animal for this response. However, the circuit and synaptic mechanisms in the NAc that may underlie this salience processing are not known. We recently discovered the neuropeptide substance *P* produces acetylcholine-dependent, excitatory long-term potentiation (LTP) selectively on NAc core dopamine 2 (D2) receptor expressing medium spiny neurons (MSNs). Substance *P* is released in response to salient rewarding and aversive information and, therefore, this plasticity provides a potential synaptic mechanism for processing salient information in the NAc. We aimed to test the hypothesis that NAc core substance P plasticity, via cholinergic signaling, is required for learning about salient cues predicting aversive stimuli.

Methods: To determine how aversive learning promotes cellular and synaptic changes in the NAc MSNs and cholinergic neurons, transgenic (Dyn-Cre, A2a-Cre, or ChAT-Cre) or wild-type mice were subjected to a Pavlovian fear conditioning paradigm. Contextual and cue-dependent freezing was analyzed in all mice. NAc c-fos expression was used as a marker of neuronal activity and was quantified in a cell-type specific manner following contextual and cue recall ($N = 10$). In this experiment, a latent inhibition procedure was used prior to conditioning to determine how this NAc activity is involved in behavioral salience. To further determine the role of NAc MSN subtype activity, optogenetic inhibition of MSN subtypes was performed during cue recall ($N = 13$). To determine the role of substance P signaling in aversive learning, a CRISPR-Cas9 conditional knockout of the main receptor for substance P, the neurokinin 1 receptor (NK1R), ($N = 28$) or pharmacological inhibition of the NK1R was used ($N = 42$). Furthermore, slice physiology was performed from NAc slices to examine for signatures of substance P plasticity (for each experiment: $n = 11$-20 cells from $N = 6$-8 mice). Finally, to examine acetylcholine dynamics, the GRAB-ACh3.0 sensor was utilized, and signals were analyzed across different phases of conditioning and recall.

Results: Diminishing salience of the cue with latent inhibition decreased expression of the activity marker c-fos selectively in NAc core D2-MSNs in response to the cue ($t(10) = 3.431$, $p < 0.01$), which strongly correlated with freezing behavior ($r = 0.854$, $p < 0.001$). This c-fos difference was not observed in NAc core D1-MSNs or in NAc shell MSNs. In accordance with this finding, optogenetic inhibition of NAc core D2-MSNs reversibly blocked freezing in halorhodopsin but not eYFP expressing mice (halo/eYFP X light on/off: $F(1,11) = 12.29$, $p < 0.001$). Systemic administration of a NK1R antagonist ($t(40) = 3.801$, $p < 0.001$) during conditioning or knockout of the NK1R in NAc core cholinergic interneurons ($t(26) = 3.332$, $p < 0.01$) suppressed cue-dependent freezing without affecting contextual freezing, suggesting NAc core NK1Rs are necessary for cue-dependent conditioning. Following fear conditioning, D2-MSNs from mice that received cue/shock conditioning, but not the cue alone displayed signatures of substance P plasticity including: inward rectification of AMPA receptor currents (holding potential X current: $F(2,20) = 4.568$, $p < 0.05$), increased calcium-permeable AMPA receptor currents ($t(9) = 2.692$, $p < 0.05$), and increased amplitude but not frequency of spontaneous excitatory post-synaptic currents ($t(15) = 2.717$, $p < 0.05$). We are currently still investigating acetylcholine release dynamics and the necessity of acetylcholine release in promoting neurokinin-dependent plasticity.

Conclusions: These results suggest NAc core substance P and cholinergic signaling drives plasticity and D2-MSN activity that is required for learning about cues predicting aversive outcomes. Suppressing substance P signaling and plasticity likely mimics suppression of salient cues predicting aversive stimuli. This work unveils an undiscovered role for the NAc in salience processing and aversive learning which may underlie related symptoms in anxiety and mood disorders such as post-traumatic stress disorder and behavioral depression.

Keywords: Substance P, Fear Conditioning, Acetylcholine, Synaptic Plasticity, Dopamine Receptor Type 2-Expressing Striatal Medium Spiny Neuron

Disclosure: Nothing to disclose.

P53. Vagal Control Moderates the Association Between Endothelial Function and Avoidance Symptoms in PTSD

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Background: Individuals with PTSD are more likely to present with cardiometabolic diseases such as type-II diabetes mellitus (T2DM), and cardiovascular dysfunction has been implicated in this link. These impairing diseases disproportionately affect women and individuals exposed to chronic environmental stressors (e.g., community violence, poverty). We examined associations among PTSD, cardiovascular indices, and metabolic function among highly trauma-exposed Black women with T2DM.

Methods: Female participants ($N = 76$) were recruited for a follow-up study of stress and T2DM as part of the Grady Trauma Project. PTSD symptoms were assessed with the Clinician Administered PTSD Scale (CAPS-IV). Cardiovascular indices included heart rate (HR), blood pressure (BP), respiratory sinus arrhythmia (RSA), and endothelial function (assessed via flow-mediated dilation; FMD). Glucose homeostasis was used as an indicator of metabolic function; this was assessed using an oral glucose tolerance test.

Results: Of the cardiovascular indices, only FMD was significantly associated with PTSD (CAPS Avoidance symptoms; $\beta = -.37$,

$p = .042$), and glucose homeostasis ($\beta = -.44$, $p = .019$), controlling for age and body mass index. The association between FMD and PTSD Avoidance was moderated by RSA such that the effect of FMD was only significant at low levels of RSA (simple slopes $\beta = -.87$, $p = .004$).

Conclusions: Our results indicate that endothelial function is strongly related to PTSD and glucose homeostasis, over and above other cardiovascular measures (HR, BP, RSA). Further, our results suggest that low RSA may be a risk factor for the link between poor endothelial function and PTSD in women with T2DM.

Keywords: PTSD, Type-2 Diabetes, Cardiovascular Physiology, Metabolic Function

Disclosure: Nothing to disclose.

P54. Preliminary Evidence That Occasionally Reinforced Extinction Reduces Acquisition of Novel Threat Responses in Patients With Pathological Anxiety: Results From a Pilot Study

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Background: Individuals with clinical anxiety are often treated with exposure-based therapies, which are thought to utilize extinction learning to overcome pathological fear associations. Yet, exposure therapies are not universally effective. This is presumed to be due in part to failures to generalize and retain extinction learning, limiting symptom improvement and leading to relapse. Recent work in rodents and healthy humans suggests that occasional presentations of the unconditioned stimulus (US; i.e., shock) during extinction trials can lead to enhanced reduction of threat responding (e.g., Bouton et al., 2004; Culver et al., 2018; Thompson et al., 2018). However, it remains unclear if these results would also be observed in individuals with anxiety disorders and whether reduced responding would extend to novel threat cues.

Methods: For the presented study, we analyzed data from a study of Pavlovian threat conditioning among individuals with clinical anxiety. Participants acquired threat responses to a face image (conditioned stimulus; CS) which was paired with an electric shock (US). The parent study investigated active avoidance (employing behavioral control over threat cues) as a strategy to enhance safety learning and included participants in a control condition who were "yoked" to participants learning to actively avoid threat cues. Some participants in the active avoidance condition immediately learned to avoid the threat cue, whereas others continued to receive shocks while they learned the behavioral sequence needed to prevent the US. Control participants were administered the same number of shocks as the participant they were yoked to in the active avoidance condition. As a result, some of these yoked participants experienced simple extinction (repetition of the CS without US), while others experienced occasional presentations of the US during the first half of extinction trials. Thus, we utilized this convenience paradigm to test the effect of occasionally reinforced extinction in a clinical sample. Data came from 32 adults diagnosed with an anxiety-related condition via structured clinical interview (SCID-5). Specific diagnoses included social anxiety disorder ($n = 10$), OCD ($n = 14$), generalized anxiety disorder ($n = 7$) and panic disorder ($n = 1$). The sample was 60% female with mean age $M = 27.11$ (SD $= 7.5$). Skin conductance responses (SCRs) were acquired during four phases collected over two visits to the laboratory separated by 24 hours. Day 1 involved initial acquisition and extinction (simple versus occasionally-reinforced). Day 2 tested extinction recall (presentation of the CS without shock) as well as threat conditioning with a novel threat cue (novel acquisition). As in past work we calculated the Spontaneous Recovery Index (average change in SCR from extinction to recall) and the Novel Acquisition Index (average change in SCR from initial acquisition to novel acquisition).

Results: We compared those who experienced simple extinction ($n = 16$) to those who experienced occasionally-reinforced extinction ($n = 16$). Values on the Spontaneous Recovery Index were lower among the occasionally-reinforced extinction group ($M = -.05$, SD $= .24$) relative to the simple extinction group ($M = .05$, SD $= .14$), but did not achieve statistical significance, $t(30) = -1.46$, $p = .14$, Cohen's $d = .52$). Scores on the Novel Acquisition Index were significantly lower among the occasionally-reinforced extinction group ($M = -.17$, SD $= .19$) than the simple extinction group ($M = .01$, SD $= .27$), $t(30) = -2.14$, $p < .05$, Cohen's $d = .76$

Conclusions: Compared to those undergoing simple extinction, participants who experienced occasional presentation of the US during extinction had significantly less threat responding to a novel threat cue 24 hours later. Participants who underwent occasionally-reinforced extinction also had somewhat less spontaneous recovery of threat responses, but this finding did not achieve statistical significance, possibly due to small sample size. These results provide preliminary data that occasionally-reinforced extinction may lead to reduced threat responding in individuals with pathological anxiety, warranting future study in this area. Replication in a larger sample could lead to future directions to improve the potency of exposure based interventions as a way to overcome pathological fear associations.

Keywords: Anxiety, Exposure Therapy, Fear Conditioning and Extinction, Extinction Learning

Disclosure: Nothing to disclose.

P55. Methylphenidate Shifts the Relationship Between Non-Threat Reinforcement Learning and Neural Response During Fear Extinction

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Background: Individuals with anxiety disorders such as posttraumatic stress disorder (PTSD) exhibit altered fear conditioning and extinction related to dysregulation of dopamine (DA) and norepinephrine (NE) signaling and activity in neural regions such as the amygdala. Recent research has suggested that the DA and NE reuptake inhibitor methylphenidate (MPH) may be effective in increasing fear extinction, and may therefore be useful in the treatment of anxiety disorders. In parallel, advances in computational psychopharmacology have clarified the role of the catecholamines dopamine (DA) and norepinephrine (NE) in regulating reinforcement learning processes via the learning rate. However, the relationship between individual indices of fear extinction and reinforcement learning in non-threat contexts, and the effects of MPH on these indices, are poorly understood.

Methods: 18 healthy males participated in two experimental sessions in which either placebo or MPH 40 mg was administered. Each subject received both MPH and placebo in separate sessions in a crossover design, with order of medication and placebo randomized in double-blinded fashion. The subjects underwent a fear conditioning and extinction procedure with functional magnetic resonance imaging (fMRI). For each subject, percent signal change in a left amygdala region-of-interest was extracted for the difference between the fear associated stimulus (CS+) and neutral stimulus (CS-) during extinction. Subjects also completed a reinforcement learning task outside the scanner with 180 total trials across 3 blocks. On each trial, subjects attempted to predict the location of a target stimulus out of 3

possible locations. Stimulus location was determined by a probability distribution in which one location was most likely to contain the target. At intervals of about 10 trials, the most likely target location changed, thereby rewarding a high learning rate on the task. A behavioral learning rate was calculated by computing the percentage of trials after an error trial on which subjects switched their first location choice to the location of the previous target. We calculated the correlation between behavioral learning rate on the reinforcement learning task with left amygdala activation during fear extinction in both the placebo and MPH conditions. Additionally, we used linear mixed effects models to assess the effect of MPH on amygdala activation after controlling for behavioral learning rate (a fixed effect) and subject (a random effect).

Results: Behavioral learning rate on the reinforcement learning task was positively correlated with left amygdala activation during fear extinction in both the placebo ($r = .55$, $p = .02$) and MPH ($r = .51$, $p = .03$) conditions. MPH reduced left amygdala activation after controlling for behavioral learning rate and subject ($X2 = 7.79$, $p < .001$).

Conclusions: Learning rate on a non-threat reinforcement learning task is related to amygdala activation during fear extinction, suggesting that there is a fundamental relationship between these two forms of learning. MPH reduced left amygdala activation during fear extinction, thus shifting the relationship between learning rate and amygdala activation. The results may have implications for the assessment and treatment of learning dysregulation in both threat and non-threat contexts in anxiety disorders.

Keywords: Methylphenidate, Computational Reinforcement Learning Model, Anxiety and PTSD, Functional Neuroimaging, Fear Conditioning and Extinction

Disclosure: Nothing to disclose.

P56. Pharmacological Treatment With a Neurogenic Compound Improves Pattern Separation

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Background: The dentate gyrus of the hippocampus exhibits continued neurogenesis into adulthood in mice and humans. Adult hippocampal neurogenesis is elevated by interventions that improve affect and cognition, such as chronic antidepressant treatment, exercise, and environmental enrichment. In mice, directly increasing neurogenesis using inducible genetic expansion of surviving adult-born neurons has been shown to improve performance in a fear discrimination task. This ability to distinguish between two similar contexts with different risk potential, referred to as pattern separation, has relevance for anxiety, mood, and trauma-related disorders, and it is also an important aspect of cognition that degrades with aging. Here, we test whether chronic treatment with a novel neurogenic compound, RO6871135, can improve pattern separation. We also test whether this effect is dependent on increased neurogenesis by ablating neurogenesis with irradiation.

Methods: Young adult c57BL/6J male mice were administered 7.5 mg/kg of RO6871135 compound by daily oral gavage. For irradiation experiments, mice were anesthetized while the hippocampus was exposed to X-irradiation. Sham irradiation was performed with anesthesia but no X-irradiation exposure. Irradiated and sham mice were allowed to recover for 8 weeks prior to initiation of drug treatment. After 21 days of treatment with the active compound or the control vehicle, mice were behaviorally tested in a contextual fear conditioning task, followed by a contextual fear discrimination task. Successful fear discrimination was achieved when animals distinguished between the conditioned fear context "A" and a similar context "B" that was not paired with foot shock. On the days of behavioral testing, animals were gavaged after completion of testing to avoid any possible acute effects of the compound. At the conclusion of the experiment, brains were perfused for immunohistochemical staining and quantification of doublecortin. ($N = 8$-9 mice/group).

Results: Both vehicle and RO6871135-treated mice showed elevated and indistinguishable levels of freezing after the initial contextual fear conditioning. Both groups also displayed low levels of freezing in a novel and dissimilar context. Additionally, both groups showed comparable generalization between the two similar contexts at the beginning of fear discrimination testing. However, the RO6871135-treated mice successfully discriminated between the similar contexts by the fifth day of exposure to both contexts. There was a significant Day x Context interaction ($p < 0.005$) in the RO6871135-treated group, and post-hoc testing using Tukey's HSD indicated significant differences in freezing starting on the fifth day of context discrimination ($p < 0.005$). Vehicle-treated mice had no significant Day x Context interaction, meaning that they failed to show significant differences in freezing in the two similar contexts on any particular days. In irradiated mice, RO6871135 treatment did not produce an improvement in context discrimination, and their performance in the task was similar to other irradiated, vehicle-treated mice. Doublecortin staining was quantified to show effects of RO6871135 treatment on neurogenesis in the dentate gyrus.

Conclusions: We demonstrated that chronic pharmacological treatment with the neurogenic compound RO6871135 improved performance in a contextual fear discrimination task, a measure of pattern separation. This was in the absence of notable effects on baseline contextual fear conditioning or generalization. This improvement in pattern separation was not seen in irradiated mice treated with the compound, suggesting that the observed effects are indeed neurogenesis dependent. These findings support the idea that pharmacological enhancement of adult hippocampal neurogenesis could be a promising direction for the development of novel therapeutics for disorders characterized by impaired pattern separation. If unwanted off-target effects, such as proliferation of non-neuronal tissues, can be circumvented, this could represent a new class of medications for the treatment of anxiety, mood, trauma-related, and cognitive disorders.

Keywords: Neurogenesis Enhancers, Pattern Separation, Novel Antidepressant

Disclosure: Nothing to disclose.

P57. Social Network Features and Peer Victimization: Relationships With Inferior Longitudinal Fasciculus Fractional Anisotropy in Posttraumatic Spectrum Women

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Background: Several prior reports by our group and others have described white matter abnormalities in occipito-temporal white matter tracts including the inferior longitudinal fasciculus (ILF) in trauma-exposed adults. We previously reported lower fractional anisotropy (FA) in the left ILF in participants with posttraumatic stress disorder (PTSD) versus trauma-exposed controls (Olson et al., 2017), though in a subsequent report we found that lower FA was associated not with PTSD diagnosis but with childhood maltreatment exposure (Olson et al., 2020). Similarly, Choi et al.

(2012) found that lower ILF FA was associated with greater exposure to witnessing interparental violence. Because the ILF is involved in connecting medial temporal lobe structures involved in emotion and salience processing (amygdala, hippocampus) with visual processing regions, disruption in social information processing is one hypothesized consequence of ILF abnormalities. We recently reported that structural features of social networks are disrupted in trauma-exposed samples, and that this disruption is related to social anhedonia (Olson et al., 2021). In the present analysis, we hypothesized that self-reported childhood/adolescent maltreatment exposure (abuse, neglect, peer victimization) would be associated with lower ILF FA, and that lower ILF FA would be associated with disrupted social network features in adulthood.

Methods: Data were analyzed from a sample of 43 women (25 symptomatic posttraumatic spectrum, 18 non-trauma-exposed healthy control). Participants completed a retrospective self-report measure of childhood maltreatment (MACE: Maltreatment and Abuse Chronology of Exposure Scale), as well as self-report measures of social network structural features (Social Network Index), social anhedonia (Revised Social Anhedonia Scale), and, for trauma-exposed participants, posttraumatic symptom severity (PTSD Checklist for DSM-5). Primary analyses considered three social network features (social network size, diversity, and embeddedness), as well as three derived scores on the MACE (abuse: sum of physical and sexual abuse; neglect: sum of emotional and physical neglect and peer victimization: sum of peer-inflicted verbal and physical abuse). Additionally, participants completed diffusion tensor imaging (DTI) on a Siemens 3.0 T Prisma (TR, 3230 ms; TE; 89.20 ms; 107 directions). Data were preprocessed in FSL and automatic probabilistic tractography was performed using FreeSurfer's TRACULA to measure DTI metrics including fractional anisotropy (FA) within the ILF bilaterally.

Results: Across the sample of 43 women, after controlling for age and total motion index, lower left ILF FA was associated with a history of having been victimized by peers, partial Spearman's $r = -0.337$, $p = 0.031$. Associations with (non-peer-related) abuse and neglect were not significant. The effect size was comparable for peer verbal abuse (partial $r = -0.297$) and peer physical abuse (partial $r = -0.252$). Peer victimization was associated with social anhedonia in adulthood, Spearman's $r = 0.60$, $p < 0.001$, and with altered social network features in adulthood, including fewer embedded networks, Spearman's $r = -0.34$, $p = 0.026$, and lower social network size, Spearman's $r = -0.34$, $p = 0.025$.

Within the posttraumatic spectrum sample ($n = 25$), lower right ILF FA was associated with low social network diversity, after controlling for age, total motion index, and PCL-5 Total Scores, Spearman's partial $r = 0.514$, $p = 0.014$. The magnitude of the correlation was comparable for the left ILF, though it did not reach significance, Spearman's partial $r = 0.407$, $p = 0.060$. Peer victimization was again associated with altered social network features in adulthood, including fewer embedded networks, Spearman's $r = -0.47$, $p = 0.018$ and lower social network size, Spearman's $r = -0.51$, $p = 0.009$, and these effects remained significant after controlling for overall posttraumatic symptom severity and social anhedonia.

Conclusions: Across all participants, ILF FA was related to self-reported exposure to verbal and physical abuse by peers during childhood/adolescence. Participants who reported higher levels of peer victimization also reported altered structural social network features in adulthood including lower social network size and participation in fewer high-contact networks ('embeddedness'). These results provide preliminary evidence that low ILF FA may be associated with social difficulties (peer victimization during childhood, abnormal structural social network features during adulthood). The mechanistic relationships between these features are unknown, but one possibility is that lower ILF FA may result in difficulties with social information processing (including visual cue processing), which may make individuals more vulnerable to peer victimization during childhood/adolescence, and cause difficulty with social network establishment and maintenance during adulthood. Together, these findings support a growing literature on ILF abnormalities in trauma-exposed individuals and raise preliminary evidence that these abnormalities may be related to difficulty in social functioning.

Keywords: PTSD, Diffusion Tensor Imaging (DTI), Social Factors and Functioning, Stress and Trauma

Disclosure: Nothing to disclose.

P58. In Vivo Imaging of Brain Cortisol Regulation: Effect of the Dexamethasone Challenge

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Background: The hypothalamic-pituitary-adrenal (HPA) axis is a central focus of the pathophysiology underlying stress, trauma, and post-traumatic stress disorder (PTSD). The HPA axis stimulates adrenal cortical secretion of cortisol in response to traumatic stress. Levels of glucocorticoids (e.g., cortisol, cortisone) present in the brain are dependent on the enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1), which catalyzes the conversion of cortisone to cortisol and amplifies the action of glucocorticoids in the brain. Glucocorticoid receptors become activated when stress hormone levels are high. These receptors and 11β-HSD1 are in brain regions critical in the negative feedback of glucocorticoids, including the caudate and amygdala. While we previously developed a novel radiotracer to measure 11β-HSD1 availability, there is currently no way to measure the function of the HPA axis system. Previous work has used the dexamethasone suppression test (DST) to examine HPA axis function. The DST measures whether cortisol secretion can be suppressed. Dexamethasone, like cortisol, lowers the amount of adrenocorticotropin (ACTH) released from the pituitary gland, and in turn, lowers the amount of cortisol released by the adrenal glands. In the present investigation, we aimed to examine whether we could use dexamethasone as a challenge to probe the HPA axis system. We used positron emission tomography (PET) imaging with the novel 11β-HSD1 specific radioligand, [18F]AS2471907, to assess changes in 11β-HSD1 availability after dexamethasone administration in healthy controls.

Methods: To date, we have imaged 6 individuals (5M, 1F, mean age of 26 years) twice, pre- and post-dexamethasone, on consecutive days with the radiotracer [18F]AS2471907 and PET. Plasma samples were taken on the pre-dexamethasone scan day to determine baseline plasma cortisol levels. Participants were then instructed to take 0.5 mg dexamethasone by mouth at 11pm, which was confirmed by phone at the time. The following day, participants returned for the post-dexamethasone PET scan. Plasma samples were also taken to determine post-dexamethasone plasma cortisol levels and to confirm dexamethasone administration. Participants received 101 □ 3 MBq and 89 ± 25 MBq [18F]AS2471907 as a bolus injection at high specific activity on the pre- and post-dexamethasone scan days, respectively. Participants were imaged for 180 minutes on the High-Resolution Research Tomograph (HRRT; 2-3 mm resolution) with arterial blood sampling to measure the metabolite-corrected input function. PET scans were conducted at the same time of day (beginning between 12 and 1pm) to control for diurnal variability. 11β-HSD1 availability was quantified by [18F]AS2471907 volume of distribution (VT; mL/cm3), the ratio at equilibrium of [18F]AS2471907 in tissue to un-metabolized [18F]AS2471907 in arterial plasma. Regions of interest included caudate, putamen,

subdivisions of the striatum, thalamus, hippocampus, amygdala, occipital, frontal and temporal cortical regions, and cerebellum.

Results: Preliminary data indicated that 11β-HSD1 levels increased following dexamethasone across regions of interest, with pre- to post-dexamethasone changes in [18F]AS2471907 ranging from 9% in hippocampus and temporal cortical regions to 16% in amygdala. Individual pre- to post-dexamethasone scan data indicated that 11β-HSD1 levels increased in $n = 3$ participants and decreased in $n = 3$ participants, across regions of interest. Pre- to post-dexamethasone 11β-HSD1 availability ranged from -12% to 36% in hippocampus and -6% to 58% in amygdala. Peripheral cortisol decreased pre- to post-dexamethasone across all participants (cortisol suppression range = 28.2% - 90.9% suppression). No relationship between cortisol suppression and change in 11β-HSD1 availability pre-to post-dexamethasone was found.

Conclusions: This is the first in vivo examination of 11β-HSD1 levels using the DST in healthy controls. These preliminary findings suggest a possible association between prefrontal-limbic 11β-HSD1 availability pre- to post-dexamethasone, including in regions critical to stress systems and stress-related disorders such as the caudate, amygdala, hippocampus, and ventromedial prefrontal cortex. However, further research needs to delineate differences (i.e., increases vs. decreases) in 11β-HSD1 levels pre- to post-dexamethasone seen in our limited sample to further develop the paradigm. Future studies will further investigate [18F]AS2471907 as a marker of 11β-HSD1-mediated HPA-axis reactivity (e.g., brain cortisol regulation) in relation to stress, trauma, and in individuals with PTSD.

Keywords: Human Neuroimaging, F-18 PET Imaging, Anxiety, Cortisol

Disclosure: Nothing to disclose.

P59. Delta-9-Tetrahydrocannabinol Moderates the Effects of Avoidance Symptom Severity on Neural Activation During Fear Renewal in Trauma-Exposed Adults

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Background: Avoiding stimuli related to a traumatic can cause the development of trauma-based disorders and perpetuate disorder severity. Long-term avoidance can interfere with fear extinction and elicit fear renewal, hallmarks of trauma-based disorders. Data from our lab indicate that an acute dose of Δ9-tetrahydrocannabinol (THC), prior to fear extinction, facilitates recall of extinction learning by increasing activation in cortico-limbic brain regions. However, it is unknown if THC can prevent fear renewal, specifically in those with greater avoidance symptoms. The present study examines the effect of avoidance symptom severity on fear-related neural activation during fear renewal and how THC moderates that relationship.

Methods: 71 adults (ages 18 – 60) participated in a randomized, double-blind, placebo-controlled, between-subjects design and completed a novel Pavlovian fear-extinction paradigm using virtual reality coupled with FMRI. During fear acquisition, two conditioned stimuli (CSs) were presented: two CS + s paired with an aversive unconditioned stimulus (US) and one CS- never paired with the US. Before fear extinction, participants were administered an oral capsule containing either 7.5 mg of THC or sugar (PBO). During fear extinction, one CS + was extinguished (CS + E), while the other was not (CS + U). 24 hours later, all CSs were presented in the fear renewal context. Avoidance symptom severity scores were measured with the Clinician Administered PTSD Scale-5

Results: THC was a significant moderator in the relation between avoidance symptom severity and left hippocampus activation during fear renewal [$\Delta R2 = .18$, $\Delta F(1,41) = 9.15$, $p < .005$]. Specifically, when participants were given THC, left hippocampus activation increased with increasing avoidance symptom severity scores. Individuals given PBO had lesser left hippocampus activation with increasing avoidance symptom severity scores. THC was also a significant moderator in the relationship between avoidance symptom severity and dorsal anterior cingulate cortex (dACC) activation during fear renewal [$\Delta R2 = .16$, $\Delta F(1,41) = 8.19$, $p < .01$]. Individuals given THC had greater dACC activation with increasing avoidance symptom severity scores, while those given PBO had lesser dACC activation with increasing avoidance scores.

Conclusions: These data suggest that THC moderates fear--related activation in trauma-exposed adults during fear renewal. However, THC's moderating effects are contradictory. While it increased hippocampus activation in those with greater avoidance symptom severity, it also increased dACC activation. Individuals with greater memory deficits (i.e., cognition) and avoidance symptoms may benefit more from THC-assisted therapies than those with greater fear expression (i.e., hypervigilance) and avoidance symptoms.

Keywords: PTSD, Endocannabinoid System, Functional MRI (fMRI), Fear Conditioning and Extinction

Disclosure: Nothing to disclose.

P60. (R,S)-Ketamine and (26,6S)-HNK Attenuate Learned Fear by Differentially Modulating Brain-Wide Neural Activity

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Background: Stress is a major risk factor for fear and anxiety disorders, such as depression and post-traumatic stress disorder (PTSD). We previously reported that a single injection of (R,S)-ketamine, an anesthetic and rapid-acting antidepressant, prior to stress decreases behavioral despair and attenuates learned fear by modulating hippocampal activity, specifically ventral CA3 activity, in male mice. Of note, (R,S)-ketamine is metabolized into different metabolites, including (2R,6R)-hydroxynorketamine (HNK) and (2S,6S)-HNK. We have recently shown that (2R,6R)-HNK reduces behavioral despair in both sexes, whereas (2S,6S)-HNK attenuates learned fear in male, but not in female mice. Electrophysiological recordings reveal that the behavioral actions of (2R,6R)-HNK and (2S,6S)-HNK correspond with distinct effects on excitatory activity in hippocampal CA3. However, other brain regions mediating (R,S)-ketamine and (2S,6S)-HNK effects on fear behavior are still largely unknown.

Methods: Here, we administered a single injection of saline, (R,S)-ketamine (30 mg/kg), or (2S,6S)-HNK (0.075 mg/kg) to adult 129S6/SvEv male mice (8-week-old, $n = 10$ per group). One week later, all mice were administered a 3-shock contextual fear conditioning (CFC) paradigm as a stressor. Five days later, mice were re-exposed to the CFC context and sacrificed 1 hour later to quantify neural activity (i.e., c-fos expression) across the entire brain by using an analysis pipeline developed in our laboratory. c-fos cell counts separated by brain region were transformed into correlation matrices to provide information on functional connectivity. Whole-brain networks were generated based on the network statistic 'average number of neighbors.' All data were analyzed using ANOVA. Post-hoc Sidak's multiple comparisons test was used to correct for multiple comparisons when a significant

effect was found in the ANOVA. Pearson correlations between regions were calculated using the Hmisc package in R.

Results: (R,S)-ketamine and (2S,6S)-HNK administration attenuated learned fear when compared to saline mice ($p < 0.01$ for both drugs). (R,S)-ketamine administration increased brain-wide neural activity ($p < 0.05$) and enhanced the connectivity within and between cortical and sub-cortically regions (e.g., hippocampal, amygdalar, and cortical regions ($p < 0.05$)), while (2S,6S)-HNK increased cortical connectivity ($p < 0.05$) and enhanced subcortical connectivity specifically between the amygdalar ($p < 0.05$), but not hippocampal regions ($p > 0.05$).

Conclusions: Our data indicate that although both (R,S)-ketamine and (2S,6S)-HNK attenuate learned fear, they do so by differentially altering network correlated activity. (R,S)-ketamine might exert its prophylactic effect by enhancing the coordination between cortical, hippocampal, and amygdalar regions, while (2S,6S)-HNK might have a similar effect by targeting specifically the amygdalar circuits. This work aims to add to the growing (R,S)-ketamine literature and aims to elucidate which neural network can be targeted to improve fear-related disorders.

Keywords: (R,S)-Ketamine, (2S,6S)-HNK, Fear Conditioning

Disclosure: Nothing to disclose.

P61. Multiomics Mapping of Posttraumatic Stress Disorder in Human Cortical Neurons

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Background: Post-traumatic stress disorder (PTSD) is a disabling mental health condition with a prevalence of 6-10% in the general population, and 25-35% in combat veterans. Recent transcriptomics studies in human postmortem brains from individuals with PTSD have shown deregulated expression of genes involved in neuroimmune and neuroendocrine function, gliogenesis, synapsis and neuron development. The gene–environment interplay, known as epigenetics, plays an important role in gene regulation. DNA methylation (5mC) has been commonly associated with transcriptional repression, particularly in the promoter regions. DNA hydroxymethylation (5hmC) is a recent interesting mechanism particularly abundant in brain tissue and associated with transcriptional activation. To date, no studies have examined 5mC and 5hmC patterns of PTSD in human postmortem brain tissue. Further, no studies have integrated 5mC/5hmC with transcriptomic data to evaluate the effect of these epigenetic mechanisms on gene expression in the context of PTSD.

Methods: This study included 38 postmortem brain samples from the orbitofrontal cortex (OFC), including 25 PTSD cases and 13 healthy controls. Genomic DNA was extracted and 5mC and 5hmC were assessed through reduced representation oxidative bisulfite sequencing (RRoxBS). methylKit R package was utilized to conduct the analysis of differentially methylated positions (DMPs) associated with PTSD. Genome-wide significant (GWS) DMPs were defined as false discovery rate (FDR) < 0.05 with a percent methylation difference larger than 25%.

Results: 528 GWS DMPs were identified for PTSD, of which 136 were differential to 5mC (59% hyper) and 392 differential to 5hmC (52% hyper). 370 DMPs were annotated to CpGs located in promoter regions (79% 5hmC). ~28% of these genes were enriched for positive regulators of metabolic process and ~15% for neurogenesis, neuron differentiation or nervous system development. Overlapped genes in the second group include BDNF, DNMT3A and NPY (hyper 5hmC), GRIN2A (hypo 5hmC), and NGFR (hyper 5mC). We then conducted an integrative analysis of GWS 5mC/5hmC DMPs with GWS differentially expressed genes of PTSD in the OFC identified in Girgenti et al., 2021. Five genes overlapped across the -omics datasets. ADAMTS2 and NFIL3 showed increased 5hmC and were upregulated in the transcriptomic analysis. ANKRD44 showed increased 5hmC and was downregulated. PRAM1 and GOLM1 showed decreased 5hmC and were downregulated and upregulated in the transcriptomic analysis, respectively.

Conclusions: Our results show differential 5mC and 5hmC for PTSD in OFC neurons. These effects are observed in CpGs genes such as BDNF, DNMT3A and NPY involved in key neuronal functions and previously associated with PTSD. Integrative multi-omics analysis showed concordance in gene regulation between 5mC, 5hmC, and gene expression in CpGs targeting ADAMTS2, NFIL3 and PRAM1. Our findings identified genes via multi-omics integrative analysis that may be involved in the pathophysiology of PTSD.

Keywords: PTSD, DNA Hydroxymethylation, DNA Methylation

Disclosure: Nothing to disclose.

P62. A Rules-Based, Natural Language Processing Approach to Identifying Trauma History From Psychiatric Notes in the Electronic Health Record

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Background: The sequelae of trauma span diagnostic categories, symptoms, and levels of severity. While post-traumatic stress disorder (PTSD) is necessarily tied to an etiology of trauma, trauma is a risk factor for nearly every psychiatric condition, including mood disorders, substance use disorders, eating disorders, psychotic disorders, attention deficit disorders, and personality disorders. With exponentially expanding amounts of multimodal data in psychiatry, there is an opportunity to examine the significance and interplay of the many biopsychosocial features associated with a range of outcomes after trauma. However, there needs to be systematized ways to accurately identify a history of trauma in clinical populations. Clinical notes-- in particular psychiatric notes-- often contain information about psychosocial factors and are being increasingly mined using natural language processing (NLP) techniques. Here we utilize a rules-based NLP system for identifying mentions of trauma in clinical notes for a large patient cohort.

Methods: The clinical note corpus from the Mount Sinai Data Warehouse EHR is drawn from psychiatric inpatient, emergency room, and hospital consult encounters which consists of 286,692 notes for 33,800 patients. Notes were only preprocessed to remove aberrant white space and to lowercase all text. First, regular expression rules were implemented in the entire corpus to identify site-specific note templates that ask about trauma. Examples include: "Does the patient have a history of experiencing or witnessing trauma?" and commonly, "trauma hx:". These templates were found 77,796 times in 52,497 notes from 26,618 patients. The templates were removed to minimize false-positives during the following lexicon search. A lexicon was developed from SNOMED Clinical Terms, which is a publicly-available systematized collection of medical terms. Twelve trauma and PTSD-related terms were searched and all the descendent terms were included. Additionally, for the list of terms that included "victim of", "survivor of" was also searched. Several site-specific terms were also added given the domain expertise of the authors, including terms related to child/adult protective services, refugees, and first-

responders. 187 terms were included in the lexicon, which was then searched in the template-removed text. For manual review, the 10 words before and after the lexicon hit were extracted to examine the context. 100 notes with lexicon hits and their contexts were reviewed. The categories of notes (e.g., "discharge", "emergency room progress") were also roughly determined with a rules-based approach by clinician manual review. Based on the presence of specific term, each note was categorized as belonging to one of 39 categories.

Results: The lexicon of trauma terms returned 81,586 hits in 51,821 notes from 23,543 patients. Removing patients with only one hit, which has a high likelihood of being a false-positive, the lexicon was found in 42,184 notes from 13,906 patients. In this group, the most common lexicon matches and their overall counts were: "physical abuse": 15,854; "trauma": 12,890; "ptsd": 11,414; "assault": 7,776; "sexual abuse,": 5160; and "domestic violence": 3626. Other notable hits included "flashbacks": 2321; "survivor: 184"; "child abuse": 126; "asylum": 50; and "victim of human trafficking": 7. The most common note categories that included lexicon terms and the number of times a term appears in any of the notes: "clinician progress": 47,383; "discharge": 13,483; "attending note": 6,883; and "inpatient arts therapy rehabilitation": 6,783. Other notable hits were "emergency room progress:" 987, "nursing:" 28, "suicide risk assessment": 25, "violence risk assessment": 15. On manual review of 100 hits, there were 14 clear false-positives for the more general terms in the lexicon. For example, "assault" and "combat" returned 7 hits with mentions of assaultive or combative behavior in the setting of agitation; "trauma" returned 3 hits in nursing notes referencing the absence of skin trauma; "abuse" had 2 hits relating to substance use, and "ptsd" was used twice to refer to a family member.

Conclusions: This pilot lexicon-based approach to identifying trauma in hospital clinical notes demonstrates feasibility with a low initial false-positive rate of 14%. In this cohort of emergency room/inpatient/hospital consult patients, 41% were identified as having trauma, which is consistent with reports of trauma exposure in at least 49% of individuals with severe mental illness. Manual review highlights future refinements in the lexicon and regular expression rules to increase specificity. However, some false-positive such as terms used to describe family members, as well as negations are difficult to capture with a rules-based approach. The next step will be to employ machine learning techniques and a more comprehensive manual chart review to improve the accuracy in identifying psychiatric hospital patients who have experienced trauma.

Keywords: Natural Language Processing (NLP), Stress and Trauma, Electronic Health Record (EHR), Translational

Disclosure: Nothing to disclose.

P63. Violence, Victimization, and Variations in Neural Network Connectivity: An ABCD Study

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Background: Six in ten American youth will experience serious interpersonal violence (IPV) before they reach adulthood. Clinicians and neuroscientists are increasingly aware of IPV's pernicious effects on the developing brain. Yet, despite growing appreciation of the brain as a holistic networked system, our collective understanding of IPV's neural effects largely derives from research limited by regional specificity and undermined by limited sample size. Novel research has only recently begun examining the effects of general adversity on neural network dynamics, yet striking effects are being revealed even among youth exposed to 'normative' forms of adversity such as low SES. Investigation of potential differences among violence exposed youth is a logical next step, given the expansive knowledge about the impacts of threat-related adversity on regional structure and function. The current work considers variation in connectivity between and within canonical networks (default mode; DMN, frontoparietal; FPN, and salience networks; SN) across a population-representative sample of youth who reported their history of exposure to violence. Hypotheses anticipated that IV-exposed youth would exhibit greater intra- and inter-network connectivity in the default mode and salience networks.

Methods: Analyses were conducted in a sample of 7,220 children (ages 9-10 years; 51% female) who participated in the Adolescent Brain and Cognitive Development (ABCD) study. Binary IPV exposure was computed from the sum of 10 violence-related exposure items (i.e., witnessed/experienced severe physical or sexual violence) included in the PTSD subscale of the parent-report Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Curated, pre-processed resting state fMRI were obtained from the ABCD-BIDS Community Collection (ABCC) and post-processed using a custom in-house pipeline incorporating tools from ABCC. Dense CIFTI timeseries were downloaded from ABCC, and parcellated using the cortical Schaefer 400 atlas. Motion contaminated frames (FD > 0.2mm) and outliers were removed. Functional connectivity matrices were computed using the Z-transformed Pearson correlations between pairwise ROIs. Intra- and inter-network connectivity was computed as the mean of correlations between ROIs in the same or different networks, respectively.

Results: Roughly 9% of youth in the ABCD sample reported exposure at least one form of IPV in their lifetime (IPV + $N = 630$, IPV-$N = 6586$), the most commonly being witness to domestic violence (7%). Independent samples *t*-tests were used to evaluate differences in network dynamics across IPV groups. IPV + youth exhibited reduced intra-network connectivity in the default mode ($t = -3.35$, $p < .001$, $d = 1.00$) and salience networks ($t = -4.24$, $p < .001$, $d = .125$), as well as reduced inter-network connectivity between the default-mode and frontoparietal networks ($t = 2.50$, $p < .05$, $d = .08$). Connectivity between the salience and default-mode networks was marginally greater among IPV + youth ($t = 1.87$, $p = .059$, $d = .05$). Network dynamics were contrasted across sex and IPV-exposure in a series of 2x2 ANOVA models, though no interaction reached significance.

Conclusions: These findings suggest that exposure to any form of serious violence in childhood may be linked to remarkable differences in the flow of information through canonical networks in the brain. Interestingly, our findings with regard to decreased intra-network connectivity in the default mode and salience networks contradict extant small-sample research with adversity-exposed youth (Patriat et al., 2016), though do align with theoretical models describing potential links between network dynamics, adversity, and precursors of mental illness (Dvir et al., 2014). The increase in inter-network connectivity between the DMN and FPN similarly contradicts recent findings related to maltreatment exposure

Keywords: Interpersonal Violence, ABCD, Neural Networks

Disclosure: Nothing to disclose.

P64. Childhood Trauma Moderates the Relationship Between Inflammation and Functional Connectivity Between the Amygdala and Ventromedial Prefrontal Cortex in Association with Anxiety in Trauma-Exposed Women

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Background: Trauma exposure has been associated with increased peripheral inflammatory biomarkers such as C-reactive

protein (CRP) and cytokines, and inflammation has been associated with diminished right amygdala-prefrontal functional connectivity (FC) in association with symptoms of anxiety in unmedicated patients with depression. However, it is unknown whether inflammation contributes to variation in amygdala-prefrontal connectivity, and whether this connectivity is associated with symptoms of anxiety in trauma-exposed women.

Methods: We conducted resting-state functional MRI in 54 African American women recruited from a high-trauma inner-city population (Grady Trauma Project), reporting exposure to five potentially traumatic events on average, to investigate whether peripheral inflammation as measured by CRP was associated with altered right amygdala-ventromedial prefrontal cortex (vmPFC) FC in relation to symptoms of anxiety as measured by the State-Trait Anxiety Inventory (STAI). Participants also completed the Childhood Trauma Questionnaire (CTQ) to assess childhood maltreatment, in order to assess the potential influence of childhood trauma on relationships between inflammation and FC.

Results: Plasma CRP was associated with lower FC between the right amygdala and the vmPFC ($R = -0.324$, $p = 0.017$), and this relationship remained significant after controlling for age, body mass index (BMI), and trauma exposure ($R = -0.378$, $p = 0.008$). Childhood trauma, as measured by the CTQ, was also associated with reduced FC between the right amygdala and vmPFC ($r = -0.322$, $p = 0.018$; $p = 0.033$ after controlling for covariates). To explore the potential influence of childhood trauma on relationship between inflammation and FC, we conducted multiple linear regression including interaction terms between CRP and CTQ and clinical covariates. We found a significant interaction between CRP and CTQ scores on the relationship with FC ($r = -0.379$, $p = 0.005$). To further interpret this interaction, women were divided based on whether or not they experienced moderate or severe childhood trauma ($n = 33/54$). We found that CRP significantly correlated with right amygdala-vmPFC FC in women with ($r = -0.458$, $p = 0.014$) but not without ($r = -0.280$, $p = 0.276$) moderate or severe childhood trauma after controlling for covariates. Reduced right amygdala-vmPFC FC was in turn marginally associated with increased levels of trait anxiety, as measured by the STAI ($R = -0.273$, $p = 0.057$). To examine whether inflammation and FC between amygdala-vmPFC interact to influence symptoms of anxiety, multiple linear regression including interaction terms and covariates were employed. Of note, we found a significant interaction between CRP and right amygdala-vmPFC FC on anxiety ($R = -0.424$, $p = 0.002$). Further examination of this relationship in women with high and low CRP, defined as having a CRP > 3 ($n = 23$) or <3 ($n = 31$), revealed a significant negative relationship between right amygdala-vmPFC FC and trait anxiety only in women with CRP > 3 ($r = -0.490$, $p = 0.011$, $p < 0.05$ after controlling for covariates) but no relationship was found in women with CRP < 3 ($r = -0.117$, $p = 0.594$).

Conclusions: These results suggest that increased inflammation in association with childhood trauma impacts amygdala-prefrontal circuitry in relation to symptoms of increased anxiety in trauma-exposed women.

Keywords: Systemic Inflammation, Anxiety and PTSD, Resting State Functional Connectivity, Childhood Trauma

Disclosure: Nothing to disclose.

P65. Neighborhood Poverty Prospectively Predicts PTSD Symptoms Six-Months Following Trauma Exposure

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Background: Individuals living in socioeconomically disadvantaged areas are disproportionately affected by posttraumatic stress disorder (PTSD). Living in areas with high rates of poverty is associated with experiencing higher rates of a variety of different types of stressors, including reduced access to quality health care, environmental stressors like noise and pollution, and exposure to traumatic events such as police violence and other violent crimes. Despite the associations between neighborhood poverty and increased stress and trauma exposure, few studies have examined the association between neighborhood poverty and risk for developing PTSD symptoms. Although recent work by our group suggests that greater neighborhood poverty exacerbates PTSD symptoms in chronically trauma-exposed Black women, it is still unknown how neighborhood poverty influences the development of PTSD symptoms in the acute aftermath of a traumatic event. Thus, in the current study we assessed the relation between neighborhood poverty and PTSD symptom development six-months following trauma exposure. We hypothesized that living in areas with higher poverty rates would predict greater PTSD symptoms six-months post-trauma in a prospective, longitudinal sample of level 1 trauma center patients.

Methods: Participants ($N = 252$, 54% female) were enrolled between 2012 and 2016 from the emergency department (ED) immediately after experiencing a traumatic event. The sample was 75% Black, 15.9% White, 4.4% Mixed, and 4.8% other. Basic sociodemographic information including income, education, and zip code where the participant lived was collected. In addition, clinicians in the ED were asked to rate the severity of the traumatic event that brought the participant to the ED. Baseline PTSD symptoms and prior trauma exposure were also assessed upon study enrollment. Neighborhood poverty was determined using the 5-year American Community Survey (2012-2016), an annual survey assessing various sociodemographic factors (including poverty) for various geographical regions within the US. Neighborhood poverty rate was defined as the percentage of the individual's zip code living below the poverty line. Baseline trauma exposure and pre-existing PTSD symptoms were assessed using the Posttraumatic Diagnostic Scale (PDS). PTSD symptoms six-months post-trauma was assessed using the modified PTSD Symptom Scale (PSS). Notably, pre-existing PTSD symptoms were assessed based on baseline trauma exposure, but PTSD symptoms six-months post-trauma were assessed based on the ED trauma.

Results: Neighborhood poverty was significantly correlated with lower income ($r = -0.236$, $p < 0.001$), less education ($r = .254$, $p < 0.001$), and baseline PTSD symptoms ($r = 0.181$, $p = 0.004$), but not clinician-rated index trauma severity ($r = .09$, $p > 0.1$) or baseline trauma history ($r = .09$, $p > 0.1$). Higher PTSD symptoms six-months after trauma exposure were associated with neighborhood poverty rate ($r = 0.163$, $p = 0.009$), higher baseline trauma exposure ($r = 0.156$, $p = 0.013$), and greater baseline PTSD symptoms ($r = 0.507$, $p < .001$). A regression analysis showed that neighborhood poverty significantly predicted PTSD symptoms six-months after trauma exposure ($R2 = 0.094$, $b = 0.132$, $p = 0.031$), even after controlling for clinician-rated trauma severity and baseline trauma exposure. However, when baseline PTSD symptoms were included as an additional covariate in a follow-up regression analysis, the association between neighborhood poverty and PTSD symptoms at six-months was no longer significant ($R2 = .303$, $b = 0.062$, $p > 0.1$).

Conclusions: Our results show that high rates of neighborhood poverty are related to higher levels of PTSD symptoms six-months after experiencing a traumatic event, even when controlling for severity of the trauma and for baseline trauma exposure. This association was not present after adjusting for baseline PTSD symptoms, suggesting that the effects of neighborhood poverty on prospective risk for PTSD is linked to pre-existing PTSD symptoms. Our results emphasize the importance of considering the impact of where an individual lives in determining risk for developing PTSD after a traumatic event, as neighborhood poverty is associated with risk factors that have been previously associated with risk for trauma exposure and PTSD. Additionally, these findings highlight the

importance of investing in and providing resources for underserved communities in order to reduce behavioral health inequities that result from trauma exposure.

Keywords: PTSD, Emergency Department, Neighborhood Poverty

Disclosure: Nothing to disclose.

P66. Adjunct Extinction and Ketamine Treatment Reverses Stress Induced Prefrontal Deficits in Male and Female Rats

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Background: Background: Treatments for stress-related psychiatric disorders are inadequate. Behavioral therapies such as exposure therapy can be effective in ameliorating cognitive dysfunction associated with PTSD and depression. We have recently established extinction learning in rats as a behavioral intervention that models the beneficial effects of exposure therapy on the detrimental effects of stress on cognition. We have shown in rats that extinction reverses chronic stress-induced deficits in cognitive flexibility on the attentional set-shifting test (AST), a medial prefrontal cortically-mediated executive process. Extinction requires the activity of pyramidal neurons in the infralimbic cortex, and BDNF signaling mediates these effects. The combined use of psychotherapy and pharmacotherapy may be more effective than either alone. Since extinction shares mechanisms exerted by ketamine, we reasoned that extinction and ketamine used in combination will have enhanced efficacy.

Methods: Methods: In these studies, we developed a model of sub-effective extinction therapy in rats that showed impairment in two readouts of prefrontal cortex function, AST and evoked local field potentials in the infralimbic cortex, following chronic unpredictable stress.

Results: Results: We found that reducing the duration of extinction attenuated its therapeutic effects on set shifting performance and activity of the infralimbic cortex in Sprague-Dawley rats after stress ($n = 6$-9/group, $p < 0.01$, $d = 1.87$). We then established sub-effective doses of ketamine on the same measures of cognition and electrophysiology. Combining sub-effective extinction with a sub-effective dose of ketamine (1mg/kg) fully reversed the effects of stress on set shifting ($n = 9$/group, $p < 0.01$, $d = 2.27$) in males and females.

Conclusions: Conclusions: We have developed a model to study adjunct treatment combining extinction and candidate drug therapies such as ketamine. Ongoing experiments will discern whether a combination of extinction and ketamine treatment enhances responsivity in the IL that is compromised by chronic stress.

Keywords: MDD, PTSD, Extinction, Ketamine

Disclosure: Nothing to disclose.

P67. Dynamic Dichotomy of Accumbal Activity Underlies Vulnerability to Stress Cue Exposure and Cocaine Sensitization

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Background: Converging epidemiological studies indicate that a history of acute life-threatening events increases the incidence of post-traumatic stress disorder (PTSD), and a diagnosis for PTSD carries 30-50% comorbidity with SUDs. Thus, patients with comorbid PTSD/SUDs have greater drug use severity and show poorer treatment outcomes than patients diagnosed with either alone. Using an animal model, we found that exposure to a single stressful event experienced 3 weeks earlier can enhance drug intake and trigger a number of enduring adaptations within corticostriatal synapses of the nucleus accumbens core (NAcore), which resemble drug induced adaptations. Furthermore, exposure to stress-conditioned stimulus (stress-CS) induce increased reactivity in the defensive burying task and evoked increases in synaptic plasticity including the pre and postsynaptic neurons, astrocytes and matrix metalloproinases (enzymes that degrade extracellular matrix and expose signaling molecules). Moreover, medium spine neurons (MSN) constitute 90-95% of the neurons in the NAcore and are chemically coded into two subtypes that selectively express D1 or D2 dopamine receptors. These two populations appear to subserve distinct behavioral functions, with D1 activation generally promoting and D2 activation inhibiting behaviors. However, the effect of stress and stress-CS exposure on accumbal population remains elusive.

Methods: We imaged calcium signals in identified accumbal neurons of freely moving male and female mice as a proxy for their activity. In order to target D1 and D2-MSN we used D1- and D2-Cre transgenic mice. We injected animals with a floxed viral construct into the NAc to express GCaMP6f. We then placed a GRIN lens above the infected area, connected a miniaturized microscope and we imaged in restraint stress, defensive burying and cocaine sensitization. We recorded calcium transients during restraint stress, and baseline before and after the stress exposure. Furthermore, while animals were immobilized, they were exposed to an odor that became a stress conditioned stumulus (stress CS), and control animals were exposed in the home-cage box to an odor, neutral stimulus (NS). Three weeks after the stressful experience animals were tested in three consecutive days on a defensive burying task that consist in a cage that contain bedding on one corner and stress-CS or NS on the opposite corner (noxious object which to be buried). Next, we recorded calcium transients in response to baseline, saline and cocaine (5 mg/kg, i.p.) injection. We calculated the locomotor sensitization index as the ratio of the distance moved between saline and cocaine injection between sham and stress animals.

Results: We examined the effects of restraint stress on the frequency and amplitude of Ca2+ events across cell types and sessions (baseline, acute stress and after stress, defensive burying and locomotor sensitization). Records were restricted to 30 min of each session. We first compared the average number of calcium events between cell types and between conditions. We found that after acute stress and stress cue exposure a fraction of D1- and D2-MSN show divergent and opposing activity. D1-MSN neurons were more active than D2-MSN neurons regardless of the session. This increased number of Ca2+ events in D1-MSN neurons was most marked during the last 30 min of the stress session, while the most marked events for D2-MSN were immediately after the stress session. Comparison of sessions within the D1-MSN population revealed that the Ca2+ event rate was increasing after each session of stress cue exposure, compared to D2-MSN. The dichotomous response was enhanced during the expression of locomotor sensitization on stress animals compared to sham, with more D1-MSN elevating their activity.

Conclusions: These results indicate that accumbal population dichotomy is dynamic and contains a subgroup of D1-MSN that drives the defensive burying response and locomotor sensitization. Insights into the stress, stress cues and drug-related activity dynamics provides a foundation for understanding the circuit-level stress and addiction pathogenesis.

Keywords: Post Traumatic Stress Disorder, In Vivo Calcium Imaging, Medium Spiny Neurons, Synaptic Plasticity

Disclosure: Nothing to disclose.

P68. Effect of a Sub-Anesthetic Infusion of Ketamine on Laboratory-Induced Stress in Healthy Subjects: A Proof-Of-Concept Translational Study

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Background: Stress exposure is a key risk factors for the development of major depressive disorder and posttraumatic stress disorder. Stress resilience is the ability to experience stress without developing significant psychopathology. Thus, enhancing stress resilience in at-risk populations could potentially protect against the development of stress-induced psychiatric disorders. Despite this, no resilience-enhancing pharmaceuticals have been identified yet. Preclinical studies showed that the administration of the NMDA receptor antagonist ketamine one week prior to an acute stressor prevents the development of depressive-like behavior in rodents. In this project we aimed to test if the stress prophylactic effect of ketamine applies also to humans.

Methods: This was a double-blind, placebo-controlled, proof of concept study wherein twenty-four healthy subjects ($n = 11$ males) were randomized to receive a single intravenous infusion of either ketamine (0.5 mg/kg) or the psychoactive placebo control condition, midazolam (0.045 mg/kg), administered one-week prior to an acute stress [the Trier Social Stress Test (TSST)]. The TSST is a validated and widely used acute stress protocol designed to evoke an acute stress response in humans. The TSST employs a combination of elements (public speaking, mental arithmetic, anticipation, social evaluation, unpredictability) that reliably produce stress in a majority of participants, and activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. Acute elevations of self-reported of negative affect and anxiety are also reliably demonstrated. The primary endpoint of the study was change from baseline (pre-TSST) in self-reported stress measured by the anxious-composed subscale of the Profile of Mood States Bipolar Scale (POMS-Bi) immediately after the TSST. Salivary cortisol and alpha amylase were also measured at 15-minute intervals following the stressor, as a proxies for HPA and SAM axis activity respectively. Effect sizes for differences in mean change from baseline (pre-TSST) to outcome (post-TSST) between treatment arms were computed as Cohen's d. The trial was registered at clinicaltrials.gov [NCT04173962].

Results: Thirty-three subjects consented to participate in the trial. Of these, 24 (72.7%) were randomized, 6 (18.2%) were screen failures, and 3 (9.1%) were exited due to COVID-19. Participants in the ketamine group ($n = 12$) showed reduced levels of anxiety (mean change: 6.8 ± 5.8) compared to the midazolam group ($n = 12$; mean change: 11.9 ± 8.6), as measured by the change in anxious-composed sub-score of the POMS from baseline (pre-TSST) to immediately following the TSST; however the difference did not reach statistical significance ($\beta = 5.66$; CI = -0.34,11.60; $p = .06$). The effect size for the difference in change in means was Cohen's $d = 0.7$, equivalent to a medium-to-large effect size. Compared with midazolam, ketamine was not associated with a significantly different trajectory in level of salivary cortisol ($p = .09$) or alpha amylase ($p = .93$) during or after the stressor. The effect size for the difference in change in means was Cohen's $d = 0.7$ and 0.3, respectively. Of note, in a subgroup of subjects who displayed a stress response following the TSST, computed as an increase of at least 20% of salivary cortisol levels from baseline (pre-TSST) to the peak (post-TSST), subjects randomized to ketamine ($n = 7$) showed reduced levels of salivary cortisol ($F = 6.1$; $df = 1,8$; $p = .038$) and salivary alpha-amylase ($F = 4.8$; $df = 1,8$; $p = .059$) compared to those randomized to midazolam ($n = 6$).

Conclusions: While this proof-of-concept study did not meet its primary endpoint, ketamine administration was associated with a medium-to-large magnitude reduction in TSST-induced anxiety levels compared to midazolam. Further, the effect of ketamine was significant on secondary biological endpoints within a subgroup of stress-responders. These findings suggest that ketamine may also exert a stress prophylactic effect in humans. Studies testing this hypothesis in larger samples are warranted in order to advance treatment discovery of preventive interventions for stress-related disorders.

Keywords: Stress Resilience, Ketamine, Stress, Cortisol

Disclosure: Institutional FCOI related to ketamine for the treatment of depression (Dr. Murrough is not named on the patent): Other Financial or Material Support (Self)

P69. Optogenetic Photo-Stimulation of Basolateral Amygdala Neurons Activated During Fear Memory Formation Promotes Anxiety-Like Behaviors

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Background: Fear-related neuropsychiatric disorders such as post-traumatic stress disorder (PTSD) often present with symptoms of anxiety. Although fear and anxiety are often considered distinct both in their behavioral manifestations and their mediating neuronal pathways, to what extent re-activation of neurons activated during fear memory formation elicit anxiety-like behaviors is unknown. Since activity of basolateral amygdala (BLA) neurons is key to formation of fear and anxiety, we hypothesized that photo-stimulated re-activation of neurons activated during fear memory formation will elicit anxiety-like behaviors.

Methods: To test this hypothesis, we used the 2nd generation of Targeted Recombination in Active Populations (TRAP2, Fos2A-iCreERT2) transgenic mice injected bilaterally with adeno-associated virus encoding Cre-dependent enhanced channelrhodopsin (ChR2-H134R) in BLA. Mice were instrumented with fiber optic cannulae above the injection sites. Nine days later mice were habituated to the fear conditioning chamber for 5 days (3 min/day) to decrease novel exploration induced BLA activation. The following day, mice underwent fear conditioning (5, 0.75 mA foot shocks in 6 min) and immediately (<1 min) thereafter were fear-TRAPed with 4-hydroxytamoxifen (4-OHT) to induce Cre recombinase expression of ChR2 driven by c-fos promoter/enhancer elements. Three weeks post TRAPing, we validated functional ChR2 expression using brain slice electrophysiology. At this same time point, mice ($n = 4$/group) underwent an open field test (OFT) while being photo-stimulated either with dummy (no light) or blue light (473 nm, 20 Hz, 5 ms) for 5 min. One hour following this test, mice underwent elevated plus maze (EPM) testing, again with or without photo-stimulation. 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.

Results: Compared to dummy pulses, photo-stimulation of fear-TRAPed BLA neurons increased thigmotaxis (time that mice spent close to the walls of the open field; blue light: 268 ± 9 s, no light: 132 ± 28 s, unpaired t test $P = 0.0040$) and decreased time spent in the open arms of the EPM (blue light: 43 ± 16 s, no light: 206 ± 12 s, unpaired t test $P = 0.0018$). Findings indicate that optogenetic

re-activation of BLA neurons that were c-fos activated (TRAPed) during fear memory formation promotes anxiety-like behaviors in two test paradigms.

Conclusions: Activation of identified fear-related BLA neurons can elicit anxiety-like behaviors. Findings could reflect activation of a functionally stable fear-coupled anxiety circuit or could require fear-conditioned plasticity induced in such a circuit. To differentiate between these possibilities, further investigation into cellular and circuit mechanisms is underway.

Keywords: Conditioned Fear Memory, Anxiety Circuitry, Basolateral Amygdala, TRAP2 Mice

Disclosure: Nothing to disclose.

P70. Sex-Dependent Predictors of PTSD Risk in the Early Aftermath of Trauma

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Background: Women are diagnosed with post-trauma psychopathology at twice the rate of men, even in the context of similar trauma types. Although social factors and the nature of the trauma contribute to this disparity, preclinical findings suggest that sex differences in the neural response to stress may also mediate risk for chronic post-stress behavioral alterations. We conducted a longitudinal study of early PTSD risk factors in a longitudinal study of Emergency Department (ED) trauma. We tested the hypothesis that neurocircuitry supporting the expression and regulation of threat responses may be differentially associated with post-trauma psychopathology in women versus men.

Methods: Patients in the ED of a large public hospital in the Southeastern U.S. were enrolled within 24 hours of a traumatic event and were assessed for PTSD symptom trajectories over the next year, with an MRI scan approximately 1-month post-trauma (female $n = 40$, male $n = 54$). Neuroimaging data included structural T1w imaging and fMRI for a social threat task comparing fearful versus neutral face stimuli. Analysis of threat-relevant regions included the amygdala, insula, dorsal anterior cingulate cortex (ACC), hippocampus, and subgenual ACC. Subcortical volumes and cortical thickness were extracted using Freesurfer 5.3, with quality control performed by 2 raters following ENIGMA 2.0 protocol. FMRI data were preprocessed in fMRIprep, and analyzed in SPM12. PTSD symptom severity (mPSS) was assessed at 1, 3, 6, and 12 months post-enrollment. Symptom trajectories were calculated using linear growth mixture modeling.

Results: More females showed a chronic PTSD symptom trajectory than males (females: 14%, males: 8%; risk ratio = 1.91). The neuroimaging findings showed female-specific links between threat neurocircuitry and later PTSD risk. Greater left dACC thickness was predictive of chronic PTSD symptom severity in females ($r = 0.65$, $p = 0.005$) but not males ($r = -0.10$, $p = 0.40$), after controlling for age, race and baseline PTSD symptoms (sex*dACC pFWE = 0.04). Similarly, bilateral dACC fMRI activation to fearful>neutral faces was negatively associated with chronic PTSD symptoms in females ($r = -0.72$) but not males ($r = 0.03$; sex*dACC $p = 0.01$). In exploratory analyses across the whole brain (14 subcortical regions for volume, 68 cortical regions for thickness, voxelwise whole-brain analyses for fMRI), no additional regions predicted PTSD trajectory in a sex-dependent manner.

Conclusions: Identifying sex-dependent risk mechanisms is a key step in the search for personalized treatment and intervention strategies. Differences in the structure and function of the dACC, involved in attention orienting to salient environmental cues, showed female-specific relationships with later PTSD. Findings suggest potential new strategies for early intervention. The structure and function of the dACC may serve as a target for novel early intervention strategies specifically targeted to recently trauma-exposed women. Furthermore, recent developments in neuromodulation approaches such as deep transcranial magnetic stimulation (TMS) may allow for direct targeting of dACC function.

Keywords: Post-Traumatic Stress Disorder, Functional MRI (fMRI), Predictive Biomarker, Sex Differences, Structural MRI

Disclosure: Nothing to disclose.

P71. Positivity Bias for Social Feedback: The Role of Perceived Memory and Social Anxiety Symptoms

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Background: Autobiographical memories are often more positive than actual events. Yet, simple alterations due to emotional memory selectivity should yield similar rates of false positive and negative memories. While a prominent literature has suggested these effects emerge from a bias towards positive information during memory encoding due to socio-emotional life history, here we propose that the positivity bias may reflect distortions resulting from schematic belief representations during recall. Although schemas influence recall of true memories, they also influence recall of false memories. To the extent recall relies on schemas rather than veridical memory, bias for true and false memories should be more similar. Thus, the level of positivity bias expressed for true and false memories should be more highly correlated among individuals will poor veridical memory. Moreover, while deficits in the positivity bias are linked to social anxiety, research on the effect rarely tests autobiographical memory in the social domain. The present research uses a novel and ecologically valid experimental paradigm to test the extent to which positivity bias manifests during memory of positive and negative social feedback, and the relation between symptoms of social anxiety and positivity bias.

Methods: Separate samples of participants completed Study 1 ($N = 76$; $M \pm SD = 17.51 \pm 5.11$ years; 55% female) and 2 ($N = 197$, 19.91 $\pm$ 2.52 years; 64.5% female). Study 2 was adequately powered to test for individual differences in social anxiety symptoms (measured via the IDAS). During a social feedback task, participants saw pairs of purported age-matched peers and selected which peer they thought would like or dislike them. Participants then received positive, negative, or neutral feedback from the selected peer. During a surprise recall task, participants were asked to which peers they had selected, and then the valence of the feedback they had received. For peers participants did not recall selecting, they were asked to predict if each peer would have liked or disliked them.

Trials were categorized based on selection recall: true memory (hits), false memory (false alarms), true prediction (correct rejections), and false prediction (misses). Bias was calculated for each category. For perceived memories (hits and false alarms), this score reflects the number of peers that participants recalled giving positive feedback, divided by the total number of peers they recalled giving positive or negative feedback. For perceived predictions (correct rejections and misses), this score reflects the number of peers that participants predicted would give them positive feedback, divided by the total number of peers they predicted would give positive or negative feedback. A non-biased participant would recall/predict an equal amount of positive and negative feedback, and would therefore have a bias score of 0.5. Thus, for both studies, independent sample t-tests were performed to compare the bias score in each memory category to 0.5. We predicted that the positivity bias would emerge based on one's perceived experience such that bias for true and false memories (hits and false alarms) would be highly correlated. Thus, a Pearson's

correlation matrix was generated to test the relation between bias scores across all four categories. We next sought to test our hypothesis that poor veridical memory would be associated with greater reliance on schemas, and thus a tighter coupling of between true and false memories (hits and false alarms). We operationalized veridical memory as d' and tested the extent to which d' mediated the relation between true and false memories. Finally, for Study 2, we also tested the relation between social anxiety symptoms and bias scores.

Results: Results replicated across both studies. Participants demonstrated a positivity bias for both true (S1: $M = 0.606 \pm 0.185$; S2: $M = 0.646 \pm 0.218$) and false (S1: $M = 0.616 \pm 0.209$; S2: $M = 0.632 \pm 0.239$) memories of social feedback (all t's > 4.80, p's < 0.001). No bias emerged for predicted feedback (all p's > 0.20). True and false memories were highly correlated (S1: $r = 0.649$, $p < 0.001$; S2: $r = 0.571$, $p < 0.001$). Moreover, veridical memory (d') moderated the association between true and false memories (S1: b = -0.64, SE = 0.28, t = -2.50, $p < 0.05$; S2: b = -0.36, SE = 0.13, t = -2.73, $p < 0.01$). Those with poor veridical memory had a stronger positive correlation between true and false memories (S1: $r = 0.779$, $p < 0.01$; S2: $r = 0.723$, $p < 0.001$) than those with better veridical memory (S1: $r = 0.423$, $p < 0.05$; S2: $r = 0.434$, $p < 0.001$). Additionally, in Study 2 we demonstrated socially anxious ($M = 0.595 \pm 0.242$), relative to asymptomatic participants ($M = 0.676 \pm 0.229$), had less positivity bias, particularly for the recall of false memories ($t(194) = 2.408$, $p < 0.05$).

Conclusions: There is a robust positivity bias for perceived autobiographical memories of social feedback - regardless of whether those memories are true or false. Moreover, the strong positive correlation between true and false memories is potentiated among those with worse veridical memory. Together, results suggest that the positivity bias may reflect reliance on schematic representations of interpersonal events, rather than mechanisms that are actually biasing selectivity during memory encoding itself. This idea is bolstered by the fact that individuals with social anxiety, who hold a negative schematic representation of interpersonal events, expressed lower levels of positivity bias.

Keywords: Social Anxiety, Memory, Social Rejection

Disclosure: Nothing to disclose.

P72. Depressive Symptom Severity Alters Quality of Sleep and Emotion Dysregulation Alters Endothelial Function in Trauma-Exposed Women With Type 2 Diabetes Mellitus

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Background: Individuals exposed to trauma are at greater risk for subsequent development of post-traumatic stress disorder (PTSD) and depression as well as cardiometabolic disorders including type 2 diabetes mellitus (T2DM) and ischemic heart disease. Emotion dysregulation, or deficits in the awareness and management of intense negative emotions, is a transdiagnostic risk factor for the development and maintenance of PTSD and depression heavily influenced by trauma exposure. Accumulating evidence suggests that insufficient sleep and endothelial dysfunction independently contribute to ischemic heart disease. However, the individual and/or combined effects of emotion dysregulation, PTSD, and depression on sleep and endothelial function remain to be elucidated. In the present study, we hypothesized that in trauma-exposed women with T2DM, endothelial function and sleep disturbances would be correlated and associated with both PTSD and depression through emotion dysregulation.

Methods: In a group of 92 Black civilian women with T2DM from an urban hospital setting, we assessed the predictive value of PTSD symptom severity, depressive symptom severity, and emotion dysregulation severity on measures of sleep quality and cardiovascular variables. PTSD symptom severity was assessed using the Clinician Administered PTSD Scale (CAPS), depressive symptom severity was assessed with the Beck Depression Inventory (BDI), and emotion dysregulation was assessed with the difficulties in emotion regulation scale (DERS). Quality of sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI). We measured baseline blood pressure (BP) and heart rate (HR) using standard methods and endothelial function using baseline flow-mediated dilation (FMD).

Results: Of the 92 women with BDI and CAPS scores, a subset of 65 had available PSQI and FMD data (age, 51 + /-10 years old; body mass index (BMI), 35 + /-6 kg/m2). Our analysis yielded significant correlations between sleep and PTSD symptoms ($r = .490$, $p < .001$); sleep and depression symptoms ($r = .634$, $p < 0.001$); and sleep and emotion dysregulation severity ($r = .409$, $p < .001$). FMD was not correlated with PTSD, depressive, or emotion dysregulation symptoms. However, FMD was correlated with blood pressure ($r = .249$, $p = .019$ and $r = .270$, $p = .012$ for systolic and diastolic respectively). We did not find a correlation between sleep and endothelial function. To further determine the predictive value of these common psychiatric outcomes on sleep and endothelial function, we conducted two hierarchical linear regression models predicting sleep and endothelial function by relevant covariates of age, body mass index, blood pressure and DERS score in step 1, and CAPS and BDI scores in step 2. The final model with emotion dysregulation, PTSD and depression scores was significant (R-square = .408, $p = .002$) at predicting sleep disturbances; with depression as the strongest predictor (beta = .505, $p = .002$). In contrast, the final model predicting FMD with systolic blood pressure, diastolic blood pressure and emotion dysregulation as predictors was also significant (R-square = .163, $p = .034$). The strongest predictor for FMD was emotion dysregulation (beta = -.264 $p = .034$).

Conclusions: Our results show that depression was the only significant predictor of sleep disturbance after controlling for severity of emotion dysregulation and PTSD. In contrast, severity of emotion dysregulation and not severity of depression or PTSD explained the variance in endothelial function as measured with FMD in trauma-exposed women. This suggests that the extent of sleep disturbance and endothelial dysfunction reported in trauma-exposed women could be driven to a significant extent by the presence of depressive or emotion dysregulation symptoms which may serve to identify individuals at risk for ischemic heart disease who may benefit from targeted interventions.

Keywords: PTSD Depression, Emotional Dysregulation, Sleep Disturbance, Endothelial Function, Blood Pressure

Disclosure: Nothing to disclose.

P73. Characterization of Distinct Neuronal Activity and Behavioral Profiles in a Novel Approach/Avoidance Conflict Assay in Mice

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Background: Reward is often present in risky environments, requiring individuals to weigh the benefits of rewards against the associated risks. There are individuals that are unable to choose an appropriate response during risky reward opportunities and thus exhibit extreme avoidance or risky behaviors that can severely impair quality of life or endanger people. It is therefore necessary to

characterize how neurons mediate reward approach and threat avoidance conflict.

Methods: Here, we used a novel approach-avoidance conflict task to characterize individual differences in behavior and neuronal activity in mice. Here, we adapted the platform-mediated avoidance conflict task (Bravo-Rivera et al 2014; Bravo-Rivera et al 2021), such that water-deprived mice could nose-poke for a light-signaled water reward (3 uL, 4 sec ITI) and avoid a tone-signaled (20 sec, 70 dB) foot-shock (0.2 mA, 2 sec co-terminating) by stepping onto a safety platform away from the reward port. Mice were trained in two different conflict contingencies; in low conflict, reward was available during safety periods (inter-tone intervals) and during the warning tone, whereas in high conflict, reward was available only during the warning tone.

Results: All mice ($n = 10$ males, 10 females) learned to actively avoid the signaled shock in >90% of trials by the tenth day of low conflict training. Interestingly, females mounted the platform earlier than males after tone onset (5 sec vs 10 sec to reach 80% mount likelihood) and had a longer latency to leave the platform after tone offset (16 sec vs 10 sec to reach 15% mount likelihood) in low conflict. Females also mounted the platform earlier than males after tone onset (15 sec vs 17 sec to reach 80% mount likelihood) in high conflict. Males received more shocks than females (5 vs 2 out of 20) and received more water reward (759 ul vs 609 ul) than females by the end of high conflict training.

Conclusions: These results suggest that females exhibit more avoidance behavior and less reward approach than males in the face of approach/avoidance conflict

Keywords: Approach/Avoidance, Motivation, Sex Differences, Ventral Pallidum, Lateral Habenula

Disclosure: Nothing to disclose.

P74. Neural Markers of Worry – Functional Connectivity Correlations Using Higher Criticism

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Background: Worry is a transdiagnostic phenotype encountered in multiple mental disorders and independently associated with increased morbidity, including cognitive impairment and cardiovascular diseases. We investigated the neurobiological basis of worry in older adults by analyzing resting state fMRI from a systems neuroscience perspective.

Methods: We collected resting fMRI on 77 participants (>50 yo) with varying worry severity. We computed region-wise connectivity across the Default Mode Network (DMN), Anterior Salience Network (ASN), and left Executive Control Network (LECN). All 22,366 correlations were regressed on worry severity and adjusted for age, sex, race, education, disease burden, depression, anxiety, rumination, and neuroticism. We employed higher criticism (HC) thresholding, a second-level method of significance testing for rare/weak features, for correlation selection. Aggregate correlations were used to summarize network-level signatures of worry.

Results: Half the relevant intra-network connections are within the DMN. Negative correlations with worry severity dominate throughout the cingulate, temporal lobe, and cuneus, while frontal regions show bidirectional associations with worry. Within the ASN, negative correlations with worry severity abound, particularly in the anterior cingulate, inferior frontal regions, and thalamus. Positive correlations with worry severity in the left posterior cingulate and right temporal lobe and negative correlations in frontal regions are notable within the LECN. Inter-network analysis reveals a rich, but complex pattern of connectivity, again heavily skewed toward connections involving the DMN.

Conclusions: Worry severity is associated with complex resting state intra- and inter-network connectivity signatures independent of other clinical and demographic variables. The majority of the relevant connections involve the DMN. The anterior cingulate, temporal lobe, and thalamus are heavily represented with overwhelmingly negative association with worry while the prefrontal regions are also strongly represented with an intricate mix of positive and negative associations with worry. Identifying the most salient and unique connections may be useful for targeted interventions for reducing morbidity associated with severe worry in older adults.

Keywords: Resting-State fMRI, Worry, Default Mode Network (DMN), Higher Criticism, Functional Connectivity

Disclosure: Nothing to disclose.

P75. An Epigenetic Contribution to Neuronal Competition During Memory Allocation

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Background: Over the past years, multiple lines of evidence have suggested that fear memories are stored in a subset of neurons, so-called engram cells (Josselyn et al., 2015, Nat Rev Neurosci; Tonegawa et al., 2015, Neuron). From these studies it is becoming apparent that only five to twenty percent of excitatory neurons are recruited to form a stable engram. Hence, as memories start to be encoded, the size constraint of the engram likely imposes neurons to compete for memory allocation. Indeed, previous studies have revealed that post-synaptic neurons with a higher excitability then their neighbours are more likely to be recruited into the memory trace (Zhou et al., 2009, Nat Neurosci; Yiu et al., 2014, Neuron).

Methods: In this project, we further explore the process of memory allocation by studying how epigenetic mechanisms contribute to neuronal competition in mice. Specifically, we are focusing on histone acetylation, one of the main epigenetic modifications studied in learning and memory (Gräff and Tsai, 2013, Nat Rev Neurosci).

Results: We find that excitatory neurons in the lateral amygdala (LA) are characterized by naturally occurring epigenetic variability and that altering such variability alters neuronal excitability; that engram allocation preferentially occurs in epigenetically altered neurons; and that such epigenetic alteration of engram cells facilitates fear memory formation. Furthermore, we show that optogenetically silencing epigenetically altered engram cells impairs memory retention, which testifies to the functional importance of engram-specific epigenetic marks for memory processing.

Conclusions: Together, these findings highlight a chromatin-templated mechanism that influences memory allocation.

Keywords: Memory Engram Cell, Epigenetic Modification, Fear Learning, Histone Acetylation, Excitability

Disclosure: Nothing to disclose.

P76. Impact of Exogenous Estradiol on Task-Based and Resting-State Neural Signature During and After Fear Extinction in Healthy Women

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Background: Fluctuations of endogenous estrogen modulates fear extinction, but the influence of exogenous estradiol is less studied. Moreover, little focus has been placed on the impact of

estradiol on broad network connectivity beyond the fear extinction circuit. Here, we examined the effect of acute exogenous estradiol administration on fear extinction-induced brain activation, whole-brain functional connectivity (FC) during the fear extinction task and post-extinction resting-state.

Methods: Ninety healthy women (57 using oral contraceptives [OC], 33 naturally cycling [NC]) were fear conditioned on day 1. Women ingested a estradiol or placebo pill prior to extinction learning on day 2 (double-blind design). Extinction memory was assessed on day 3. Task-based functional MRI data were ascertained on days 2 and 3 and resting-state data were collected post-extinction on day 2 and pre-recall on day 3.

Results: Estradiol administration significantly modulated the neural signature associated with fear extinction learning and memory, consistent with prior studies. Importantly, estradiol administration induced significant changes in FC within multiple networks, including the default mode and somatomotor networks during extinction learning, post-extinction, and during extinction memory recall. Exploratory analyses revealed that estradiol impacted ventromedial prefrontal cortex (vmPFC) activation and FC differently in the NC and OC women.

Conclusions: The data implicate a more diffused and significant effect of acute estradiol administration on multiple networks. Such an effect might be beneficial to modulating attention and conscious processes in addition to engaging neural processes associated with emotional learning and memory consolidation.

Keywords: Fear Conditioning and Extinction, Functional MRI (fMRI), Resting State Functional Connectivity, Women's Health

Disclosure: Nothing to disclose.

P78. Anxious Temperament is Associated With Transcriptional Alterations in the Primate Orbitofrontal Cortex

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Background: Anxiety is an adaptive state that facilitates the engagement of defensive systems in order to avoid encounters with potential threats. However, when expressed in a manner that is extreme and out of context, anxiety can become maladaptive. The early-life tendency to experience an exhibit extreme anxiety in response to novelty and/or uncertainty, which is indicative of an anxious temperament (AT), is associated with the emergence of anxiety disorders later in life. We have developed a nonhuman primate (NHP) model of AT, indexed by a composite score which includes threat-related behavioral inhibition as well as reactive cortisol, a measure of pituitary adrenal activity. Using this model, we have characterized a brain circuit, which includes the posterior orbitofrontal cortex (pOFC), in which increased threat-related glucose metabolism is associated with high AT. To further characterize molecular alterations related to individual differences in this region, we combined selective capture of neurons within the pOFC with sequencing techniques to reveal molecular alterations associated with individual differences in AT.

Methods: The sample for this study consisted of brain tissue collected from $n = 71$ young rhesus monkeys ($n = 23$ females, $n = 48$ males, mean age $= 2.56 +/- 0.71$ years) that had undergone extensive AT-related phenotyping. Using laser capture microdissection (LCM) in combination with a rapid immunohistological staining protocol, we collected neurons from the deep and superficial cortical layers of the pOFC and characterized gene expression levels using RNA sequencing (RNAseq). Alignment and analysis of RNAseq data was performed using a custom pipeline written in Python.

Results: A principal components analysis revealed that the first principal component (PC1), which described 9.4% of the total variance in the data, was strongly associated with laminar identity ($r = 0.91$). Differential expression analyses revealed 2,535 transcripts that were differentially expressed across laminae at FDR corrected $p < 0.05$. Permutation testing was used to determine if AT or any of its components were associated with transcriptome-wide expression beyond the effect of random chance in either the deep or superficial layers. AT was marginally associated with transcriptome-wide alterations in the deep ($p = 0.06$, $n = 10{,}000$ permutations) but not superficial layers ($p = 0.45$, $n = 10{,}000$ permutations) of the pOFC. On the other hand, threat-related cortisol, a component of the composite AT score, was marginally associated with transcriptome-wide alterations across both cortical layers (deep layers: $p = 0.06$, superficial layers: $p = 0.03$, $n = 10{,}000$ permutations). Pathway analyses revealed that the genes associated with threat-related cortisol were enriched for catecholamine systems (dopamine and serotonin signaling), as well as for corticotrophin releasing factor (CRF) signaling. These analyses also pointed to several interesting novel candidates for investigation, including caldesmon (CALD1), a molecule that is under the transcriptional control of the glucocorticoid receptor (GR) and mediates changes in cytoskeletal architecture following glucocorticoid administration. Interestingly, the expression levels of the transcript for the GR (NR33C1), as well as several other GR-associated molecules, were associated with individual differences in AT. Finally, as the sample for this group included both males and females, sex differences in pOFC neuron gene expression were tested. Beyond differential expression of several sex-linked transcripts, we observed differential expression with respect to sex of the transcripts for apoptosis inhibitor 5 (API5) ($t = 5.03$, FDR corrected p value $= 0.0045$), which is an anti-apoptotic factor that regulates mRNA export, and glycogenin 2 (GYG2), an enzyme involved in glycogen synthesis that is subject to regulation by brain estradiol ($t = -5.6$, FDR corrected p value $= 0.0006$).

Conclusions: Overall, these results, focused on the pOFC, represent the largest characterization to date of the transcriptional profile of cells within the primate frontal cortex. As the primary source of variance was related to laminar identity, these data suggest that neurons within the superficial and deep layers of the pOFC are divergent in terms of their gene expression, recapitulating documented differences in connectional and functional properties. Furthermore, distinct transcriptome-wide relationships were observed between AT and the deep and superficial layers, suggesting that the transcriptional profile of the primarily feedback neurons residing within the deep layers of the pOFC may be more relevant with respect to AT than the feedforward neurons residing in superficial layers. Irrespective of laminar identity, and consistent with work in rodents, transcriptional alterations of molecules associated with the glucocorticoid system were related to individual differences in threat-reactive cortisol. Importantly, these findings suggest that alterations in the function of the glucocorticoid system are not only associated with acute stress-related challenges and stress-induction protocols employed in rodent models, but also with innately occurring, genetically mediated individual differences in anxiety-related temperaments.

Keywords: Anxiety, Nonhuman Primates, RNA-Sequencing, Prefrontal Cortex

Disclosure: Nothing to disclose.

P79. Inhibitory Control Brain Regions Implicated in the Development of Chronic Posttraumatic Stress Disorder Following Acute Trauma Exposure

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Background: Identifying neurobiological phenotypes that may predispose individuals to develop posttraumatic stress disorder (PTSD) following acute trauma exposure is critical in efforts to improve mental health outcomes for trauma survivors. Inhibition is a critical executive control process and an established neurobiological phenotype of PTSD that may be a relevant risk factor for the development of PTSD, and impaired hippocampal, ventromedial prefrontal cortex (vmPFC) and right inferior frontal gyrus activation (rIFG) during response inhibition have been observed in PTSD patients in prior studies. There are two types of inhibition to consider; reactive inhibition is the direct stopping of a response via inhibition of the motor areas, whereas proactive inhibition is the anticipation of stopping based on contextual cues. To date, no prospective studies have examined inhibition as a risk factor for the development of PTSD using a contextual cue task that enables measurement of behavioral response and neural activation patterns across both proactive and reactive inhibition.

Methods: The current longitudinal study utilized functional magnetic resonance imaging (fMRI) to examine whether deficits in proactive and reactive inhibition predicted chronic PTSD symptoms at 6 months post-trauma. Twenty-four (64% males) medical patients receiving acute medical care from a level 1 trauma center located in an Emergency Department were enrolled in the study and invited for an MRI scan 1-2-months post-trauma. To be eligible for study inclusion, participants had to be between the ages of 18 and 65 years and have experienced a DSM-IV criterion A trauma within the last 24 hours. Participants also needed to be able to provide informed consent, understand and speak English, and have blood obtained by ED care staff. PTSD symptoms were measured dimensionally using a self-report measure, the Post-traumatic Stress Scale (PSS), at time of scan and at 6 months post-trauma. Twenty-one percent of the sample met for likely PTSD at 6 months. A stop-signal anticipation task (SSAT) in an fMRI scan was used and measured proactive and reactive inhibition behavioral response and neural activation patterns. Given the small sample size, only regions of interest (ROI) based and specific hypothesis-driven analyses that directly follow prior work were performed. ROIs included the right inferior frontal gyrus (rIFG), ventromedial prefrontal cortex (vmPFC), and bilateral hippocampus. We hypothesized that impaired proactive and reactive inhibition behavioral measures would be associated with higher levels of PTSD at 6 months. We also hypothesized lower activation levels of rIFG and hippocampal activation during proactive inhibition and lower activation levels of vmPFC and rIFG during reactive inhibition would be related to higher levels of PTSD at 6 months.

Results: No significant associations were found between proactive and reactive inhibition behavioral responses and 6-month PTSD ($p > .05$). Bivariate correlation analyses showed significant negative correlations between both rIFG and vmPFC activation during reactive inhibition and 6-month PTSD symptoms ($r = -0.57$, $p = .005$ and $r = -0.45$, $p = .033$, respectively). Follow-up linear regression analyses revealed reduced rIFG activation accounted for 32% of the variance ($F1,21 = 9.97$, $p = .005$) and reduced vmPFC activation accounted for 20% of the variance ($F1,21 = 5.19$, $p = .03$) in 6-month PTSD symptoms; these associations remained significant even when demographic variables and baseline PTSD symptoms were included in the model. No significant associations with proactive inhibition were observed.

Conclusions: Our findings suggest that impaired rIFG and vmPFC activation during reactive inhibition may predict the development of chronic PTSD and impaired inhibition serves as an important risk factor for PTSD development following acute trauma exposure. This is one of the first studies showing the rIFG as a potential target for (early) interventions in addition to vmPFC. Along with behavioral interventions to improve mechanisms related to response inhibition, the rIFG could be an interesting target for neurostimulation interventions for (the development of) PTSD. Given the small sample size, future replication studies are needed to further clarify unique pathways of risk related to proactive versus reactive inhibition.

Keywords: Posttraumatic Stress Disorder, Inhibition, Human Neuroimaging

Disclosure: Nothing to disclose.

P80. Female-Specific 3D Genome Dynamics in the Brain: Implications for Anxiety Disorders and Depression

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Background: Male and female brains differ significantly in both health and disease, as a result of the interplay of sex hormones and sex chromosome-linked genes. From puberty to menopause, cyclical sex-hormone fluctuations represent a female-unique experience, which is associated with substantial brain plasticity and the increased female risk for certain brain disorders such as anxiety and depression. However, little is still known about molecular mechanisms underlying the sex hormone-induced, dynamic nature of the female brain. We previously implicated neuronal chromatin reorganization, a major mechanism controlling gene expression, as part of the mechanism regulating hippocampal plasticity and anxiety-related behavior across the estrous cycle in female mice. However, whether sex hormones are able to dynamically change the higher-order chromatin organization in post-mitotic neurons of the brain remains unknown. Three-dimensional (3D) genome organization allows interactions of genes with their distant cis-regulatory elements and is thought to play a major role in transcriptional regulation. Within the brain, 3D genome remodeling has only recently been implicated in neuronal function but whether there are sex differences and sex hormone-mediated influences on this regulation is unknown.

Methods: We profiled 3D genome organization in adult ventral hippocampal (vHIP) neurons across the estrous cycle and by sex using an unbiased chromatin conformation capture (Hi-C) method combined with candidate-loci DNA fluorescence in situ hybridization (FISH). Hi-C was performed in triplicates ($N = 6$ animals/group) on vHIP neurons isolated from 11 week-old male and female mice using fluorescence-activated nuclei sorting. We included females in two estrous cycle stages: proestrus (high estrogen-low progesterone) and diestrus (low estrogen-high progesterone), mimicking the human follicular and luteal phase, respectively. Bioinformatics analysis explored three levels of 3D chromatin organization: compartments (using Pearson correlation), CTCF loops (using SIP), and enhancer-promoter interactions (using FitHiC2). The role of 3D genome organization in gene regulation was assessed by integrating Hi-C data with chromatin accessibility (ATAC-seq) and gene expression (RNA-seq) data on the same biological samples generated in triplicates ($N = 6$ animals/group). Enriched motifs were obtained by meme-chip. Gene ontology and pathway analyses were performed by EnrichR and the Ingenuity Pathway Analysis software ($q < .05$).

Results: We provide the first evidence that 3D genome organization in the brain differs between males and females and undergoes dynamic remodeling during the female ovarian cycle. In females, we found significant sex hormone-driven dynamism in 3D chromatin organization, including in X-chromosome compartments, autosomal CTCF loops, and enhancer-promoter interactions, all of which are enriched for estrogen response elements. With rising estrogen levels in the proestrus phase, the female 3D genome organization becomes more similar to the male 3D genome organization. Differential estrous cycle-dependent

enhancer-promoter interactions are partially associated with transcriptional changes and enriched for brain disorder-relevant genes and pathways including the Serotonin and Anxiety pathway as the top enriched pathway.

Conclusions: This study shows that 3D genome organization in the female brain undergoes multi-level dynamic remodeling during the ovarian cycle, with a potential functional and priming role in female-specific gene regulation, brain plasticity, and disease risk. In particular, these findings provide a candidate molecular mechanism for the increased female vulnerability to anxiety and depression and establish a foundation for the development of sex-specific treatments for these disorders.

Keywords: Chromatin, Epigenetics, Sex Hormones, Sex Differences, Anxiety and Depression

Disclosure: Nothing to disclose.

P81. Impact of Oral Contraceptive Use on Psychological Distress During the COVID-19 Pandemic

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Background: Women are at greater risk than men to suffer from affective disorders such as depression, anxiety, and post-traumatic stress. Sex differences also emerge in the context of disease outbreaks, with women reporting higher distress. To account for this important sex difference, various mechanisms have been studied. Notably, the use of hormonal contraceptives (HC) has been identified as a potential vulnerability factor. So far, studies have mostly investigating the acute effects of HC, without considering whether this chronic modulation of sex hormone secretion could have long-lasting impact that would linger after HC cessation. Taking advantage of the COVID-19 context, this study aimed to investigate both acute and long-term effects of HC on psychological distress over a one-year period.

Methods: As part of a COVID-19 study launched in the laboratory, we recontacted participants who took part in studies in our laboratory between 2017 and 2020. At four time points during the COVID-19 pandemic in Montreal, Canada (June 2020 (T1), September 2020 (T2), December 2020 (T3), March 2021 (T4)), we collected self-reported data of psychological distress, assessing symptoms of post-traumatic stress (via the Impact of Event Scale-Revised (IES-R)), and symptoms of depression, anxiety, and stress (via the three subscales of the Depression Anxiety Stress Scales (DASS-21)). General distress levels were also assessed using the total score of the DASS-21. Linear mixed models were conducted to compare men ($n = 49$), naturally cycling women ($n = 73$), and current HC users ($n = 32$) across time (first set of analyses). Then, to examine potential long-lasting effects of HC, secondary analyses were restricted to women, comparing current HC users ($n = 32$), past users ($n = 56$), and never users ($n = 17$) (second set of analyses).

Results: The first set of analysis revealed a significant Time X Group interaction for the PTSD symptoms ($F(6, 243.87) = 2.26$, $p = .039$), with women using HC reporting stable levels of PTSD symptoms across the four timepoints ($F(3, 41.36) = 0.486$, $p = 0.694$) relative to naturally cycling women and men who showed a significant decrease from T1 to T2 (both ps < .01). The analysis also revealed a significant Time X Group interaction for the DASS total score ($F(6, 194.84) = 2.28$, $p = 0.038$), with HC users reporting increasing levels of general distress from T1 to T3 ($F(3, 38.74) = 3.43$, $p = 0.026$) compared to naturally cycling women and men. Importantly, a group effect was found for both stress ($F(2, 173.2) = 5.42$, $p = 0.005$) and anxiety symptoms ($F(2, 159.4) = 3.09$, $p = 0.048$), both effects being driven by the fact that women using HC report significantly higher symptoms than men. With regards to the second set of analyses, results showed a significant group effect for anxiety ($F(2, 105.27) = 5.23$, $p = 0.007$) and stress symptoms ($F(2, 108.89 = 4.01$, $p = 0.021$), as well as for general distress ($F(2, 108.11) = 3.22$, $p = 0.044$). Irrespective of time, current users and past users exhibited similar levels of symptoms. Current users were always more symptomatic than never users and past HC users also exhibited significantly higher anxiety symptoms than never users.

Conclusions: Our results suggest that HC users report increased distress during the pandemic relative to both naturally-cycling women and men. Furthermore, these preliminary results suggest a long-lasting effect of HC use, highlighting the importance of considering not only the current use of HC but also its history. This could provide some insight on potential avenues for explaining why women are prone to higher psychological distress than men.

Keywords: Psychological Distress, The COVID-19 Pandemic, Sex Differences, Hormonal Contraceptive Use

Disclosure: Nothing to disclose.

P83. Effects of Intranasal (S)-Ketamine on Veterans With Co-Morbid Treatment-Resistant Depression and PTSD: A Retrospective Case Series

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Background: Ketamine is a glutamatergic drug with potent and rapid acting effects for the treatment of depression. Racemic ketamine contains a mix of the (R) and (S) enantiomers. Little is known about the effectiveness of intranasal (S)-ketamine for treating patients with comorbid depression and comorbid PTSD.

Methods: We retrospectively analyzed clinical outcomes in 35 patients with comorbid depression and PTSD referred for (S)-ketamine treatments at the VA San Diego Neuromodulation Clinic between Jan 2020 to March 2021. Outcomes were calculated across the first 8 treatments (4 weeks) based on changes across time (repeated measures ANOVA), and overall reduction in symptom scales (PHQ-9 and PCL-5). In a smaller sub-group ($n = 19$) we analyzed stability of treatment effects across the first 16 treatments (~ 3 months). Sub-group analyses based on anti-depressant response and general linear models were also performed to identify predictors of treatment response.

Results: Across the first 8 treatments (4 weeks), there was an absolute reduction of 4.6 + /- 0.9 on the patient health questionnaire-9 (PHQ-9) rating scale for depression, from 19.6 + /- 0.8 at treatment 1 to 14.9 + /- 0.9 at treatment 8 (week 4) ($F(7,238) = 6$, $p < 0.001$), with 17% meeting criteria for a clinically meaningful response (reduction in symptoms > 50%) at treatment 8. There was an absolute reduction of 12.1 + /- 2.5 on the patient checklist 5 (PCL5) rating scale for PTSD, from 54.4 + /- 2 at treatment 1 down to 42.3 + /- 2.5 at treatment 8 ($F(7,238) = 10.8$, $p < 0.0001$). 34% Veterans showing a clinically meaningful response (reduction in symptoms by > 30%) at this time-point. Over a longer (3 month) time period, we found stable effects on depression and continued improvements on PTSD symptoms. Three pieces of evidence suggest that the effects on depression and PTSD are distinct. First, improvements on depression were observed early, while improvements on PTSD symptoms occurred late and continued to trend downwards even during the 3-month period. Second, (S)-ketamine improved re-experiencing, avoidance, arousal and mood/cognition domains of PTSD, effects

beyond just the mood/cognition domains. Finally, participants with a minimal antidepressant response still showed a significant reduction in PTSD symptoms.

Conclusions: Our results show that (S)-ketamine can improve both depression and PTSD symptoms in Veterans with dual-diagnoses. The effects of (S)-ketamine on PTSD were temporally and individually distinct from those on depression, suggesting potentially different modes of action on the two disorders. This work warrants further research and RCTs studying intranasal (S)-ketamine for PTS. Further research is warranted.

Keywords: Esketamine, MDD, PTSD, Novel Therapeutics

Disclosure: Nothing to disclose.

P84. Amygdalar Protein Synthesis Supports Persistent Trauma-Induced Shifts in Negative Valence

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Background: In addition to traumatic stress producing robust associative memories about the traumatic experience, trauma leaves individuals more vulnerable to future stressors. This vulnerability is thought to emerge in part via trauma's capacity to augment subsequent learning about aversive events. However, while much is known about the biology of aversive learning, little is known about how aversive learning is modified by prior traumatic experience. Defining the mechanism through which this change occurs may shed light on new treatment avenues for conditions like post-traumatic stress disorder, which are often predated by a history of stressful experiences.

Methods: In Experiment 1, mice were exposed to a brief 'traumatic' experience in which they received 10 foot-shocks, or not. A week later, anxiety-like behavior was assessed in a light-dark test and sensitization of aversive learning was assessed by exposing them to a loud auditory stressor in a distinct conditioning chamber. In Experiments 2 and 3, we assessed whether trauma altered expression or learning of aversive memories. This was done by pairing a tone with a weak foot-shock either before (Experiment 2), or after (Experiment 3), trauma. Fear of the tone was assessed in all animals after trauma. In Experiment 4, we utilized intra-amygdala infusions of anisomycin just after trauma to examine the contribution of protein synthesis in this region to the lasting sensitization of aversive learning and anxiety-like behavior observed following trauma. All groups were composed of 8-12 male mice. After confirming that data conform to GLM assumptions, group differences in behavior were examined with ANOVA and planned contrasts.

Results: We found that a single acute traumatic event is able to persistently increase measures of anxiety-like behavior in the light-dark test, as well as learned fear in response to a novel aversive experience (Experiment 1). Examining the impact of trauma on aversive memories, trauma had no effect on the expression of an aversive memory acquired before trauma (Experiment 2), but greatly enhanced a fear memory formed after trauma (Experiment 3), indicating an interplay of trauma and subsequent aversive learning. Analysis of the learning curves for the post-trauma aversive experience indicated that trauma heightened the perceived valence of the aversive stimuli, reflected in an increase in asymptotic freezing, rather than the rate at which learning occurred, and was independent of peripheral sensitivity to aversive stimuli. Lastly, the ability of trauma to induce these learning changes was dependent upon protein synthesis within the amygdala just after trauma (Experiment 4).

Conclusions: This work highlights the essential role of amygdalar protein synthesis in inducing lasting changes in aversive learning after trauma, by augmenting the perceived intensity of future aversive events. Current work is ongoing to determine how this augmented valence is encoded within the amygdala, using a combination of in vivo calcium imaging and immediate early-gene tagging. By dissecting how trauma alters both the psychological process (i.e., enhanced valence), and neural function (i.e., how the amygdala processes subsequent aversive events), this work will hopefully render insights into why some are more vulnerable to trauma than others.

Keywords: Fear, Amygdala, Trauma

Disclosure: Nothing to disclose.

P85. Global Reductions in White Matter Integrity are Associated With Worsening Anxiety Symptoms in Preadolescent Girls

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Background: Anxiety is dimensional and, when extreme, becomes maladaptive and is pathological. Anxiety disorders (ADs) are among the most common childhood psychiatric illnesses, affecting up to 30% of youth. In addition, numerous children have subclinical and persistent anxiety symptoms that do not meet DSM-5 criteria. Like children with ADs, these children also suffer considerably and are at increased risk to develop more significant stress-related psychopathology later in life. Because anxiety is dimensional in nature, studying the full range of anxiety may provide insights into the factors that contribute to the varying degrees of distress and disability experienced by children with pathological anxiety. Understanding the factors underlying the development and expression of anxiety in young girls is of particular interest because after the transition to adolescence there is a two-fold increase in the prevalence of ADs in adolescent girls compared to boys that persists throughout the reproductive years. The current study examines longitudinal relations among anxiety symptoms and white matter (WM) microstructure in 182 preadolescent girls, studied over three years with diffusion tensor imaging (DTI) as they enter adolescence.

Methods: Preadolescent girls with varying levels of anxiety were enrolled between ages 9-11 and characterized using clinical, behavioral, and diffusion tensor imaging (DTI) assessments. Based on the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) and Clinical Global Impression Scale-Severity (CGI-S), participants were categorized into three groups: 1) controls, 2) subthreshold-AD, and 3) AD. Control participants exhibited very minimal, if any, symptoms of anxiety and did not meet criteria for any DSM-V diagnoses (CGI-S = 1, normal/not at all ill). Subthreshold-AD participants exhibited subsyndromal but persistent levels of generalized, separation, and/or social anxiety but did not meet DSM-V criteria for these disorders (CGI-S = 2, borderline mentally ill; or CGI-S = 3, mildly ill). AD participants met full DSM-5 criteria for generalized anxiety disorder, separation anxiety disorder, and/or social anxiety disorder (CGI-S ≥ 4, moderately ill or worse). Children's anxiety symptoms were rated by both the child and a parent using the Screen for Child Anxiety and Related Emotional Disorders (SCARED). The final sample ($n = 182$) included 49 controls, 82 subthreshold-AD, and 51 AD girls that completed the initial year of the study. Girls with pathological anxiety (subthreshold-AD and AD, $n = 133$) were followed longitudinally for up to 3 years with repeated clinical and imaging assessments. Images were collected on a 3T scanner using a 32-channel head coil, and deterministic tractography was performed to delineate whole-brain WM and seven bilateral tracts of interest across the

brain (uncinate fasciculus, superior longitudinal fasciculus, corpus callosum, cingulum, stria/fornix, inferior fronto-occipital fasciculus, internal capsule). Cross-sectional analyses in the full sample assessed group differences in DTI metrics (fractional anisotropy [FA], mean diffusivity [MD], radial diffusivity [RD]) in the 7 WM tracts and whole-brain WM. In the sample of girls with pathological anxiety (subthreshold-AD and AD participants), linear mixed-effects models (LMEMs) assessed longitudinal within-participant relationships between WM microstructural parameters and child-rated SCARED scores. Analyses controlled for age and pubertal status (i.e., Pubertal Development Scale (PDS) scores).

Results: Cross-sectional ANCOVAs comparing controls, subthreshold-AD and ADs girls revealed no statistically significant associations between anxiety and FA in any of the WM tracts of interest or in whole-brain WM. In longitudinal LMEMs, child-rated SCARED scores exhibited a significant negative correlation with whole-brain FA at the individual level (Std. β (95% CI) = -0.06 (-0.09 to -0.03), F(1,46.24) = 11.90, $P = 0.001$), such that increases in a child's anxiety level predicted decreases in her whole-brain FA, independent of developmental status. As expected, both age (Std. β (95% CI) = 0.08 (0.05 to 0.12), F(1,64.60) = 24.75, $P < 0.001$) and PDS scores (Std. β (95% CI) = 0.07 (0.03 to 0.10), F(1,51.68) = 13.39, $P < 0.001$) were positively correlated with whole-brain FA on the individual level, and our LMEMs controlled for both variables.

Conclusions: In summary, we present one of the largest longitudinal neuroimaging studies of pediatric anxiety, demonstrating that, on an individual level in girls with pathological anxiety, worsening of anxiety symptoms is associated with a global decrease in WM microstructural integrity. Importantly, this relationship is independent of age and puberty. An extensive body of literature has shown that childhood and early adolescence are periods of significant WM growth. Our results demonstrate that within this overarching developmental pattern, individual variations in whole-brain WM are dynamically linked to anxiety symptom severity. The longitudinal within-subjects approach that was used underscores the value of assessing brain structure and function at an individual-level and over time in studying neural correlates of psychopathology. The findings support future studies investigating the possibility of targeting WM as a modality to aid in the prevention and treatment of childhood anxiety disorders.

Keywords: Childhood Anxiety, Dimensional Psychopathology, White Matter Microstructure, Diffusion Tensor Imaging (DTI), Longitudinal Study

Disclosure: Nothing to disclose.

P86. Elucidating the Role of BNST PKCdelta Cells in Stress- and Anxiety-Like Behaviors

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Background: Chronic stress exposure is implicated in psychiatric disorders such as PTSD, anxiety, depression, and addiction. The Bed Nucleus of the Stria Terminals (BNST) is part of the extended amygdala known to mediate many stress responses and anxiety-like behaviors that may contribute to these disorders and the cycle of relapse characteristic of substance use disorders. The BNST contains numerous cell types distinguishable by the expression of distinct neuropeptides and proteins, and evidence suggests that cell-type contributes unique facets to stress responses. For example, one of the most well-characterized BNST cell types expresses corticotropin-releasing factor (BNST(CRF)) and is known to promote anxiety-like behavior and reinstatement of drug seeking in rodent models. However, attempts to target the CRF system in addiction treatments have been largely unsuccessful, underscoring the necessity of exploring alternative therapeutic targets and gaining a more thorough understanding of the heterogeneity within the region. BNST cells expressing Protein Kinase C-delta (BNST(PKCd)) are an equally abundant but largely distinct population from the BNST(CRF) cells. We have found that expression of this kinase is dynamically regulated by stress, and that these cells show increased activity during active stress coping, but further studies are needed to dissect the role of PKCd and BNST(PKCd) cells in stress responses and anxiety-like behaviors.

Methods: We have begun to better understand the function of BNST(PKCd) cells by first situating them in their broader circuit context. I used rabies-mediated tracing in conjunction with brain clearing and whole-brain light sheet microscopy to examine the brain-wide inputs to BNST(PKCd) cells, and we are using synaptophysin-based tracing to examine the brain-wide outputs of this population. We are also discerning the electrophysiological profile of BNST(PKCd) cells in order to learn more about the basal and input-specific properties of this understudied population. Finally, I used in vivo optogenetics to determine the effect of BNST (PKCd) cell activation, injecting DIO-ChR2 in the BNST of PKCd-Cre mice and measuring behavioral effects during real time place preference (RTPP), open field (OF), elevated plus maze (EPM), and novelty-suppressed feeding test (NSFT.) My ongoing studies are also using the inhibitory opsin iC ++ to investigate the effect of PKCd cell inhibition on anxiety-like behaviors in the presence or absence of stress.

Results: I have found that mice receiving activation of BNST(PKCd) cells in RTPP show a mild aversion to the stimulation side compared to YFP controls ($p = 0.046$). Optogenetic stimulation also decreases time spent in the open arms of the EPM ($p = 0.01$) and results in a trend toward increased latency to first bite in the NSFT ($p = 0.09$). Preliminary results suggest that BNST(PKCd) cells receive inputs from brain structures involved in a variety of processes including affective responses and danger signals such as the CeA, BLA, and PBN, consumption behaviors such as the lateral hypothalamus, and sensory processing such as the thalamus as well as auditory and olfactory processing regions. Investigation of their output regions is ongoing. Electrophysiologically, we are observing a trend for this population to rest at more hyperpolarized membrane potentials and have a higher rheobase than other cells in the BNST, and further investigation is also ongoing.

Conclusions: Initial results suggest that BNST(PKCd) cells may be involved specifically in fine-tuning the response to particularly stressful or salient stimuli. In vivo optogenetic data show that when this population is activated, it results in mild aversion and increased anxiety-like behavior. Our previous work has found that BNST(PKCd) cells express little-to-no cfos following stress, but there is a significant increase in calcium signaling during active stress coping in this population as measured by fiber photometry via GCaMP. This in combination with preliminary electrophysiological profiling suggesting this population requires significant stimulation to fire action potentials, and anatomical data suggesting they receive significant input from both affective/danger signal and sensory processing regions, together suggest these cells may serve as a coincidence detector for salient negative environmental stimuli. By elucidating the dynamic, cell-type specific role of BNST(PKCd) cells in the BNST, we will provide a more comprehensive understanding of the mechanisms regulating anxiety-like behaviors and other stress-related disorders.

Keywords: Anxiety and Stress, BNST, PKCdelta

Disclosure: Nothing to disclose.

P87. Acute Ketamine Facilitates Fear Memory Extinction in a Rat Model of PTSD Along With Restoring Glutamatergic Alterations and Dendritic Atrophy in the Prefrontal Cortex

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Background: Stress represents a major risk factor for psychiatric disorders, including Post-Traumatic Stress Disorder (PTSD). Here we assessed the effects of single subanesthetic administration of ketamine on the alterations of the excitatory glutamate system in the prefrontal cortex (PFC) and behavior induced by acute footshock (FS)-stress.

Methods: Male rats were subjected to FS-stress and racemic ketamine (10 mg/kg) was administered before or after FS. Basal and depolarization-evoked release of glutamate/GABA in PFC was measured with the method of purified synaptosomes in superfusion. Patch-clamp recordings were used to assess synaptic transmission. Dendritic morphology was measured in Golgi-Cox stained sections and in vitro. Behavioral alterations were also evaluated.

Results: Ketamine, while inducing a mild increase of glutamate release in the PFC of naïve rats, blocked the acute stress-induced enhancement of glutamate release when administered 24 or 72 h before, or 6 h after FS-stress. The treatment with ketamine 6 h after FS-stress also reduced the stress-dependent increase of spontaneous excitatory postsynaptic currents (sEPSCs) amplitude in prelimbic cortex. Moreover, ketamine injection 6 h after FS-stress was found to rescue apical dendritic retraction of pyramidal neurons induced by acute stress in the prelimbic cortex and facilitated contextual fear extinction.

Conclusions: These results show rapid effects of ketamine in animals subjected to acute FS-stress, in line with previous studies suggesting a therapeutic action of the drug in PTSD models. Our data are consistent with a mechanism of ketamine involving re-establishment of synaptic homeostasis, through restoration of glutamate release, and structural remodeling of dendrites.

Keywords: (2R,6R)-hydroxynorketamine, Glutamate Homeostasis, Acute Stress, Dendritic Remodeling, Fear Extinction

Disclosure: Hoffmann-La Roche: Employee (Spouse)
Johnson and Johnson: Consultant (Self)

P88. Data Driven Intrinsic Connectivity Subtypes Identify PTSD and mTBI

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Background: There is considerable diagnostic overlap across posttraumatic stress disorder (PTSD) and symptomatic mild traumatic brain injury (mTBI) as well as within-condition symptom and neurobiological heterogeneity. Brain connectivity is a promising biomarker for understanding heterogeneity in psychopathology, but the extent to which these conditions are characterized by shared versus distinct resting state patterns has not been established. We used a data-driven analysis of intrinsic network connectivity to identify neural subgroups present in individuals with PTSD, mTBI, or their comorbidity. We sought to identify neurobiological patterns, agnostic of clinical label, that reflect commonalities in brain dysfunction that can then be linked to phenotypic traits. This unsupervised approach is advantageous in cases where the same clinical phenotype can be derived from multiple biological pathways.

Methods: One hundred and sixty-seven individuals completed a resting state functional magnetic resonance imaging scan, clinical symptom measures, and neuropsychological assessments as part of the Injury and Traumatic Stress Clinical Consortium (INTRuST). Directed functional connectivity between large-scale intrinsic connectivity networks relevant to PTSD and/or mTBI were calculated using Subgroup-Group Iterative Multiple Model Estimation (S-GIMME). S-GIMME is a data driven causal search algorithm used to model directed functional connectivity of fMRI BOLD signal between predefined regions. We conducted S-GIMME with functional connectivity across 9 networks implicated in PTSD and/or mTBI: salience, default mode, dorsal and ventral attention, cingulo-opercular, visual, frontoparietal, sensorimotor, and subcortical networks. Subgroups were compared across diagnostic, clinical severity, and neuropsychological features. Associations between functional connectivity and clinical measures was conducted within observed subgroups.

Results: Two subgroups emerged: subgroup 1 was characterized by a greater number of subgroup-specific paths than subgroup 2, which included connections between the dorsal attention to sensory network, cingulo-opercular to dorsal attention, and default mode network to salience network. Subgroup 2 had two unique subgroup paths between the ventral attention and visual networks and salience to subcortical networks. Subgroup 1 demonstrated relatively lower connectivity strength than subgroup 2 in paths that were observed across both subgroups. Neurally-derived subtype was modestly but statistically associated with clinical grouping, $\chi^2(2) = 6.67$, $p = .036$. Subgroup 1 was characterized by higher PTSD re-experiencing symptoms $F(1,157) = 7.44$, $p = 0.007$ but no statistically significant differences were observed on neuropsychological variables. PTSD re-experiencing symptoms and arousal symptoms were positively correlated with lagged functional connectivity between the default mode and salience network in subgroup 1.

Conclusions: Results underscore the potential utility in identifying homogeneous neural subgroups that are related to, but not fully redundant with, diagnostic classification. The observed associations between default mode-salience network connectivity and PTSD re-experiencing and hyperarousal symptoms are consistent with proposals that communication between these two networks underlies hypervigilance and intrusive symptoms. This connectivity may reflect an inability to appropriately balance attention to internally focused thoughts and memories and salient, potentially threatening cues in the environment. Given the high degree of symptom overlap that poses diagnostic challenges, using brain-based groupings may better identify neural substrates that are unique and diverging across condition.

Keywords: Anxiety and PTSD, Mild Traumatic Brain Injury, Resting and Task fMRI

Disclosure: Nothing to disclose.

P89. Role of Direct Prefrontal Cortical Projections to the Central Amygdala in Mediation of High Fear States

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Background: In the face of threat, organisms display a continuum of defensive behaviors and flexibly shift between survival

strategies; however, maladaptive responses to perceived threat are associated with several mental illnesses. Previous work has shown that fear learning and expression of defensive behavior is mediated by neuronal circuits in the central nucleus of the amygdala (CEA) -- with a mutually inhibitory circuit motif in the CEA regulating transitions between defensive states. The source of excitation to these CEA GABAergic neurons driving intense defensive responses, such as flight, is unknown. Because cortical dysfunction is observed in clinical populations with panic disorder, we sought to test the role of direct cortical projections to the CEA in the regulation of high fear responses. Here, we describe a novel projection from the dorsal peduncular nucleus (DP), a subdivision of the ventromedial prefrontal cortex, to the CEA in mediating high-intensity defensive responses.

Methods: Male and female C57BL/6J, or Vglut (1/2)-Cre mice, aged 10-12 weeks old, were stereotaxically injected with retrograde fluorescent beads into the CEA, or anterograde AAV-DIO-mCherry virus in the DP, respectively, to study anatomical connectivity. FOS expression was analyzed in DP → CEA projectors to evaluate the activation of neurons following conditioning in a paradigm we developed to study freezing and flight responses within subjects. We used an intersectional viral vector approach to express GCaMP6f specifically in DP → CEA projection neurons, and we performed freely moving in vivo calcium imaging using custom-built open source miniscopes. For chemogenetic and optogenetic manipulation of the DP → CEA pathwayem, CAV2-Cre virus was injected into the CEA and either Cre-dependent DREADD vectors (Gq/Gi), halorhodopsin, or channelrhodopsin, were injected into the DP. To activate DREADDs, CNO (5 mg/kg, i.p.) was injected 30 min prior to behavioral tests. Optic fibers were targeted to the CEA for optogenetics. Mice were then subjected to avoidance tests (open field test, OFT and elevated plus maze, EPM) and serial compound stimulus fear conditioning for 2 days, with recall on next day, to test defensive responses (freezing and flight).

Results: Retrograde tracing studies show that the DP, as compared to infralimbic and prelimbic cortex, sends substantial projections to the CEA (One-way ANOVA, F (2,15) = 5.512, $P < 0.05$). These projections innervate the medial subdivision of the CEA (CEm) and are Vglut1-positive (Two-way ANOVA, CEM vs CEL, F (1, 50) = 25.82, $P < 0.001$; Vglut1 vs Vglut2, F (1, 50) = 121.5, $P < 0.001$). FOS expression is significantly greater in this pathway following fear conditioning, as compared to homecage control, or shock-only groups (One-way ANOVA, F (2,34) = 20.41, $P < 0.001$). Miniscope recordings of Ca2+ activity show that DP → CEA projectors are activated specifically by high-intensity threats. Furthermore, threat-responsive cells are positively and negatively correlated with escape speed and freezing, respectively (Pearson correlation, $r = 0.9723$ and -0.9883, respectively; both $P < 0.05$). We did not observe any significant difference in neuronal responding to different cues during recall in a low-threat context. Optogenetic and chemogenetic inhibition experiments suggest that the DP → CEA pathway is necessary for avoidance behavior, and for generating learned flight responses. Inhibition of the DP → CEA pathway increased the time spent by animals in the center zone of the OFT and in the open arm of the EPM (One-way ANOVA, OFT, F (3,19) = 8.023, EPM, F (3,19) = 8.813; both $P < 0.001$), without affecting the total distance travelled, suggesting anxiolytic effects. Finally, results from in vitro recordings demonstrate that these DP □ CEA projectors have excitatory effects on CEm neurons.

Conclusions: Our data suggest that the DP → CEA pathway is necessary to induce behavioral switching during high fear states. These results are the first demonstration that the prefrontal cortex exerts direct top-down control over the CEA in the regulation of defensive responses and could be an important avenue of investigation for treatment of PTSD and panic disorders.

Keywords: Amygdala, Defensive and Motivated Behaviors, Fear Conditioning, Medial Prefrontal Cortex, Anxiety and PTSD

Disclosure: Nothing to disclose.

P90. Complementary Roles for the Medial and Orbito-Frontal Cortex in Learning of Probabilistic Punishment

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Background: The ability to learn the relationship between reward and risk of harm is critical for survival and a process commonly compromised in mood and addictive disorders. For example, perseverative reward seeking despite negative consequences is a hallmark of addiction whereas excessive suppression of behavior due to exaggerated perceived risk of harm is seen in anxiety disorders. While there have been recent advances in assessing this relationship, the neuronal basis of how probability of harm influences reward processing and action selection remains poorly understood.

Methods: We designed a novel behavioral model to assess how instrumental responses are modified by varying probabilities of punishment. Male and female rats ($n = 8$) were trained to perform a chained seek-take procedure whereby two successive and spatio-temporally distinct instrumental actions were reinforced by sucrose pellets. The "risky" seek link of the chain was probabilistically punished by mild foot shock, while the "safe" take link of the chain deterministically resulted in reward delivery. We used fiber photometry to record neural calcium activity in two regions of the prefrontal cortex, the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC), during the learning of this task to inform how action encoding adapts to the learning and extinction of probabilistic punishment contingencies. The emphasis on these regions was supported by a large literature implicating them in outcome and harm probability processing. Significant differences described in Results were determined by permutation tests or analysis of variance comparing activity after learning to either no risk periods or before the task was learned.

Results: Rats decreased instrumental responding for reward as the probability of punishment increased with females being more sensitive to punishment than males. Different patterns of learning-related changes in neural encoding were observed in mPFC and OFC. While the mPFC modified its response to risky actions (i.e. punishment contingencies), OFC modified its response to safe actions and punishing outcomes. Moreover, the positive correlation in OFC-mPFC activity observed during seek action execution when there was no risk of punishment was attenuated with increased probability of punishment. The change in action encoding and disruption of correlated activity were normalized when punishment contingencies were removed.

Conclusions: We have designed a behavioral paradigm for assessing punishment resistance that may be relevant to reckless behavior and some aspects of learned anxiety. Using this paradigm we find that prefrontal cortex subregions play unique and complimentary roles in adapting to the risk of harm. While the mPFC may be important in learning punishment contingencies, the OFC may update the value of rewarded actions and punishment when risky contingencies are learned. These findings provide mechanistic insight about adaptive changes in cortical networks that support learned anxiety.

Keywords: Anxiety, Orbitofrontal Cortex, Fiber Photometry, Addiction, Impulsivity

Disclosure: Nothing to disclose.

P91. Systems Biology Dissection of PTSD in Diverse Populations: From Geneticsto Cell-Type Specific Mechanisms

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Background: Many advances have been made towards understanding the genetic and pathophysiological architecture of stress-related psychiatric disorders such as post-traumatic stress disorder (PTSD). Perturbations in dorsolateral prefrontal cortex (dlPFC) function have been implicated in the development of PTSD. Transcriptome imputation leverages tissue-specific cell-type-specific genotype-expression reference panels to build databases of genetically regulated gene expression. These models can be applied to GWAS to conduct transcriptome-wide association studies (TWAS) to prioritize gene-trait associations (GTAs) with functional importance. Available TWAS models exhibit both technical and methodological limitations, including limited expression data in diverse ancestries and extensive validation with observed data.

Methods: We developed PEC.db - a new family of dlPFC reference databases built from ~453 adult healthy control samples of European ancestry (EA), and 165 samples of African ancestry (AA) from the PsychENCODE consortium (PEC). In addition to gene expression and splicing predictions, databases were constructed for isoforms, relative cell type abundance-expression interactions.

Prediction accuracy was evaluated using external bulk-tissue and single-cell datasets. The new models were applied in meta-analyses of PTSD GWAS from PGC and MVP consortia (EA ~400K, AA ~70K). We (i) analyzed bulk-tissue transcriptomes from postmortem dlPFC tissue of PTSD, and control subjects (110/group), and 600K single-nucleus transcriptomes from postmortem dlPFC tissue of PTSD, and control subjects ($n = 16$/group) to identify cell-type-specific transcriptional changes associated with PTSD and/or MDD.

Results: PEC DLPFC gene expression predictions were accomplished for 10013 genes in EA

ancestry and 4033 genes in AA ancestry. The PEC DLPFC models significantly outperform available dlPFC reference panels in prediction accuracy [e.g., PEC EA vs GTEx-v8 Cortex: $t = -17.928$, df = 10054, p-value < 2.2e-16 and PEC AA vs GTEx-v8 Cortex: $t = -16.437$, df = 9478.3, p-value < 2.2e-16] andin correlation with observed expression in an external sample [e.g., PEC EA vs GTEx-v8 Cortex: $t = 6.658$, df = 8960.6, p-value = 2.938e-11 and PEC AA vs GTEx-v8 Cortex: $t = 6.8949$, df = 6616.2, p-value = 5.888e-12] . These improvements resulted to increases in the number of total GTAs across the two largest EA PTSD GWAS in ~400K [PEC DLPFC (nGTAs = 23) vs GTEx-v8 Cortex (nGTAs = 15); 53% increase], thus identifying a large number of novel gene-disease associations. While the EA TWAS analysis did not have significant power to detect GTAs, we observed no significant relationship between EA and AA TWAS effect sizes (Rho = 0.016, df = 2860, ns). CRHR1-IT1 (intronic transcript of CRHR1) and other genes of 17q21.31 locus had Bonferroni-significant DLPFC PTSD GTAs and were significant neuronal snDEGs for PTSD.

Conclusions: We developed and validate developed TWAS models across ancestries and use them to confirm dlPFC involvement in PTSD. Discovered GTAs were overlayed with DEGs in postmortem brains at the bulk and single-cell level.

Keywords: Transcriptome, Genetics, PTSD, Single Cell, Cell Type Specific

Disclosure: Nothing to disclose.

P92. Abnormal Dynamic Functional Connectivity During Fear Extinction Learning in Anxiety Disorders

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Background: The ability to extinguish the conditioned fear is critical for preventing fear and anxiety. Exploring the neural circuits of extinction learning can facilitate the understanding of the psychopathology underlying fear- and anxiety-related disorders. The field has focused on a limited number of brain regions including the medial prefrontal cortex, insular cortex, hippocampus, and amygdala in fear conditioning and extinction, with the other systems overlooked. Here we explored the dynamic changes of large-scale functional connectivity (FC) across the extinction learning, examined how is the FC altered in anxiety disorders.

Methods: Nighty-one individuals with at least one anxiety disorder (ANX) and 92 controls without an anxiety disorder (CT) underwent a two-day fear conditioning and extinction paradigm in a functional magnetic resonance imaging (fMRI) scanner. We estimated the trial-by-trial functional connectivity across the brain during extinction learning and compared the two groups using network-based statistic analysis. We conducted correlation analysis to link the extinction learning-induced functional connectivity with neural data during extinction memory recall and with clinical measures (anxiety sensitivity index, beck anxiety inventory, beck depression inventory, and state trait anxiety inventory-trait form). The reported p-values were familywise error-corrected.

Results: The CT exhibited increased FC from early to late extinction learning specifically to a conditioned stimulus. The ANX group, in contrast, showed widespread dysconnectivity compared with CT (cluster-level $p < 0.001$), with the reductions predominantly affecting interactions between the default mode network, somatomotor network, frontoparietal control network, and the rest of the brain. The increase of extinction-induced FC negatively correlated with FC principally within the same systems in ANX ($r = -0.63$, $p < 0.001$), and positively correlated with ventromedial prefrontal cortex activation in CT ($r = 0.37$, cluster-level $p < 0.05$), during extinction recall in next day. The increased FC during extinction learning correlated with clinical measures (canonical correlation analysis $r = 0.51$, $p = 0.002$).

Conclusions: These findings provide evidence supporting recent studies implicating distributed brain regions in attention, conscious processes, learning and consolidation of fear extinction memory in the human brain. The disfunction of anxiety disorder may associate with the widespread altered functional connectivity across different stages of extinction learning.

Keywords: Fear Extinction, Dynamic Functional Connectivity, Anxiety Disorder, fMRI

Disclosure: Nothing to disclose.

P93. Protein Pathways Underlying PTSD and Stress-Related Disorders

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Background: PTSD is a severe, debilitating and prevalent disorder occurring in the aftermath of significant trauma exposure. Despite a rapidly expanding understanding of the genetic architecture of PTSD and neural circuit mechanisms underlying fear-based disorders such as PTSD, there have been no large postmortem brain studies elucidating the molecular biology underlying this disorder. The neurobiology of PTSD with regard to trauma-associated genetic, epigenetic and transcriptional mechanisms is increasingly understood, yet many critical questions remain. Recent developments including the creation of large scale GWAS consortia to identify genetic variants associated with increased risk for PTSD require postmortem human brain tissue to elucidate the molecular biological mechanisms. The paucity of postmortem brain studies of PTSD reflects the fact that there have been few

postmortem brains from PTSD subjects for this purpose. The recent acquisition by the Lieber Institute for Brain Development (LIBD) of a large, well characterized cohort of postmortem human brains from PTSD subjects and controls has created a unique opportunity to correct this shortcoming while advancing our knowledge of the molecular biology of PTSD.

Methods: Differential proteomic analyses is being performed, including targeted proteomics (epigenetic readers and writers and the inflammasome) as well as Mass Spec-based large-scale proteomic profiling of brain areas comparing PTSD+, PTSD-/MDD+, and healthy control tissue. We hypothesize that there will be differences in the PTSD proteome that varies by brain region. Additionally, we hypothesize that differences at the level of the transcriptome and epigenome will be translated into a differentially expressed proteome within PTSD relevant biological pathways. Our approach will confirm translated protein level findings simultaneously identifying novel protein targets and pathways (i.e. proteins not directly related to differences in the transcriptome) of relevance to PTSD.

Results: We present ongoing collaborative work, utilizing Genetic consortium based PWAS analyses as well as MS proteome analyses to identify novel protein pathways associated with PTSD, followed by targeted validation in post-mortem brain samples.

We integrated human brain proteomes with PTSD GWAS results to perform a proteome-wide association study (PWAS) of PTSD. Deep human brain proteomes ($N = 528$) were profiled from the dorsolateral prefrontal cortex using isobaric tandem mass tag mass spectrometry. The PTSD GWAS from the Million Veteran Program (MVP; N~214,000) was used for the discovery PWAS and the PTSD GWAS from the Psychiatric Genomics Consortium (PGC; N~175,000) for the confirmation PWAS. The discovery PWAS identified > 10 genes whose cis-regulated brain protein abundances were associated with PTSD at FDR $p < 0.05$.

Separately, using MassSpec Proteomics, proteins in amygdala, PFC, and hippocampus which survive study-wide multiple corrections have been identified separating PTSD from Depression from healthy controls. We validated a number of these pathways with independent western blot.

Conclusions: Using both large-scale PWAS approaches combined with direct MassSpec-based proteomic identification, we have identified a number of protein pathways related to risk for PTSD, based on neural circuit regions known to be involved in fear- and threat-related disorders. These protein pathways provide novel and tractable targets for further mechanistic studies to elucidate the pathogenesis of PTSD and develop effective therapeutics.

Keywords: PTSD, Brain, Proteomic, Therapeutic Target

Disclosures: Alto Neuroscience, Brainsway,: Grant (Self)
Bioxcel, Bionomics: Consultant (Self)
Janssen: Advisory Board (Self)

P94. Mechanisms of PTSD Molecular Pathology: Integration of Single Cell-Type Genomics

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Background: Post-traumatic stress disorder is a multigenic disorder occurring in the aftermath of severe trauma exposure. Recent studies have begun to detail the molecular biology of the postmortem PTSD brain using bulk-tissue transcriptomic and epigenetic analyses. However, given the array of PTSD-perturbed molecular pathways identified thus far (i.e. glucocorticoid signaling, GABAergic transmission, and inflammatory signaling), it is unlikely that a single cell type is responsible. It is therefore necessary to uncover the individual cell type contributions to the molecular pathology of PTSD.

Methods: We isolated ~1.2M nuclei from human postmortem dorsolateral prefrontal cortex cases and controls for single nucleus RNA sequencing across three diagnostic cohorts: PTSD, MDD (Psychiatric control), and normal controls to identify neuronal and non-neuronal cell type clusters and cell type-specific gene expression changes. We then performed ATAC-sequencing, to measure chromatin accessibility from these same nuclei. We identified open genomic regions harboring risk alleles for PTSD and integrated our RNA and ATAC datasets.

Results: We identified 25 distinct cell type clusters including neuronal and non-neuronal cell types. We identified over 800 FDR significant differentially expressed genes across many cell types and confirmed expression changes of several genes implicated in PTSD pathophysiology including ELFN1, FKBP5, and SGK1. By adding an additional molecular modality- chromatin accessibility, we were able to improve our transcript based clustering and identify a consistent relationship between chromatin accessibilities and mRNA levels providing unparalleled molecular resolution at the individual cell-type level.

Conclusions: This work is the first step in the creation of a cell type-specific atlas of stress disorders. These findings provide a global picture of the cell type-specific molecular regulatory mechanisms that govern stress effects on the human frontal cortex. Additionally, applying functional genomic approaches to characterize risk alleles within specific cell types may help determine which neurotypical processes are most impacted by stress.

Keywords: PTSD, Postmortem Brain Tissue, Genomics, MDD, Single Cell Omics

Disclosure: Nothing to disclose.

P95. Single-Nucleus RNA Sequencing of Amygdala During Fear Conditioning and Extinction

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Background: Post-Traumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder with profound social burden and few effective treatments. Fear extinction deficits are thought to contribute to PTSD pathogenesis. Research from animal models and from human neuroimaging studies implicate medial prefrontal cortex (mPFC) and amygdala, among other structures, as playing a crucial role in fear extinction memory formation. The molecular fingerprints of cell-types that are necessary and sufficient for fear extinction processes in these regions are incompletely understood but could lead to the identification of novel drug targets for PTSD.

Methods: Methods: We used single nuclear sequencing (InDrops) to sequence over 100,000 nuclei from both mPFC and amygdala from three behavioral groups of mice, home cage, fear conditioning, and fear extinction ($n = 8$ groups of $n = 2$-3 male mice). We identified clusters of cells in both regions and tested for differential gene expression analyses using the Seurat package. We have used fluorescent in situ hybridization (FISH) and immunohistochemical techniques to confirm markers for cell clusters found with single nuclear sequencing.

Results: Results: We previously presented results from mPFC: here we present results from the amygdala dataset. We have identified over 20 distinct cell-type populations within the amygdala, including glutamatergic neurons, GABAergic interneurons, astrocytes, microglia, and endothelial cells. Many of these

clusters express known cell-type specific markers, but we identify additional novel cell-type specific markers, and we have also identified rare populations of neurons with incompletely described molecular signatures. Marker analysis demonstrates that kappa-opioid receptor (Oprk1), a significant antidepressant receptor candidate is nearly exclusively expressed within FearOn Rspo2+ projection neurons within the basolateral amygdala. We identify both known differentially expressed genes with fear conditioning (Akap5), as well as novel cell-type specific gene expression changes (Igf1 in VIP interneurons), which we have confirmed with RNAscope (fold change 1.8, Unpaired *t*-test, home cage vs. fear conditioning, $p = 0.0008$).

Conclusions: Conclusions: We provide data to begin construction of a comprehensive map of cell-types within the mouse amygdala. We have identified both known and uncharacterized cell-types. Some of these cell-types possess transcriptional changes that may be necessary for fear memory formation. Follow-up studies will assess the functional role of these cell-types in the process of fear memory and fear extinction formation.

Keywords: Auditory Fear Conditioning, Amygdala, Single-cell RNA Sequencing

Disclosure: Nothing to disclose.

P96. Spatial Transcriptions

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Background: A coordinated transcriptional response across defined neuronal circuits integrating sensory, motor, autonomic, neuroendocrine, cognitive, and emotional functions is critical to re-establish homeostasis after exposure to stress and to store relevant memory information. Evidence suggests that maladaptive transcriptional alterations within a complex neurocircuitry are central to many stress- and trauma-related disorders. However, how different brain regions, their subdivisions and nuclei interact on the level of spatial transcriptomics influencing behavioral outcomes remains for the most part unknown. Here we test the hypothesis that fear learning induces highly specific, spatially defined, and brain-wide transcriptional differences across -and beyond- the stress neurocircuitry. BulkRNA-seq and single cell RNA-seq approaches are powerful tools to identify gene expression pattern in tissues and individual cell populations. However, both approaches insufficiently delineate the morphological context of gene expression. Recently, technologies that profile gene expression in-situ have been developed to overcome these limitations and provide genome-wide transcriptome data with high spatial resolution.

Methods: We generated spatial transcriptomics data in C57BL/6 mice exposed to a standard auditory fear conditioning paradigm (30 sec 75dB tone co-terminating with a 1 sec 0.6mA mild foot shock; total of 5 tone shock pairings or tone only control; $n = 8$ per group). Brains were harvested in the early memory consolidation period, 2 hrs after the last CS-US pairing. Sections targeting the amygdala, hippocampus, thalamus, hypothalamus, and cortical regions were placed on capture areas of 10X Genomics Visium chips. After H and E staining and high resolution brightfield imaging an on-slide permeabilization and library preparation was performed followed by Illumina sequencing targeting 50,000 reads per spot. Due to the paucity of off the shelf analysis pipelines, we developed custom scripts in *R* to process sequencing data and perform differential expression analysis.

Results: As expected, unsupervised clustering analysis of the obtained expression data (total $n = 16$) reveals anatomically correct clustering into 10 major brain regions. We performed differentially expressed gene (DEG) and enrichment analyses using data from the Allen Brain Atlas confirming the identity of the identified clusters. For example, the top differential expressed genes at pFDR < 0.05 for cluster 8 (representing the hippocampal area) are Hpca, Wipf3, Cabp7 and Neurod6, all highly expressed in the mouse hippocampus. Further sub-clustering yielded a total of 33 subregions and nuclei including, for example, a stratification of the hippocampus into CA1, CA2/CA3 and the dentate gyrus. We also integrated single-cell RNA-seq reference data from the Allen Brain Institute or DropViz to enhance resolution. Next, we piloted the detection of DEGs between fear conditioned (FC) and control (CTRL) animals using the Visium platform. After data QC, normalization and clustering, differential gene expression analysis between FC and CTRL animals across all 33 subregions/nuclei was performed. We detect a total of $n = 344$ DEGs across subregions/nuclei with e.g. $n = 50$ DEGs in the hippocampus and $n = 76$ DEGs in the isocortex (all pFDR < 0.05). Interestingly, the top differential expressed genes in the hippocampus are all related to neuropsychiatric disorders with impairment of learning and memory. We also performed a network analysis with weighted gene correlation network analysis (WGCNA) providing evidence for a concerted transcriptional regulation in multiple brain regions and pathway in response to fear learning.

Conclusions: Our results show the successful implementation of the Visium spatial transcriptomics platform and suggest broad differential gene expression in response to fear conditioning. We provide for the first time evidence for a concerted and extensive transcriptional response in most of the brain regions investigated.

Keywords: Spatial Transcriptomics, Fear Learning, Gene Co-Expression Networks

Disclosure: Alkermes Inc: Consultant (Self)

P97. Cerebellum Structural Covariance Networks in PTSD and Depression

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Background: The cerebellum is historically known for its role in sensorimotor function, but it is also critical for cognition and emotion. Recent neuroimaging studies have reported altered cerebellum activation, functional connectivity, and volume in posttraumatic stress (PTSD) and related disorders, such as depression. In this study, the structure-function relationship of the cerebellum was explored using neuroimaging meta-analysis. The aim of the study was to identify the structural covariance networks of the cerebellum in PTSD and depression based on previously published neuroimaging papers. The hypothesis was that these networks would have shared and disorder-specific nodes.

Methods: The BrainMap structural/VBM database was searched for studies reporting volume reductions in gray and white matter with at least one coordinate in the cerebellum. Anatomic likelihood estimation (ALE) meta-analyses were conducted separately for PTSD (130 subjects, 8 experiments, 58 coordinates) and depression (606 subjects, 24 experiments, 307 coordinates) using GingerALE (voxel-level $p < 0.001$, cluster-level FWE $p < 0.05$). Spherical (12 mm) regions of interest were defined around the significant nodes, and the BrainMap functional database was used to identify the functional paradigms and behavioral domains most associated with activation in the cerebellum structural covariance networks (z-score > 3).

Results: The PTSD network included nodes in the left posterior lobe of the cerebellum, left superior and middle temporal gyri, left middle frontal gyrus, and bilateral medial frontal gyri. The functional paradigms associated with this PTSD network were

theory of mind and emotion induction. The depression network included nodes in the left inferior and superior frontal gyri. The functional paradigms associated with this depression network were semantic monitoring/discrimination, reading, word generation, phonological discrimination, naming, and *n*-back.

Conclusions: Contrary to expectations, the cerebellum structural covariance networks were distinct with no overlapping nodes between PTSD and depression. The PTSD network represents volume reductions in regions associated with social cognition, whereas the depression network represents volume reductions in regions associated with language, memory, and speech. These findings reveal unique alterations in structural networks in PTSD and depression and demonstrate the need for further studies of cerebellum's role in the pathophysiology of these disorders.

Keywords: PTSD, Depression, Cerebellum, Meta-Analysis

Disclosure: Nothing to disclose.

P98. Linguistic Markers of Chronic PTSD in World Trade Center Rescue and Recovery Workers: A Computer-Based Natural Language Processing Study

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Background: An emerging literature suggests the value of automated natural speech analysis in characterizing posttraumatic stress disorder (PTSD). Automated analyses of speech transcripts aim to identify linguistic patterns differentiating individuals with PTSD from trauma-exposed individuals who did not develop the disorder, with the ultimate goal of improving diagnostic characterization and treatment interventions for this chronic and disabling disorder. Studies to date have generally included heterogeneous samples of individuals with PTSD stemming from a range of trauma exposures and with varying degrees of chronicity. In the present study, we applied automated language processing methods to participant responses during open-ended interviews with World Trade Center (WTC) rescue and recovery workers, who were asked to describe their experience during the 9/11 terrorist attacks and their aftermath. Novel aspects of this study include a unique sample of WTC responders all exposed to a single, shared, and well-documented trauma, and the inclusion of a comparison group of highly resilient WTC responders.

Methods: WTC responders recruited from the WTC Health Program Responder Cohort (group-matched by age, race, marital status, education, and word count) completed in-person diagnostic interviews, including the Structured Clinical Interview for DSM-5 (SCID-5) and the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), administered by trained clinicians. Participants were also recorded during open-ended interviews while responding to the following prompt: "Please describe your experience of the 9/11 attacks and your experience during your involvement in the Work Trade Center recovery work". Interviews were designed to be non-directive; interviewers could further prompt participants by stating, "Is there anything more you'd like to say about your WTC recovery experiences?". Participants ($n = 10$ per group) were classified into "highly resilient" [high WTC-related exposure severity, no lifetime psychiatric disorders, mean (SD) past-month CAPS-5 = 1.4 (1.2) and "chronic PTSD" [met past-month DSM-5 criteria for WTC-related PTSD; mean (SD) past-month CAPS-5 = 30.7 (10.7)]. Analyses of interview transcripts were conducted using Language Inquiry and Word Count (LIWC) software. Bivariate analyses were conducted to identify linguistic categories that differed between groups at the $p < 0.20$ level. These categories were then entered into a multivariate analysis of variance to identify between-group differences in linguistic categories used in interview responses. We then conducted LASSO regression analyses to examine associations between individual PTSD symptoms and linguistic categories. Analyses were adjusted for full-scale IQ and responder type (police vs. non-traditional [e.g., construction worker]).

Results: Bivariate analyses revealed 19 linguistic categories that differed between groups. In a multivariate model, 3 categories reflecting biological processes (i.e., body words [e.g., cheek, hands, spit], Cohen $d = 2.0$); perceptual processes (i.e., feel words [e.g., feels, touch], $d = 1.7$); and drives (i.e., affiliation words [e.g., ally, friend, social], $d = 1.3$) showed large magnitude between-group differences, with WTC responders with PTSD using a greater proportion of feel and body words, and a lower proportion of affiliation words than highly resilient responders. Sleep disturbance was associated with a greater proportion of body ($\beta = 0.67$) words; intrusive thoughts about the WTC disaster with a greater proportion of feel ($\beta = 0.61$) words; and feeling distant or cut off from others with a lower proportion of affiliation words ($\beta = -0.53$).

Conclusions: This study identified potential linguistic markers of chronic PTSD in a sample of individuals exposed to a common traumatic event. Findings point to specific differences in speech patterns in responders with WTC-related chronic PTSD, compared to highly resilient WTC responders. Further, preliminary evidence indicates a close alignment between certain linguistic markers and specific PTSD symptom dimensions, suggesting that linguistic markers might map to specific underlying biological abnormalities. Further study in larger samples, in combination with biomarker studies (e.g., neural circuitry function), has the potential to deepen our understanding of this heterogeneous disorder and enhance personalized treatment interventions for individuals with chronic PTSD.

Keywords: PTSD, Automated Natural Speech Analysis, World Trade Center Responders, Linguistic Markers, Resilience

Disclosure: Nothing to disclose.

P99. Longitudinal Effects of COVID-19 Related Occupational Stressors on Health Care Workers and First Responders: Implications for Wellbeing, Workplace Retention, Suicidality, and the Relationship of Acute Stress Symptoms to PTSD

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Background: Elevated rates of psychiatric symptoms in health care workers working during the Covid-19 pandemic have been identified in multiple contexts. Less is known regarding the specific Covid-19 related occupational stressors associated with these psychiatric symptoms, and their impact on workplace functional impairment, professional retention, and suicidality.

Here, we report results from an ongoing longitudinal study of health care workers (HCW) and first responders (FR) working in the United States during the COVID-19 pandemic.

Methods: Participants were recruited via targeted outreach and paid advertising on social media, and assessments were completed using online surveys. Participants were assessed at baseline, then every 2-12 weeks for up to 9 months.

Exposure to COVID-19 related occupational stressors was assessed using a 13-point assessment scale assessing the frequency of potential COVID-19 related stressors, such as caring for patients severely ill with COVID-19, not having sufficient PPE, or experiencing an increased risk of infection with COVID-19 for one's

self or one's family members. These items could be summed to create a COVID-19 occupational stressors total score (CROS total). A factor analysis also identified 3 independent factors within the measure, corresponding to items emphasizing the total volume of COVID-19 related care provided ("Volume factor"), items emphasizing risk of infection for oneself or one's family ("Risk factor"), and items emphasizing a lack of support from one's workplace or feelings of futility ("Demoralization factor").

Psychiatric symptoms were assessed using standard psychiatric rating scales (PTSD Checklist [PCL5], General Anxiety Disorders-7 [GAD7], Insomnia Severity Index (ISI), and the Patient Health Questionnaire 9 [PHQ9] for depression). Impairment in occupational functioning and likelihood of leaving one's current field were each assessed using 2-item scales. Thoughts of suicide and self-harm were assessed via item 9 of the PHQ9.

Results: Results were obtained from $N = 543$ participants ($N =$ 339 HCW, 206 FR) representing 47 states. Among all respondents, a majority reported psychiatric symptoms in the clinical range at baseline assessment (37% for PTSD, 75% for depression, 75% for anxiety, 34% for insomnia). Symptom burden was strongly associated with the intensity of exposure to COVID-19 related occupational stressors (CROS total: $R = .54$ for PTSD, $R = .48$ for depression, $R = .43$ for insomnia, $R = .46$ for anxiety, all $p < 2.2e\text{-}16$).

Rates of endorsing thoughts of suicide or self-harm were significantly higher than the general population, with 21% of FR and 13% of HCW reporting such thoughts in the past two weeks. Score on this item was significantly related to CROS total for both FR ($R = .36$, $p < 1e\text{-}4$) and HCW ($R = .36$, $p = .01$).

A majority of health care workers (53%) and 39% of first responders indicated that their experiences working during the COVID-19 pandemic had somewhat or significantly decreased their likelihood of continuing to work in their current field. 22% of HCW and 14% of FR reported difficulty completing important work tasks. Both trouble completing work tasks and likelihood of leaving one's current field were significantly related to CROS total for HCW ($R = .26$, $p = 9.2e\text{-}6$; and $R = .26$, $p = 8.2e\text{-}6$, respectively), while only trouble completing work tasks was related to CROS total for FR ($R = .38$, $p = 3.5e\text{-}7$).

The relationship of the volume, risk and demoralization factors to psychiatric symptoms, along with covariates including gender, age, personal history of COVID-19 infection, and prior history of traumatic stress exposure, were evaluated using multivariable models. Across all participants, the volume, risk, and demoralization factors were all significantly related to all four psychiatric symptom domains, as was prior history of traumatic stress exposure and (for depression and anxiety) female gender. However, for all four psychiatric symptom domains, the demoralization factor was the strongest predictor. Similarly, the demoralization factor was the strongest predictor of adverse occupational outcomes, and thoughts of suicide or self-harm.

Of the psychiatric symptom domains, only PTSD symptoms were significantly associated with increase likelihood of leaving one's current field and trouble completing work tasks. Both PTSD and depression symptoms were significantly associated with thoughts of suicide or self-harm. In the longitudinal data, intrusive and hyperarousal symptoms at baseline were strongly and significantly associated with PTSD symptom burden 90 days later.

Conclusions: Working during the COVID-19 pandemic has been associated with significant adverse effects on the mental health and occupational functioning of both health care workers and first responders, and is associated with a significantly increased self-reported likelihood of leaving one's current field and thoughts of suicide or self-harm. Personal risk of infection, volume of care delivered, and demoralization are all significantly associated with psychiatric symptom burden and adverse occupational outcome, but demoralization shows the strongest associations. Of psychiatric symptom domains, PTSD is the most strongly associated with exposure burden and with adverse outcomes. Hyperarousal and intrusive symptoms at baseline assessment are predictive of sustained PTSD symptom burden.

Keywords: COVID-19, PTSD, Insomnia, Acute Traumatic Stress, Health Services

Disclosure: Nothing to disclose.

P100. Consistency Checks to Improve Measurement with the Clinician Administered Post Traumatic Stress Disorder Scale (CAPS)

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Background: CAPS is regarded as the "gold standard" in PTSD assessment. It is a structured

interview that yields a categorical diagnosis of PTSD and also a measure of the severity of PTSD symptoms. It can be administered in 30-60 minutes by a trained rater. The first 17 items of CAPS IV elicits ratings on Frequency (0=never; 1=once or twice; 2=once or twice a week; 3=several times a week; 4-daily or almost every day) and intensity (0=no distress; 1=mild; 2=moderate; 3=severe; 4=extreme) of symptoms and are used to compute a total severity score. The next 4 items measure duration, subject distress and functional impairment. A scoring algorithm is applied to these 21 items to arrive at a diagnosis. The CAPS also includes 3 global ratings and ratings of 5 associated features. To improve the reliability and validity of measurement in clinical trials, we previously developed consistency checks "flags" for the Montgomery-Asberg Depression Rating Scale(MADRS)(Rabinowitz et al.,2019), Positive and Negative Syndrome Scale (PANSS) (Rabinowitz et al,, 2017; 2021) and the Personal and Social Performance scale (PSP) (Rabinowitz et al, 2021). The objective of the current effort was to derive consistency flags for the CAPS-IV. Since a PTSD diagnosis in some settings could be connected to getting benefits, scoring inconsistencies may be more abundant with this rating scale as they not only reflect raters carelessness but intentional inaccurate reporting by the subject.

Methods: We systematically deconstructed CAPS scoring instructions and anchors to identify potential scoring inconsistency flags. These inconsistency flags were reviewed and confirmed by expert raters.

To test the ability of the flags to identify careless responses the flags were applied to Monte Carlo simulated data of 100,000 CAPS administrations.

Results: Twelve flags were derived. Two flags applied to most of the 17 symptom items (Flag 1: Frequency = 0 and Intensity>0 and Flag 2: Frequency>0 and Intensity = 0). The remaining 10 flags pertained to individual items. Five flags were rated as "High" flags, representing very probably or definitely incorrect rating, one as medium, reflecting probably incorrect rating. Flags were raised for 95% of the 100,00 Monte Carlo simulated CAPS administrations, 78% of the administrations had 4 or more flags and 60% 5 or more. Two high flags, Flag 1 and 2 were raised in more than 85% of the administrations.

Conclusions: Scoring consistency flags for the CAPS may be useful in the quest to improve

reliability and validity of clinical trials. Modified flags are currently being developed to cover the CAPS-V. Further testing using clinical trial data is planned.

Keywords: Psychiatric Measurement, PTSD, Clinical Trial Rating Methods

Disclosures: JNJ, Minerva: Consultant (Self) Lundbeck: Advisory Board (Self)

P102. Low Dose Ketamine and Ketorolac and OPRM1 A118G in Chronic Pain Patients

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Background: The OPRM1 A118G genotype has been associated with pain (Pecina et al. 2015) and stress vulnerability (Lovallo et al. 2015). A large number of US armed force members who terminated active service continues to have chronic pain (CP). Dadabayev et al. (2021) summarized our initial research that ketamine and ketorolac were effective analgesics in both patients with CP and CP + PTSD. The present manuscript describes the effects of OPRM1 A118G genotype on the analgesic, plasma cortisol and prolactin levels in the same group of patients.

Methods: A total of 35 of 40 participants were separated into four groups according to their OPRM1 genotype and infusion drug types (Genotype: AA or *G, drug: ketamine or ketorolac). A single low dose of ketamine (0.5 mg/kg) or ketorolac (15 mg) was administered. VAS scores were collected before infusion (baseline), 15, 40, 120, 240 min and 1 day after infusion. In addition, venous blood samples were collected at 40 min after drug infusion. The samples were centrifuged at 1200 rpm for 10 min at 4 °C and stored frozen at −80 °C until assay for plasma cortisol, prolactin and OPRM 1 A118G genotypes. To quantify cortisol and prolactin in plasma, a rapid highly sensitive and precise semi-automated chemiluminescent assay was conducted using Immulite (Siemens, Inc.), according to the manufacturer's directions (Siemens Healthcare Diagnostics, Tarrytown, NY). The intra-assay and inter-assay variability was < 5% for both cortisol and prolactin detection. OPRM1 genotypes were determined by the same methods as Hirasawa-Fujita et al. (2017). VAS scores, time of VAS score assessment and genotypes were analyzed by 3 way ANOVA. Cortisol and prolactin data were analyzed by 2 way ANOVA. Only p values that are less than 0.05 is considered significant.

Results: A total of 35 of 40 participants in Dadabayev et al., (2020) were divided into four groups according to their OPRM1 genotype and infusion drug type. There were 11 AA and 6 *G carriers given ketamine, and 16 AA and 2 *G carriers given ketorolac. Average VAS scores were compared between the chronic pain patients with AA and *G (AA + GG) at baseline, 15, 40, 120, 240 min and 1 day after either ketamine or ketorolac administration. All four groups had similar VAS scores at all the time points (as illustrated in Figure 1).

The analgesic effects of ketamine were confirmed in AA carriers at 15 ($p = 0.027$), 40 ($p = 0.011$) and 120 min ($p = 0.012$) as well as *G carriers at 120 min ($p = 0.034$) compared to baseline. The anesthetic effects of ketorolac were confirmed in AA carriers at 40 ($p = 0.032$) and 120 min ($p = 0.013$) compared to baseline. However, ketorolac anesthetic effects in *G carriers significantly weakened at 120 min ($p < 0.0001$) compared to 15 min after drug administration.

AA and *G carriers had similar cortisol and prolactin levels at 40 min after drug administration (either ketamine or ketorolac).

Conclusions: Both ketamine and ketorolac are effective analgesic agents. The effects of ketamine are somewhat greater than those of ketorolac. However $N = 35$ in the present study is very small. The small number of *G carriers may affect the results. Additional studies should be done to confirm these results.

Keywords: Ketamine, Ketorolac, Analgesic, OPRM1

Disclosure: Nothing to disclose.

P104. Age-Associated Differences in Resting State BNST Connectivity

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Background: The bed nucleus of the stria terminalis, or BNST, has emerged as a critical region for regulating key neural processes including stress response, anxiety, and social behaviors. Alterations in BNST connectivity has been associated with multiple psychopathologies, particularly anxiety and trauma-related disorders. Anxiety disorders have a peak onset in adolescence, raising the question of whether BNST changes occur across development.

Methods: This is a secondary analysis of resting state MRI data collected as part of the Philadelphia Neurodevelopmental Cohort (PNC). Participants were between the ages of 8 and 20 years old and met quality assurance (e.g. low motion). The final analyses included 1134 male and female participants. Whole brain connectivity analyses were performed with the left and right BNST as the seed regions. First, regression analyses were performed with age (linear) as the predictor (FWE corrected, voxel-wise $\alpha = 0.001$, FWE cluster-correction $\alpha = 0.05$). Second, the age-independent BNST network was evaluated by controlling for age (FWE corrected, voxel-wise $\alpha = 0.001$, FWE cluster-correction $\alpha = 0.05$).

Results: Older participants had stronger resting state connectivity between the right BNST and multiple cortical control regions including the posterior cingulate cortex, the supplemental motor area, and the orbitofrontal cortex (all clusters FWE $p < 0.05$). Younger participants had associated with stronger resting state connectivity between the right BNST and multiple regions associated with emotion processing, including the anterior cingulate cortex, the nucleus accumbens, and the hippocampus (all clusters FWE $p < 0.05$). The age-independent BNST network included robust connections with the dorsal amygdala, rostral and dorsal medial prefrontal cortex, and the insula.

Conclusions: This study is, to our knowledge, the first to describe differences in age-associated BNST resting state connectivity. Our findings suggest that in younger children have weaker connectivity between the BNST and cognitive control regions but greater connectivity with emotion-related regions. This imbalance of control and emotion are consistent with a critical period for the development of anxiety disorders prior to the onset of adolescence.

Keywords: BNST, Resting State Connectivity, Age Effects

Disclosure: Nothing to disclose.

P105. Parent Cognition and Behavior Predict Variable Outcomes in Children With Ras/mitogen-Activated Protein Kinase (RMK) Pathway Pathogenic Mutations

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Background: Mounting evidence supports the role of the Ras/mitogen-activated protein kinase (RMK) pathway in neurodevelopmental disorders. RMK pathogenic mutations affect physical, cognitive, and behavioral phenotypes, resulting in specific neurogenetic disorders collectively termed RASopathies. Noonan syndrome (NS) is the most common RASopathy. Despite knowledge of specific genetic mutations that cause NS, there is significant phenotypic variability in cognition and behavior traits. Here we examine the correspondence between non-carrier parents and children (probands) with NS across and within cognitive and behavioral phenotypic traits. We also examine how RMK pathogenetic mutations modify trait correspondence.

Methods: Participants included 45 families of children age 4-12 years with NS and either PTPN11 ($N = 33$) or SOS1 ($N = 10$) mutation. Parent (one per family) and proband cognition were

assessed with Weschler full-scale IQ (FSIQ). IQ subtest data were examined to understand parent/proband correspondence patterns across verbal and performance domains. Parent/proband behavior was assessed with the Achenbach scales for depression, anxiety, somatic, and attention deficit hyperactivity (ADHD) problems. Most families ($N = 37$) provided behavioral data from both parents, which was averaged. Five families provided behavioral data from one parent, and three families were missing parent behavioral data. For each trait, we used effect sizes to assess offsets (parent - proband scores), stepwise regressions to examine how trait correspondence is modified by RMK mutation, slopes to estimate variable penetrance within a trait.

Results: Offsets indicated that proband cognition (FSIQ scores) was shifted down relative to parent scores: mean difference = 12.535, $p < 0.001$, Cohen's $d = 1.04$. For behavior, proband scores were shifted up (indicating greater levels of behavior problems) relative to parent scores for depression ($d = -0.82$), anxiety ($d = -0.82$), and ADHD problems ($d = -0.82$, all p's < 0.001, survive Bonferroni correction) but not somatic problems $p > 0.10$, $d = -0.57$).

Regression results indicate that parent FSIQ was a significant predictor of proband IQ after controlling for proband gene mutation (PTPN11 or SOS1, $F = 3.270$, ß = 0.344, $p = 0.048$, $\Delta R2 = 109$, $p = 0.030$). Upon examination of verbal and performance subtests subtest data, the model and change in R2 were significant only for block design ($F = 6.361$, ß = 0.471, $p = 0.004$, $\Delta R2 = 0.206$, $p = 0.002$).

Subsequent regression results indicated that parent behavior was a significant predictor of proband behavior after controlling for proband gene mutation (PTPN11 or SOS1) and parent FSIQ. Results were significant for depression ($F = 7.643$, ß = 0.607, $p < 0.001$, $\Delta R2 = 0.363$, $p < 0.001$), anxiety ($F = 3.971$, ß = 0.421, $p = 0.015$, $\Delta R2 = 0.165$, $p = 0.008$) and ADHD problems ($F = 4.153$, ß = 0.395, $p = 0.013$, $\Delta R2 = 0.154$, $p = 0.01$). Specifically, parent FSIQ did not account for a significant proportion of variance in proband behavior (ADHD problems $\Delta R2 = 0.075$, $p = 0.064$, anxiety and depression problems p's > 0.10).

Conclusions: We demonstrate that parent cognition and behavior are useful in predicting proband outcomes, specifically in children with NS. First, the offsets or differences between parent and proband scores indicate that the penetrance of NS varies depending upon the trait examined (between traits). Offsets and corresponding effect sizes were greatest for FSIQ, yet most traits examined (FSIQ, depression, anxiety, and ADHD) demonstrated large effect sizes.

Regression results demonstrate significant relationships between parent and proband traits and variable penetrance within traits after accounting for gene mutation. Slopes for cognition (FSIQ and block design) were significantly less than 1, indicating variable penetrance; higher parent scores were associated with a greater difference between parent and proband scores. IQ subtest data revealed a significant predictive relationship between parent/proband block design and lack of significant relationships with parent/proband verbal subtests. This result contrasts with previous findings in other neurogenetic syndromes and the general population, which indicate significant relationships across IQ domains and stronger relationships between verbal relative to performance domains. The present results may indicate that, in addition to shifting IQ below expected based on age-norms, NS also disrupts the parent/child heritability of verbal IQ domains.

Parent depression, anxiety, and ADHD were significant predictors of proband behavior. Furthermore, parent behavior traits may hold a unique role in understanding proband behavior that is over and beyond the contribution of parental IQ. For behavior traits, the slopes were not significantly different from 1, suggesting that the difference between parent and proband behavior does not vary with parent scores (no evidence for variable penetrance).

Our results demonstrate that a variety of parent traits are useful in estimating variable penetrance in NS. Utilizing parent traits in a predictive framework affords control for various environmental and genetic factors and thus provides a more individualized estimate of expected proband outcomes. Further refinement of predictive modeling to estimate penetrance will advance a precision medicine approach to treating NS and other neurogenetic syndromes.

Keywords: Genetic Disorder, Neurodevelopmental Disorders, Rare Neurodevelopmental Disorders, ADHD, Behavior Predictor

Disclosure: Nothing to disclose.

P106. Multivariate Modeling of Maternal Inflammatory Pathways by Which the Prenatal Environment Influences Offspring Neurobehavioral Development With Independent Dataset Replication

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Background: Preconceptional and prenatal psychological stress, demographics, trauma, health, and nutrition all have potential to alter offspring neurodevelopmental outcomes. These aspects of the prenatal environment are hypothesized to influence the developing fetal brain via stress-sensitive aspects of maternal-placental-fetal biology (MPF), such as immune and endocrine functioning. A growing body of literature has established an important role for inflammation as a common pathway through which multiple aspects of the preconceptional and prenatal environment have the potential to alter the developing fetal brain and increase subsequent risk for poor neurodevelopmental outcomes and psychiatric disorders. Elevated maternal inflammation during pregnancy is associated with neonatal brain alterations that have been linked to poorer neurodevelopment in early childhood, including poorer executive functioning, increased negative affect, and delayed cognitive development. Several studies have also identified certain cytokines that mediate the pathway between maternal health during pregnancy and offspring neurobehavioral development in early childhood. However, the majority of research in this area has utilized univariate analyses that do not account for the highly interactive, multidimensional nature of the maternal inflammatory milieu and prenatal factors with potential to alter fetal brain development during pregnancy. Further, studies in this area of research utilizing longitudinal, clinical datasets often struggle to replicate their findings in independent datasets. We seek to add to this research by utilizing innovating multivariate analyses to examine potential inflammatory pathways by which the prenatal environment influences offspring neurodevelopment. Additionally, work is underway to replicate our findings across several independent datasets.

Methods: Biological samples were collected at 2 timepoints during pregnancy to derive the average across pregnancy of 34 stress-sensitive biological markers. Features of maternal life history, demographics, and lifestyle were surveyed throughout pregnancy. Offspring were assessed at 2 years of age utilizing parent reports of behavioral and emotional functioning, in addition to two performance-based tasks to measure the child's working memory and impulse control.

Results: We first employed a canonical correlation analysis (CCA) to examine the relationship between 1) maternal

preconceptional and prenatal psychosocial and health factors and 2) multiple biomarkers of stress and inflammation during pregnancy, using three independent datasets to validate results. Preliminary results from these analyses showed that multiple factors in the maternal psychosocial environment, including childhood physical neglect and income, as well as several health factors, including pre-pregnancy BMI and arm circumference during pregnancy, were associated with a latent factor that showed positive loadings for multiple pro-inflammatory cytokines. The final analysis examined the relationship between 1) multiple maternal psychosocial factors in the preconceptional and prenatal environment, and 2) multiple indicators of offspring behavioral, emotional, and executive functioning at 2 years of age using data from two independent longitudinal datasets ($n = 138$; $n = 446$) to cross validate a canonical correlation analysis (CCA). Results from this analysis showed a psychosocial canonical variate with positive loadings of maternal anxiety, depression, and history of childhood maltreatment, and negative loadings of maternal relative economic standing. The canonical variate representing offspring outcomes showed positive loadings of problem behaviors and negative affect and negative loadings of working memory performance.

Conclusions: This work has promising implications for improving reproducibility and using multivariate approaches to better understand multiple, interacting prenatal influences and candidate biological pathways through which the prenatal environment can influence offspring neurodevelopment.

Keywords: Multivariate, Prenatal Immune Exposures, Reproducibility

Disclosure: Nothing to disclose.

P107. Longitudinal Characterization of Myelination in the Healthy Human Brain From Age 7 to 40 in Vivo Using Quantitative Myelin Imaging

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Background: Development of the white matter of the human brain is a complex process that begins in fetal life but can continue well into adulthood. In addition to axonal formation and synaptogenesis, myelination (the forming of a lipid sheath around axons) is critical to proper conduction of action potentials and can be temporally linked to the emergence and maturation of specific cognitive abilities. Foundational work in the late 1800s and early 1900s by Flechsig used classic histopathological methods and postmortem samples to characterize regional myelination patterns during fetal life and early development. That work documented that white matter underlying primary, unimodal cortical regions is the first to myelinate, followed by white matter underlying association cortices, and then by that underlying transmodal regions. In the 1960s, Yakovlev and Lecours significantly extended these findings to show that myelination, particularly in the cortex, extends at least into the fourth decade. These early studies highlighted the importance of understanding the process of myelination throughout the lifespan, particularly because these events are temporally linked with the emergence of some neuropsychiatric diseases. With technological advances in MR imaging came the ability to measure white matter in vivo. Initial studies showed white matter volume increases into the fifth decade before declining, suggesting that white matter maturation continues for longer than previously believed. As newer methods have become available to measure myelin in vivo using MRI, interest has been renewed in this process, particularly as it relates to both neurodevelopment and neuropsychiatric disease. Over the past decade multiple groups have elegantly demonstrated that ratios of T1 to T2 in the cortex seem to match early work by Flechsig; however, this MRI method is not necessarily quantitative and, therefore, may not be comparable across individuals. Other methods that do quantitatively measure myelin have also been developed and have produced results that, at least in early development, also resemble early histopathological studies. However, longitudinal, quantitative measurement of myelination changes in vivo, through the adolescent period and beyond, have not been completed. Here, we use a quantitative measure of myelination, myelin water fraction (MWF) derived with the mcDESPOT method, in a large, healthy, longitudinal sample spanning ages 7-40 to characterize the changes in myelination in both the cortex and underlying white matter through development.

Methods: We carried out 586 imaging sessions on 237 healthy individuals (mean age 13.9 + /-6.0 years, range 7-40; 122F/115M) using a 3T GE MRI scanner. mcDESPOT data acquisition includes 8 flip angles of a Spoiled Gradient recalled echo (SPGR) MR sequence, 8 flip angles of Steady State Free Precession (SSFP) MR sequences at phase 0 and phase 180, and an inversion-recovery SPGR sequence. Voxel-wise MWF maps were calculated using a three-pool model for each participant and were first spatially normalized within each participant across sessions and then to a study-specific template. AFNI's 3dMSS tool was used to model MWF trajectories throughout the age range, taking into account longitudinal information from each participant. Results were examined in a voxel-wise manner and within white matter tracts as defined by the JHU white matter atlas distributed with FSL. Additionally, change in myelination from age 7 was determined by subtracting the average MWF estimated by 3dMSS at each voxel for age 7 from each age in the range of 8-40 years for the cortical ribbon and examined across time.

Results: Modeling of the relationship between age and MWF was found to be accurate throughout the brain parenchyma at nearly every voxel ($p < 0.001$ at >91% of voxels in brain). MWF averaged across the entire white matter showed a linear increase from age 7 into late teenage years before plateauing until age 40. Similar curves were seen for individual white matter tracts, though corticospinal tracts and anterior thalamic radiations peaked earlier, around the ages of 12-15, while uncinate fasciculus, superior longitudinal fasciculus and inferior frontal-occipital fasciculus appeared to peak at around age 20 and then plateaued. Cortical MWF was examined as change in MWF from age 7. Consistent with descriptions from both Flechsig and Yakovlev, we found that primary cortices, including sensory motor regions (i.e., pre/postcentral gyri), primary visual, and primary auditory regions were the first to show increases in myelination (i.e., greater than 2% change in MWF) occurring at 12-13 years, while lateral frontal and temporoparietal junction regions were the last, occurring in the early 20s.

Conclusions: Here, in a large, longitudinal sample, we characterize the process of myelination across a period of development known to be important for the emergence of neuropsychiatric diseases, and beyond. These results, measured in vivo, largely recapitulate the myelination patterns of white matter seen by Flechsig in postmortem samples more than 100 years ago. Further, the temporal pattern of gray matter myelination over the modeled age range demonstrated that myelination of cortex during adolescence follows the same regional pattern as myelination of the underlying white matter during fetal development and infancy. Finally, these data in healthy individuals provide a critical base from which to search for changes in individuals with neuropsychiatric diseases.

Keywords: Myelin Imaging, Neurodevelopment, Longitudinal MRI, White Matter Development, Cortical Myelination

Disclosure: Nothing to disclose.

P108. Neural Epigenetic Signatures of Early-Life Adversity and Post-Hoc Exercise Underlying Hippocampal Memory Function in Adulthood

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Background: Poverty, neglect, abuse and displacement are all examples of early life adversity experienced by millions of children worldwide. Across species, early life adversity can lead to impairments in cognitive functions, placing children at risk for academic difficulties, poorer school performance, and memory impairments with aging. Accessible interventions and therapeutic strategies are needed to offset these cognitive impairments and improve quality of life. Our lab has demonstrated that in rodents, physical activity taking place during a sensitive, postnatal juvenile period can enable hippocampal memory and synaptic plasticity (Ivy et al., 2020). We thus consider whether early-life exercise (ELE) can be employed as a post-hoc intervention to offset the negative consequences of a rodent model of early-life stress (ELA) on hippocampal memory. By using unbiased next-generation sequencing approaches, as well as evaluating histone modifications influencing memory- and exercise-associated genes, we investigate the underlying neural epigenetic mechanisms that may contribute to the lasting consequences of stress and exercise on hippocampal memory. We hypothesize that juvenile exercise introduced after ELA can buffer the negative consequences of ELA on hippocampal memory in adulthood. Furthermore, we predict that there are specific histone modifications influenced by both ELE and ELA that influence memory-associated gene expression programs critical for hippocampal cognition.

Methods: We crossed Emx1IRES-cre females with males harboring the NuTRAP cassette (loxP-flanked Gt(ROSA)26Sortm1 (CAG-birA,-mCherry/Rangap1,-EGFP/Rpl10a)Evdr transgene; "Emx1-NuTRAP" mice). This novel transgenic line allows for the simultaneous isolation of nuclear chromatin and translating mRNA from Emx1-expressing hippocampal neurons. ELE mice were housed in voluntary running wheel cages during postnatal days (P)21-41. On P42 ELE and sedentary male mice were taken down and hippocampi removed and processed for RNA- and CUT and RUN-sequencing for histone marks H4K8Ac and H3K27me3 ($n = 4$ mice/group). Female dams were placed in normal-bedded or limited bedding and nesting (ELA) cages with their litters during P2-9. On P10, ELA mice were returned to normal-bedded cages, and ELE was then introduced to a subset of male and female ELA offspring during P21-41. During young adulthood (P60-90), mice underwent a battery of behavior tasks: 1) spatial y-maze, 2) object location memory task, 3) open field exploration (OFE), and 4) elevated plus maze (EPM) ($n = 6$-8 mice/group). Middle-aged mice (8-10 month) were also tested in the objects in updated locations (OUL) task (Wright et al, 2020). During memory re-consolidation in the OUL task, mice were rapidly sacrificed and dorsal hippocampi collected for RNA-Seq, ATAC-Seq, and CUT and RUN-seq evaluating for H4K8Ac and H3K27me3. RT-qPCR and CUT and RUN-PCR were also performed to evaluate the above histone modifications at specific memory-associated genes.

Statistical analyses: For behavior, $n = 6$-8 mice per sex, per group. All results were analyzed using one-way ANOVA and post-hoc Bonferroni corrections. RNA-seq reads were trimmed and aligned to Mm10 mouse genome. Differential gene expression was analyzed using DESeq2. CUT and RUN-seq analysis for significant peaks against an IgG control using SEACR and counts for the significant peaks and analyzed for differential occupancy using DESeq2. RNA-seq data was also analyzed using Ingenuity Pathway Analysis (Qiagen) and Gene Set Enrichment Analysis. RT-qPCR: $n = 3$-4 mice per group, one-way ANOVA.

Results: Using Emx1-NuTRAP mice, performance in tasks of anxiety (elevated plus maze, open field) were not significantly different across groups (four groups: Control, ELA, ELE, ELA + ELE; $p > 0.05$). We found impaired object location memory in ELA mice (as measured by discrimination index), and this was rescued by post-hoc exercise (one way ANOVA, main effect; $p = 0.0194$; post-hoc comparison revealed significant difference between ELA and control, $p = 0.029$; and ELA vs early-exercise, $p = 0.04$). RNA-seq studies revealed differential sets of highly and lowly expressed genes in ELE mice vs sedentary, and gene candidates and upstream transcription factors were identified as potentially activated by ELE. CUT and RUN-seq showed site-specific, differential enrichment of genes bodies with H4K8ac and H3K27me3 resulting from ELE. The genes BDNF and Nr4a1 were significantly increased in ELE compared to sedentary ($p < 0.05$). RT-qPCR and CUT and RUN-PCR studies demonstrated that ELE increases expression of BDNF exon 1 (overall effect, $p = 0.0014$; ELE vs sed, $p = 0.0012$), BDNF exon 4 (overall effect, $p = 0.0036$; ELE vs sed; $p = 0.011$) and Nr4a1 (overall effect, $p = 0.006$; ELE vs sed, $p = 0.03$). Sequencing studies for the ELA and ELE + ELA groups, as well as RT-qPCR gene expression data, are currently being analyzed.

Conclusions: The cognitive consequences of early-life adversity can be mitigated by post-hoc, juvenile physical activity, thus providing an experimental approach for which mechanistic targets can be identified and targeted for exercise-based mechanistic studies. NGS studies using the novel Emx1-NuTRAP mouse allow for cell-type specific pairing of genomic and epigenomic information to identify these molecular targets. Our data suggest that epigenetic mechanisms of early-life exercise may modulated programs of gene expression in order to reduce or prevent impairments in hippocampal long-term memory after ELA.

Keywords: Neuronal Epigenome, Aerobic Exercise, Early-Life Adversity, Dorsal Hippocampus, Juvenile Critical Period

Disclosure: Nothing to disclose.

P109. Selective Inhibition of Prelimbic Medial Prefrontal Cortex During Adolescence Increases Susceptibility to Helpless Behavior in Adult Male Rats

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Background: Background: Major depressive disorder (MDD) is a disabling mental disorder that may be related to vulnerability to stressors. Stress and circuit dysfunction of stress regulation are risk factors that are related to the emergence of depression. Stress-based protocols are extensively used to model circuit-based disruption of depression in rodents, such as the learned helplessness (LH) protocol, which leads to anhedonia and a hypodopaminergic state. In fact, the prelimbic portion of the mPFC (plPFC) is important for stress regulation and plays an important role in the modulation of helpless behavior. plPFC dysfunction during development does increase vulnerability to helpless behavior, and this is potentially due to a dysregulated stress response. However, whether this requires a persistent or transient loss of plPFC function is unknown. This study aimed to investigate the impact of selective plPFC chemogenetic inhibition only during adolescence on the susceptibility to adulthood helpless behavior and its corresponding effects on VTA DA system activity in rats.

Methods: Methods: Male and females Sprague-Dawley juvenile rats (PND 22-23) were subjected to surgery for injection of plasmid for Designer Receptors Exclusively Activated by Designer Drugs (DREADDs; pAAV-CaMKIIa-hM4D(Gi)-mCherry or pAAV-CaMKIIa-

eGFP, 300nL) in plPFC to induce rapid DREADD expression. The animals were treated with clozapine *N*-oxide (CNO; 3mg/kg) or Vehicle (Saline, 1ml/Kg) injection i.p. twice a day during adolescence (PD31-40). At PD70, the rats were tested for anxiety in the elevated plus-maze (EPM) and at least one day later subjected to the LH model (Day 1, inescapable footshock; Day 2 escape session) to evaluate helpless behavior during adulthood (PD > 72). Electrophysiology recording of VTA DA neurons was performed after four days of LH. All procedures were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh.

Results: Results: The selective chemogenetic inhibition of excitatory neurons in the plPFC during adolescence decreased the percentage of time and entries in the open arms (%Time in open arms, $F4,55 = 5.42$, $p < 0.05$; %Entries in open arms, $F4,55 = 6.34$, $p < 0.05$; Females, %Entries and %Time, $p > 0.05$) only in male rats. In LH, the proportion of animals showing helpless behavior at adulthood was higher in male rats injected with pAAV-M4h plasmid in the plPFC treated with CNO (Helplessness, Naïve 29.41%; eGFP-Veh 33.33%; eGFP-CNO 33.33%; M4h-Veh 27.27%; M4h-CNO 54.54%; Chi-square, 22.18, $df = 4$, $p < 0.05$). No significant effect was found regarding the helpless behavior in all female groups (Helplessness, Naïve 26.32%; eGFP-Veh 25%; eGFP-CNO 30.8%%; M4h-Veh 26.67%; M4h-CNO 40%; Chi-square, $p > 0.05$). Moreover, a decreased number of spontaneously active DA neurons was observed in rats showing helpless behavior across all groups (Behavior, $F19,125 = 5.335$, $p < 0.05$; no treatment and sex effect, $p > 0.05$). No effect of condition/treatment was found for average firing rate ($p > 0.05$) and percentage of spikes in bursts ($p > 0.05$) in male and female rats.

Conclusions: Conclusion: These data suggest that the inhibition of plPFC excitatory activity selectively during adolescence increases anxiety and susceptibility to helpless behavior only in male adult rats. Female adolescent rats were found to be resistant to plPFC inhibition with respect to either anxiety and helplessness. Therefore, a gender-dependent predisposition of early life adverse events that impair plPFC activity may enhance susceptibility to affective disturbance in adulthood.

Keywords: Medial Prefrontal Cortex, Adolescence, DREADDs, Depression and Anxiety, Dopamine

Disclosure: Nothing to disclose.

P110. Ghosts in the Fear Circuitry? Mother's Child Abuse History Impacts Activation of Their School-Aged Children's Fear Circuitry

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Background: The prospect of intergenerational effects of trauma exposure on neurobiology suggests an important risk factor for psychopathology. Multiple studies indicate that maternal trauma history increases exposure to glucocorticoids in utero and in infancy. Recent evidence also suggests that mother's own trauma history may impact their children's brain global structure and function within emotion circuitry in infancy, but it is unclear that these intergenerational effects persist later in development. The current study examined associations between maternal child abuse history and school-aged children's resting-state functional connectivity (rsFC) between the amygdala (AMY) and anterior cingulate cortex (ACC), two structures involved in emotion response and psychopathology. We hypothesized that maternal childhood abuse history would be associated with increased connectivity within this emotion circuitry.

Methods: Black mother-child dyads, $N = 52$, completed interviews. Mothers completed the Childhood Trauma Questionnaire, which assesses experiences of childhood physical, sexual, and emotional abuse. Children reported their exposure to traumatic events via the Traumatic Events Screening Inventory for Children. The children (27 girls; 8- to 14-years-old, $MAge = 10.74$, $SD = 1.61$) also underwent resting-state functional MRI with eyes open for 7min. Separate hierarchical regressions assessed the impact of each type of maternal child abuse (physical, sexual, and emotional) on rsFC between AMY and ACC. For each model, child age and sex were entered in Block 1, child trauma exposure in Block 2, and maternal child abuse in Block 3.

Results: Mean rsFC between left and right AMY to ACC was positive, $MLeft = .173$, $SDLeft = .213$, $MRight = .140$, $SDRight = .185$. For left AMY-ACC rsFC, all models were significant for the Block 1 and 2 predictors, all ps < .003. Maternal physical abuse explained additional variance, $\Delta R2 = .101$, $\Delta F(1,39) = 7.642$, $p = .009$, and was associated with increased connectivity, $B = 0.343$, $t = 2.764$. Emotional abuse explained marginally more variance, $\Delta R2 = .056$, $\Delta F(1,39) = 3.884$, $p = .056$, and was linked to increased rsFC, $B = 0.251$, $t = 1.971$. Sexual abuse was not significantly associated with left AMY-ACC rsFC, $p > .350$. In contrast to these associations in the left hemisphere, right AMY-ACC rsFC was not significantly associated with any type of maternal childhood abuse, all ps > .09. Parallel models with maternal post-traumatic stress symptoms entered in Block 3, rather than maternal child abuse, did not explain significant variance in either left or right AMY to ACC connectivity, ps > .966.Block 1, child trauma exposure in Block 2, and maternal child abuse in Block 3.

Conclusions: These results provide novel evidence that maternal childhood abuse history is associated with increased left frontoamygdala connectivity in school-aged children. Importantly, maternal post-traumatic stress symptoms were not associated with connectivity in either hemisphere, suggesting that the impact of childhood abuse exposure may be independent of mental health problems related to that trauma exposure. These results suggest that trauma may have intergenerational effects and highlight the need for further study of how maternal trauma exposure confers risk via biological pathways that modulate neurocircuitry.

Keywords: Intergenerational Transmission of Trauma, Resting State Functional Connectivity, Brain Development, Child Abuse and Neglect, Childhood Trauma

Disclosure: Nothing to disclose.

P111. Impact of Prenatal Cannabis Exposure on Frontolimbic White Matter Pathways in Children: Results From the ABCD Study

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Background: Some pregnant people use cannabis to assuage symptoms of morning sickness or anxiety, and some cannabis-using individuals may have not known they were pregnant. However, research shows that approximately 1/3 of cannabis constituents, such as delta-9-tetrahydrocannabinol (THC) undergoes cross-placental transfer upon use by a pregnant person and may therefore disrupt fetal neurodevelopment. In particular, THC may disrupt the endocannabinoid system, which plays a key role in neurodevelopment across the lifespan. Indeed, endocannabinoids and cannabinoid receptors are expressed in the fetal brain, including white matter, as early as 5 weeks into gestation. Further, prenatal cannabis exposure is associated with learning, memory, motor, and socioemotional deficits that last into the adulthood of

offspring. Here, we use data from the ongoing large-scale NIH Adolescent Brain Cognitive Development (ABCD) study to examine the impact of prenatal cannabis exposure on integrity of frontolimbic white matter pathways. We focused on frontolimbic pathways because they are susceptible to cannabis use in adolescents and adults, and because variation in endocannabinoid signaling modulates frontolimbic development.

Methods: This study reports on diffusion tensor imaging (DTI) data collected from 10,570 youth ($M \pm SD = 9.92 \pm 0.62$ years; 48% female; 55.1% White, 13.2% Black, 19.8% Hispanic, 1.9% Asian, 10.1% Other). Prenatal cannabis use was measured via parent retrospective report and fractional anisotropy (FA) and mean diffusivity (MD) was estimated for ten frontolimbic white matter tracts, including left and right: (1) fornix, (2) cingulum bundle, (3) parahippocampal cingulum, (4) uncinate fasciculus, and (5) inferior fronto-occipital fasciculus. Linear regression was used to test for associations between prenatal cannabis exposure before or after knowledge of pregnancy and white matter integrity (FA or MD) and FDR was used to adjust for multiple comparisons (40 tests). Follow-up analyses covaried for race/ethnicity, age, parental education, family income, prenatal alcohol, and prenatal tobacco exposure, and included both sex and the interactions between sex and cannabis exposure as predictors.

Results: Four hundred ten parents (3.9%) reported using cannabis prior to knowledge of pregnancy, and 1.1% ($n = 119$) reported using after knowledge. Prenatal cannabis exposure before knowledge of pregnancy was associated with lower FA of the right and left fornix, the left inferior fronto-occipital fasciculus, and the left parahippocampal cingulum ($p < .012$). FA of the right fornix was the only tract that remained significant after adjusting for covariates ($R2 = .001$, $F[1,10,577] = 15.69$, $p < .001$, standardized beta = -.04). Sex was also a significant predictor of right fornix FA (beta = -.086, $p < .001$) such that female sex was associated with lower FA than non-female sex, and there was no sex x cannabis exposure interaction ($p = .9$). Prenatal cannabis exposure after knowledge of pregnancy was associated with lower FA in seven out of the ten tested tracts; however, these associations were no longer significant when adjusting for covariates.

Conclusions: These data add to the growing body of evidence linking prenatal cannabis exposure to altered neurodevelopment in offspring. In particular, our results suggest that cannabis exposure early during gestation affects microstructure of the fornix during childhood. The fornix connects the hippocampus to the hypothalamus and plays a key role in learning, memory, and emotional processes. Therefore, developmental alterations of the fornix may contribute to elevated risk of neurobehavioral and mental health problems following exposure to cannabis in utero. These findings should encourage individuals to abstain from using cannabis during pregnancy or pre-conception.

Keywords: Cannabis, Endocannabinoid System, Frontolimbic Network, Children, White Matter

Disclosure: Nothing to disclose.

P112. Oxytocin Normalizes Functional Connectivity Between Salience and Visual Networks in Autism Spectrum Disorder

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Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized by deficits in social interaction and communication. Oxytocin enhances the salience of social stimuli in preclinical models and may improve social functioning in ASD. Clinical trials with intranasal oxytocin (IN-OT) in ASD have been inconsistent. To improve efficacy of this therapeutic approach, we need a better understanding of how IN-OT dose-dependently modulates brain communication across networks. Therefore, we conducted a dose response study with IN-OT in adults with ASD to examine its effects on resting-state functional connectivity (rsFC) between areas involved in salience and visual processes.

Methods: A total of 50 ASD subjects (male, 18 to 45 years old) were recruited from the Emory Autism Center, 32 adults met eligibility criteria and completed the study. An additional 17 age and IQ matched neurotypical (NT) participants (male, 18 to 45 years old) were also recruited from the general population. ASD subjects received 4 doses of IN-OT (Syntocinon, 8IU, 24IU and 48IU) and IN-placebo in a randomized, double-blind, within-subject, placebo-controlled design. NT subjects only received intranasal placebo (IN-PL). All subjects were scanned during resting-state in the MRI scanner (3T, Siemens) 40 minutes after nasal spray administration. All subject visits were separated by a one-week interval. fMRI data analysis were performed using the AFNI and FSL software packages, and the GIFT toolbox for group analysis. We performed a group independent component analysis (ICA) to identify independent brain functional networks using a data-driven approach. We also used machine learning analysis to identify the most important independent components (ICs) that best differentiate ASD and NT, and to identify dose-dependent effects of IN-OT on resting-state connectivity.

Results: When comparing rsFC between NT and ASD adults, we found that subjects with ASD have a deficit in rsFC between a salience IC network (including the anterior cingulate cortex, insular cortex), and a visual IC network (including visual occipital cortex). Feature importance analysis revealed that there are several IC networks that highly differentiate ASD from NT. For instance, the machine learning analysis revealed hypo-connectivity between salience and visual networks in ASD compared to NT subjects, as well as hyper-connectivity between reward and sensorimotor networks. Interestingly, IN-OT normalized the rsFC deficits between the salience and visual IC networks in a dose-dependent manner in ASD subjects ($p < 0.05$). Additionally, machine learning analysis suggested that a high dose of IN-OT (48IU) also normalizes rsFC connectivity the reward and sensorimotor IC networks.

Conclusions: Our findings suggest a potential mechanism by which IN-OT may enhance the salience of visual social cues in ASD by normalizing the functional connectivity between salience and visual networks. Additionally, machine learning and feature importance are useful techniques to identify resting-connectivity features that differentiates ASD and NT subjects as well as those that are modulated by drug treatment. These results have implications for improving efficacy of OT therapy to treat social deficits in ASD.

Keywords: Autism Spectrum Disorder, Machine Learning, Salience, Functional Connectivity, Resting-State Functional Connectivity

Disclosure: Nothing to disclose.

P113. Examining the Synergistic Effect of Stress During Puberty and Pregnancy-Related Hormones on PVN Chromatin Landscape and Transcription

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Background: Women who undergo adverse childhood experiences are at risk for developing lasting biological changes, including affective disturbances and stress dysregulation. As the pubertal transition is marked by dynamic hormonal changes and

ensuing reorganization of the brain, it represents a window of sex-specific vulnerability to adverse experiences. Periods of hormonal flux in the female lifespan, including pregnancy, exacerbate the risk for affective disturbances and promote stress dysregulation, a key feature of affective disorders. We have previously shown that pubertal adversity is associated with a blunted glucocorticoid response within the hypothalamic-pituitary-adrenal (HPA) axis in both peripartum humans and mice. In mice, we have examined puberty-stress reprogramming in the paraventricular nucleus (PVN) of the hypothalamus, the brain region that initiates the HPA axis response. We found that pubertal stress led to alterations in both the chromatin and transcriptional landscapes of the PVN, specifically when females were pregnant. The chromatin landscape was found to be more open, and therefore permissive to transcription, in the PVN of pubertally stressed females. Binding motif analysis suggested a potential role for histone acetylation in this altered chromatin state. Separately, we found that pubertal stress led to aberrant transcription of immediate early genes (IEGs) in the PVN of adult, pregnant mice. IEGs are stimulus-dependent transcription factors that have important downstream targets. We hypothesized that pubertal stress and the pregnancy-related hormone allopregnanolone have a synergistic effect in altering the chromatin landscape and permitting altered transcription in pubertally stressed females.

Methods: Male and female mice were exposed to chronic variable stress (CVS) from postnatal day 21–34 using our previously established paradigm. CVS consisted of two stressors (tactile, olfactory, or auditory) per day. In one set of mice, females were exposed to chronic variable stress or not (Control) and brains were collected from virgin or pregnant adults at 12 weeks of age ($n = 8$/group). PVN extraction was performed, and proteins were isolated and quantified. Western blot analysis was used to quantify several acetyl post-translational modifications that are known to be associated with permissive chromatin states, including histone 3 lysine 9 acetylation (H3K9ac). In another set of mice, 12 week old male and female mice that had undergone CVS or not ($n = 10$/group) were given either allopregnanolone or vehicle (25% w/v HPβCD) treatment via two separate subcutaneous injections: 3 mg/kg of allopregnanolone 20 hours and 1 mg/kg 2 hours, as previously, before brain collection. PVN micropunches were obtained from brains, RNA was isolated, and gene expression was measured using quantitative PCR. Data were analyzed by ANOVA with Tukey post-hoc tests when necessary.

Results: Initial examination of the level of H3K9ac showed a trend towards an increase of this post-translational modification by pubertal stress in the PVN of pregnant, pubertally stressed mice ($p = 0.07$). Examination of additional histone marks and the inclusion of virgin females allows for the identification of chromatin modifications that are dependent upon pubertal stress, pregnancy, or requiring both. In examination of the transcriptional landscape in the PVN, allopregnanolone treatment had divergent impacts on the IEG expression in the PVN of adult females based on pubertal stress experience. Specifically, peripheral administration of allopregnanolone resulted in a nearly significant reduction in Fos expression in control females ($p = 0.058$), while pubertally stressed females were unaffected ($p = 0.93$). Examination of males allows for the determination of whether males undergo the same reprogramming of the PVN by pubertal stress, and therefore are similarly sensitive to the effects of pregnancy-related hormones in altering transcription.

Conclusions: These findings will clarify the role for histone acetylation as part of the mechanism by which pubertal stress alters the PVN and leads to lasting changes in the transcriptional landscape. These findings are consistent with our previous work, whereby pubertal stress leads to divergent responses to future stimuli at the level of the chromatin, transcription, and physiology. Together, these studies support a role for long-term alterations in the chromatin landscape of the PVN that interact with later life experiences, such as pregnancy, to alter how the PVN responds to input. This translationally-relevant mouse model provides the opportunity to understand the molecular underpinnings of risk for stress dysregulation, a central endophenotype of affective disorders.

Keywords: Pubertal Stress, Epigenetics, Risk and Resilience

Disclosure: Nothing to disclose.

P114. Impaired Microglial Pruning of Excitatory Synapses on Developing CRH-Expressing Hypothalamic Neurons Exacerbates Stress Responses Throughout Life

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Background: The developmental origins of stress-related mental illnesses are well-established, and early-life stress/adversity (ELA) is an important risk factor. We and others have found that early-life exposure to an impoverished environment and unpredictable maternal care (in a limited bedding and nesting [LBN] paradigm) provokes major alterations in cognitive and emotional function, including anhedonia, accompanied by aberrant connectivity between the hippocampal-limbic system and reward/pleasure-related regions. Within the hypothalamus, this early-life adversity causes an increase in the number of excitatory synapses onto corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus (PVN). Such synaptic changes suffice to induce large-scale and enduring epigenomic changes in the expression of neuronal genes, including Crh. However, the mechanisms by which early-life adversity modulates synapse development or persistence in developing brain circuits remain unknown. We hypothesize that microglia contribute to normal synapse reduction on CRH + neurons in the developing PVN, and that adverse early-life experiences interfere with this function, leading to lifelong stress vulnerabilities.

Methods: To interrogate microglial function, we employed dual-reporter transgenic mice with visible CRH + neurons and microglia and two-photon time-lapse imaging in acute slices of the PVN. We obtained these hypothalamic slices from P8 male and female mice ($n = 8$-10/group) that were reared in LBN or control cages from P2 to P8. We then visualized live microglial process dynamics and their interactions with CRH neurons. In fixed tissue, we utilized 3D-reconstruction confocal microscopy and immunodetection of pre- and post-synaptic markers to quantify in high-resolution the developmental trajectory of synapse density and engulfment by microglia in the PVN ($n = 8$-10/group). To probe whether microglial function is required for normal synapse development, we inhibited microglial phagocytosis with a targeted Mer tyrosine kinase inhibitor and assessed synapse number on CRH + neurons ($n = 5$-8/group). In a final mechanistic experiment, we capitalized on cell type-specific DREADD technology to express activating Gq-DREADDs in microglia and delivered CNO continuously via a subcutaneous slow-release pellet from P3 to P10 ($n = 6$-12/group). We then probed whether this exogenous activation of microglia prevented the effects of ELA on microglial function, synapse number on CRH + neurons, and lifelong stress responses. Statistical analyses included *t*-tests, or one-way or two-way ANOVA, as appropriate.

Results: Here we find that ELA increases the number and function of excitatory synapses onto stress-sensitive hypothalamic corticotropin-releasing hormone CRH + neurons ($t[12.44] = 2.95$, $p = 0.01$), and implicate disrupted synapse pruning by microglia as a key mechanism. Microglial process dynamics in live imaging,

and engulfment of synaptic elements by microglia, were both attenuated in ELA mice ($t[16] = 2.79$, $p = 0.01$), associated with deficient signaling of the microglial phagocytic receptor Mer. Accordingly, selective chemogenetic activation of ELA microglia (with CX3CR1-Gq-DREADDs) increased microglial process dynamics and reduced excitatory synapse density to control levels ($F[2,23.8] = 3.76$, $p = 0.04$). In terms of functional outcomes, selective early-life microglial activation also mitigated the adrenal hypertrophy and prolonged stress responses in adult ELA mice ($F[3,24] = 11.11$, $p < 0.0001$).

Conclusions: These findings establish microglial actions during development as powerful contributors to experience-dependent sculpting of stress-related brain circuits. The manipulation of microglial function during development to prevent stress-related emotional disorders in adulthood may provide novel targets for therapeutics or preventative interventions in neuropsychiatric disorders.

Keywords: Microglia, CRH + Neurons, chemogenetics, 2-photon Techniques, Synaptic Pruning

Disclosure: Nothing to disclose.

P115. Differential Neural Responses to Subliminal and Supraliminal Faces Associated With Mood Disorders, Sex, and Self-Injurious Thoughts and Behaviors

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Background: Mood disorders have often been associated with disruptions in both subliminal and supraliminal emotion processing that can be represented neurobiologically. Further, neural responses to these stimuli vary depending on the emotion being presented (happy, sad, neutral), mood disorder diagnosis (major depressive disorder (MDD) versus bipolar disorder (BP)) and sex. Further, it is possible that there is additional variation among individuals with histories of self-injurious thoughts and behaviors (SITBs) including suicidal ideation (SI) or self-injurious behaviors (SIBs). However, these studies have primarily focused on these patterns in samples of individuals who are currently experiencing an active mood disorder episode, thus limiting our understanding as to whether these neural processing differences persist when these individuals are not experiencing active symptoms. This study examines the relationships between neural responses to subliminal and supraliminal facial stimuli and diagnosis, SI and SIBs, and sex.

Methods: Seventy-eight participants with any mood disorder (AMD; remitted MDD and euthymic BP) and 29 healthy controls completed a diagnostic evaluation and an MRI scan. During the MRI scan, the participants completed a task consisting of 2 4-minute runs in a mixed event/block design. They were shown images of shapes and faces of different people expressing happy, sad, and neutral expressions. For each block, participants were shown a supraliminal (overt) face near continuously, with 2-3 very brief presentations (33ms) of subliminal faces and shapes. We completed preprocessing and first level models using SPM12 and FSL. For our second level model, we examined activation of 3 salience and emotion network regions of interest (ROIs; subgenual anterior cingulate cortex (sgACC), amygdala, and anterior insula) during the different conditions and contrasts. In SPSS, we conducted repeated measures GLMs by entering group (HC vs. AMD) and sex as between subjects factors. Condition (subliminal vs. supraliminal), ROI and ROI hemisphere (left vs. right) were entered as within subjects factors. We repeated these analyses with just the AMD group and entering SITB group (No SITBs, SI Only, SI + SIBs) as the between subjects factor. We did not include sex for the SITB analysis due to small sample size.

Results: Supraliminal faces elicited greater activation than subliminal across HC and AMD groups $F(1) = 13.197$, $p < .001$, partial $\eta 2 = .119$, observed power = .949. The amygdala showed greater activation in response to both subliminal and supraliminal faces in the HC group relative to AMD, while the AMD group shows greater sgACC blunting in response to sad faces relative to HC, $F(1) = 7.040$, $p = .009$, partial $\eta 2 = .067$, observed power = .748. The left ROIs showed greater activation in response to sad faces relative to the right, and males showed lower activation in response to sadness relative to happiness, which was not evident in females. emotion by ROI by side by gender, $F(1) = 4.242$, $p = .042$, partial $\eta 2 = .041$, observed power = .532, in which the left ROIs exhibited greater activation in response to sad faces relative to right and males showed lower activation in response to sadness relative to happiness across ROIs, which was not evident in females. For the SITB analyses with only AMD participants, the SI Only group showed increased amygdala activation to supraliminal stimuli relative to No SITBs or SI + SIBs groups and the SI Only and SI + SIB groups showed less sgACC blunting relative to the No SITB group, $F(4) = 6.284$, $p = .003$,partial $\eta 2 = .149$, observed power = .885. Across all conditions, the No SITB group showed lower insula activation and greater sgACC blunting than the SI Only and SI + SIB groups, $F(2) = 3.173$, $p = .047$, partial $\eta 2 = .081$, observed power = .591. The SI Only and SITB + SIB groups showed greater insula activation and less sgACC blunting for supraliminal faces relative to the No SITB group, $F(2) = 3.936$, $p = .024$, partial $\eta 2 = .099$, observed power = .691.

Conclusions: In contrast with prior work, we did not find greater activation in response to subliminal emotional stimuli relative to supraliminal. Compared to HC, the AMD group showed blunted sgACC activation in response to sad faces and lower amygdala activation in response to happy faces, the latter of which is consistent with prior research. Reduced amygdala activation in response to happy stimuli may be a characteristic of mood disorders that persists regardless of disease state (active vs. remitted). Level of sgACC activation in response to sad stimuli may be an indicator of disease state, with greater activation indicating active and blunted activation indicating remitted illness. This is further supported by the reduction in sgACC activation found post-treatment in mood disorders. We also found a sex effect in which males exhibited lower activation in response to sad faces across all ROIs compared to females. Finally, the presence of SITBs was associated with greater insula activation and reduced sgACC blunting in response to supraliminal stimuli, suggesting greater emotional engagement and awareness among these individuals. Findings highlight that some neurobiological features of mood disorders persist beyond remission and the importance of examining heterogeneity within these diagnoses.

Keywords: Non-Suicidal Self-Injury (NSSI), Subliminal Emotion, MRI

Disclosure: Nothing to disclose.

P116. High Fat, High Sugar Diet in Adolescence Predicts Memory and Executive Functioning in Young Adulthood

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Background: Exposure to a high fat, high sugar (HFHS) diet during adolescence has been associated with long-term cognitive impairments in animals. No human studies have examined the relationship between adolescent nutrition and cognition in adulthood. The current study examined whether adolescent HFHS intake predicts performance on memory and executive function tasks in young adulthood using longitudinal data from the National Longitudinal Study of Adolescent to Adult Health.

Methods: Participants provided data regarding dietary intake in adolescence and underwent cognitive assessments in young adulthood. A HFHS score was calculated by adding the number of HFHS food or beverage items (e.g., soda, candy, pizza, French fries) adolescents reported consuming in the past day. Regression analyses tested whether adolescent HFHS intake predicted word and backward digits recall in young adulthood.

Results: 2,827 participants provided relevant data in adolescence (mean age 15 years [SD 1]) and young adulthood (mean age 28 years [SD 1]). HFHS scores significantly, negatively predicted immediate ($p < 0.01$) and delayed word recall scores ($p < 0.01$) as well as backward digits recall scores ($p < 0.05$) after controlling for age, sex, race, income, education, and body mass index (BMI).

Conclusions: HFHS consumption in adolescence may be associated with poorer memory and executive function later in life even after controlling for other relevant covariates such as BMI and SES. Potential mechanisms for these animal and human findings include reductions in neurogenesis as well as increased neuroinflammation, synaptic remodeling, microglial activation, apoptosis and changes in both neurotransmission and synaptic plasticity observed after HFHS exposure, which may affect cognition. Moreover, diet-induced changes in gastrointestinal hormones (e.g., insulin, leptin, and ghrelin) thought to alter neural reward and learning systems may be implicated. These results add to a growing literature suggesting the importance of nutrition during adolescent development and support research questioning whether this effect can be modified by dietary changes.

Keywords: High Fat Diet, Neurodevelopment, Cognitive Functioning

Disclosure: Nothing to disclose.

P117. Astrocytes in the Medial Amygdala Regulate Playfulness in Real Time in Juvenile Rats

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Background: The medial amygdala (MeA) is the site of masculinization of juvenile social play behavior in rats. We have established that during neonatal development, microglia in the male amygdala phagocytose more newborn astrocytes than in females. By the juvenile age, males have fewer astrocytes in the MeA. The sex difference in MeA astrocyte number is inversely related to both the activation of MeA neurons as well as the amount of play, as males display more frequent and vigorous rough-and-tumble play as juveniles and have more immediate early gene expression following a play bout (VanRyzin et al., Neuron, 2019). Whether the developmental determination of a sex difference in astrocyte number has direct implications on play as it is occurring has been unknown. Astrocytes are potent modulators of neural activity via gliotransmitter signaling, leading us to hypothesize that astrocytes in the MeA regulate rough-and-tumble play by influencing the activity of play-relevant neurons.

Methods: To test this hypothesis, we selectively modulated MeA astrocytes using the astrocyte-specific DREADD viruses AAV5-GFAP-HM3D-mCherry and AAV5-GFAP-HM4D-mCherry. Viruses were injected bilaterally into the MeA on postnatal day 21 (P21) and animals were given CNO (3mg/kg) or saline 30 minutes prior to play each day from P27-30. To identify a potential gliotransmitter, we bilaterally cannulated the MeA on P21 and infused the adenosine receptor 1 agonist, nCPA (4.5 nmol) or saline 20 minutes prior to play each day from P27-30. Finally, we used RNAscope to determine the neurochemical phenotype of play-active cells by co-labeling the immediate early gene Egr1 with VGAT (GABAergic cells) and Vglut2 (glutamatergic cells).

Results: We found that HM3D stimulation of MeA astrocytes decreased juvenile play ($n = 14$, $p < 0.001$) while HM4D stimulation increased play ($n = 14$, $p < 0.001$). Furthermore, infusing nCPA via bilateral cannulation similarly and decreased play ($n = 10$, $p = 0.002$), suggesting that astrocytes may be regulating neural activity and behavior through this gliotransmitter. RNAscope phenotyping of play-active cells found that males had significantly more Egr1+ cells in the MeA than females ($n = 8$ per sex, $p = 0.002$) and the majority of play-active cells in both sexes were VGAT + (> 80%, $n = 8$ per sex).

Conclusions: These findings suggest that astrocytes in the MeA provide real-time modulation of GABAergic neural activity which drives play behavior, and identify adenosine signaling as a putative mechanism by which this occurs.

Keywords: Brain Development, Astrocytes, GABA Neuron, Adenosine Signaling

Disclosure: Nothing to disclose.

P118. Prenatal Stress Effects on Placenta and the Role of Maternal IL-6

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Background: Prenatal stress is associated with increases in neurodevelopmental disorders. The cytokine interleukin-6 (IL-6) also has a critical role in the pathogenesis of neurodevelopmental outcomes, with IL-6 signaling in the placenta of particular interest. How specifically the placenta is impacted by prenatal stress, and how those impacts are mirrored by increased prenatal IL-6, is currently unknown. The current study assessed placental changes due to maternal prenatal stress and assessed the sufficiency of IL-6 for these effects using transcriptomic, gene expression, cellular, and morphological perspectives.

Methods: CD1 mice were time-mated. On embryonic day 12 (E12) dams were assigned to one of three groups ($n = 6$ per group): naïve + saline injections, chronic restraint stress + saline injections, or naïve +IL-6 injections (100 ng in .9% saline). IP injections or stress occurred three times per day, 3-4 hours apart. Stressed dams were restrained under bright light for 45-minutes. On E13, a final injection and/or stress session was administered before tissue collection. Placentae were collected and bisected: half was stored in RNALater for molecular studies, and half in 10% formalin for histology. One male and one female placenta (jarid genotyped) from each litter was assessed. Differentially-expressed genes (DEGs) were determined by mRNA-seq. The Kallisto-Sleuth workflow and Wald test were used to evaluate statistical differences between groups with FDR < 0.05. Overrepresentation of IL-6 DEGs in stress DEGs was determined by Fisher's exact test. Pathway analysis was performed with Ingenuity Pathway Analysis (IPA), Protein Analysis Through Evolutionary relationships (PANTHER), and Jackson Labs Mouse Genome Database (MGD). Placentae were H and E stained and immunostained for Iba1. Morphology and Iba1+ macrophages (Hofbauer cells) were quantified by digital microscopy, and expression of relevant genes was assessed with qPCR with t-tests used for assessment of differences.

Results: From unbiased transcriptomics, a significant ($p < 0.001$) overlap in DEGs was found for prenatal stress and IL-6, suggesting the sufficiency of IL-6 for a component of the placental response to stress. Prenatal stress and IL-6 transcriptomics also shared similar over-represented pathways including "glutathione redox reactions I" and immune-related pathways, including "virus entry via endocytic pathways" and natural killer cell signaling. Prenatal stress and IL-6 both also decreased expression of labyrinth-zone

associated genes (MGD). By histology, total placental area and junctional but not labyrinth zone area were decreased by both prenatal stress and IL-6 ($p < 0.01$; $p < 0.05$) in males but not females ($p > 0.05$). Lox, a critical gene for trophoblast migration was trend decreased due to both stress ($p = 0.06$) and IL-6 ($p = 0.09$) in males only (females: $p > 0.1$). Other genes associated with junctional zone morphology, Phlda2 and Plac1, were unchanged; further analyses are ongoing.

Prenatal stress had impacts on placenta independent of IL-6, with DEGs showing decreased expression of decidua-associated genes (MGD) and over-representing glucocorticoid receptor signaling and additional immune pathways. Because immune pathways were implicated, we assessed placental resident immune cells - Hofbauer cells - and found a trend lower density ($p = 0.07$) with stress but not IL-6 in male placenta. Stress also led to increased expression of B2M (both sexes: $p < 0.05$; males: ns, $p > 0.05$; females: $p = 0.06$), a gene with a role in MHC-1 and T-cell development and commonly used as a placental housekeeping gene. The expression of the junctional zone progesterone receptor gene, Pgr was decreased (both sexes: $p < 0.05$; males: ns $p > 0.05$; females: $p < 0.05$). These gene expression differences unique to stress exposure were largely found in females, not males. Conversely, the junctional zone developmental gene Igf2 was trend decreased ($p = 0.09$) with stress but not IL-6 in male placenta.

Interestingly, IL-6 led to placental alterations that were not shared with effects of prenatal stress. IL-6, independent of stress, led to differences in pathways related to redox reactions, such as NAD signaling, superoxide radical degradation, and eNOS signaling. In morphological analysis, male labyrinth zone area was only decreased due to IL-6, not stress ($p < 0.05$). In both sexes, IL-6 also led to significantly downregulated expression of the cell cycle arrest gene, Cdkn1a ($p < 0.05$), and the endothelial proliferation repressor gene, Timp2 ($p < 0.05$). In male placenta only, IL-6 led to a trend decrease in the endogenous antioxidant, Sod1 ($p = 0.09$).

Conclusions: Stress and IL-6 led to overlapping placental transcriptomics and, in males, a reduction in placental junctional zone size. Despite these similarities, stress had unique effects on placental Hofbauer cells and some junctional zone-specific gene expression, suggesting complex effects from the broad physiological changes of maternal stress. Preliminary findings suggest that male morphological and cellular changes occurred in conjunction with changes in genes contributing to cellular development, and female functional changes involved hormone receptor and immune functioning. Whether stress and IL-6 overlapping placental changes underlie common effects on offspring neurodevelopment is unclear, as are the effects on male and female placentae. Further work is needed to assess the impacts of these stress-related placental alterations on offspring brain and behavior.

Keywords: Placenta, Prenatal Stress, IL-6

Disclosure: Nothing to disclose.

P119. Historical and Developmental Risk Associations With Future Orientation

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Background: Adolescent substance initiation and use trajectories are multifactorial[1–3] whereby both historical and developmental factors increase or decrease the likelihood of substance use difficulties (SUD). Historical putative risk factors for SUD development include family density of SUDs[4,5] history of adverse childhood experiences [3,6,7], child history of mental health diagnoses[8], and early substance initiation[9]. Developmentally, increasing impulsivity among adolescents also increases the risk of substance initiation and SUD[10,11]. However, these risk factors are not obligate and understanding protective factors is imperative to characterizing SUD trajectories. One such factor is future orientation (i.e., one's ability to think about the future and future consequences). Adolescent future orientation, often viewed as a stable trait-like factor, is associated with both behavioral (e.g., delayed discounting rates[12]) and functional (e.g., reduced SUDs [13–15]) outcomes. Recent literature also indicates adolescent future orientation actually changes over time as it is sensitive to proximal factors[15]. However, it is unclear how historical and developmental risk and current stress symptomology is associated with future orientation. Aim: Describe the association among historical and developmental risk factors, current reported stress symptoms, and future orientation.

Methods: Adolescents ($N = 127$, 13.60 years + 1.69 years, 55% identify as female) who demographically represent the larger local community (79% white) completed a structured clinical interview, questionnaires, and neuroimaging procedures. Historical risk factors included 1) family history of SUD, 2) child maltreatment history, 3) mental health diagnosis history, and 4) previous substance initiation. For interpretability, we split number of risk factors (0, 1-2, 3-4) into terciles for a composite score. Using Python 3, we entered the historical risk composite and scores for stress, impulsivity, and future orientation into a Generalized Linear Model. Interactions among historical risk, impulsivity, and current stress symptoms were tested for associations with adolescent future orientation.

Results: Tests of multivariate direct effects indicated higher historical risk ($p < .001$) and more impulsivity (i.e., dysfunction in attention ($p < .001$), acting without thinking ($p < .001$), and inability to plan ahead ($p < .001$)) was associated with adolescent preference for immediate outcomes while stress symptoms were not associated with preference for immediate outcomes. However, adolescents with higher historical risk ($p < .001$ - .01), more stress symptoms ($p < .01$ - .07), and more impulsivity ($p < .001$) also reported higher future orientation. Results indicate interactions among these variables are complex. For example, attentional dysfunction is associated with increased preference for immediate outcomes among adolescents with fewer than 3 risk factors, but not those with 3-4 risk factors. Similarly, attentional dysfunction and non-planning were negatively associated with future orientation among adolescents with fewer than 3 risk factors, but positively associated for adolescents with 3-4 risk factors. Variance explained in preference for immediate outcomes ranged from 24 – 30%. The variance explained in future orientation varied by type of impulsivity (i.e., attention: 8%, motor: 5%, planning: 35%).

Conclusions: Consistent with previous literature, preference for immediate outcomes was positively associated with historical risk, stress symptoms, and three different domains of impulsivity [16,17]. Future orientation was negatively associated with stress symptoms and impulsivity, but only for adolescents with less than 3 historical risks. These complex interactions among risk, developmental processes, and future orientation suggests researchers should continue to take an individual differences approach to the study of risk and protective factors. Additionally, the amount of variance accounted for in future orientation and preference for immediate outcomes is dependent on type of impulsivity indicating research should continue to delineate impulsivity domains in order to better understand the development of future orientation. Overall, understanding complex interactions among risk and protective factors including future orientation is essential for characterizing developmental trajectories of substance initiation and SUD. Participants also underwent resting-state and delay discounting fMRI neuroimaging tasks, which will be utilized in future work to characterize the neural connectivity and functional representations underlying these complex interactions.

References: [1]PMC2581497
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[3]PMID20472211
[4]PMC5241101
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[12]PMID28645750
[13]PMC4517266
[14]PMC5376625
[15]PMC6546100
[16]PMC3445337
[17]PMC6214760

Keywords: Risk and Resilience, Future Orientation, Adolescents

Disclosure: Nothing to disclose.

P120. Maternal Medications in Pregnancy and Risk of Autism in the Offspring

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder affecting 1 in 56 children in the US. Studies have established the contribution of several genetic and environmental factors to the etiology of ASD. Despite this progress, a significant proportion of ASD cases remains unexplained. To address this gap and advance prevention efforts, several studies have focused on the role of modifiable risk factors. Maternal health and medication use during pregnancy have received mounting attention. Given the advancing age at pregnancy and polypharmacy attributable to the changes in demographic characteristics and disease patterns, knowledge of the potential role of maternal medication in the risk of ASD becomes even more critical. Several studies have pointed to associations between maternal exposure to certain medications in pregnancy and the risk of ASD in offspring. Nevertheless, methodological limitations often hamper observational studies into the effects of maternal medications, particularly confounding by indication. Moreover, the effects of many medications on the risk of offspring ASD have not been studied. To address these lacunae, we propose a novel methodological approach to minimize the potential role of confounding by indication and illustrate its application to evaluate the associations between maternal medications during pregnancy and offspring ASD.

Methods: We used a nationally representative matched cohort study design based on electronic health records from a health maintenance organization in Israel, covering all children born from 1997 to 2008. Medications prescribed to mothers during the 12 months (three months before and nine months of the pregnancy period) served as exposure variables. All medications with identical active ingredient/s but different brand names were unified into a single (generic) medication category. The study outcome was ASD diagnosis among children by the end of the follow-up (2015). The study protocol was reviewed and approved by the Helsinki Ethics Committee of the Meuhedet and the Institutional Review Board of the University of Haifa.

Medications prescribed to less than 10 mothers of individuals with or without ASD were excluded to minimize sparse data bias. We performed a medication-wide association study (MedWAS), whereby each medication was tested in a separate Cox proportional hazard model by comparing the risk of ASD among children with maternal exposure to the medication in pregnancy with that in unexposed children. The MedWAS models adjusted for child's sex and year of birth, maternal age, the total number of maternal diagnoses during the 12 months before the child's birth, and all indications based on the Anatomical Therapeutic Chemical classification. Next, we assessed the independent effects of the targets influenced by all the medications that were statistically significantly associated with ASD.

Results: The analytical sample consisted of 96,148 individuals (1,401 children with ASD and 94,747 unaffected children). Of the 564 unique medications in our sample, 141 medications had a frequency of ≥ 10 in mothers of children with and without ASD. Of the 141 medications analyzed, 21 were statistically significantly associated with ASD (8 with reduced risk and 13 with increased risk). After adjusting for the indications underlying prescription of these medications, the direction or magnitude of several of these associations changed, suggesting the potential confounding effect of indications in unadjusted associations between maternal medication use and ASD. Of the initial 21 statistically significant associations, 6 remained statistically significant. In further analysis, we examined the associations between the underlying targets inflected by these medications and ASD. The study results pointed to previously reported (e.g., fluoxetine: HR = 1.86; 95%CI = 0.72 – 4.80), and potentially novel associations, including medications associated with lower risk of ASD (e.g., α-tocopherol acetate (a form of vitamin E): HR = 0.76; 95%CI = 0.55 – 1.05, propranolol: HR = 3.85; 95%CI = 1.03 – 14.38).

Conclusions: Harnessing on a national cohort study, our results provide novel insights into potentially modifiable risk factors of ASD, offering the potential to enhance our understanding of the disease etiology and optimizing prevention. Our systematic and rigorous approach minimizes confounding by indication, while the multidimensional strategy and triangulation of findings from different steps of the analyses decrease the likelihood of false-positive results. The study findings draw attention to the importance of maternal exposures, specifically around pregnancy, in the risk of offspring ASD. The implications of the study findings and the application of the proposed methodology for investigating the intended and unintended effects of medications beyond the context of ASD risk, are discussed.

Keywords: Autism Spectrum Disorder, Pharmacoepidemiology, Epidemiology, Neurodevelopmental Disorders

Disclosure: Nothing to disclose.

P121. Motor Activity Declines Across Adolescence in Humans and Monkeys

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Background: There is emerging evidence for a substantial decline in motor activity (MA), a core feature of several human disorders, across adolescent development. However, elucidation of the mechanisms is complicated by contextual factors that constrain MA in human studies. The availability of accelerometry as an unobtrusive tool to obtain objective indices of MA in both humans and non-human primates provides an ideal opportunity for cross species research on MA without the social restrictions in human samples. The aims of this poster are: (1) to evaluate the contribution of age, sex, pubertal status and contextual factors on changes in MA in a human sample of adolescents; and (2) to examine biologic, genetic, and environmental factors associated

with MA in non-human primates in a natural environmental context.

Methods: Human: 1520 youth (mean age 10.2; range 5-21) from the Healthy Brain Network, a study of a broad range of behavioral, emotional, and cognitive assessments in youth in the New York area. Accelerometry was assessed for one week with the Actigraph (wGT3X-BT). Two features derived from accelerometry including Total Log Transformed Activity Count (TLAC) across 24 hours (TLAC), and Total Sedentary Time (TST).

Monkeys: 145 monkeys ($n = 69$ females; 76 males) from the Oregon National Primate Research Center assessed with a neck worn Actical device for 3-10 days at two time points (ages 23-30 mo- pre-pubertal) and (34-43 mo-peri/post pubertal). TLAC and TST were compared at pre-pubertal and post pubertal time points among male and female monkeys.

Results: In the human sample, there was a monotonic decline in TLAC and an increase in TST in both male and female adolescents across ages 8-12. Analyses yielded significant effects for changes in both age and pubertal status, but pubertal status was more influential in males than in females. Likewise, there was a significant decrease in TLAC and an increase in TST across the pre and post pubertal assessments in monkeys, with females having higher TLAC and lower TST than males at both time points. Conversely, there was an increase in sleep time and sleep efficiency in monkeys across adolescence, with similar patterns in the human sample, who also exhibited an increase in sleep midpoint.

Conclusions: These findings demonstrate the importance of the influence of both contextual and biologic factors involved in pubertal development on the decline in motor activity in adolescents. Use of the common phenotype and measure of motor activity facilitates our ability to pursue cross species studies of the genetic, environmental and developmental influences on motor activity. The adolescent decline in MA may provide etiologic insight several human disorders that emerge at adolescence.

Keywords: Motor Activity, Adolescence- Critical Period, Mood Disorders

Disclosure: Nothing to disclose.

P122. Cognitive Neurostimulation of Dopaminergic Midbrain via fMRI Neurofeedback Training Increases Willingness to Exert Effort in ADHD

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Background: The willingness to exert effort is a key driver of motivated behavior. In attention-deficit hyperactivity disorder (ADHD), impairments in cognitive performance have been theorized to arise together with reduced motivation and disrupted effort allocation, all associated with dysregulated dopaminergic functioning. Consistent with this account, pharmacotherapy that increases availability of dopamine has been shown to increase the willingness to exert effort in ADHD subjects. Our prior work has shown that neurofeedback training using fMRI enables healthy young adults to volitionally engage dopaminergic midbrain using only internal imagery. Here, we investigated whether adults with ADHD subjects would show enhancements in effort-based decision-making following neurofeedback training to volitionally engage the dopaminergic midbrain.

Methods: ADHD adults ($N = 11$, 5 Females, Mean age = 30.5yrs) performed the Effort Expenditure for Rewards Task (EEfRt), in which they were presented with the choice of high and low effort tasks, each providing a monetary reward of varying magnitude, with different reward probability. Depending on their choice, participants were required to make a different number of speeded button presses, followed by feedback about whether they successfully completed the task and whether they earned the reward for the trial. This task has been used previously for repeated measures designs.

We compared participants' performance on the EEfRt task before versus after volitional activation of dopaminergic midbrain using real-time fMRI neurofeedback. Training occurred in sessions over four separate days. Training consisted of midbrain neurofeedback during imagery of motivated states, bracketed by Pre- and Post-Tests conducted with no neurofeedback to demonstrate transfer, as in our prior published work (MacInnes, Dickerson, Chen and Adcock, Neuron 2006).

Statistical analysis was performed using 2 x 2 repeated-measures ANOVA implemented in *R*.

Results: Across all sessions (both baseline and post-training), participants were more likely to choose the high-effort option when reward probability is high ($F(2,20) = 16.03$, $p < .001$), indicating that participants were sensitive to expected value during effort-based decision making.

Comparing baseline and post-neurofeedback-training EEfRT performance (within session), participants were more likely to choose the high-effort option after the neurofeedback training session ($F(1,10) = 6.2$, $p = .032$); thus, participants showed significantly greater willingness to choose to exert effort to obtain high rewards following midbrain neurofeedback training. There was no significant interaction between session and reward probability ($F(2,20) = 1.69$, $p = .21$). We also compared actual effort expenditure, based on participant's button presses during EEfRTexecution. Consistent with the results for effort-based decisions, participants also made a higher number of button presses in the EEfRT in post-training sessions versus during the baseline sessions ($F(1,10) = 7.01$, $p = .024$), indicating significantly greater ability to recruit the required effort to implement their choice following midbrain neurofeedback training.

Conclusions: Drawing parallels to results obtained by increasing availability of dopamine pharmacologically, our findings provide preliminary evidence that volitional activation of the dopaminergic midbrain can enhance motivated behavior after the training session, as evidenced by the willingness to exert effort. Current ongoing work examines whether efficacy of volitional midbrain activation during training is predictive of individual effortful behavior, and whether this increase is related to ADHD symptom severity.

Our cognitive neurostimulation approach to changing a neuromodulatory neurotransmitter system with behavior could avoid the side effects associated with chronic medication, and offers the novel possibility of dynamic, rapid neuromodulation according to behavioral context.

Keywords: ADHD, Effort Based Decision Making Task, Motivation, Real-Time fMRI Neurofeedback, Midbrain

Disclosure: Nothing to disclose.

P123. Transcriptome and Proteome Dysregulation in iPSC-Derived Neural Progenitor Cell (NPC) Model of Smith-Magenis Syndrome

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Background: Smith-Magenis Syndrome (SMS) is a rare neurodevelopmental disorder with a global incidence of ~1/15,000. Clinically, patients are observed to have distinct facial features, self-injurious behaviors, circadian rhythm dysfunction, and intellectual disability. In majority of patients with SMS, a heterozygous interstitial deletion of chromosome 17p11.2 is identified. However, in 10% of patients, mutations in retinoic acid induced 1 (RAI1), a gene encoded by this region, underlie the genetic basis for the syndrome. RAI1 has also been implicated in schizophrenia and ASD; though, its function remains to be fully defined. To investigate the neurobiology of SMS and the effects of RAI1 mutations, we are conducting studies on iPSC-derived NPCs, to model early neural development.

Methods: Dermal fibroblasts from 3 unrelated SMS cases, each carrying its unique, deleterious RAI1 mutation, and 5 neurotypical controls were reprogrammed to iPSCs using non-integrating Sendai virus vector. Differentiation into NPCs was performed then checked for immunostaining with Nestin and PAX6. Total RNA and protein lysates were extracted to obtain transcriptome and proteome profiles in SMS- and control-derived NPCs and were analyzed through RNA sequencing and mass spectrometry respectively.

Results: Out of 15233 genes reliably detected, RNA sequencing identified significant differential expression of 347 genes, of which 231 are upregulated and 116 are downregulated. Gene expression was compared to neurotypical developing brains from the Allen Brain Collection, which showed close similarity to early development brains. Significant overlaps with gene modules implicated in schizophrenia and autism spectrum disorder were observed when differentially expressed gene set was compared with PsychENCODE data.

In the proteome dataset, 186 proteins were significantly expressed – 106 were in the cytosolic extract, while 80 were in the membrane-bound extract. Although overlap between the genes in the two data sets were not significant, similar networks were significantly enriched in both data sets, that included cell adhesion, extracellular matrix organization, cell motility, and immunity biological processes.

Conclusions: Novel implicated pathways in SMS were revealed through iPSC-based disease modeling. In this study, mutations in RAI1 were shown to dysregulate diverse cellular processes that may also shed light on SMS-related phenotypes in schizophrenia and ASD. Overall, these investigations illuminate disrupted neurobiological mechanisms that could reveal targets for novel therapeutics.

Keywords: Induced Pluripotent Stem Cells (iPSCs), Rare Neurodevelopmental Disorders, Transcriptomics

Disclosure: Nothing to disclose.

P124. Prediction of Intellectual Disability From Developmental Milestones in Large-Scale Autism Datasets

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Background: Intellectual Disability (ID) is present in approximately one-third of newly diagnosed individuals with Autism Spectrum Disorder (ASD). Past research has demonstrated both (a) with decreasing cognitive ability, risk creating de novo variation is more common in ASD cases, and (b) the genome-wide common variant influences on ASD and ID are largely unshared. These findings motivate a genome-wide association study (GWAS) of ASD without ID, aiming to better isolate ASD's common variant risk factors. However, IQ/ID data are not collected in many large ASD studies due to time and resource constraints. In this project, we aim to fill that gap by predicting the presence of ID in ASD using commonly available, parent-reported developmental milestone data. Ability to predict the presence - or absence - of ID in ASD cases would be useful across several research disciplines, particularly those that necessitate very large samples.

Methods: We began by searching for parent-reported developmental milestone variables common to most large, existing genetics collections. We trained a random forest model to predict ID status from those milestones (First Words, Walking, First Phrases, Bowel Training), age, and sex, using half of the Simons Simplex Collection ($N = 951$). We then tested our model in the remaining half of the Simons Simplex Collection ($N = 951$) as well as a subset of the Simons Powering Autism Research dataset ($N = 1160$).

Results: The model was able to successfully predict the absence of ID in ASD cases. In the Simons Simplex Collection test half and in the SPARK dataset, we achieved negative predictive values (i.e., how often ASD individuals labelled as "no ID" in fact did not have ID) of 87% and 89%, respectively ($p < 0.001$, permutation test). Per-person model confidence estimates also predicted continuous IQ ($r = 0.54$, $p < 0.001$). Permutation testing revealed that First Phrase Age and Bowel Training Age made the largest contribution to model predictions. The model could not successfully predict ASD with ID (positive predictive values 43% and 51% in Simons Simplex Collection test half and SPARK, respectively), likely reflecting lower prevalence of the +ID phenotype among cases and greater variability in the developmental trajectories associated with low measured IQ in ASD.

Conclusions: Using simple developmental phenotypes and machine learning approaches, we were able to successfully predict the absence of ID amongst ASD probands. The present results outperform large-scale electronic medical record registries as tools for identifying ASD probands without ID. This approach enables generation of ID labels for thousands of individuals from large scale ASD genetic association studies that lack the neurocognitive testing data necessary for ID diagnosis. These labels will expand capacity to perform ASD genetic and imaging studies, and enhance ASD risk variant discovery.

Keywords: Autism, Intellectual Disability, Neurodevelopmental Disorders

Disclosure: Nothing to disclose.

P126. Psychophysiological Markers Predict the Effect of Propranolol on Conversational Reciprocity in Autism Spectrum Disorder

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Background: Autism spectrum disorder (ASD) is characterized by impaired social interaction and communication as well as repetitive behaviors and restricted interests. Current pharmacotherapy typically targets psychiatric comorbid conditions, and no agent is proven to target the core features of ASD. Past efforts to target core features in ASD are frequently characterized by a high degree of individual variability in response to the drug. Propranolol is a non-selective beta-adrenergic antagonist that is often used to treat performance anxiety. Our previous work found that propranolol improved conversational reciprocity in patients with ASD with a single dose psychopharmacological challenge study. We have recently completed a double-blind placebo-controlled trial for propranolol in ASD. Most participants participated in an open-label extension study upon completion

of the trial, where psychophysiological assessments were done to determine if they predicted response to propranolol on conversational reciprocity in ASD.

Methods: Forty-seven participants with ASD, age 7-24 participated in the 12 week open label extension study, where propranolol was titrated to 100mg a day in divided doses, or a body weight adjusted dose in younger children. Baseline heart rate variability (HRV) was assessed at baseline. At baseline and at 12 weeks, the social reciprocity subscale of the General Social Outcomes Measure (GSOM) was administered, as used in our previous single dose psychopharmacological challenge study, where participants were rated on six domains for aspects of conversational reciprocity during a semi-structured social interaction. HRV measures were correlated with change in performance on the social reciprocity subscale of the GSOM with propranolol. Analysis was performed separately for participants ages 7-14 and ages 15-24 due to changes in psychophysiology across development.

Results: In the open label study, improvements in social measures were observed over the 12 weeks of the trial. For the participants in the 7-14 year old group, there was a significant negative correlation between the conversational reciprocity change score on the GSOM and baseline standard deviation of the heart rate (Pearson's $r = -0.490$, $p = 0.018$, $n = 24$). However this correlation was not observed in the older participants.

Conclusions: Improvements on social measures need to be interpreted with extreme caution in the open label setting, given the high degree of placebo response in trials in the ASD population. However, psychophysiological markers associated with arousal and sympathetic/parasympathetic balance do appear to predict response to propranolol on aspects of social interaction. Subsequent larger trials will need to revisit this issue to determine whether the apparent specificity of this effect to the younger population is still observed, and to establish a broader understanding of the markers that predict the best responders to propranolol in ASD.

Keywords: Autism Spectrum Disorder, Propranolol, Noradrenergic, Heart Rate Variability, Social Interactions

Disclosures: YAMO Pharma, Impel Phrama, MA Pharma: Consultant (Self)
Quadrant Biosci, Stalicla Biosci: Advisory Board (Self)
Biogen: Speakers Bureau (Self)

P127. Artificial Intelligence-Based Prediction of Aggressive Behavior in Children With Attention Deficit Hyperactivity Disorder

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Background: Attention deficit hyperactivity disorder (ADHD) can be associated with disruptive behavior, including aggression. Episodes of aggressive behavior, whether verbal or physical, may occur without noticeable triggers. This study aims to develop an artificial intelligence (AI)-based model to predict aggressive behavior by monitoring physical activity. We used decision tree-based AI model as its predictions are interpretable similar to human decision making.

Methods: Physical activity was continuously monitored in a home setting in 11 children (Age $= 8.5 \pm 1.0$ years, Female $=$ 27.3%) with ADHD showing frequent aggressive behavior. The wearable sensor (ActiGraph GT3X+, Pensacola, FL, USA) was attached to the waist for a week. A decision tree was trained with collected physical activity data, with the caregiver reporting the time and nature of the aggressive events. The identified parameters were used as the input features for the decision tree-based AI model, which was trained to recognize aggressive events labelled by the caregiver.

Results: Energy expenditure ($p < 0.01$, Cohen's $d = 0.23$), percent of light activity ($p < 0.01$, $d = 0.5$), and step count ($p < 0.01$, $d = 0.4$) were distinguished an event of aggression from non-aggressive behavior. The decision tree-based model showed 75% accuracy, 74% specificity, 90% sensitivity and 20% precision.

Conclusions: This study provides initial support for a decision-tree based classification model to predict aggressive behaviors in children with ADHD. Overall, the combination of energy expenditure, percent of light of activity, and step count can predict aggressive behavior. Future work must seek to improve precision, allowing broad clinical application.

Keywords: ADHD, Artificial Intelligence, Aggression

Disclosure: Nothing to disclose.

P128. Early-Life Adversity Disrupts Reward Responsiveness and Underlying Circuit Activity

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Background: Anhedonia, the loss of pleasure or lack of reactivity to pleasurable stimuli, is a trait marker for vulnerability to depression. Early-life adversity have been associated with higher anhedonic symptoms and increased risk for depression later in life. Rodent models of early-life adversity results in reward deficits later in life. However, the nature of early-life adversity-induced reward deficits and the neural basis of these deficits remain unknown. Here, we dissected the reward processes affected by the early-life adversity and then tested the role of nucleus accumbens (Nac) activity and several projections to Nac in mediating these reward deficits.

Methods: Early-life adversity was induced by placing mice (C57BL/6J) pups and dam in a cage with limited-bedding and nesting during P3-10. Control mice were left undisturbed in their cages during the same period. We tested adult male and female mice for their willingness to work in a progressive ratio task. Further we examined reward responsiveness by measuring lick responses to gradients of palatable rewards. To control for effects of food/water deprivation, we also measured voluntary consumption of palatable rewards. To determine the role of Nac in early-life adversity-induced reward deficits, we performed single-unit and local field potential recordings in Nac as mice responded to rewards. To test the role of projections to Nac in early-adversity-induced reward deficits, inhibitory and excitatory opsins were retrogradely expressed in the ventral pallidum (VP) or orbitofrontal cortex (OFC) neurons projecting to Nac. We analyzed the data using custom MATLAB scripts. Statistical analyses were conducted using repeated measures ANOVA and Wilcoxon signed-rank test.

Results: Reward responsiveness was associated with an emergence of a low-frequency oscillation at 4Hz range in Nac. Interestingly the strength of this oscillation correlated with the hedonic value of the reward. Nac single-units responded to rewards in a diverse fashion, with excitation and inhibition. Excited, but not inhibited, units that were locked to 4Hz oscillation phase showed significantly higher responses to reward in a value-dependent manner, suggesting that reward-induced 4Hz oscillation amplify Nac single-unit responses to the hedonic value of reward. Interestingly, early-life adversity reduced reward responsiveness and reward-induced 4Hz responses in Nac (ANOVA, $p <$ 0.05). Moreover, the inhibition of VP, but not OFC, to Nac, projection resulted in deficits in reward responsiveness and

reward-induced 4Hz oscillation similar to those observed after early-life adversity (rm-ANOVA, $p < 0.05$).

Conclusions: These findings suggest that Nac single-unit activity and 4Hz oscillation as well as VP-Nac projection activity are essential for reward responsiveness. Early-life adversity produces deficits primarily in reward responsiveness and in the underlying neural circuit activity.

Keywords: Early-Life Adversity, Reward Deficit, Anhedonia, Nucleus Accumbens, Neural Circuitry

Disclosure: Nothing to disclose.

P129. Modulating Social Behavior via Manipulation of the Gut Microbiome and Activation of the Dopamine System in a Mouse Model of Prenatal Toxicant/Stress Exposure

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Background: A wealth of epidemiological work suggests that perinatal exposure to air pollution is associated with risk for autism spectrum disorders (ASD). Moreover, psychosocial stressors activate the maternal immune system, making mothers more sensitive to toxicants. Yet, the mechanism by which stress and pollutants synergize to produce risk has yet to be determined. ASD is characterized by impaired social interaction and social communication and is male-biased. Importantly, ASD is often accompanied by gastrointestinal disfunction and fecal microbiota transfer therapy has yielded promising amelioration of behavioral symptoms in ASD. In a novel mouse model of combined prenatal diesel exhaust particles (DEP) and maternal stress (MS) we have found that male but not female offspring have deficits in social behavior, changes in the gut microbiome, and altered neuroimmune interactions within the mesolimbic reward system. Here, we aim to investigate the causal links between the microbiome, brain, and social outcomes.

Methods: First, we aimed to test whether restoring healthy gut microbiota could rescue social behavior following DEP/MS. Thus, we used a) a cross-fostering procedure to assess intervention at birth and b) co-housing with naïve cage mates at weaning to assess intervention later in life. These manipulations have been shown to shift the composition of the gut microbiome. In cross-fostering experiments, DEP/MS exposed male and female pups were fostered on the day of birth to either a DEP/MS or a VEH/CON exposed dam. For co-housing, DEP/MS exposed male offspring were housed at weaning with either 3 littermates or 3 wild-type cage mates. In both experiments, social behavior was assessed during adolescence using a 3-chambered social preference test and 16S sequencing was used to assess the gut microbiome. Second, we used a chemogenetic approach to test whether activation of the dopamine system could rescue social behavior. DAT-cre mice were prenatally exposed to either VEH/CON or DEP/MS. At postnatal day 23, males of both treatments received stereotaxic microinjection of either AAV-hSyn-DIO-mCherry (control virus) or AAV-hSyn-DIO-hM3Dq-mCherry (virus encoding the excitatory DREADD receptor) into the ventral tegmental area. Clozapine-N-oxide (CNO) was administered peripherally 30 min before social behavior testing 10 days later.

Results: Our results show that cross-fostering of DEP/MS exposed male pups to VEH/CON dams on the day of birth prevents deficits in sociability ($t(1,13) = 3.334$, $p < 0.01$). Similarly, co-housing with naïve cage mates reverses social behavior impairments in male offspring ($t(1,20) = 2.177$, $p < 0.05$). Finally, chemogenetic activation of VTA dopamine neurons restores sociability in DEP/MS-exposed male offspring ($F(2,26) = 4.253$; $p < 0.05$).

Conclusions: These results suggest that the gut microbiome may causally contribute to the changes in social behavior observed in male offspring following DEP/MS exposure. Furthermore, driving activity of the mesolimbic dopamine system is sufficient to rescue these social behavior impairments. Importantly, this work also suggests that intervening during either the perinatal or adolescent period may be effective at reducing social behavior impairments. We are currently investigating whether microglia act as key intermediaries between the gut microbiome and the dopamine system in the developmental sculpting of these social circuits.

Keywords: Autism, Social Behavior, Microglia, Dopamine, Gut Microbiome

Disclosure: Nothing to disclose.

P130. Fear-Potentiated Startle as a Biomarker of Trauma-Related Psychopathology in Youth Resettled as Refugees of Syria

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Background: Youth resettled as refugees of Syria in Southeastern Michigan report experiencing an average of 5 traumatic events prior to age 17 (including war, forced migration, and racial/ethnic discrimination), and such exposure can have life-long effects on health and behavior. Fear and safety learning are behaviors affected by trauma exposure that may provide an indication of trauma-related psychopathology—including post-traumatic stress symptoms. More specifically, arousal and vigilance behaviors represented in the hyperarousal symptom cluster may be adaptive in the context of stress and danger, but could become maladaptive and contribute to pathophysiology. In Pavlovian fear conditioning, a neutral cue is repeatedly paired with an aversive stimulus (unconditioned stimulus, US) resulting in a conditioned fear response to this reinforced conditioned stimulus, (CS +, threat cue). Another neutral cue that is never paired with the US is also presented (CS-, safety cue). Fear-potentiated startle (FPS) combines Pavlovian fear conditioning and the acoustic startle response (ASR) to measure fear and safety learning. The startle response is a ubiquitous, cross-species response to strong exteroceptive stimuli, recorded in humans using electromyogram (EMG) of the orbicularis oculi (eye blink muscle) contraction. The fear response component is reflected in the increased magnitude of the startle response to the acoustic startle probe during presentation of the CS + relative to the startle probe alone (in the absence of either CS). The goal of the present research was to measure FPS to threat and safety cues in Syrian youth resettled as refugees in the United States, and determine the relation between FPS and PTSD symptom severity—more specifically, hyperarousal symptoms (Frederkis et al 2021, Biological Psychiatry; Michopoulos et al 2015, Arch Womens Ment Health). Identifying objective biomarkers that can guide early intervention is critical in developing youth, and especially in the context of public health to funnel resources towards individuals that may be at greater risk for psychopathology.

Methods: Youth exposed to civilian war trauma and forced migration were enrolled in a longitudinal study of refugee health within one month of resettlement in the United States. EMG data from a FPS paradigm and self-report posttraumatic stress symptom severity were obtained from $n = 35$ refugee youth (17F; Mage = 12.9 years) assessed 2.5 years after resettlement. The startle probe was a 106 dB, 40 ms white noise burst delivered binaurally through headphones. The CSs were colored shapes presented on a monitor, and the US was an air blast directed at

the larynx, paired with CS + 100% of the time. The acquisition phase consisted of 3 blocks, each with 3 CS + trials, 3 CS- trials, and 3 noise alone (NA) trials (no CS presented during the startle probe), for a total of 27 trials. EMG data were acquired at a sampling rate of 1000 Hz using Biopac MP160.

Results: The results of a 4x3 RMANOVA indicated a significant effect of Block ($F(3,102) = 3.61, p = .02$), Trial Type ($F(2,68) = 5.58, p = .01$), and Block x Trial Type interaction ($F(6,204) = 4.96, p < .001$), such that the startle responses to the NA trials habituated over the course of the fear conditioning session, while startle response to the threat cue, CS +, increased over the session. The startle response to the safety cue, CS-, initially increased and then declined. During the last block of conditioning, startle response to CS + was significantly greater than to the NA ($F(1,34) = 7.51$, $p = .01$), indicating that startle response was potentiated by threat. The startle response to CS + was also significantly greater than to CS-, $F(1,34) = 4.62$, $p = .04$. There were no significant effects of age or sex on startle responses. We then calculated a threat and safety discrimination variable, which was the difference in the startle magnitude between CS + and CS-. Discrimination between cues was positively correlated with total posttraumatic stress symptoms ($r(33) = .41$, $p = .02$) and hyperarousal symptoms ($r(33) = .54$, $p < .001$). In a 3-block hierarchical multiple regression where symptom severity was the predictor and startle response was the outcome, we found that neither severity of total posttraumatic stress symptoms nor hyperarousal symptoms explained a significant portion of variance in startle response to the threat cue above and beyond that of age, sex, and trauma exposure. However, hyperarousal symptoms did explain a significant portion of variance in startle response to safety cue after controlling for the above variables, $F(4,34) = 2.73$, R2change = .16, pchange = .016. pmodel = .047. The same was true for hyperarousal and discrimination score, $F(4,34) = 3.58$, R2change = .24, pchange = 003. pmodel = .019, but not total posttraumatic stress symptoms.

Conclusions: These preliminary findings suggest greater reactivity towards threat cues for youth with elevated hyperarousal symptoms. Having experienced civilian war trauma and forced migration, such behaviors may have been initially adaptive, however persistence of threat vigilance and hyperarousal may become maladaptive and drive cognitive resources away from important non-trauma stimuli in the developmental space. Trauma-exposed youth who exhibit high threat reactivity may benefit from interventions that target the sympathetic responses and emotion regulation.

Keywords: Childhood Trauma, Fear Conditioning, Fear-Potentiated Startle, Adolescent PTSD, Hyperarousal

Disclosure: Nothing to disclose.

P131. Prediction of Mid Adolescent Suicide Attempt Using Multidimensional Data Collected in Early Adolescence

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Background: Suicide is the second leading cause of death in youths and a major health concern. Clinical research has shown that clinicians' capacity to predict suicide attempt (SA) is limited. Therefore, there is hope that predictive analytics can improve SA prediction. While preliminary data from studies applying machine learning (ML) algorithms to predict SA in adults is promising, there is a specific gap in predictive analytic research for youth SA. Here we used longitudinal dataset of youths with data collected in early adolescence to predict SA in mid-late adolescence. We aimed (1) to compare the relevance of different data types (e.g., demographic, clinical, neurocognitive, environmental exposures) for the prediction; (2) to investigate whether use of selected features can outperform models that use all of the available data; and (3) to provide a proof-of-concept for the potential utility of ML based approach to predict youth SA using data collected in early adolescence.

Methods: We analyzed data on youths who participated in the Philadelphia Neurodevelopmental Cohort (PNC) for whom we obtained longitudinal data regarding a history of SA. PNC assessment was conducted from 2009-2011. A convenience subsample of PNC participants remained in the Children's Hospital of Philadelphia (CHOP) health network where screening for depression and history of SA has been added to routine practice as part of well child visits since 2014. We integrated PNC data with CHOP electronic health record to create a PNC longitudinal dataset including $N = 922$ participants (mean age 10 years at PNC assessment [T1]) with longitudinal data on SA in mid-late adolescence (T2, mean age 16.2, of which $n = 49$ [5%] reported a history of SA). We applied ML algorithms using a total 193 features collected at T1 to predict endorsement of SA at T2. In line with the study aim to identify features that are important for the prediction, we chose ML algorithms that allow identification of features and their ranking (i.e., their relative importance for the prediction). Examples of such algorithms include regularized regression (e.g., LASSO), advanced feature-selection algorithms (e.g. Relieff), and other ML approaches (e.g., Random Forest). We used a 3-stage study design. First, we separated the data to domains (i.e., demographic, clinical symptoms, family factors, census-derived neighborhood factors, neurocognitive performance) and used each data domain, as well as the total 193 features, to predict SA. Thereafter, we applied algorithms to allow feature selection based on their relative importance for the SA prediction. Lastly, we evaluated whether a subset of selected features yields better prediction than using the entire 193 features. In all stages, we used Ridge Regression and Random Forest (RF) to generate Area Under the Curve (AUC), sensitivity and specificity as metrics to compare algorithm performance. All prediction models were cross-validated (10-fold) by performing all feature-selection and model estimation in a training sample before being used to generate predicted values in a validation sample.

Results: Inclusion of all dataset 193 features showed superior prediction (higher AUC) than models relying on specific data domains, with AUCs of 0.73 for Ridge and 0.72 for RF. Comparison across data domains indicated that the "clinical" domain yielded the highest prediction metrics with AUC of 0.69 for Ridge and 0.67 for RF. A few domains showed inferior performance, such as "Individual-level trauma exposure" with AUC of 0.46 for Ridge and 0.53 for RF; "Demographics" with AUC of 0.6 for Ridge and 0.48 for RF; and "Neurocognitive" with AUC of 0.56 for Ridge and 0.55 for RF. "Family-level characteristics" (AUC of 0.64 for Ridge and of 0.52 for RF) and "Neighborhood-level socioeconomic environmental characteristics" (AUC of 0.6 for Ridge and 0.59 for RF) showed comparable predictive performance.

Feature selection algorithms revealed that overall, the top ranked features (i.e., those of most importance for the prediction) were of different data domains, and that a selected subset of 25 features yields greater predictive capacity than that relying on all features. In addition, we found that when using different types of algorithms, the top ranking features differ, and often belong to different data domains. The top performing prediction reached an AUC of 0.813, with a balance between sensitivity/specificity with 0.792/0.778.

Notably, the highest-ranked predictive feature was the clinical feature "Have you ever thought about killing yourself?". Sensitivity analysis omitting this feature yielded similar prediction as the main analyses.

Conclusions: We show that data collected early in adolescence can help predict endorsement of a suicide attempt in mid-late

adolescence with predictive capacity that may be relevant for future clinical use as a decision supporting tool for clinicians. A key finding is that different data types from multiple levels of analysis (i.e., demographic, clinical, cognitive, family, neighborhood) are important for generating SA prediction. Our findings provide a proof-of-concept for the potential of using ML algorithms for SA prediction, and suggest that multiple data types, some of which can be easily obtained in real world settings, can contribute to improve and optimize SA prediction in adolescence.

Keywords: Suicide Prediction, Children and Adolescents, Multimodal Data

Disclosures: Taliaz Health: Advisory Board (Self)
Taliaz Health: Stock / Equity (Self)

P132. Early Life Stress Modulates the Gene-Brain-Cognition Pathway in Children

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Background: Childhood early life stress is related to psychopathology. It remains unclear the mechanism of the impact of early life stress on cognition and behaviors in humans. We hypothesized that early life stress modulates the genetic influence on brain development, which then affects cognitive development. We tested this genes-early life stress relationship on the brain and cognition using the integrated data of DNA genotype, brain imaging, and behavioral assessments in large epidemiological, developmental samples (Adolescent Brain Cognitive Development Study, $N = 4{,}992$, ages of 9 to 10).

Methods: Early life stress was measured through questionnaires about household challenges, neglect, and abuse. Genetic influences on general intelligence were estimated using Genome-wide Polygenic Scores (GPS) of Cognitive Performance and Educational Attainment. We identified the brain structural correlates of the cognitive GPSs. For cognitive outcomes, NIH toolbox was used.

Results: Causal mediation models showed the significant genetics-brain-cognition causal pathway, such that brain structure mediated significantly the effects of cognitive GPSs on intelligence (mediation effect = 0.013). Of note, we found a significant moderation effect of early life stress-abuse on the genetics-brain-intelligence pathway (Index of Moderated Mediation = -0.006; 95% CI = -0.011 ~ -0.002; P bonferroni < 0.05). All effects were adjusted for covariates (sex, age, ethnicity, parental marital status, family income).

Conclusions: In sum, this study shows the negative modulatory effects of ELS on the genetic influence on brain structural development, which then have a negative impact on cognitive development. We suggest this as a novel mechanism of early life stress on neurocognitive development.

Keywords: Polygenic Risk Score, Early life Stress, Neurocognition

Disclosure: Nothing to disclose.

P133. Prevalence of Suicidal Ideation and Attempt in Youth: An International Meta-Analysis

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Background: The prevalence of suicide among American youth has increased in recent years (Curtin and Heron, 2019). This is despite significant investment to better understand and prevent suicide. Hypotheses about this increase include time spent on social media and academic pressure, but data are inconsistent. Exploring global trends in suicidal thoughts and behaviors (STB) could provide valuable insights; if cultural differences in hypothesized risk factors correspond with the prevalence of STB, it would inform intervention strategies. However, international trends in STB have not yet been compared. In order to address this gap, we conducted a meta-analysis of epidemiological studies that report on STB in youth worldwide.

Methods: Systematic searches were conducted in PubMed and PsycINFO using the terms "suicid*" AND ("community" OR "epidemiolog*") AND "prevalence." Eligible studies included prevalence of active suicidal ideation (SI) or suicide attempt (SA) in community youth ages 21 and younger. All studies were double coded and all discrepancies reviewed. Analyses were conducted using the metafor package in *R*. Mixed models accounting for shared methods were used to examine the influence of hypothesized moderators (year of data collection, minimum age, percentage of female participants, reporter [youth alone Y/N], self-report [Y/N], school-based [Y/N], lifetime rate [Y/N], region [North America as reference], whether the assessment was a self-report or an interview, what time period was reported [lifetime Y/N]). Additionally, prevalence rates were compared across age, gender, and racial/ethnic groups.

Results: Searches yielded 1930 potential articles; 346 effect sizes for SI met criteria, as did 291 effect sizes for SA. Year of data collection ranged from 1981 to 2020. There were 137 countries and regions represented. Participants ranged from 6 to 21 years old.

The average prevalence of SI was 15.8% (95 % CI 14.3-17.4%). Studies that assessed lifetime active suicidal ideation had higher rates ($B = 0.43$, $p = .0007$), as did those that included only the child as reporter ($B = 0.87$, $p = .031$). More recent studies were associated with lower rates ($B = -0.01$, $p = .022$). The moderators explained 25% of the variance in SI prevalence rates.

The average prevalence of SA was 5.9% (95 % CI 5.2-6.6%). Studies that assessed lifetime suicide attempt had higher rates ($B = 0.42$, $p = .004$). School-based studies ($B = -0.59$, $p = .010$). and those from Western Europe ($B = -0.59$, $p = .011$) or Asia ($B = -0.75$, $p = .0002$) were associated with lower rates. The moderators explained 9% of the variance in SA prevalence rates.

Younger samples (ages 13-and-under), compared to those aged 14 +, were associated with lower rates of SI (8.7% vs. 16.3%, $p = 0.010$), but not SA (3.5% vs. 6.1%, $p = 0.110$). Females were more likely than males to report SI (19.5% vs. 13.3%, $p < .001$) and SA (7.8% vs. 4.7%, $p < .001$). Among the few studies that reported prevalence rates for individual racial/ethnic groups, rates of SI were largely equivalent between White (15.3%) and Black (16.4%) youth, but were higher (but did not reach statistical significance) for Asian (25.9%) and Hispanic (22.2%) youth . The prevalence of SA was statistically equivalent across racial/ethnic groups (Hispanic 10.0%, Asian 8.0%, Black 7.2%, White 4.8%). SI prevalence rates varied by region from 13.5% in Asian countries to 26.0% in Eastern European countries. Rates of suicide attempt ranged from 4.6% in Asian countries to 15.8% in South Pacific Islands.

Conclusions: Although youth suicide deaths in the US are increasing, there has not been a corresponding increase in SI or SA over time. This suggests that access to information about fatal suicide methods, as well the availability of means, may be influencing the rate of fatal attempts more than other hypothesized factors. For example, studies of the association between social media use and youth suicide show mixed results; with a link between social media and suicide found primarily among social media users who specifically seek self-harm or suicide-related content (Daine et al., 2013; Mars et al., 2015; Sedgwick, Epstein, Dutta, and Ougrin, 2019). This type of content is associated with a contagion effect (Arendt, Scherr, and Romer, 2019; Dunlop, More,

and Romer, 2011; Marchant et al., 2017). It may be that easy online access to information about how to die by suicide plays a bigger role in the observed increase in suicide deaths than a change in psychological distress due to social media use.

The results also show that rates of suicidal ideation and suicide attempt – like suicide death rates – vary widely around the world. This suggests that there are important cultural and/or socio-economic drivers of youth suicide. For example, WHO data show that low-income countries account for the vast majority of suicides among young people. However, some higher income countries, like South Korea, have been singled out for having a high rate of suicide, which is often attributed to academic pressure put on young people (among other factors; Kwak and Ickovics, 2019). Although our analyses investigated a number of hypothesized moderators, they accounted for a small proportion of the variance in SI and SA prevalence rates across studies.

Significant effort has been levied against youth suicide, but further work is necessary to better understand the factors that contribute to youth suicide risk – and how these factors vary based on individual and environmental characteristics.

Keywords: Suicide, Epidemiology, Meta-Analysis, Youth

Disclosure: Nothing to disclose.

P134. Limited Bedding Combined With Maternal Separation During Early Life Induces Abnormal Brain Metabolism, Memory Impairments and mPFC Transcriptomic Signature

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Background: Exposure to adverse experiences during early life is considered a risk factor for the development of cognitive impairments. The prefrontal cortex (PFC) is directly involved in regulating working memory, and due to its late development, it is considered vulnerable to the effects of early life stress (ELS). Nevertheless, there are still gaps in the literature in order to fully unravel the molecular underpinnings associated with those ELS-induced cognitive deficits. Considering the multifactorial and polygenic characteristics of these impairments, a global approach is increasingly necessary to comprehend such conditions. For this reason, we aimed to investigate the impact of a novel ELS model on PFC-dependent memory function, brain metabolism and potential biomolecular targets via RNA-seq analysis.

Methods: BALB/cJ mice were simultaneously exposed to limited bedding and maternal separation (3h per day) from postnatal day (PND) 2-15 (LBMS protocol) or left undisturbed (CT group). During late adolescence (PND 50), one cohort of male offspring ($n = 13$/group) were tested in the Y-maze and Object-in-Place (OIP) to evaluate PFC-dependent memory function. Following behavioral testing, the medial PFC was dissected. Total RNA was isolated and mRNA was enriched in order to conduct RNA-seq transcriptomic analysis ($n = 4$/group). RNA-seq data was aligned to the GRCm39 mus musculus reference genome using the STAR aligner. FeatureCounts was utilized to quantify gene-level expression of transcripts followed by differential gene expression analyses with DeSeq2. Adjusted *p*-value cutoff (FDR) was used to identify differentially expressed genes. Two outliers were removed (one from each experimental group) using the PcaGrid method. We also conducted microPET/CT scans on a second cohort ($n = 10$/group) to gather information on brain metabolism using the uptake of [(18)F]Fluoro-2-deoxy-2-d-glucose (FDG) as a marker. The 18F-FDG uptake in the right and left striatum, cortex, right and left hippocampus, thalamus, basal forebrain/septum, hypothalamus, right and left amygdala, olfactory areas, cingulate gyrus, superior colliculi, right and left midbrain, and right and left inferior colliculi were normalized for the injected dose and body weight. The standardized uptake value (SUV) was calculated for the whole brain and each individual region.

Results: Regarding behavioral data, we observed that animals exposed to ELS showed impaired performance in the Y-maze ($p = 0.001$) and OIP ($p < 0.001$) compared to CT group. Transcriptome analysis of differentially expressed genes showed that Hba-a2 ($p < 0.001$), Ly6c1 ($p < 0.001$), Fkbp5 ($p = 0.001$), Fam107a ($p = 0.001$), Cables1 ($p = 0.005$), Tsc22d3 ($p = 0.007$), Echdc2 ($p = 0.012$), Slc2a1 ($p = 0.014$), and Hif3a ($p = 0.018$) were downregulated in animals exposed to ELS when compared to CT group. We also found increased glucose uptake in the whole brain in ELS group ($p = 0.0092$).

Conclusions: Our data provides significant evidence that ELS induces long-term PFC-dependent memory impairments in male mice. We found evidences of brain hypermetabolism within animals exposed to LBSM. Furthermore, we conducted an extensive molecular characterization, which identified a lower expression of targets related to stress and immune system.

Keywords: Early Life Stress, Maternal Separation, microPET, Transcriptomics, mPFC

Disclosure: Nothing to disclose.

P135. A General Psychopathology, "*p*" Factor Identified in Preschool Age Children Predicts Longitudinal Psychiatric Symptom Trajectory and Functioning

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Background: A "*p*" factor, representing the overarching shared variance among all psychiatric symptoms may help explain the liability for developing psychiatric problems, the comorbidity between diagnoses, as well as the persistence and severity of symptoms (Caspi and Moffitt, 2018). A *p* factor has been found in school age children, adolescents, and adults and recently in a cross-sectional analysis of preschool children (Michelini et al., under review). Here, we assess the impact of the preschool *p* factor (PS *p*) on adolescent outcomes in a 17-year longitudinal study of children enriched for early onset psychopathology.

Methods: Factor structure was defined using structured clinical interview items from parent interviews in a group of 1253 preschool children (Michelini et al., under review), including $n = 306$ 3 to 5 year-old children from the preschool depression study (PDS), which demonstrated a robust common *p* factor as well as multiple correlated subfactors. In the PDS participants, multilevel models were used to calculate the trajectories (intercept and slope) of internalizing and externalizing symptoms, peer relationships, and general functioning as measured by the MacArthur Human Behavior Questionnaire (HBQ). Linear regressions were used to predict these HBQ intercepts and slopes from PS *p*, both individually and when covarying for IQ and adverse experiences ($n = 145$).

Results: As expected from prior studies, PS *p* was significantly correlated with adverse experiences ($r = 0.27$, $p < 0.001$) and IQ ($r = -0.23$, $p < 0.001$). However, PS *p* predicted the intercept of externalizing (est = 0.11, $t = 5.22$, $p < 0.001$) and internalizing symptoms (est = 0.08, $t = 4.65$, $p < 0.001$), as well as overall peer relations (est = -0.09, $t = -2.13$, $p = 0.03$) and functional impairment (est = 0.09, $t = 4.19$, $p < 0.01$), even when covarying for IQ, adverse experiences, participant reported sex, age, and lifetime diagnosis of depression.

Conclusions: As early as preschool age, the *p* factor describing common variance shared amongst multiple psychiatric symptoms

can be identified and predicts having increased internalizing and externalizing symptoms across development, worse peer relationships and increased impairment, even when covarying for other transdiagnostic factors such as adverse experiences and IQ. Thus, children with high burden of psychiatric symptoms in early childhood should be followed closely and considered for early intervention programs that target social, emotional, and behavioral development. Moreover, understanding the developmental course of the *p* factor may help elucidate the biological constructs underlying such shared variance.

Keywords: Early Childhood, P Factor, Longitudinal Analysis

Disclosure: Kirkwood Medication Assisted Treatments: Founder (Spouse)

P136. Dynamic Changes in PVN Neuronal Activity In Vivo in Response to Acute Stress

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Background: Stress dysfunction and HPA axis dysregulation are associated with vulnerability to neuropsychiatric disorders. Adverse events or trauma experienced during vulnerable developmental periods such as during pubertal maturation increase disease risk across the lifespan. The paraventricular nucleus of the hypothalamus (PVN) integrates critical information regarding stressful stimuli, and the output of PVN corticotropin-releasing factor (CRF) neurons regulates hormonal and autonomic stress responses required for survival. While adult PVN CRF neurons are highly plastic and quickly return to baseline activity during stress recovery, determination of when this homeostatic setpoint is established during postnatal development is not understood. Further, despite the vulnerability of adolescents to stress-related neuropsychiatric disease, juvenile PVN anatomy and function has received limited attention. The current study utilized in vivo fiber photometry to measure calcium activity of PVN neurons in mice of both sexes during exposure acute stress, to determine how the activity of the adult PVN varies in response to qualitatively different stress paradigms. Developing an understanding of the typical neuronal stress response in the adult brain is an important first step for future investigation of how PVN neuron activity correlates with the hormonal stress response, how PVN CRF neurons mature relative to HPA axis function throughout development, and how adversity experience during this vulnerable period alters this trajectory.

Methods: To measure the calcium activity of hypothalamic PVN neurons in vivo in adult mice (3 to 6 months) of both sexes, we employed stereotaxic injection targeting the PVN for bulk loading of the calcium sensitive fluorescent dye Cal-520 AM ($n = 4$ mice) or delivery of pAAV-syn-FLEX-jGCaMP7c in Sim1-cre animals ($n = 7$ mice). Mice subsequently received fiber optic implants targeting the PVN for fiber photometry recordings. Following acclimation to experimenter handling and the optical patch cord, PVN calcium activity was recorded using a Neurophotometrics FP3002 fiber photometry system during exposure to an acute stressor. We utilized four different stress paradigms: tail restraint stress, forced swim test, predator odor exposure, and acute restraint. Raw fluorescence data was corrected and processed using custom Python scripts. Behavioral videos were manually scored. Behavioral events were aligned in time with corrected fluorescence signals to quantify changes in ΔF/F in Python for statistical comparison in GraphPad Prism using paired and unpaired t-tests ($\alpha < 0.05$) where appropriate.

Results: Both bulk-loading of the calcium-sensitive dye Cal-520 AM and viral expression of the calcium indicator jGCaMP7c were found to be viable strategies for measuring the response of PVN neurons to stressful events, exhibiting calcium events of similar peak amplitude during the tail restraint test ($p > 0.05$). All four acute stress-inducing conditions increased the calcium activity of PVN neurons relative to the pre-stress baseline ($n = 3$-8 trials per condition; $p < 0.05$ for all). We also observed that different stressors produced distinct patterns of PVN activity. The tail restraint test and acute restraint were associated with distinct peaks of calcium activity. In contrast, the forced swim test and exposure to predator odor were associated with a prolonged increase in baseline fluorescence, suggesting a protracted increase in PVN activity.

Conclusions: Our study was focused on establishing an understanding of the stress-induced changes in activity of neurons in the adult PVN. Stress rapidly induces plasticity in PVN CRF neurons, increasing CRF levels, excitability, and firing rate, and leading ultimately to increased glucocorticoid release from the adrenal glands. Our data indicate that neuronal activity within the PVN during acute stress is dynamic and dependent on the nature of the stressor, a factor that should be considered in the design and interpretation of experiments assaying HPA axis function. Characterizing the typical response of adult PVN to stress also provides a starting point for investigating neuronal response to stress in the PVN during juvenile development, when stress response and HPA axis function are changing dynamically. Future investigations will determine the relationship between PVN activity and hormonal stress response and define the developmentally-programmed trajectory of PVN activity and HPA axis activation.

Keywords: Acute Stress, HPA Axis, Fiber Photometry, Paraventricuar Nucleus, Hypothalamus

Disclosure: Nothing to disclose.

P137. Mapping the Neuroconnectional Landscape in Autism via Cross-Species fMRI

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Background: Autism is a complex neurodevelopmental disorder characterized by high etiological heterogeneity. Brain imaging studies have revealed atypical connectivity in individuals with autism as measured by resting state functional MRI (rsfMRI). In keeping with the large etiological and biological variability of the disorder, diverse and diverging patterns of connectivity alterations have been reported in individuals with autism (Hull et al., 2017). However, the significance of clinical heterogeneity in rsfMRI connectivity remains largely debated. For one, it remains unclear whether clinical rsfMRI atypicalities can converge to define a brain signature of autism, or whether they should be expected to differ. Moreover, while encouraging attempts to use connectivity mapping as a stratifier for autism have been published (Tang et al., 2020), controversy remains as the contribution and control of physiological noise, environmental and genetic heterogeneity, and the identification of suitable control population to which autism-related atypicalities can be contrasted.

By back-translating rsfMRI mapping in physiologically accessible species like the mouse, we recently showed the possibility to reliably map autism-related connectivity alterations with exquisite etiological and genetic specificity, negligible contributions from environmental confounds, and leveraging the use of appropriately matched control population. Importantly, when expanded to a sufficient number of etiologies, this approach offers the unprecedented opportunity to define a "ground-truth" etiologically-relevant neuroconnectional landscape of autism, which may guide and inform analogous effort in relevant clinical populations. To this aim, here we leveraged our rsfMRI database of 20 mouse

models of highly relevant autism-related genetic etiologies. We next used rsfMRI connectivity metrics to map the corresponding space in clinical autism rsfMRI databases.

Methods: Mice: All experimental protocols were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals. A total of 306 mice with 20 autism-related genetic alteration and 310 control littermates underwent rsfMRI mapping at 7T. Thirteen etiologies were scanned at IIT Rovereto (Italy) and 7 etiologies were scanned at ETH Zürich (Switzerland). RsfMRI connectivity mapping was carried out by using spatially unbiased global connectivity mapping (Cole et al., 2010). Functional alterations associated to each etiology were computed by carrying out intergroup comparisons (transgenic mice vs. control littermates). Humans: Global connectivity mapping was carried out on $n = 1123$ individuals with ASD and $n = 1166$ controls (6-30 yo) from ABIDE1 (Di Martino et al., 2014), ABIDE2 (Di Martino et al., 2017) and an additional independent dataset. Scans with median FD < 0.2 mm were included in the analysis. Preprocessing was carried out by using CPACv1.6 (Craddock et al., 2013) and time-series underwent multi-site harmonization by using COMBAT (Johnson et al., 2007). Replicability of findings was assessed by splitting our sample in discovery and replication datasets, matched by age and head-motion.

Results: To probe the neuroconnectional landscape produce by multiple, unrelated autism-relevant genetic etiologies, we investigated 20 autism-relevant mouse models via rsfMRI connectivity mapping. Consistent with our recent work (Zerbi et al., 2020), we found that most etiologies had robust connectivity alterations, and many exhibited subtle and distinctive functional dysconnections. Cross-etiological convergences were, however, notable. When grouped together they defined a pseudo-continuous connectivity landscape characterized at its extremes by etiologies exhibiting dominant functional hypo- or hyper-connectivity, and by multiple intermediate phenotypes in which weaker mosaic patterns of dysconnectivity were appreciable. To assess whether this variability can be parsed in functionally-meaningful subtypes, we used hierarchical cluster analysis. Results revealed at least two subtypes showing diverging patterns of connectopathy. We next turned to human rsfMRI imaging to obtain an analogous assessment of the connectional landscape. Here we found that rsfMRI connectivity mapping in subjects with idiopathic ASD defined a pseudo-continuous landscape of connectivity alterations remarkably similar to the one mapped in the mouse database. The extremes were characterized by broad hypo- or hyper-connectivity and a wide range of varying mosaic patterns laid in between these diverging profiles. Notably, we found an analogous landscape of ASD-related atypicalities in the replication dataset, suggesting robust reproducibility of our findings.

Conclusions: Our cross-species approach suggests that atypical functional connectivity in autism can be conceptualized by a pseudo-continuous neuroconnectional landscape defined by prominent global hyper- or hypo-connectivity at the extremes, and varying mosaic patterns of functional dysfunctions between these two outmost boundaries. These findings together support the notion that there is not unique signature of connectopathy in for the disorder.

Keywords: Autism, Functional MRI (fMRI), Resting State Functional Connectivity, Translational Imaging

Disclosure: Nothing to disclose.

P138. Investigating the Effects of Prenatal Alcohol Exposure on the Developing Cortex Using Single Nucleus RNA Sequencing

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Background: Fetal Alcohol Spectrum Disorder (FASD) encompasses the array of conditions associated with prenatal alcohol exposure (PAE), including physical dysmorphism, cognitive deficits, and behavioral issues. The effects of PAE on the brain include excessive cell death and impaired proliferation and differentiation, but how individual cell types may be differentially affected is still poorly understood. In this study, we use single nucleus RNA sequencing (snRNAseq) to investigate whether first trimester PAE alters cell type proportion and the transcriptomic profiles of individual cell types of the developing cortex in a model for FASD.

Methods: Pregnant C57BL/6J dams were treated with 2.5 mg/kg ethanol (EtOH) or saline daily from embryonic day 8 (E8) to E13. On E14, cortices from embryos were harvested ($n = 5$-6). Nuclei were extracted and processed for snRNAseq (10X Genomics). Transcriptomic libraries were sequenced (Illumina), and cluster analysis, differential gene expression analysis, and pathway analyzes was performed using Seurat.

Results: snRNAseq in embryonic cortices revealed the expected cell types at this developmental time, including progenitor, interneuron, and excitatory neuron subtypes. Among these major cell types, unsupervised cell cluster analysis revealed 23 individual cell subtypes. While PAE did not significantly alter the proportion of cells per identified cell type, individual cell types displayed differential patterns of gene expression in response to PAE. In particular, Layer V-VI excitatory neurons demonstrated the largest number of differentially expressed genes. Pathways implicated include those involved with neuronal differentiation and brain development.

Conclusions: The PAE paradigm used in this study did not alter the proportion of cells of different cell types; however, different cell types displayed different transcriptomic profiles in response to PAE, suggesting specific cell types of the cortex may be more vulnerable to the effects of PAE at this time in development.

Keywords: fetal alcohol spectrum disorder, Single-cell RNA sequencing, Cortical Development, Prenatal alcohol exposure

Disclosure: Nothing to disclose.

P139. Maternal Stress During Pregnancy and its Impact on Gyrification and Cognition in Young Adulthood: Findings From a Prenatal Birth Cohort

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Background: Maternal stress during pregnancy has been associated with elevated risk of cognitive impairments in the offspring such as worse cognitive ability in the attention, language and executive functioning domains, but the mechanisms underlying these relationships are incompletely understood. Cortical gyrification can serve as an index of early brain development and convey information about prenatal developmental disruption well into adulthood. We previously conducted a neuroimaging follow-up of a prenatal birth cohort and showed that prenatal stress is associated with temporally and sex-specific differences in cortical gyrification across frontal, temporal, and parietal regions in offspring at the age 23-24. Here we conducted further longitudinal follow-up analyses to test whether cortical gyrification differences identified at age 23-24 may predict cognitive performance at age 28-29 and mediate the link between exposure to prenatal stress and cognitive ability in adulthood.

Methods: A total of 85 young adults (44% women, all White Caucasians) from the European Longitudinal Study of Pregnancy and Childhood, a prenatal birth cohort born between 1991 and 1992, participated in the neuroimaging follow-up Biomarkers and Underlying Mechanisms of Vulnerability to Depression (VULDE) at the age of 23-24 and had complete information on early life stress. Out of these, 54 (50% women) participated in an ongoing follow-up Health Brain Age (HBA) at the age of 28-29. Maternal stress was assessed using a 40-item questionnaire at four different time points in the early 1990s to evaluate the number and impact of stressful life events experienced during the first and second half of pregnancy, the first six months after birth, and during 6-18 months after birth. As previously described, structural magnetic resonance imaging (MRI) was performed on a 3T Siemens Prisma MRI scanner at the age of 23-24 and T1-weighted data were processed using Freesurfer to estimate local gyrification index (LGI). Cognitive abilities in the young adult offspring (age 28-29) were measured using the Wechsler Adult Intelligence Scale (WAIS), which allowed us to calculate separate measures capturing Performance and Verbal intelligence quotient (IQ). While Performance IQ reflects processing speed and perceptual organization, Verbal IQ reflects measures of verbal comprehension and working memory performance. Statistical analyses used multiple regression to assess whether stress during early life (4 measurements) and sex of the offspring might predict Verbal and Performance IQ in young adulthood. Next, linear regression assessed whether cortical gyrification in clusters previously associated with prenatal stress might prospectively predict Verbal and Performance IQ assessed at age 28-29. Finally, a mediation analysis using bootstrapping evaluated whether altered gyrification might mediate the relationship between maternal stress during pregnancy and Verbal and Performance IQ in the offspring.

Results: Higher maternal stress during the first half of pregnancy was associated with lower Performance IQ (Adj $R2 = 0.05$, beta = -0.42, $p = 0.032$), while higher maternal stress during the second half of pregnancy was associated with lower Verbal IQ (Adj $R2 = 0.08$, beta = -0.44, $p = 0.009$) in offspring at the age of 28-29. These findings were independent of sex and maternal stress experienced during the rest of pregnancy, as well as maternal stress experienced during the first 18 months of the offspring's postnatal development. Further analyses demonstrated that Performance IQ at the age of 28-29 was predicted by lower gyrification of a cluster in the right middle temporal lobe assessed at the age of 23-24 and previously associated with maternal stress during the first half of pregnancy ($R2 = 0.07$, beta = -0.27, $p = 0.047$). Verbal IQ at the age of 28-29 was predicted by higher gyrification of distinct clusters in the right inferior parietal lobe and pars opercularis, which were previously associated with maternal stress during the second half of pregnancy ($R2 = 0.10$, beta = 0.32, $p = 0.020$ and $R2 = 0.10$, beta = 0.32, $p = 0.017$, respectively). Finally, a mediation analysis revealed that the relationship between maternal stress during the second half of pregnancy and Verbal IQ in the young adult offspring was mediated by gyrification of the right inferior parietal lobe (ab = -0.93, 95% CI [-2.18, -0.10]) and pars opercularis (ab = -0.28, 95% CI [-2.66, -0.06]). No similar mediation was present for the relationship between maternal stress during the first half of pregnancy and Performance IQ (ab = -0.78, 95% CI [-2.17, 1.57]).

Conclusions: We identified novel time-specific effects of prenatal stress on Performance and Verbal IQ in young adult offspring. While higher stress experienced during the first half of pregnancy was associated with lower Performance IQ, higher stress during the second half of pregnancy was associated with lower Verbal IQ. We also demonstrated that altered gyrification measured at ages 23-24 mediated the relationship between exposure to stress during the second half of pregnancy and Verbal IQ at age 28-29. Thus, we speculate that the time-specific effects of prenatal stress on cognitive performance in adulthood might be driven by distinct patterns of spatiotemporal sensitivity of the cortical gyrification developmental process, differentially impacting frontal, parietal and temporal regions essential for these cognitive skills.

Keywords: Prenatal Stress, Cognitive Skills, Gyrification

Disclosure: Nothing to disclose.

P140. Adolescent Data-Driven Neural Networks Prospectively Predict Adult Anxiety Symptoms Related to COVID-19 Economic Adversity

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Background: Stressful events, such as the COVID-19 pandemic, are major contributors to anxiety and depression, but only a subset of severely stressed individuals develop psychopathology. Characterizing neural signatures that underlie differential susceptibility can inform targeted prevention and intervention efforts. Using conventional aggregated group-level methods, fMRI research has identified modest predictive links between brain function and later anxiety and depression; however, recent evidence suggests that traditional analytic techniques may conceal substantial heterogeneity in brain networks. Modeling functional connectivity using advanced person-specific approaches reveals individualized features that better capture heterogeneity for predicting clinical outcomes. In this study, we utilized a person-specific approach to connectivity mapping that included an embedded unsupervised community-detection algorithm to derive data-driven subgroups in adolescent fMRI data. In an existing population-based sample with a substantial representation of African Americans and low-income families who were disproportionately impacted during the pandemic, we addressed two questions: 1) Do adolescent neural network subgroups predict anxiety and depression symptoms six years later in adulthood during COVID-19? and 2) Are the neural network subgroups differentially susceptible to anxiety and depression related to COVID-19 economic adversity?

Methods: Functional neuroimaging data during an emotional faces task were collected from 174 adolescents (mean age 15.9, 54% females, 70% African Americans, 47% reported family income of < $30,000) recruited from the longitudinal Fragile Families and Child Wellbeing Study. Subgroup Group Iterative Multiple Model Estimation (S-GIMME) was applied to individual-level functional data extracted from 7 bilateral regions of interest (ROI; 4mm radii) linked to emotion processing as well as anxiety and depression: amygdala, dorsal anterior cingulate (dACC), dorsomedial prefrontal (dmPFC), insula, orbitofrontal (OFC), subgenual anterior cingulate (sgACC), and ventral striatum (VS). All ROI central coordinates were preregistered on Open Science Framework. Anxiety and depression were self-reported at ages 15 and 17 (using Screen for Child Anxiety Related Emotional Disorders, Mood and Feelings Questionnaire), and 21 (during COVID-19; using Beck Anxiety Inventory, Beck Depression Inventory). At 21, participants reported on pandemic-related economic adversity (i.e., job loss, income loss, financial hardship, food insecurity). Differences across neural network subgroups were first examined, then subgroup membership was utilized to predict anxiety and depression symptoms using hierarchical regression. Finally, interactions between subgroups and economic adversity were examined to predict symptoms. Additionally, person-specific node degree centrality (i.e., number of connection involving a given ROI) was examined in relation to symptoms using Bonferroni-adjusted

alpha levels of .004 (0.05/14). Sex was used as a covariate in subsequent sensitivity analyses.

Results: Person-specific networks fit the data well, and S-GIMME identified two neural subgroups: subgroup A ($n = 80$) characterized by hyperconnectivity among the emotion processing regions; and subgroup B ($n = 94$), with fewer overall connections (average fit indices: RMSEA = .051; SRMR = .050; CFI = .952). Subgroup A showed significantly greater node centrality in the right amygdala, right dACC, bilateral sgACC, and right VS.

Regarding the first research question, relative to subgroup B, subgroup A had greater anxiety during COVID-19, and these findings were significant when adjusting for ages 15 and 17 anxiety (b = .47; 95% CI = [.167, .768]; $p = .003$). Group differences in anxiety were particularly linked to the left sgACC: greater left sgACC centrality at age 15 was predictive of greater anxiety at age 21 (b = .12; 95% CI = [.039, .197]; $p = .004$).

Regarding the second research question, greater COVID economic adversity was related to greater anxiety across all participants (b = .21, 95% CI = [.112, .300], $p < .001$); but there was a significant adversity-subgroup interaction (b = .44; 95% CI = [.104, .783]; $p = .011$) such that subgroup A reported greater anxiety in response to COVID economic adversity relative to subgroup B. Individuals across subgroups did not differ demographically (e.g., sex, race, income) and reported equivalent economic adversity, and these effects remained after adjusting for sex and other relevant demographic variables.

Conclusions: An unsupervised community detection algorithm embedded within a person-specific functional connectivity mapping framework identified two neural network subgroups from adolescent fMRI data: one subgroup exhibited hyperconnectivity across emotion-related ROIs and the other subgroup had fewer connections among all ROIs. Prospectively, six years later in adulthood, the hyperconnected subgroup experienced greater anxiety symptoms during COVID-19 and was more susceptible to anxiety from COVID-related economic adversity relative to the other subgroup. All effects remained when adjusting for covariates. These results highlight the importance of considering heterogeneity in neural network modeling and suggest that hyperconnectivity in emotion networks may predispose individuals to anxiety when experiencing highly stressful adverse events.

Keywords: Anxiety and Stress, COVID-19, Differential Susceptibility, Neural Network Connectivity, Biomarker Prediction

Disclosure: Nothing to disclose.

P141. Association of Maternal Mood Postpartum With Electroencephalography Patterns of Infant Speech Development at 2 and 6 Months

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Background: Postpartum depression has been associated with language development delays in infants. This may be due to a reduction in infant-directed speech use of mothers suffering from depression, characterized by reduced mean pitch and pitch range, slower verbal responses and less positive valence in the mother's voice. Given the wide spectrum of postpartum depression severity and the high prevalence of subclinical depressive symptoms postpartum (i.e., "baby blues" in up to 70 percent of recent mothers), it is important to understand if and how subclinical depressed maternal mood affects early infant speech perception development. It remains an unresolved question whether subclinically depressed mood in healthy recent mothers associates with early infant speech perception. Moreover, it is unclear whether such an association can be detected during early infancy on the neural level. We hypothesized that lower maternal mood postpartum would be associated with a lower likelihood of developing a more mature infant Mismatch Response (MMR) to acoustic stimuli.

Methods: We recorded longitudinal electroencephalography (EEG) data during an event-related potential (ERP) Mismatch Negativity (MMN) paradigm. We assessed infants' brain responses to different phonological feature changes relevant for speech perception at 2 ($n = 46$) and 6.5 months ($n = 36$), covering the age range in which a shift from a positive to a negative MMR typically appears. As an initial evaluation of infant speech perception abilities, we first tested the infant MMR to different phonological features at both assessments. To avoid bias, the dropouts at the follow-up assessment ($n = 10$) were compared to the remaining sample ($n = 36$). Maternal questionnaires for postpartum mood (Edinburgh Postnatal Depression Scale, EPDS) and perceived stress (Perceived Stress Scale, PSS-10) were assessed at 2 months postpartum. We analysed the correlation between maternal postpartum mood (at 2 months) and infant MMR as a measure of speech perception at the age of 2 months as well as in the same infants at the age of 6.5 months. Assumptions for metric statistical tests were proven and, if not otherwise specified, data and residuals of regression analyses were normally distributed (Kolmogorov-Smirnov Test). Reported p-values are two-sided. For ANOVAs, Greenhouse-Geisser-Correction was used, p-values were corrected for multiple comparisons, and ηp^2 is given for ANOVAS and $f2 = [(R2/(1–R2)]$ for regression analyses as effect sizes.

Results: All mothers were physically healthy, did not smoke, had no history of neurotoxin use, and did not meet criteria for current or past Axis I diagnosis. All infants were healthy and full-term born without any diagnosed hearing deficit or neurological condition. At age 2 months, we found a significant linear model fit for the syllable-pitch MMR (300–400 ms) [$F(1,43) = 5.66$; $p < .03$; $f2 = 0.13$; 12% explained variance] with EPDS as the only surviving predictor (inclusion criterion: $p \leq .05$). Higher EPDS scores were associated with a more positive syllable-pitch MMR. At age 6.5 months, we also found a significant linear model fit for the syllable-pitch MMR (200–300 ms) [$F(1,34) = 5.64$; $p < .02$; $f2 = 0.21$, 17% explained variance] with EPDS as the only significant predictor. Again, higher EPDS scores were associated with a more positive syllable-pitch MMR in infants. A one-factorial repeated-measures ANCOVA with the change in syllable-pitch MMR amplitude (from 2 to 6.5 months) as between-subject factor and maternal mood (EPDS scores) as a covariate of interest, revealed a statistical trend for a main effect of change in syllable-pitch MMR [$F(1,34) = 3.68$; $p = 0.063$; $\eta p^2 = 0.09$], indicating a change to a more negative MMR at 6.5 months. Further, a significant interaction between the change in MMR and maternal mood [$F(1,34) = 5.54$; $p < 0.03$; $\eta p^2 = 0.14$] was revealed. Following this interaction, a correlation between MMR change (delta syllable-pitch MMR = MMR 6.5 months–MMR 2 months) and maternal mood was calculated, revealing a positive correlation ($r = .37$; $p < .03$).

Conclusions: This longitudinal infant electroencephalographic dataset during an early speech perception paradigm and records of their mothers' subclinical mood range reveals an association of maternal mood at 2-months-postpartum with infant syllable-pitch perception. Lower maternal mood postpartum was associated with a more positive infant MMR to the syllable-pitch deviant. This association was still present for the MMR to the syllable-pitch deviant in infants at age 6.5 months. We show that syllable-pitch MMR was less likely to maturate (i.e., become more negative) when their mothers reported lower mood at 2-months-postpartum. Given that the infant's brain response is expected to shift from a positive, immature MMR to a negative, more adult-

like MMR within the first year of life, while a delayed shift enhances the risk of developing language impairments, our findings indicate that subclinically depressed mood in postpartum mothers may modulate infant developmental speech perception trajectories. Our findings lay the groundwork for future research on whether early support for caregivers experiencing low mood may positively affect children's language development.

Keywords: Postpartum Mood, Infant Electroencephalography, Speech Development

Disclosure: Nothing to disclose.

P142. Developmental Pyrethroid Pesticide Exposure Causes Autism-Related Behavioral and Neurological Changes in Prairie Voles

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Background: Autism Spectrum Disorder is a cluster of incurable neurodevelopmental disorders with a prevalence of 1 in 54 people. Although autism is commonly thought of as a genetic disorder, up to 50% of autism risk derives from environmental sources. Exposure to pyrethroid pesticides during pregnancy has recently been linked to autism risk by epidemiology studies. Our previous experiments in mouse suggest that developmental exposure to pyrethroid pesticides causes an autism-related phenotype, including decreased vocalizations, repetitive behaviors, learning deficits, and hyperactivity.

Methods: In this study, we exposed female prairie voles to the EPA reference pyrethroid, deltamethrin, throughout pregnancy and lactation, and tested the resulting offspring for autism-related phenotype. Route of administration mimicked human exposure by being consumed in food at a concentration below the EPA benchmark dose (3 mg/kg every 3 days in peanut butter). One pup per litter was used for each test in a behavioral battery that included ultrasonic vocalizations, marble burying, repetitive behaviors, 24-hour mobility, operant conditioning, partner preference, consoling behavior, and fear conditioning. Biological samples were collected for FOS immunochemistry and omics applications.

Results: Developmentally exposed vole showed alterations in repetitive behaviors, USVs and other behaviors consistent with autism-related phenotype. Alterations in behavior and brain are consistent with disruptions of 24-hour movement cycles and circadian rhythm pathways.

Conclusions: Behavioral and molecular changes induced by developmental pesticide exposure are consistent with autism-related behaviors and pathways, suggesting a causal role of this exposure in autism risk.

Keywords: Prairie Voles, Prenatal Exposure, Autism

Disclosure: Nothing to disclose.

P143. Affective Theory of Mind Impairments in Youth With Callous-Unemotional Traits: The Role of Cognitive Control

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Background: Impaired affective theory of mind for complex stimuli predicts violent criminal behavior amongst adolescents with callous-unemotional (CU) traits[1-6]. CU traits are a youth antisocial phenotype counterpart to adult psychopathy[7, 8] present between 17-26% of community youth[9] that cost U.S. society over $2 trillion annually[10]; yet, available treatments for these youth have limited efficacy[11].

Cognitive control is a potentially important, yet understudied, treatment target to address CU trait impairments in complex affective theory of mind. Affective theory of mind involves making inferences about others' emotions[12] that can be basic (e.g., happy, sad, mad) or complex (e.g., nervous, shame, annoyance). Complex affective states are subtle[13], which, to process, require greater cognitive control resources[14]. Cognitive control modulates theory of mind[15, 16]; and research on CU traits demonstrates impairments in both cognitive control[17-21] and complex affective theory of mind[5, 6]. Despite the connections made in the literature[22], the impact of cognitive control impairments on affective theory of mind amongst youth with CU traits remains understudied. The failure to process other's complex affective states may explain how those with CU traits callously harm others and engage in criminal acts[22]; therefore, investigating cognitive control's impact on affective theory of mind impairments can reveal neurocognitive targets that inform new evidence-based therapeutics. Given that adult psychopathy is considered a neurodevelopmental disorder[23], it is critical to examine early adolescents, the earliest that theory of mind is consistently accurate[24], to capture mechanisms of these core impairments early. There is considerable evidence that CU traits are present on a continuous scale amongst community samples, which demonstrate the same neurocognitive impairments as clinical/forensic samples[25]. Thus, we examined a community sample of early adolescents in a pilot study designed to determine cognitive control's impact on theory of mind as a function of CU traits.

Methods: We recruited 87 early adolescents (ages 12-14) from the community (1:1 ratio of sex) oversampled for high CU traits to participate in behavioral tasks. Behavioral tasks included an affective theory of mind task with basic and complex emotions [26] and an inhibitory processing task (to tax cognitive control) [27]. For recruitment, we determined high versus normal CU traits using the inventory of CU traits low prosocial emotion specifier [28]. Given that cognitive control depends on the current load on cognitive resources[29], cognitive control can be manipulated by placing a cognitive load on cognitive resources[e.g., 27]. Thus, the design involved a baseline theory of mind, then a cognitive load, and a final post-cognitive load theory of mind task.

We conducted three separate analyses. First, to test effects of taxing cognitive control, we used a linear mixed-effects model across repeated measures of complex theory of mind as a function of CU traits specifying random effects for individuals. Second, to test response to cognitive load, we used a linear regression with the maximum amount of cognitive load responded to as a function of CU traits. Third, we used linear regressions with basic and complex affective theory of mind as functions of CU traits. For all analyses we adjusted for sex, age, and race. A priori 80% power calculations using a two-tailed test with $p < 0.05$ revealed a mixed-effects model required 62 participants and regressions required 81 participants.

Results: Mixed-effects model revealed that increases in CU traits associated with a greater mean difference from baseline to post cognitive load on complex affective theory of mind ($F = 4.07$, $p = 0.021$), and the cognitive load had a higher impact on the slope for complex affective theory of mind judgments ($\beta = -0.11$, $p = 0.018$, marginal $R2 = 0.113$, conditional $R2 = 0.591$). Second, increases in CU traits associated with lower levels of cognitive load responded to ($\beta = -21.57$, $p = 0.032$, $R2 = 0.100$). Third, increases in CU traits did not associate with basic emotions but did associate with significantly lower accuracy during complex affective theory of mind ($\beta = -0.102$, $p = 0.009$, $R2 = 0.149$).

Conclusions: Results suggest 1) higher levels of CU traits associated with general impairments in cognitive control resources, 2) impairments in complex affective theory of mind

are accentuated after placing a cognitive load on cognitive control, and 3) these effects are specific to complex affective theory of mind. Future research could examine neural mechanisms underlying these findings by taking this behavioral paradigm into an fMRI, which will set the stage for refining neural targets for new evidenced-based therapeutics targeting affective theory of mind in early adolescents with CU traits.

Keywords: Callous-Unemotional Traits, Cognitive Control, Affective Theory of Mind, Adolescence

Disclosure: Nothing to disclose.

P144. Quantitative EEG Markers of Suicide Implicit Association Test in Adolescents

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Background: Implicit Association Test (IAT) has been used in cognitive neuroscience to measure implicit biases toward different concepts. In suicide research it has been shown that positive implicit associations between self and death/suicide was associated with approximately six-fold increase in the odds of making a suicide attempt at 6-month follow-up (Nock et al. 2010). Yet a little known about the neural correlates of implicit cognitive processes associated with suicidality and to our knowledge no previous study has investigated quantitative EEG correlates S-IAT. Therefore, in this study we aimed to investigate qEEG markers of Suicide-Implicit Association Test (S-IAT) in inpatient adolescents with suicidal ideations and behaviors as compared to healthy controls.

Methods: Thirty adolescents between ages 13-18 admitted to the Mayo Clinic child and adolescent psychiatry unit with suicidal ideations and suicidal behaviors (screened by Columbia-Suicide Severity Rating Scale (C-SSRS)) and thirty adolescents with no prior psychiatric diagnoses were recruited. All participants underwent diagnostic assessments and EEG recordings. Primary outcomes were correlations between the behavioral outcomes of S-IAT (d-score) and event-related potentials elicited during S-IAT, and the group differences between healthy controls and patients. Hierarchical GLMs (ANCOVA) with spatiotemporal clustering were used to identify significant event-related potentials associated with S-IAT and group differences.

Results: Behavioral results (d-score) showed that the patient group had stronger implicit associations between "death" and "self" as compared to the healthy group ($p = .007$). Within the patient group the intensity of suicidal ideations in the past 2 weeks (based on C-SSRS) was higher in those who had stronger implicit associations between "death" and "self" ($p = .043$). ERP analysis showed that there was a significant correlation between d-scores and N100 component over the left occipito-parietal cortex, in a way that incongruent trials yielded larger visual N100 components. Significant group differences were present for later ERP components (>600 ms, LPP) over this region (occipito-parietal cortex), but d-scores did not correlate with the ERP activity at these later latencies. Other significant group differences were found over the centro-parietal areas (also N100) and left dorsolateral pre-frontal cortex (P200).

Conclusions: Our results suggest that N100 may be a marker of attentional resources allocated to the discrimination of the stimulus that is congruent or incongruent to one's associations between death and self. Group differences over centro-parietal areas and prefrontal cortex may be explained by other factors such as emotional salience (N100), selective attention (frontal P200), and semantic processing (LPP) independent of the behavioral effect of S-IAT.

Keywords: Suicide, qEEG, Implicit Association Test

Disclosure: Nothing to disclose.

P145. Neurofeedback Augmented Mindfulness Training Elicits Distinct Responses in the Subregions of the Insular Cortex in Healthy Adolescents

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Background: Mindfulness training (MT) fosters present moment awareness of thoughts, feelings, behaviors, and physical sensations, and as such, it has been shown to improve and sustain psychological well-being. Given that adolescence represents a sensitive developmental period of emergence of psychopathology, delineating the precise mechanisms by which MT exerts its effects will be crucial for improving mental health prevention and intervention efforts in this population. It has been proposed that MT leads to changes in interoception, that is, the process of integrating cognitive and affective states with the current body state to select and motivate regulatory behaviors. Previous research has shown that the insular cortex (INS) is the key hub of interoceptive processing, but little experimental data links MT to INS activity. Thus, the present study examined INS activity during MT and its modulation with real-time fMRI neurofeedback (rtfMRI-nf) augmented mindfulness training targeting the posterior cingulate cortex (PCC), a key brain region involved in MT that is also significantly interconnected with INS during affective-somatosensory processing. We hypothesized that INS would show reduced activity during MT relative to active control (i.e., self-referential processing), and that this activation will be further modulated consequent to PCC rtfMRI-nf. We further hypothesized that decreased INS activity during PCC rtfMRI-nf would relate to greater subjective awareness of mind and body, propensity to experience more positive and less negative affect, and better emotion regulation.

Methods: Thirty-five healthy adolescents [age: mean(sd) = 14(1) years; 43% female] were enrolled in and completed the rtfMRI-nf protocol targeting the PCC during mindfulness practice. The rtfMRI-nf experiments were conducted on the GE MR750 3T MRI scanner (TR/TE = 2000/30ms, SENSE acceleration $R = 2$, matrix 96×96, 46 axial slices, $2.5 \times 2.5 \times 2.9$ mm3 voxels). The rtfMRI-nf PCC region-of-interest (7mm sphere, MNI coordinates = -7, -52, 23) was meta-analytically derived from default mode network and mindfulness meditation studies, including neurofeedback, and adjusted further during pilot testing. Adolescents first underwent mindful breathing training outside of the scanner. Next, they completed the neurofeedback augmented mindfulness training (NAMT) task, consisting of three conditions: Focus, Describe, and Rest. In the "Focus" condition, participants received ongoing rtfMRI-nf signal from the PCC presented as variable-height bar and were instructed to lower it by focusing on the physical sensations of their breath wherever they most strongly felt it. In the "Describe" (i.e., active control) condition, participants engaged in self-referential processing by mentally deciding whether an adjective described them. In the "Rest" condition, participants were not presented with any task. Each of three rtfMRI-nf runs (NF-1, NF-2, NF-3) started with a 66s "Rest" block, followed by alternating blocks of "Rest" (30s) "Describe" (20s) or "Focus" (70s) blocks. Prior to and after rtfMRI-nf runs, there were "Observe (OBS)" and "Transfer (TRS)" runs during which no neurofeedback was provided. Regression coefficients estimated from the GLM were extracted from both hemispheres of all three probabilistic cytoarchitectonic segmentations of the insular regions defined by the Brainnetome atlas: anterior (aINS), mid- (mINS),

and posterior insula (pINS). Averaged across hemisphere, the average beta values the Focus – Describe contrast were extracted. Linear mixed effects (LME) analyses examined the effect of run on INS activity, with run (OBS, NF-1, NF- 2, NF-3, TRS) entered as fixed effects and subject ID number as a random effect. Clinicaltrials.gov identifier: NCT04053582.

Results: LME analyses revealed the main effect of run for the Focus – Describe contrast in the aINS [$F(4, 134) = 4.33$, $p < .005$; $R2 = .34$] and pINS [$F(4, 135) = 11.95$, $p < .001$; $R2 = .33$], but not mINS subregions [$F(4, 135) = 1.31$, $p = .27$; $R2 = .32$]. Post-hoc analyses performed for aINS and pINS subregions revealed significant differences between neurofeedback and non-neurofeedback runs. Specifically, neurofeedback runs elicited greater activation than the OBS run in the aINS ($p < .05$), while in the pINS, neurofeedback runs elicited lower activation than OBS and TRS runs ($p < .05$). Awareness of thoughts/emotions and physical sensations negatively related to both aINS and pINS activity across neurofeedback runs, while propensity to experience positive affect and better emotion regulation negatively related to aINS activity across neurofeedback runs ($p < .05$).

Conclusions: These findings provide initial evidence for the role of INS in MT. The data also showed a relation between INS activity during neurofeedback augmented mindfulness practice and self-reported cognitive/affective/sensory processing. The divergent effect of PCC rtfMRI-nf on anterior vs. posterior INS subregions during mindfulness practice relative to self-referential thinking may support previous findings whereby the aINS is involved in the experience of cognitive-affective states, while the pINS plays a more prominent role in somatosensory processes. Future studies are needed to directly examine how distinct mindfulness practices modulate INS along the proposed subregion specializations. Finally, studies with larger and clinical samples will determine whether MT impacts INS activity and interoceptive processes to improve clinical outcomes.

Keywords: Real-Time fMRI Neurofeedback, Adolescence, Mindfulness Meditation, Insula, Posterior Cingulate Cortex

Disclosure: Nothing to disclose.

P146. Characterizing De Novo Damaging Coding Variants in Attention-Deficit/Hyperactivity Disorder

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Background: Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable psychiatric condition. Identifying genes that contribute to ADHD risk is a critical step in understanding underlying mechanisms and developing novel treatments. However, decades of candidate gene studies have not identified reproducible findings, and only recently have the first genome-wide significant common variants been identified in a large genome-wide association study. Similar to other childhood-onset neuropsychiatric conditions, it is likely that rare genetic variants with larger effects also play an important role in the etiology of ADHD. In the largest case-control DNA sequencing study, a similar burden of ultra-rare protein truncating variants in evolutionary constrained genes was observed in individuals with autism spectrum disorder (ASD) and ADHD, suggesting that study designs that have led to risk gene identification in ASD may also be successful in ADHD. In the field of autism, DNA sequencing studies of parent-child trios with de novo variant detection have identified a plethora of high-confidence risk genes, which are already impacting clinical care. This approach has also been successful in discovering risk genes in Tourette's disorder and obsessive-compulsive disorder but has yet to be leveraged to find risk genes for ADHD. This is because the only published DNA sequencing studies of parent-child trios with ADHD have small sample sizes. Here, we address this gap in the field by conducting whole-exome DNA sequencing in a larger cohort of parent-child trios impacted by ADHD to shed light on the etiology of this impairing condition.

Methods: Whole-exome DNA sequencing was performed in 80 parent-child trios (240 individuals total) where the child had a primary diagnosis of ADHD. Exclusion criteria included a diagnosis of ASD, intellectual disability, psychosis, mood disorder, or clinically significant medical or neurological disease. Exome capture was performed using the IDT xGen Exome Panel, followed by whole-exome sequencing on the Illumina NovaSeq with 80x coverage. These results were compared to 225 previously sequenced unaffected parent-child trios. After quality control, we examined 73 ADHD trios and 224 control trios for de novo single nucleotide variants and indels following the Genome Analysis Toolkit (GATK) best practice guidelines. We focused on variants that were rare in reference databases and that were either likely gene disrupting (including variants causing premature stop-codons, altered splice sites, and frameshifts) or missense variants that were predicted to be damaging based on a "missense badness, PolyPhen-2, constraint" (MPC) score >2. We then explored overlap with high-confidence risk genes for other conditions and conducted exploratory pathway analyses.

Results: Our results show a trend towards an increased rate of de novo likely gene disrupting variants and missense variants predicted to be damaging in ADHD cases compared with controls (Rate ratio = 1.6, $p = 0.13$), suggesting that further study of de novo variation in larger cohorts may lead to risk gene discovery. Furthermore, we found that genes harboring de novo damaging variants in the ADHD cases overlap with known risk genes for other disorders. Of note, two unrelated individuals with ADHD have de novo likely gene disrupting variants in the lysine demethylase 5B gene (KDM5B), which is a previously identified high-confidence risk gene for ASD. This highlights the potential role of pleiotropy in these childhood neuropsychiatric conditions. Exploratory network analyses show enrichment of genes with de novo damaging variants in several canonical biologic pathways. Given these promising findings, we are currently sequencing an additional 70 parent-child trios impacted by ADHD. We will plan to present these combined sequencing results examining de novo and rare inherited variants in 150 ADHD parent-child trios at ACNP.

Conclusions: Whole-exome DNA sequencing of parent-child trios with ADHD can be used to identify de novo damaging variants. These damaging variants occur in genes that overlap with risk genes for other related neuropsychiatric conditions and are enriched for canonical biological pathways. Overall, our results demonstrate that whole-exome DNA sequencing with de novo variant detection provides a powerful and previously unexplored path for identifying new risk genes for ADHD and relevant biologic pathways. By increasing our sample size, we hope to provide additional insights into the underlying biology of this common and impairing condition.

Keywords: ADHD, Whole Exome Sequencing, Genomics

Disclosure: Nothing to disclose.

P147. The Genetic Underpinnings of Pubertal Timing in 7q11.23 Copy-Number-Variation: Age at Menarche, Pituitary Volume, and the Relation of Predicted STAG3L2 Expression to Gray Matter Volume

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Background: Williams syndrome (WS) is a rare neurodevelopmental disorder caused by hemideletion of ~25 genes at

chromosomal locus 7q11.23. It has been clinically noted that children with WS (having one copy of affected genes) enter puberty early, whereas individuals with the 7q11.23 duplication syndrome ([Dup7]; three copies of these same genes) have delayed puberty. We, therefore, hypothesized that the differential gene dosages underlying these two contrasting copy number variations (CNVs) could impact the timing of menarche. We also noted that a previous GWAS study of ~370,000 women identified 389 significant independent signals that contributed to age at menarche (AAM), and that the "stromal antigen 3-like 2 gene" (STAG3L2), which resides in the low copy repeat region flanking the WS 7q11.23 locus, accounts for one of these signals (rs2267812, $p = 1.69$ x 10-17). This gene is ubiquitously expressed, though particularly in testes, and is similar in structure to other STAG3 genes, which are known to be involved in meiotic chromosome pairing. Though the exact function of this particular gene is not well understood, mutations in other similar STAG3 genes have been implicated in disorders of reproductive functions in both males (spermatogenic impairment) and females (primary ovarian insufficiency). Here, we first examined how 7q11.23 CNVs affect AAM and STAG3L2 gene expression. Second, because there is evidence that pituitary morphology in children with early puberty differs from controls, we also looked for an association between 7q11.23 copy number and pituitary volume. Third, in an exploratory analysis, we tested for a relation between imputed cortical expression of the STAG3L2 gene and brain architecture in healthy adult women.

Methods: Study 1: AAM was reported by 19 girls with 7q11.23 CNVs (ten with WS and nine with Dup7) and 42 typically-developing (TD) girls. We calculated polygenic scores (PGSs) for AAM for the 42 TD girls, based on previously reported GWAS summary statistics, and correlated the results with AAM. Additionally, transcription of STAG3L2 was computed in 23 children with WS, 40 TDs, and 13 children with Dup7 using RNASeq of blood lymphocytes, and regression was used to test for step-wise group differences. Study 2: for 32 individuals with WS, 51 TD children, and 17 individuals with Dup7, investigators blinded to diagnostic group determined the volume of the pituitary by manual segmention on T1-weighted ME-MPRAGE scans collected on a GE 3T MRI scanner. Group difference in pituitary volumes across 7q11.23 CNVs was assessed using linear regression. Study 3: In 145 healthy adult women, genetic data and structural MRIs were collected, and PGSs predicting cortical-expression of STAG3L2 were calculated using GTEx postmortem cis-eQTL data as weights for each SNP and correlated with gray-matter volume (GMV) for each voxel ($p < 0.005$).

Results: Study 1: AAM (WS $= 10.8 \pm 1.0$ years; TD $= 12.6 \pm 1.25$; Dup7 $= 15.8 \pm 2.7$) significantly differed across 7q11.23 CNV groups such that greater gene dosage was associated with older AAM ($p = 6.15$ x 10-8). Further supporting a role for genetic contributions to AAM, PGS for AAM tended to correlate with AAM in TDs ($p = 0.06$); and RNASeq data showed that STAG3L2 expression decreased with increasing copy number (i.e., WS > TD > Dup7, $p = 0.036$). Study 2: Pituitary size was also significantly associated with 7q11.23 copy number such that individuals with WS had the smallest pituitary glands while individuals with Dup7 had the largest ($p = 0.002$). Study 3: In healthy adult women, imputed cortical expression of STAG3L2 was associated with increased GMV in posterior cingulate, medial prefrontal cortex, and insula, but with decreased GMV in dorsolateral prefrontal cortex and inferior parietal lobule.

Conclusions: We found that AAM, pituitary volume, and STAG3L2 gene expression are all moderated by 7q11.23 CNVs. The finding that increased STAG3L2 RNA expression was associated with WS is contrary to what one might expect with hemideletion and suggests that a regulatory element may be present in 7q11.23 CNV region. These findings are particularly intriguing because of a reported link between STAG3 loss-of-function mutations and delayed puberty, which is consistent with the findings of delayed puberty in Dup7 (wherein expression is decreased) and early puberty in WS (wherein STAG3L2 expression is increased). Additionally, our findings indicate that the size of the pituitary is also, at least in part, genetically mediated and may be associated with the effects of 7q11.23 CNVs on the timing of puberty. Finally, GTEx-estimated STAG3L2 brain expression is associated with cortical architecture in regions that are previously implicated in 7q11.23 CNV, particularly the prefrontal cortex, insula as well as parietal lobe, and are important for neurodevelopment which may have cognitive/behavioral implications.

Keywords: Human Genetics, Williams Syndrome, Puberty, Gray Matter Volumes

Disclosure: Nothing to disclose.

P148. Developmental Coupling of Cerebral Blood Flow and fMRI Fluctuations in Youth

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Background: The functions of the human brain are metabolically expensive: despite only weighing 1.5kg on average, the brain utilizes a disproportionate one-fifth of bodily energetic requirements and receives 20% of cardiac output (1). In healthy people, the relationship between brain activity and cerebral blood flow (CBF), or neurovascular coupling, is tightly linked at the local level, allowing the neurovascular unit to maintain appropriate energy balance (2). Neurovascular coupling in vivo is often characterized by relating two neuroimaging-derived measures: CBF and the amplitude of low frequency fluctuations (ALFF) in resting-state blood oxygen level dependent (BOLD) fMRI (3). Previous studies in adults have indeed reported high CBF-ALFF coupling in healthy subjects, and have also demonstrated that aging and medical illness can disrupt neurovascular coupling (4,5). Though CBF and ALFF have been studied independently in youth, it is currently not known how neurovascular coupling as measured by CBF-ALFF evolves in childhood and adolescence. Here we explore regional variation and development of CBF-ALFF coupling in youth.

Methods: Data from 831 youth (478 females, ages 8-22) in the Philadelphia Neurodevelopmental Cohort were used for this study (6). As previously detailed, each participant underwent T1-weighted magnetic resonance imaging (MRI), arterial spin labeled (ASL) MRI and resting-state fMRI (rs-fMRI) on a Siemens Tim Trio 3T scanner with a 32-channel head coil. After detailed image quality assurance, ASL and rs-fMRI scans were co-registered to the structural scan and preprocessed using standard tools (8). We used ASL to quantify CBF using standard methods. We used spontaneous fluctuations in the BOLD signal at 0.01-0.08Hz during rs-fMRI as our measure of ALFF. Images were projected to the surface using Freesurfer. Local coupling between CBF and ALFF was first quantified using locally weighted regressions on the cortical surface. We then used generalized additive models to evaluate how CBF-ALFF coupling was associated with age, sex, and executive function, while controlling for in-scanner motion. Enrichment of effects within canonical functional networks was evaluated using spin-based permutation tests (8,9). Analyses were corrected for multiple comparisons by controlling the False Discovery Rate (FDR, $Q < 0.05$).

Results: We found evidence of tight CBF-ALFF coupling across the brain. Whole-brain CBF-ALFF coupling decreased with age,

largely driven by coupling decreases in the inferior frontal cortex, precuneus, visual cortex, and temporoparietal cortex (Pfdr < 0.05). Development-related enrichment was highest in the dorsal attention network ($P = 0.014$). Females had stronger coupling than males (Pfdr < 0.05), with enrichment in the frontoparietal network ($P = 0.034$). Better executive function was associated with decreased coupling in sensorimotor cortex and increased coupling in areas within the default mode network (Pfdr < 0.05); enrichment within the somatomotor network was noted ($P = 0.040$).

Conclusions: CBF-ALFF coupling evolves in development, differs by sex, and is associated with individual differences in executive function. Coupling changes coincide with known structural development changes including synaptic pruning and increases in myelin and perineuronal nets (10,11). Our results may indicate that developmental maturation leads to changing metabolic requirements that are supported by regionally-specific neurovascular coupling. Future studies will investigate relationships between maturational changes in CBF-ALFF coupling and the presence of psychiatric symptoms in youth.

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Keywords: Adolescent Development, Sex Differences, Neurovascular Coupling, Arterial Spin Labeling, fMRI Resting State

Disclosure: Nothing to disclose.

P149. Maternal Childhood Maltreatment: Intergenerational Effects on Offspring Brain and Behavior

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Background: The deleterious effects of early life adversity are likely intergenerational, such that one generation's adverse experiences can affect the next1,2. Understanding the intergenerational effects of adversity may thus open new avenues for intervention with broad-reaching influence in deterring psychiatric illness in subsequent generations. Epidemiological studies link maternal adversity to offspring depression and anxiety, possibly via epigenetic mechanisms that impact offspring fronto-limbic connectivity3-5. However, identifying intergenerational transmission effects independent of the postnatal environment – often termed "indirect mechanisms" – has proven difficult in human research. Further, studies have not thoroughly considered the role of offspring sex. In the present study, we extend our understanding of the intergenerational effects of maternal childhood maltreatment by examining regional brain volumes and structural connectivity in infants of women with and without a history of childhood maltreatment. The present study represents a significant expansion of the literature by examining structural connectivity. We hypothesized that maternal childhood maltreatment would be related to increased fronto-limbic connectivity in infancy, and that, in line with preclinical studies, males would be more susceptible. We examine white matter connectivity in a socioeconomically diverse sample of two cohorts and explore relationships between white matter connectivity and behaviors in childhood better elucidating the impact of adversity, its intergenerational transmission, and its persistence from infancy to early childhood.

Methods: Ninety-two infant-mother dyads participated (32 mothers with a history of childhood maltreatment (CM+), 60 without (CM-); 40 infant males, 52 females). The study combined data from two cohorts: Cohort 1 was based at the Universidade Federal de São Paulo, Brazil and Cohort 2 in New York City6,7. Pregnant women were recruited through obstetricians, midwives, and psychiatrists and invited to participate in prenatal interviews, biospecimen collections, and infant MRIs. Interested participants were screened for eligibility and consented. Prenatal interviews included reports of childhood maltreatment (via the Childhood Traumatic Questionnaire (CTQ)) and perinatal stressors, clinical interviews, and demographic questionnaires. Non-sedated sleeping infants were scanned at 2.44 ± 2.74 weeks post birth. Brain volumes were estimated via structural MRI and white matter structural connectivity (fiber counts) via diffusion MRI with probabilistic tractography. A subset of mothers reported on children's behaviors using the Child Behavior Checklist at age 6.26 ± 0.68. To account for potential confounders, inverse probability of treatment weighting using propensity scores was implemented using the following variables: maternal age, pre-pregnancy body mass index, prenatal medication use, infant weight at scan, infant gestational age at delivery, birth type, and socioeconomic status. Dimension reduction of MRI data was conducted using principal components analysis (PCA).

Results: Weighted linear regressions controlling for the aforementioned confounders, prenatal maternal distress, and prenatal alcohol, tobacco, and substance use revealed a male-specific association between maternal CM and a PCA component indexing intra-hemispheric fronto-limbic connectivity, with males in the CM+ group demonstrating greater values in this component compared to males in the CM- group, ($b = 0.96$, $p = 0.008$, [95%CI 0.25 – 1.66]). No maternal CM-related differences were detected for females on this component, and the interaction between maternal CM and offspring sex was significant suggesting meaningful differential effects by sex. Exploratory analyses ($n = 29$) revealed that intra-hemispheric fronto-limbic connectivity

was related to childhood depressive symptoms ($r = 0.386$, $p = .039$).

Conclusions: This study adds to a growing body of literature suggesting that childhood maltreatment can exert effects on the next generation, perpetuating cycles of hardship and adversity. It represents a significant advancement in our understanding of the intergenerational effects of maternal childhood maltreatment on offspring neurodevelopment, documenting associations between maltreatment and intra-hemispheric fronto-limbic connectivity in newborn males. Although the mechanisms underlying sex-dependent effects require elucidation, sexual dimorphism in the placental response to glucocorticoids8 may play an important role. However, our understanding of these processes remains limited, and because not all human studies of intergenerational adversity find increased susceptibility in males9, longitudinal studies will be required. As our understanding of risk develops, so should our understanding of resilience. Research on intergenerational resilience is strikingly underdeveloped yet identifying the mechanisms underlying resilience will be crucial when developing early intervention and policy. This study also suggests (via exploratory analyses) that these increases in fronto-limbic connectivity are related to later childhood depressive symptoms. Although the underlying mechanisms require elucidation, our findings underscore the critical need for policy aimed at childhood maltreatment prevention and early intervention.

Keywords: Childhood Adversity, Intergenerational Transmission, Brain Development

Disclosure: Nothing to disclose.

P150. Using Causal Discovery Analysis to Explore Sex Differences in Restricted/Repetitive Behaviors and Other Features of Autism

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Background: Autism Spectrum Disorder (ASD), a complex neurodevelopmental disorder, includes restricted and repetitive behaviors (RRBs) along with challenges in the social communication and social interaction domains (DSM-5, 2013). While a strong male bias in ASD prevalence has been reported consistently, researchers have yet to reach consensus on mechanisms and clinical features that may underlie differences in females (Halladay et al. 2015). Numerous factors may contribute to observed sex differences in the ASD literature. For example, females may be under-diagnosed because of differing symptom presentation; diagnosed boys may exhibit more behaviors (e.g., hyperactivity, aggression) that prompt clinical evaluation whereas ASD features in girls may be masked or misdiagnosed because of sex-specific characteristics or societal expectations in typically-developing (TD) males and females (e.g., memory, cognitive flexibility, verbal fluency). Interactions with intelligence quotient (IQ) and developmental stage as well as inconsistencies in diagnostic/ascertainment procedures further contribute to variability in prevalence data.

Applying network theory to frame the complex symptomatology of ASD, we attempted to extract data-driven (Borsboom and Cramer, 2013), clinically-relevant insights from a large dataset (Simons Simplex Collection v15.3; SSC) ascertained strictly for genetics studies. We used causal discovery analysis (CDA) to investigate causal relationships between factors subserving core characteristics of ASD. Restricting our focus to RRBs (instead of the multilayered complexities inherent to social development) for this exploratory approach helped reduce our data dimensionality, and enabled us to investigate differences and similarities in girls and boys when key factors (IQ, age) were controlled.

Methods: Drawing from the SSC database which provides extensive diagnostic confirmation, we identified 2509 ASD youth (Males: $N = 2175$, Ages $= 8.9 \pm 3.5$ years; Females: $N = 334$, Ages $= 9.2 \pm 3.7$ years) with completed IQ assessments and parent questionnaires (Repetitive Behavior Scale-Revised; RBS-R, Social Responsiveness Scale; SRS, Aberrant Behavior Checklist-Community Version; ABC-CV). Given overlap across phenotypic measures, we applied exploratory factor analysis (EFA) with maximum likelihood factor extraction and oblimin rotation to reduce data dimensionality (161 total items) and correct for correlated measurement error; we used parallel analysis to determine which factors to retain for continued analysis (95th percentile eigenvalue). From these 23 retained factors, we reduced the data further by first ordering factors from highest to lowest variance, excluding items with loadings $= |x| < 0.30$, and removing lower variance factors if an item previously appeared in a higher variance factor. These steps yielded 15 final factors that we labeled by clinical consensus. Consistent with the literature, our sample was predominantly male (86.7%) rendering observed sex differences difficult to interpret. Hence, to offset some of the inherent confounds (e.g., variability) of an imbalanced sample, we identified a subset of males matched to females on age and IQ, factors that associate highly with RRBs. With this multivariable matched comparison approach, we applied data-driven CDA using Greedy Fast Causal Inference (GFCI) for three groups (All Females (AF), $N = 334$; and Matched Males (MM), $N = 331$, and remaining Unmatched Males (UM), $N = 1844$) to generate models relating EFA-selected factors and participant characteristics. Using structural equation modeling (SEM), we extracted measures of model fit and effect sizes for causal relationships.

Results: CDA uncovered effects indicating causal influences of age on EFA-selected factors capturing motor overflow and odd social behaviors. Further, causal influences propagated from motor overflow to factors capturing oppositional behaviors which, in turn, proceeded to self-injurious behaviors in both the AF:MM and UM:MM comparisons. We also found relationships for each group comparison that suggest distinct constellations of factor influences for males and females matched on IQ and Age. For example, verbal IQ was causally linked to severity of repetitive speech in females and related to factors encompassing physical isolation in males, specific to MM is the link of verbal IQ to both factors. Additional CDA results will be presented using factors derived from clinical assessments to explore how RRBs relate to other symptoms.

Conclusions: By implementing an analytical methodology originally designed for causal discovery from observational data broadly, we unveiled sex-specific causal relationships between multiple clinically-derived variables that may illuminate targets for intervention. Future steps will involve broadening our focus to additional domains, refining our identified factors of interest for RRBs, and exploring closely related subphenotypes in ASD.

Keywords: Autism Spectrum Disorder, Sex Differences, Causal Discovery Analyses

Disclosure: Nothing to disclose.

P151. Assessing COVID-19 Effects on Neurodevelopment (ACEND): Preliminary Findings in 12-Month-Old Children Exposed to Maternal SARS-CoV-2 Infection During Pregnancy

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Background: Substantial data now indicate that SARS-CoV-2 exposure during pregnancy does not confer risk for gross

neurological defects at birth, nor does the virus routinely cross the placenta. However, whether such exposure confers more subtle effects on early brain development, potentially via maternal immune activation, has remained uncertain. Exposure to numerous viral illnesses in utero has been associated with detrimental effects on fetal brain development and risk for mental health problems in childhood, even in the absence of vertical transmission. Maternal exposure to psychosocial stressors has likewise been associated with poorer neurodevelopmental outcomes. As such, COVID-19 poses dual concerns for the long-term brain health of children who gestated during the pandemic. The Assessing COVID-19 Effects on NeuroDevelopment (ACEND) study combines maternal survey data and perinatal biospecimens to identify direct effects of prenatal SARS-CoV-2 exposure, as well as broader psychosocial effects of the COVID-19 pandemic, on neurodevelopmental and behavioral outcomes through age 2. Here we report initial results on how prenatal SARS-CoV-2 exposure and broader pandemic-related stressors affected developmental milestones at 12 months of age.

Methods: ACEND is enrolling recently postpartum mothers who participated in COVID-19 biorepository protocols at Mass General Hospital during pregnancy via direct contact, as well as new participants who gave birth at MGH during the pandemic via provider referral. To examine the effects of SARS-CoV-2 infection and/or exposure on early brain development, we are administering neurodevelopmental batteries to mothers in English or Spanish when their child reaches 6, 12, 18, and 24 months of age. At present, 50 mothers and 53 babies have been enrolled (3 twin sets), with ongoing recruitment averaging 5 new families per week. For this analysis, we analyzed Ages and Stages Questionnaire (ASQ) and Baby Pediatric Symptom Checklist (BPSC) data at 12-months from $n = 19$ babies (average age = 12.3 months) whose mothers tested positive for SARS-CoV-2 during pregnancy and $n = 15$ demographically matched babies (average age = 13.3 months) whose mothers had no known SARS-CoV-2 positivity during pregnancy and tested negative at the time of delivery. Frequency of ASQ domain scores ≥1 SD below normative means was the primary outcome in this initial study.

Results: A total of 68% of children born to SARS-CoV-2-infected mothers and 53% of children born to uninfected mothers performed at least 1 standard deviation (SD) below the normative mean for at least 1 of the 5 ASQ constructs (communication, gross motor, fine motor, problem-solving, and personal-social) 12 months after birth. Deficits were most widespread in the gross motor domain (42% of the SARS-CoV-2-exposed and 40% of the unexposed sample scored at least 1 SD below the normative mean); however, across all domains children exposed to SARS-CoV-2 showed significantly greater likelihood of scores ≥1 SD below normative means compared to non-exposed children (chi squared = 5.90, $p = .015$). Results from the BPSC indicated that 53% of children in the SARS-CoV-2 exposed cohort and 53% of children in the SARS-CoV-2 unexposed cohort passed the threshold of clinical concern (defined as a score of 3 or above in any one of the 3 constructs – irritability, inflexibility, and difficulty with routine) at 12 months, with irritability being the most widespread behavior in each group.

Conclusions: Initial data from the ACEND study suggest that SARS-CoV-2 exposure in utero may correlate with deficits in fine motor, problem solving, and personal-social skills, while exposure to either SARS-CoV-2 or broader COVID-19 pandemic-related stressors may be associated with worsened gross motor skills and increased irritability in infants at 12 months of age. Existing results must be interpreted with caution due to sample size and age differences between SARS-CoV-2-exposed and non-exposed infants at completion of the 12 month survey. Ongoing recruitment of mothers exposed to SARS-CoV-2 during pregnancy and demographically-matched negative controls will (1) further explore effects of SARS-CoV-2 infection on neurodevelopmental outcomes; (2) disambiguate effects of SARS-CoV-2 from those of broader pandemic-related stressors; and (3) delineate underlying biological mechanisms through perinatal biospecimen studies.

Keywords: COVID-19, Pregnancy, Neurodevelopment, Maternal Stress

Disclosure: Nothing to disclose.

P153. A Three-Factor Model of Commonly Comorbid Early Onset Psychiatric Disorders: Temperament, Adversity, and Dopamine

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Background: Commonly comorbid early onset psychiatric disorders might reflect the varying expression of overlapping risk factors (1-4). The mediating processes remain poorly understood, but three factors show some promise: adolescent externalizing (EXT) traits, early life adversity (5), and midbrain dopamine autoreceptors (6,7). In the present study, we investigated whether these features acquire greater predictive power when combined.

Methods: Participants were transitional aged youth who had been followed since birth and lived in the area of Montreal and Quebec City. They were invited to participate in the current study based on EXT trait scores between the ages of 10 to 16 (8), as measured with the Social Behavioural Questionnaire (9,10).

In early adulthood (age 18.5 ± 0.6 y.o.) participants were assessed with the Structured Clinical Interview for DSM-5, completed the Childhood Trauma Questionnaire (CTQ), and had a 90-min high-resolution positron emission tomography scan with [18F]fallypride. Fifty-two psychotropic medication-free young adults (30F, 22M) completed the study. Follow-up interviews were conducted 1, 2 and 3 years later.

Binomial logistic regression analyses tested whether midbrain [18F]fallypride BPND values, EXT and CTQ scores predicted the presence of lifetime DSM-5 diagnoses. All analyses were run for lifetime diagnoses at the time of or prior to the PET scan and again including diagnoses obtained during the follow-up interviews.

Results: At the index interview, 23% of participants met criteria for at least one lifetime DSM-5 disorder. The three-factor model predicted their presence with an overall accuracy of 90.4% ($p = 0.000024$) and explained 91.5% of the area under the receiver operating characteristic curve [95% CI: .824, 1.000]. When limited to EXT disorders specifically, the model was not more powerful than when targeting all disorders ($p = 0.54$). The model was independent of sex and remained significant upon addition of new diagnoses that developed during the follow-up period ($p = 0.000035$).

Conclusions: A combination of EXT traits, early life adversity, and poorly regulated dopamine transmission might increase risk for diverse early onset psychiatric disorders. The data reported here raise the possibility that these features can predict susceptibility prospectively.

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Keywords: Vulnerability Traits, Dopamine, Stress and Trauma, Impulsivity

Disclosure: Nothing to disclose.

P154. A Phase 2 Randomized Controlled Trial (RCT) of Balovaptan (BAL) in Pediatric Participants With Autism Spectrum Disorder (ASD)

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Background: Objectives: The aV1ation study assessed the efficacy and safety of balovaptan (BAL) vs placebo (PBO) in pediatric autism spectrum disorder (ASD).

Methods: Methods: This phase 2, double-blind, 24-week (wk) RCT (NCT02901431) enrolled pediatric participants with ASD, confirmed by Autism Diagnostic Observation Schedule, aged 5–17 years, IQ ≥ 70 and Clinical Global Impression (CGI)-severity scale ≥4. Participants were randomized to daily BAL 4 mg or 10 mg, or PBO. The 4 mg dose was later cancelled due to lower than predicted levels. The primary endpoint was change from baseline (CfB) in Vineland™-II Adaptive Behavior Scale (VABS) 2-Domain Composite (2DC Social and Communication domains) score at wk 24 assessed by Mixed Model Repeated Measurements.

Results: Results: Participants ($N = 167$) received BAL 10 mg ($n = 86$) or PBO ($n = 81$). At baseline, participants were 83% male with mean age of 12.1 years and mean IQ of 98. BAL 10 mg did not differ from PBO at wk 24 on the primary endpoint VABS 2DC CfB (difference in adjusted LSMeans [LSM] −0.16; 90% CI −2.56, 2.23). BAL 10 mg did not differ from PBO at wk 24 in CfB of standard scores VABS composite (LSM −0.23; 90% CI −2.67, 2.22); VABS communication (LSM 0.71; 90% CI −1.60, 3.02); VABS socialization (LSM − 0.61; 90% CI -3.74, 2.51); VABS daily living skills (LSM 0.18; 90% CI −2.87, 3.22) and Pediatric Quality of Life Inventory generic (LSM 2.28; 90% CI −0.73, 5.29) and family impact scores (LSM −3.43; 90% CI −7.52, 0.65). BAL 10 mg and PBO had a similar participant response at wk 24 in CGI-improvement (31% vs 31%) and CfB of CGI-severity (36% vs 40%). Exploratory analysis of Aberrant Behavior Checklist – subscale scores for irritability (LSM 0.60; 90% CI −1.08; 2.27) and lethargy (LSM −0.59; 90% CI −2.33, 1.16) did not differ for BAL 10 mg vs PBO. No relationship between efficacy and increasing exposure of BAL was seen. BAL vs PBO had a similar % of ≥1 adverse event (77% vs 75%).

Conclusions: Conclusions: No difference was seen between BAL 10 mg vs PBO in any efficacy measures. No BAL exposure–response relationship was seen. BAL and PBO had similar types and frequencies of adverse events. BAL had no safety concerns.

Keywords: Autism Spectrum Disorder, Vasopressin 1a Receptor Antagonist, Social Deficits, Phase III Trial

Disclosure: F. Hoffmann-La Roche Ltd: Advisory Board (Self)

P156. Cognitive Behavioral Psychosocial Intervention Improves Impulsivity in Children With Disruptive Behavior Disorders and Increases Frontotemporal Grey Matter Volume: Preliminary Results of a Clinical Trial

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Background: Disruptive behavior disorders (DBDs) are characterized by symptoms of conduct-disordered behaviors and oppositionality that are among the most prevalent classes of problems affecting young children. Among the negative consequences of DBDs include risk for later life psychopathology, family dysfunction, and criminality. Stop, Now, and Plan (SNAP) is an evidence-based psychosocial intervention aimed at 6-11 year-olds who present with externalizing behavior. The 13-week program teaches physiological awareness of emotional responding that may promote aggressive behaviors, and it also helps to improve self-control and impart problem-solving skills to help children make more adaptive choices. It is based on a cognitive behavioral therapy (CBT) model and parent management training. CBT promotes efficient regulation of emotion and impulses through strategies such as cognitive restructuring, problem-solving, role-playing, social and token reinforcements, and generalization activities. Parent management training imparts positive parenting practices, including skill encouragement, problem-solving, and monitoring in addition to substitution of coercive or lax discipline strategies with mild sanctions addressing misbehavior. Improving self-control is a key theoretical mechanism for change in the SNAP intervention. Self-control has been described as a distinctive individual concept that is reliably associated with individuals' capacity to override immediately rewarding behaviors and engage in continued, effortful goal-directed behavior. In impulsive choice, self-control relates to the ability to delay gratification and select the larger, delayed reward. Here, we conducted a clinical trial of SNAP in DBD youth to test whether SNAP participation could improve behavioral measures of impulsivity and also whether increased grey matter (GM) volume would become apparent by structural magnetic resonance imaging (sMRI) results in brain regions associated with impulsivity.

Methods: Thus far, 10 male children with DBDs underwent SNAP and have completed the study. Twelve male typically developing children without externalizing behaviors have also completed the study. SNAP participants were assessed at the start of SNAP treatment (Time 1) and then 13 weeks later post-SNAP (Time 2). Healthy control participants were assessed at Time 1 and Time 2, which were separated by 13 weeks. They did not receive

any intervention. At Time 1 and Time 2, all participants completed the computerized Two Choice Impulsivity Paradigm, which is a discrete-choice task used to assess preference for a smaller, immediate reward or a larger, delayed reward. Participants were instructed to earn as many points as possible, such that a proportional amount of points was rewarded according to the amount of time the participant chose to wait to make the selection. Variables of interest for the TCIP included the number of immediate choices, the proportion of immediate choices, and the highest maximum consecutive number of immediate choices. We operationalized higher values for these variables as indicative of greater impulsivity. Participants also underwent structural MRI scanning at Time 1 and Time 2. Pre-processing and voxel-based morphometry (VBM) analyses were completed in Statistical Parametric Mapping 12. GM volume differences in the SNAP group between time 1 and time 2 were analyzed with a multiple regression factorial design in the VBM option of SPM12. Change in brain volumes following SNAP treatment were calculated by subtracting the VBM results at Time 1 from Time 2. Age and total intracranial volume (TIV) were included as covariates in the analyses. Voxel extent threshold was set at $p < 0.001$ and clusters were considered significant at $p < 0.05$ FDR.

Results: Regarding demographic variables, the SNAP participants were older than the healthy participants (10.6 ± 1.3 versus 8.9 ± 1.8 years, $p = 0.022$). Therefore, age was used as a covariate for all subsequent analyses. There was no significant difference between groups for any of the other demographic variables. In order to elucidate group $\times$ interaction effects for the impulsivity measures, we utilized a generalized estimating equation. There were two levels for each variable: SNAP participant and healthy control and Time 1 and Time 2. Results revealed that SNAP participants significantly improved on all three impulsivity measures (p-values ranged from 0.006 - 0.01), whereas healthy controls did not change. VBM indicated that improvement for the impulsivity measure "maximum consecutive number of immediate choices" was positively and significantly associated in the SNAP participants with increased GM volume in the right superior frontal gyrus, right temporal pole, right inferior temporal gyrus, and left middle temporal gyrus (all p-values < 0.001)

Conclusions: These preliminary results suggest that the SNAP intervention was able to improve a behavioral measure of impulsivity in SNAP participants that showed no difference from healthy controls at Time 2. At the same time, improvement on a behavioral measure of impulsivity was associated with increased GM volumes in frontotemporal regions. Reduced frontotemporal volumes have been implicated in a variety of clinical populations with high impulsivity as well as healthy controls with higher levels of impulsivity. We tentatively suggest, therefore, that SNAP was able to improve brain correlates of impulsive choice in DBDs.

Keywords: Impulsivity, Disruptive Behavior Disorders, Psychosocial Intervention, Magnetic Resonance Imaging, Voxel-Based Morphometry (VBM)

Disclosure: Nothing to disclose.

P157. Early Life Adversity Alters Infant Communication in Ways That Predict Adolescent Oxytocin Receptivity and Behavior

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Background: Early life adversity (ELA) can impact social behavior throughout the lifespan, largely due to aberrant development of regions controlling affective regulation, such as the prefrontal cortex (PFC). However, later-life effects of ELA often evade early identification of vulnerable individuals. The oxytocin system plays an important role in social behaviors, as its activation of receptors in the PFC enhances the salience of both positive and aversive social interactions. Notably, stress exposure affects oxytocin signaling, and ELA has been shown to alter the developmental trajectory of oxytocin systems. Here, we investigated early life indicators of oxytocin dysfunction and associated social behaviors in male and female rats. Males and females experience sex-specific consequences of early adversity, which may be due to sex-dependent developmental trajectories or to sex-specific experiences within the same early life environment. Therefore, we examined a species-typical neonatal measure of communication, namely isolation-induced ultrasonic vocalizations (USV) as a potential indicator of atypically developing oxytocin systems and social behavior.

Methods: Male and female pups ($n = 10$-11) were reared either in a control environment or with ELA in the form of resource scarcity (limited bedding) from postnatal day 2-14. Pups were weaned from their mother at P21. On postnatal day 10, each pup was placed individually in a cage with home bedding for 5 min while USVs were recorded using an Avisoft-Bioacoustics ultrasound microphone positioned 10cm above the cage. Spectrograms for each recording were created using the DeepSqueak system for Matlab, and 9 unique sonographic structures were identified. Individual USVs were classified by type, and duration, peak frequency, and bandwidth were calculated in DeepSqueak. On the morning of postnatal day 35 (adolescence), rats underwent a 10-min dyadic social interaction test to determine the effects of rearing condition on social approach and play behaviors. Brains were taken 24 hours following the behavioral test and the PFC was collected for qPCR analyses of oxytocin (OR) and vasopressin receptors. 2-way (sex x rearing) ANOVA were conducted using Prism software to detect group differences in total USV, specific call types, social play behaviors, and receptor mRNA expression. Multiple regressions were conducted using R to detect significant relationships between infant USV and either play behaviors or receptor expression with sex and rearing as mediating factors.

Results: Both males and females being reared in a limited bedding environment emitted fewer total USVs over a 5 min period of isolation at postnatal day 10 (Main effect of Rearing $F1,36 = 17.1$; $p = 0.0002$; $\eta 2 = 0.47$). Play behaviors in adolescence were affected by ELA in a sex-specific manner, with males exposed to ELA displaying more nose-to-tail interactions with a conspecific (Main effect of Rearing $F1,36 = 8.052$; $p = 0.0074$; $\eta 2 = 0.224$; post-hoc Sidak's test in males adjusted $p = 0.0165$) and females exposed to ELA displaying fewer bouts of boxing (Main effect of Sex $F1,36 = 6.018$; $p = 0.019$; $\eta 2 = 0.167$; post-hoc Sidak's test in females adjusted $p = 0.04$). However, both males and females exposed to ELA expressed higher levels of PFC OR in adolescence (Main effect of Rearing $F1,36 = 12.31$; $p = 0.0013$; $\eta 2 = 0.264$). No differences were seen in vasopressin receptor expression. Regardless of sex or rearing, individual differences in infant USV emissions predicted adolescent behavior and OR expression. Specifically, more total USVs emitted during 5 min of isolation predicted more social exploration (sniffing conspecific) during a dyadic social interaction ($p = 0.0005$; $\eta 2 = 0.289$). Higher peak frequencies of USV predicted fewer instances of overall social interaction ($p = 0.015$; $\eta 2 = 0.1537$). Engagement in play behaviors specifically during adolescence were positively correlated with the number of flat-type USVs ($p = 0.019$; $\eta 2 = 0.1436$), and negatively correlated with the number of short-type USVs ($p = 0.0304$; $\eta 2 = 0.1236$). Complex-type USVs predicted OR expression in adolescence, with fewer complex USVs predicting higher PFC OR ($p = 0.021$; $\eta 2 = 0.147$).

Conclusions: These data suggest that ELA through neonatal resource scarcity can impact infant USV, and that these early measures of communication may serve as early indicators of ELA-attributable changes in social behavior and oxytocin signaling. Our findings warrant further examination of sex-specific and

experience-specific impacts on affective circuits and the ability to identify vulnerable individuals with behavioral measures in early life.

Keywords: Early-Life Adversity, Ultrasonic Vocalization, Oxytocin Receptor, Adolescence

Disclosure: Nothing to disclose.

Disclosure: Nothing to disclose.

P159. CYP2C19 Metabolizer Status Predicts Sertraline and Escitalopram Pharmacokinetics in Children and Adolescents

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Background: The selective serotonin reuptake inhibitors (SSRIs), sertraline and escitalopram are commonly prescribed for anxiety and depressive disorders as well as obsessive compulsive disorder in children and adolescents. Both SSRIs are primarily metabolized by cytochrome P450 2C19. Importantly, the gene that encodes this enzyme, CYP2C19, is highly polymorphic and these polymorphisms have been associated with altered pharmacokinetics in adults and small samples of children and adolescents. To date, few studies have evaluated the impact of polymorphisms in CYP2C19 on sertraline or escitalopram pharmacokinetics in children and adolescents. With this in mind, we sought to evaluate the impact of CYP2C19 phenotype on sertraline and escitalopram pharmacokinetics in a large sample of pediatric patients.

Methods: Using remnant samples from hospitalized children and adolescents ($N = 211$), aged 10 to 20 years who received either of these medications during inpatient hospitalizations, we determined plasma sertraline/desmethylsertraline ($n = 107$, mean age: 14.5 ± 2.1 years, 73% female), escitalopram and desmethylescitalopram ($n = 104$, mean age: 15 ± 1.8 years, 69.2% female) concentrations were determined. From buccal swabs or whole blood, genomic DNA was isolated and patients were genotyped for 7 no function alleles (*2, *3, *4, *5, *6, *7, *8) and the increased function allele (*17); *1 genotype was inferred from the absence of the previous alleles. CYP2C19 phenotypes were determined based on CPIC guidelines and dose-specific pharmacokinetic models were utilized to determine exposure (area under the curve [AUC]) and Cmax for each phenotype.

Results: The sample consisted of poor ($n = 4$), intermediate ($n = 65$), normal ($n = 77$), rapid ($n = 55$) and ultrarapid ($n = 10$) metabolizers. Dose to drug concentration ratios were significantly decreased in patients with faster CYP2C19 metabolism relative to those with slower metabolism for both sertraline (ANOVA test for linear trend, $p = 0.002$) and escitalopram (ANOVA test for linear trend, $p < 0.001$). Faster CYP2C19 metabolizers also had significantly lower ratios of escitalopram to its primary metabolite desmethylescitalopram ($p = <0.001$) but ratios of sertraline to its primary metabolite, desmethylsertraline were not associated with metabolizer status (ANOVA test for trend, $p = 0.17$). Individual patient specific models revealed associations between CYP2C19 and the Cmax and AUC for both sertraline and escitalopram.

Conclusions: In children and adolescents, CYP2C19 significantly affects sertraline and escitalopram pharmacokinetics across the dosing range. These data raise the possibility that CYP2C19-informed dosing could normalize sertraline and escitalopram exposure in adolescents. These data also lay the groundwork for studies that minimizing CYP2C19-related variability in exposure and clearance to decrease concentration-dependent adverse effects in adolescents who require treatment with sertraline or escitalopram.

Keywords: SSRI, Pharmacokinetics, Precision Medicine for Mood and Anxiety Disorders, Adolescent Anxiety

Disclosure: Myriad, AbbVie: Grant (Self)

Genomind, Neuroscience Education Institute, CMEology, MedScape: Honoraria (Self), UpToDate, Springer Publishing: Royalties (Self)

P160. New Analyses in the Development of an Abbreviated PANSS for Pediatric Trials: Criterion Validity and Treatment Sensitivity of an Abbreviated PANSS Using an NIMH Adolescent Schizophrenia Study Sample

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Background: What are the psychometric properties of the PANSS in a pediatric sample, and do they support abbreviation of this instrument for pediatric trials? Pediatric schizophrenia trials, with few exceptions, have used for primary efficacy assessment the PANSS, a complex and lengthy 30-item (adult) measure that has been extensively studied and shown to pose ratings challenges even when used with the adult patients for whom it was designed. For adult populations, there have been a variety of efforts to shorten the PANSS while retaining its clinical and research value. As presented to ACNP in 2020, we developed a psychometrically sound abbreviated 10 item pediatric PANSS derived from the baseline data of the NIMH Treatment of Early Onset Schizophrenia (TEOSS) study. The present study extends this work by testing the criterion validity and treatment sensitivity of our 10-item version compared with the original 30-item version using TEOSS on-treatment observations and associated measures.

Methods: As part of a NIMH multisite study (completed and previously described), 118 male and female youths with schizophrenia/schizoaffective disorder (mean age = 14.26, SD = 2.41 years) were administered the 30 item PANSS, the Brief Psychotic Rating Scale for Children (BRPS-C), and the Clinical Global Impressions – Severity (CGI-S) at baseline and weekly throughout an 8-week randomized double-blind study of three antipsychotic agents. In the present study, we examined the baseline correlation of our psychometrically derived 10-item abbreviated PANSS (Busner et al, ACNP 2020 poster) with the BPRS-C and CGI-S scales and then compared these with the BPRS-C and CGI-S correlations obtained using the 30-item PANSS. To examine treatment sensitivity, we computed effect sizes for the 30-item vs 10- item PANSS LOCF change from baseline. We also examined the correlation of the CGI-S LOCF changes from baseline with those of the 30-item and 10-item PANSS.

Results: Convergent correlations of the 10-item PANSS version with the BRPS-C and the CGI-S were similar to those found with the original 30-item PANSS. The 10-item version correlated .71 with the BPRS-C (versus .75 for the 30-item version); this difference was not statistically significant, $t = 1.43$, $p = .155$, per Steiger's test. Similarly, the CGI-S correlations were .57 with the 10-item versus .62 with the 30-item versions, also not significantly different per Steiger's test, $t = 1.69$, $p = .093$. The 10-item and 30-item versions produced essentially identical estimates of treatment effects: the eta-squared for baseline to LOCF change was .55 for the 30-item PANSS and .51 for the 10-item version, both indicating large treatment effects. The time-by-treatment interaction was not significant, eta-squared < .01, for either version (consistent with published results, finding no separation between active comparators). CGI-S change from baseline correlated similarly with LOCF change from baseline for both the 10-item (.63) and 30-item (.66) PANSS versions.

Conclusions: The results support the utility of our previously reported 10 item "optimized" PANSS for use in pediatric trials. For pediatric trials, the 10-item PANSS should maintain treatment sensitivity and precision while reducing costs, shortening interviews, and reducing burden. In this randomized and blinded adolescent schizophrenia treatment study, the proposed 10-item empirically derived version of the PANSS performed similarly to the original 30-item version with respect to treatment sensitivity and measures of criterion validity. Next steps include examination of the optimized pediatric PANSS in larger samples and placebo-controlled trials.

Keywords: Childhood-Onset Schizophrenia, Adolescent Schizophrenia, Clinical Trials Methodology, Novel Assessment Tools for Clinical Trials

Disclosure: Signant Health: Employee (Self)

P161. Adolescent Alcohol Exposure Produces a Persistent Neuroinflammatory Response Resulting in Increased Pain Sensitivity During Adulthood

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Background: Chronic episodic binge drinking is a significant public health concern, resulting in deleterious, long-lasting effects on behavior and brain function. Chronic intermittent ethanol exposure (CIEE) can exacerbate anxiety and heighten sensitivity to mechanical and thermal stimuli, leading to repeated cycles of alcohol and other drug-seeking behavior to alleviate these symptoms. The adolescent brain may be particularly sensitive to the damaging effects of CIEE as it is still developing. Chronic cycles of binge drinking may predispose the individual to changes in neural adaptations, or stimulate a persistent neuroinflammatory response, resulting in diverse behavioral sequelae including persistent pain or drug seeking behavior during adulthood. Recently the immune system has been suggested to play a role in ethanol-related neurotoxicity and behavioral alterations.

Methods: Male and female adolescent C57BL/6J mice were subjected to a voluntary intermittent access to 20% ethanol for four weeks, spanning the period of adolescent development. Following CIEE, animals entered a chronic withdrawal period during which sensitivity to mechanical and thermal stimuli was investigated in the Hargreaves and von Frey assays. This was accompanied by an examination of neuroinflammatory markers in brain regions associated with pain processing: Raphe Nuclei, Amygdala, Anterior Cingulate, and Thalamus.

In a subset of animals, CIEE was followed by systemic treatment with minocycline - a tetracycline antibiotic commonly used to inhibit microglial activation. After 3 weeks of minocycline treatment, sensitivity to pain stimuli was investigated. To further examine the role of microglia in specific nuclei, we used chemogenetic strategies to target cx3cr1-cre positive cells (primarily microglia) within the Dorsal Raphe Nucleus (DRN)– a nucleus in the descending pain pathway. Using this approach, we examined the role of DRN microglial activation in the sensitivity to pain stimuli in ethanol naïve animals. Unless otherwise stated, sample sizes ranged from 9-11 animals per group.

Results: Adolescent CIEE produced a persistent hypersensitivity to mechanical and thermal stimuli in male and female mice. This was accompanied by increased microglial (P2Y12 cell marker) and macrophage activity (CD68) in brain regions associated with pain processing. Chronic treatment with minocycline during chronic withdrawal reversed the persistent pain response observed in ethanol treated animals.

To investigate the specific role of the DRN microglia in the production of pain responses, we employed chemogenetic approaches to activate cx3cr1+ cells. Treatment with CNO (3mg/kg, i.p.) produced a hypersensitivity to mechanical and thermal stimuli in ethanol naïve animals.

Conclusions: Our results demonstrate the long-lasting influence of chronic neuroinflammatory insults on behavior and microglial activity later in life. In on-going experiments, we are using two-photon laser scanning microscopy to investigate how chronic neuroinflammatory insults, such as adolescent CIEE, influence microglial responses to acute inflammatory stimuli later in life.

Keywords: Adolescent Alcohol, Neuroinflammation, Pain Sensitivity

Disclosure: Nothing to disclose.

P162. The Importance of Race/Ethnicity for Brain-Environment Associations in Adolescence

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Background: Adolescence is characterized by substantial brain reorganization that is shaped, at least in part, by environmental factors. Race/ethnicity is known to be associated with environmental exposures, but it is currently unknown whether it modifies brain-environment associations during development. To address this question, we leverage the large and epidemiologically informed dataset provided by the Adolescent Brain Cognitive Development (ABCD) Study.

Methods: We analyzed data from 7879 unrelated ABCD study participants (47% females), aged 9-10 years identified as one of the four common ethnicities (White, Black, Hispanic, or Asians). Independent Component Analysis (ICA) was applied to decompose 40 variables representing environmental exposures pertaining to encompassing early life, parental and family characteristics, school engagement, and neighborhood deprivation. The association between environment and brain structural measures (cortical thickness and surface area as well as subcortical structures) were assessed using kernel based regularized least squares with site, age, sex, race, and handedness as covariates. The interaction between environmental exposures, and race/ethnicity were tested by examining their partial derivatives in a linear model.

Results: ICA identified three stable components (stability = 0.95) representing perinatal-developmental environment (PD), family/school environment (FS) and socioeconomic (SE) environment; with higher scores representing more advantageous environmental conditions. A pattern of spatially diffuse brain-environment associations was identified for the PD and SE components (all *P*-values < 0.000001) but not for the FS component; specifically, the PD component was negatively associated with cortical thickness (std beta = -0.025) and was positively associated with cortical surface area (std beta = 0.09). The SE dimension was positively associated with cortical thickness (std beta = 0.062) and surface area (std beta = 0.14,). Race/ethnicity modified the association between the PD component and cortical thickness, with this association being more marked in black participants (std beta = 0.009, $p < 0.000001$). Race/ethnicity modified the association between the SE component and on cortical thickness, with this association being less pronounced in black (std beta = -0.02, $p < 0.000001$) and Hispanic participants (std beta = -0.009, $p < 0.000001$). Race/ethnicity modified the

association between the SE component and surface area, this association being less pronounced in white (std beta = -0.006, $p = 0.005$) and black participants (std beta = -0.009, $p = 0.001$).

Conclusions: Perinatal and socioeconomic environment are linked to cortical structural development during adolescence; their associations are modified by race/ethnicity, suggesting differential susceptibility of these groups to environmental exposure during development.

Keywords: Adolescence, Adolescence- Critical Period, Human Neuroimaging, Structural MRI, Environment

Disclosure: Nothing to disclose.

P163. The Region-Specific Relationship Between Cortical GABA Levels and Social Cognition Deficits in Autism Spectrum Disorder and a Preliminary Study of the Effect of Gabapentin on These Levels

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Background: Autism spectrum disorder (ASD) is characterized by an imbalance in excitatory and inhibitory neurotransmission. Magnetic resonance spectroscopy (MRS) data suggests decreased GABA levels as a possible neuroimaging biomarker for social cognition deficits in ASD. Gabapentin has been shown in typically developing individuals and individuals with epilepsy to increase GABA acutely in the occipital cortex. Abnormalities in the anterior cingulate cortex (ACC) and anterior insula (AI) (components of the salience network) are associated with the underlying deficits seen in ASD. We sought in an exploratory study to determine what clinical characteristics of ASD were associated with GABA levels in the ACC and right AI, and whether an acute dose of gabapentin could alter these levels.

Methods: We recruited 15 adolescents ages 13-17 (14 M, 1 F) with a diagnosis of ASD, confirmed by ADOS-2 and ADI-R. We used a Mesher-Garwood Point Resolved Spectroscopy Sequence (MEGA-PRESS: TE 68 ms, TR 2 s) to measure GABA levels in two voxels that were 4 cm X 2.5 cm X 2.5 cm in dimension: one covering the bilateral pregenual ACC and one centered on the right AI. We assessed correlation coefficients of GABA levels in the ACC and right AI with two a priori selected measures of social cognition: the Social Responsiveness Scale (SRS) total score, and Reading the Mind in the Eyes Test (RMET) score. We also conducted exploratory assessments of correlations with SRS subscale scores, ADOS-2 scores, and Theory of Mind Inventory scores as additional social cognition measures, as well as dimensional assessments of anxiety symptoms, depressive symptoms, and ADHD symptoms (Multidimensional Anxiety Scale for Children, Children's Depression Inventory, and ADHD-Rating Scale IV, respectively). Finally, we administered a single dose of gabapentin to 12 of the 15 participants (fixed dose of 900 mg for the first 8 participants, weight-based dosing of 17-25 mg/kg for the last 4 participants after a protocol change due to preliminary evidence of a dose-dependent effect). We repeated the GABA MRS measurements 2 hours, 4 hours, and 6 hours after administration of gabapentin, and calculated the percent change in GABA from pre-dose to the average of the post-dose measurements. We used a generalized linear model to assess the relationship of percent change in GABA in the ACC and right AI to the weight-normalized dose of gabapentin (mg/kg), controlling for age, IQ, and baseline GABA level.

Results: GABA levels in the ACC were inversely related to the SRS Total Score ($r = -0.48$, $p = 0.08$), primarily driven by the Social Communication subscale ($r = -0.63$, $p = 0.02$, all other subscales $p > 0.1$). There was no correlation with the RMET scores, and exploratory analysis of other social cognition measures showed no significant correlations. GABA levels in the right AI were not correlated with the SRS or RMET scores, but exploratory analyses identified an inverse correlation with Restricted and Repetitive Behavior scores on the ADOS-2 ($r = -0.72$, $p = 0.002$). There were no correlations of GABA levels with age, IQ, anxiety symptoms, depressive symptoms, or ADHD symptoms. After gabapentin administration, there was a dose-related 1.4% increase in GABA (95% Confidence Interval – 0.4% - 2.4% increase, $p = 0.013$) in the right AI, but not in the ACC, for every mg/kg increase in gabapentin dose after controlling for age, IQ, and baseline GABA levels.

Conclusions: We found evidence suggesting that adolescents with ASD who have greater social deficits as measured by the SRS tended to have lower GABA levels in the ACC but not the right AI, with the social communication subscale driving the correlation. Other social measures were not related to GABA levels in either the ACC or right AI. GABA levels in the right AI may be related to restricted and repetitive behaviors in ASD. An acute single dose of gabapentin caused a dose-related increase in GABA in the right AI but not the ACC. The excitatory-inhibitory imbalance postulated for ASD may be region-specific as measured by cortical GABA levels, and gabapentin action on GABA levels has a different region-specificity. Future studies will be necessary to determine whether gabapentin has any clinical effect on ASD symptoms.

Keywords: Autism Spectrum Disorder, Magnetic Resonance Spectroscopy, GABA, Biomarkers

Disclosure: Nothing to disclose.

P164. Emotion Processing in Pre-Adolescents With Prenatal Drug Exposure and Childhood Trauma and its Association With Psychopathological Symptoms: Findings From the ABCD Study

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Background: Development of emotion regulation may inform predisposition or resilience to affective psychopathologies. While small cohort studies have identified prenatal drug exposure (PDE) and childhood trauma (CT) as factors that impact such development, a large-scale assessment of their interactive impact is warranted. The NIH ABCD Study is ideally suited for such examination. We hypothesize that PDE and CT independently and interactively will alter emotion processing and associated "top-down" and "bottom-up" cortico-limbic regions of interest, while accounting for psychosocial covariates. Furthermore, we predict brain and behavioral changes will be associated with clinical correlates of psychopathology.

Methods: Subjects from the Release 3.0 of the ABCD Study (ages 9-10 years) with complete data, including fMRI data on the Emotional *N*-back task, were included ($N = 6612$). Of them, 323 had prenatal exposure to alcohol, cigarettes, or marijuana as assessed from mothers' self-report (i.e., "PDE + "), 912 were "CT + " as assessed from the PTSD module of the KSADS, and 118 were both PDE + and CT + (or "double-hit"). Dependent variables included behavioral (i.e., mean reaction time and accuracy) and brain (beta-weight BOLD-response in select regions-of-interest) data from the emotional versus neutral ("arousal") and negative versus positive ("valence") contrasts of the Emotion N-back task. The PDE and CT main effects and their interaction were analyzed using linear and robust mixed effects models in R. Correlations between the significant brain and behavioral variables with clinical

variables (CBCL, Difficulties in Emotion Regulation, and BIS/BAS scales) were assessed using the Spearman Rank correlations.

Results: The PDE + showed reduced activation in the right ventromedial prefrontal cortex (vmPFC; CE = -0.1, $p = 0.044$) compared to PDE- in the valence condition, such that lower vmPFC activation was correlated with greater CBCL-assessed anxious-depressive ($r = -0.12$, $p = 0.043$), withdrawn-depressive ($r = -0.13$, $p = 0.025$), and internalizing ($r = -0.11$, $p = 0.045$) symptoms. Also in the valence condition, CT + showed higher activation of the left amygdala (CE = 0.052, $p = 0.036$) compared to CT-, which was correlated with greater BIS score ($r = 0.07$, $p = 0.033$). Moreover, again in the valence condition, the "double-hit" group showed reduced activation of the left vmPFC (CE = -0.2, $p = 0.023$) compared to other groups, which was correlated with greater withdrawn-depressive symptoms ($r = -0.22$, $p = 0.02$). In the arousal condition, the "double-hit" group showed greater activation of the left caudal anterior cingulate cortex (cAcc; CE = 0.056, $p = 0.03$) compared to other groups, which was correlated with higher somatic complaints ($r = 0.2$, $p = 0.048$). Correlations were FDR-corrected for multiple comparisons.

Conclusions: Given comparable task behavior between groups, we observed main effects of PDE and CT on neural correlates of emotion processing in the valence conditions, both corroborating previous literature and adding to it by accounting for several confounding variables not typically considered in smaller studies. Additionally, the size and diversity of the ABCD cohort allowed for an investigation of interaction effects of the PDE and CT insults, which resulted in additional findings in the "double-hit" group. Overall, correlations between brain activation and clinical scales showed that brain activations seen in PDE+, CT+ and in the "double-hit" groups are associated with greater severity of psychopathological symptoms, specifically as it relates to depressive and somatic domains. Future research is required to explore if these two exposures might confer a modifiable vulnerability where an intervention might target and normalize amygdala and vmPFC activation that might ameliorate problematic behaviors.

Keywords: Prenatal Drug Exposure, Childhood Trauma, Emotion Processing, ABCD Study

Disclosure: Nothing to disclose.

P165. A Longitudinal Examination of Presynaptic Dopamine in a Nonhuman Primate Model of Maternal Immune Activation

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Background: Epidemiological evidence suggests that prenatal, maternal immune activation (MIA) may be a risk factor for future psychotic illness in offspring. Accordingly, rodent MIA models have found alterations in adolescent neuroanatomical and neurochemical markers, including enhanced dopamine (DA) agonist sensitivity following a period of normal development. A previous pilot study from our group found that rhesus monkeys treated with Poly IC: IC during the first or second trimester gave birth to offspring that showed increased striatal presynaptic dopamine using [18 F]fluoro-l-m-tyrosine (FMT) PET during adolescence. As part of the UC Davis Conte Center focusing on neuroimmune mechanisms in psychiatric disorders, a new, MIA NHP cohort has undergone longitudinal PET studies examining striatal dopamine levels. Here we present longitudinal results from PET imaging conducted yearly from the first through fourth years of life.

Methods: Twenty-four pregnant rhesus macaques carrying male fetuses were randomly assigned to MIA (polyIC:IC, $n = 14$) or control ($n = 10$ saline) treatment at the end of the first trimester. Untreated male offspring were added to the control group ($n = 4$) and all offspring were characterized PET imaging at 12 months, 24 months, 36 months, and 45 months of age. FMT PET was used to measure striatal dopamine synthesis capacity. Animals were injected with benzeracide (2 mg/kg) 30 mins prior to FMT injection. FMT uptake in the bilateral caudate, putamen, and nucleus accumbens was measured using the Patlak reference tissue model (reference = cerebellum).

Results: MIA dams showed expected increases in temperature and sickness behavior as well as increases in IL-6 and other pro-inflammatory cytokines. Two MIA animals were removed from analysis as they did not undergo scanning at all 4 timepoints. A significant main effect of time and group*time interaction were observed for the bilateral caudate. The time effect was driven by an overall increase in FMT signal over time. The interaction effect was driven by higher FMT uptake at 24 months in the MIA group vs. the saline group but no group differences at other timepoints.

Conclusions: These results suggest that presynaptic dopamine is increased in the caudate prior to adolescence in MIA-treated offspring and then normalizes with maturity, consistent with a neurodevelopmental phenotype. Implications for understanding the MIA model in the context of brain disorders are discussed.

Keywords: Dopamine, Maternal Immune Activation, PET, Macaque, Dorsal Caudate

Disclosure: Nothing to disclose.

P166. Ontogeny of Recognition Memory Tasks in Mice

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Background: Childhood and adolescence are the predominant age of onset for the majority of mental disorders. Early life is also a time when key brain areas implicated in these disorders, such as the hippocampus and prefrontal cortex, are maturing. Several theories posit a connection between neural changes occurring in early life and the early onset of mental disorders. Importantly, to effectively interrogate the link between brain circuit development and the etiology of mental disorders, robust behavioral tasks must be optimized for use with young subjects. Recognition memory tasks assess the what, when and where components of episodic memory, and have increasingly been used in rodents to assess cognitive function in animal models of neurodevelopmental and neurodegenerative disorders. One such recognition memory task, object-place, explores the connection between object location and identity, and has been shown to rely on the hippocampus-prefrontal cortex circuit in rats. Nevertheless, its use in young rodents has never been reported. Here we have optimized the use of the object-place recognition memory task in mice, elucidated its developmental expression and circuit requirements.

Methods: We tried three experimental designs: (1) 4-Objects, One Sample Phase ($n = 9$ females, 8 males); (2) 4-Objects, Two Sample Phases ($n = 10$ females, 10 males), and (3) 2-objects, One Sample Phase ($n = 11$ females, 8 males). In all versions of the task, C57/129J mice (C57BLK/6J x 129S1/SvImJ) undergo a sample phase, in which they explore a combination of 3D-printed objects for 5 minutes, followed by a 3-minute test phase, in which novelty is introduced through a change in object placement. Recognition memory is assessed by quantifying the time spent exploring the novel (displaced) object(s) compared to the non-displaced. In the 4-Objects, One Sample Phase design, mice interacted with four different objects during the sample phase, two of which swapped location on the test phase. In the 4-Objects, Two Sample Phases design an additional,

identical, sample phase took place before the test phase. In the 2-objects, One Sample Phase design, mice interacted with two objects (dome and step) during the sample phase. In the test phase, one of the objects was replaced by an identical copy of the remaining object (e.g. dome and dome). For the inactivation experiment ($n = 9$ hM4D, 8 mCherry), mice were injected with either pAAV5-hSyn-DIO-hM4D (Gi)-mCherry or control pAAV5-hSyn-mCherry onto intermediate CA1 (iCA1). Ten days later, animals were injected with compound C21 thirty minutes prior to object-place (2-Object design). For the ontogeny experiment, C57/129J mice were tested at postnatal day (*P*)25, P28, or P35 (P25 $n = 9$ females, 10 males; P28 $n = 11$ females, 9 males; P35 $n = 11$ females, 15 males). Potential sex differences and object/side bias were assessed using a two-way, rm ANOVA. Object exploration time was analyzed by two-way, rm ANOVA followed by Sidak's post-hoc tests.

Results: To standardize the use of the object-place recognition memory task in mice, we tried some of the most commonly used experimental designs published with rats. While most rat object-place studies use a 4-object, one sample phase version of this task, we found that C57/129J mice were unable to display a preference for the displaced objects under this paradigm ($t(16) = 1.74$, $p = 0.10$). We then tested whether an additional, identical, sample phase would lower the difficulty of the task, as had been shown for P90 CD1 mice (Ricceri et al., 2000). Under this experimental design, C57/129J mice also failed to recognize the displaced objects ($t(19) = 0.39$, $p = 0.70$). Next, we tested a simpler, 2-object version of the object-place task used in rats. Under this experimental design, C57/129 mice successfully displayed a preference for the displaced object ($t(24) = 2.15$, $p = 0.042$). We found no sex differences in any of the tasks. Chemogenetic inactivation of intermediate hippocampus abolished preference for the displaced object ($t(12) = 3.56$, $p = 0.004$) in the 2-object version of this task. Finally, we proceeded to interrogate the developmental onset of 2-object object-place recognition memory at postnatal day (*P*)25, P28, or P35. We found that object-place memory is first expressed between P25 and P28 in C57/129J mice (two-way ANOVA, $F(1,68) = 13.82$, $p = 0.0004$; P25: $t(68) = 0.74$, $p = 0.84$; P28: $t(68) = 2.61$, $p = 0.033$; P35: $t(68) = 3.26$, $p = 0.0052$).

Conclusions: Here we have standardized a successful paradigm to probe object-place recognition memory in mice across the lifespan. We established that this 2-object variation of the object-place task is dependent on the hippocampus and can be used to assess cognitive function in young mice. We found that the onset of object-place memory takes place in juvenility, between P25 and P28 in C57/129J mice. This timeline is identical to that of the ontogeny of other recognition memory tasks which rely on hippocampus and prefrontal cortex, such as temporal order recognition, suggesting a coincidence between circuit requirements and developmental onset. Early life is a critical window for brain circuit development which overlaps with the predominant onset of anxiety, mood, impulse-control, and substance use disorders. Diversifying behavioral tools to probe circuit function in early life is a critical step towards understanding the relationship between brain circuit maturation and the onset of mental and neurodevelopmental disorders.

Keywords: Cognitive Development, Recognition Memory, Mice, Hippocampus

Disclosure: Nothing to disclose.

P167. Longitudinal Hippocampal Circuit Change Differentiates Persistence and Remission of Pediatric Posttraumatic Stress Disorder

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Background: Previous studies have identified functional brain abnormalities in pediatric posttraumatic stress disorder (pPTSD) suggesting altered frontoparietal-subcortical function during emotion processing. However, little is known about the development of functional brain substrates underlying recovery versus persistence of PTSD.

Methods: This longitudinal study recruited 23 youth with PTSD and 28 typically developing (TD) youth. Within the PTSD group, 9 remitted by the one-year follow-up (Remit) while the remaining 14 persisted (PTSD). At each visit, youth completed an emotional processing task in which they viewed threat and neutral images during functional magnetic resonance imaging (fMRI). Voxelwise activation analyses using linear mixed-effects regression were conducted using a group (TD, Remit, PTSD) by time (baseline, follow-up) by valence (threat, neutral) design. Based on activation findings, a subsequent analysis of hippocampal functional connectivity was performed using a similar model.

Results: In a pattern more closely resembling TD youth, Remit youth exhibited longitudinal decreases in hippocampal activation while viewing threat-related stimuli over time, while youth with persisting PTSD exhibit longitudinal increases. Subsequent hippocampal functional connectivity analyses reveal remitters diverging from PTSD youth through longitudinal increases in hippocampus-visual cortex (V4) functional connectivity while viewing threat stimuli.

Conclusions: These findings represent one of the first reports of functional brain substrates of persistence and remission in pPTSD. Notably, decreased hippocampal activation to threat and increased connectivity in the hippocampal-V4 network over time may contribute to reduced threat encoding leading to remission. These findings suggest potential biomarkers that could be utilized to advance the treatment of pediatric PTSD.

Keywords: PTSD, Adolescent PTSD, Human Neuroimaging

Disclosure: Nothing to disclose.

P168. Neighborhood Crime Exposure During Pregnancy Relates to Functional Connectivity in Neonates

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Background: Living in a neighborhood with high crime rates is associated with poor cardiovascular health, sleep disturbances, mental health problems, and altered brain development. Specifically, neighborhood crime exposure has been associated with decreased functional connectivity between limbic and prefrontal regions in children and adolescents. These connectivity changes are potentially meditated by stress pathways, given the chronic and acute stress associated with living in dangerous neighborhoods. The timing of exposure to violence seems to be important though, with some evidence that early exposure is more detrimental. Thus, we predicted that exposure to violence in-utero might be particularly important as pregnancy is a crucial time for brain development and sensitivity to stress. The aims of this study were to (1) examine the relationship of prenatal exposure to neighborhood crime to functional connectivity within and between limbic and control networks in neonates and (2) investigate whether any observed functional connectivity changes were mediated by psychosocial stress. The hypothesis was that living in a high crime area during pregnancy would be associated with decreased functional connectivity between the amygdala, hippocampus, thalamus, default mode network (DMN), and anterior frontal parietal network (aFPN) in neonates and that psychosocial stressors would mediate the relationship between neighborhood crime exposure and early brain function.

Methods: A total of 399 pregnant women were recruited as part of the Early Life Adversity and Biological Embedding study at Washington University. Prenatal addresses were collected and coded by census block group. Crime data for each block group was obtained from Applied Geographic Solution's CrimeRisk Database, which is a commercial dataset that combines data from over 16,000 law enforcement agencies. Violent crimes (e.g., murder, rape, aggravated assault, robbery) and property crimes (e.g., burglary, larceny, vehicle theft, arson) were examined separately. In the neonatal period (mean postmenstrual age at scan = 41 weeks), 319 non-sedated infants (male = 55%, mean gestational age = 38 weeks) were scanned using a resting-state functional MRI sequence (TR = 800 ms, TE = 37 ms, Voxel size = 2.0 × 2.0 × 2.0 mm3, MB = 8) on a Prisma 3T scanner and had at least 10 minutes of high-quality resting-state data after pre- and post-processing, including stringent motion correction. Linear regressions were used to examine the relationship of block-tract group crime to the functional connectivity of hypothesized networks. A composite measure of adversity, which included mom's income-to-needs ratio, Area Deprivation Index, education, insurance status, and Healthy Eating Index, was used to determine whether the observed effects were specific to neighborhood crime. Mediation models were used to investigate whether psychosocial stress, a composite measure of the Perceived Stress Scale, Edinburgh Postnatal Depression Scale, Stress and Adversity Inventory, and Everyday Discrimination Scale, mediated these results. Analyses were corrected for multiple comparisons using an FDR procedure.

Results: Prenatal exposure to neighborhoods with high rates of property crimes was related to decreased neonatal functional connectivity between the hippocampus-DMN ($p = .002$) and thalamus-DMN ($p = .008$) when controlling for other types of adversity. Functional connectivity between the thalamus-DMN ($p < .001$), thalamus-aFPN ($p = .005$), amygdala-hippocampus ($p = .005$) and amygdala-thalamus ($p = .002$) were decreased in babies born to mothers living in areas with high rates of violent crime; however, only the amygdala-thalamus ($p = .005$) and thalamus-DMN ($p = .01$) connectivity was specifically related to crime exposure and not adversity, after correcting for multiple comparisons. Finally, psychosocial stress mediated the direct relationship between thalamus-DMN connectivity and rates of violent crime (indirect effect; $p = .002$), as well as direct relationships between thalamus-DMN and both violent and property crimes (indirect effects; $p = .02$ and $p = .03$, respectively), though this mediation only held for thalamus-aFPN after controlling for adversity (indirect effect; $p = .03$).

Conclusions: These findings provide evidence that living in a high crime area during pregnancy is associated with decreases in certain neonatal functional relationships within and between limbic areas and control networks even after controlling for other adversity variables. The specific association of neighborhood crime may be related to differences in the biological processing of threats as opposed to deprivation. Furthermore, mother's psychosocial stress mediated the decrease in connectivity between crime and thalamus-aFPN and thalamus-DMN functional connectivity, indicating that mother's subjective assessment of their own stress levels may be particularly important for the development of those relationships. However, the lack of mediation with many of the functional connectivity measures specific to neighborhood crime indicates that alternative pathways, either through chronic biological stress or other mechanisms, may mediate the effects of neighborhood crime on brain development.

Keywords: Pregnancy, Brain Development, Functional MRI (fMRI), Neighborhood Crime, Stress

Disclosure: Nothing to disclose.

P169. Brain Mechanisms of Perceived Discrimination in Black Youth: Results From the ABCD Study

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Background: Social discrimination, a psychological stressor, has been linked to poorer mental and physical health outcomes. These relationships therefore may contribute to the underlying mental health disparities observed in marginalized populations, such as racial minorities. Less is known, however, about the impact of discrimination on neurobiology. Given the significant brain remodeling evident during adolescence, particularly in brain regions and networks that contribute to mental wellness, it is critical to examine early impacts of discrimination on neural function during this period of neurobiological vulnerability. Using data from the Adolescent Behavior Cognitive Development (ABCD) study, the objective of the current study was to examine perceived discrimination and mental health disparities in black, relative to white, youth. Resting state functional connectivity (rsFC) data were examined to test whether connectivity differs by race, discrimination and mental health, in networks linked with psychiatric symptomatology. Networks examined included the default mode network (DMN), dorsal attention network (DAN) and salience network (SN).

Methods: Methods: This is a secondary analysis of pre-existing data from the ABCD study. From the baseline sample of 11,875 participants, 9387 youth had resting state functional connectivity data that met quality assurance criteria, and thus, were included in the current analyses. This sample was then stratified by race, those identifying as black ($n = 1850$) or white ($n = 7537$). Data from youth of other racial groups were available ($n = 1899$), however was beyond the scope of this study. Baseline rsFC data, mental health symptoms and diagnoses, and perceived discrimination were examined.

Results: Results: Black youth had a statistically significantly higher rates of depressed mood symptomatology, including major depressive disorder ($p < .0001$), self-injury ($p = .006$), suicidal ideation ($p = .038$), and suicide attempt ($p = .002$). Black youth also reported significantly higher levels of perceived discrimination ($p < .0001$). There was a significant main effect of race on rsFC, weaker connectivity in DMN and weaker DMN-DAN and DMN-SAL connectivity in black relative to white youth (all $p < .0001$). Perceived discrimination and depressive symptoms were linked to weaker DMN connectivity. There also were main effects of race ($p < .001$), discrimination ($p < .05$), and depressed mood symptomatology ($p < .01$) and a significant interaction between discrimination and depressed mood symptomatology ($p < 0.05$), but did not interact with race for DMN rsFC, but not for DAN or SAL.

Conclusions: Conclusions: Mental health symptoms, such as depression, often manifest during adolescence, with significantly higher rates occurring in minority youth. Significant differences in DMN rsFC connectivity in black versus white participants suggest a potential neural substrate, weaker DMN connectivity, of perceived discrimination that could contribute to poorer mental health in minority youth. This novel study will help fill a major gap in identifying neurobiological correlates of psychological stressors, such as perceived discrimination, shedding light on interactions between biology and environmental factors associated with mental health disparities. Future work will examine longitudinal changes in these youth, followed over the course of the ABCD study.

Keywords: Adolescence, Resting State Functional Connectivity, ABCD Study, Racism and Discrimination Stress, Depressive Disorders

Disclosure: Nothing to disclose.

P170. Childhood Trauma Exposure is More Impactful Than HIV on Glucocorticoid-Related Gene Expression and Immune Cell Levels in Black Women

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Background: People living with HIV experience increased immune activation and chronic inflammation that increase risk for adverse physical and behavioral health outcomes. One experiential factor that may exacerbate the physiological consequences of chronic HIV infection is childhood trauma exposure, which people living with HIV are exposed to at higher rates than the general population. Additionally, Black women living in poverty and urban environments tend to be exposed to high levels of trauma and are at increased risk for HIV infection. Thus, it is important to understand how HIV infection interacts with childhood trauma exposure to influence the stress-related physiology, including the immune system. Given the role of glucocorticoids in mediating stress responses, there is a potential for the expression of stress related genes to be altered by the interaction of HIV and childhood trauma history. NR3C1 also known as the gene that encodes the glucocorticoid receptor; along with its positive and negative co-chaperones- FKBP4 and FKBP5 respectively are of particular interest. The overall goal of the current study was to characterize the extent to which HIV interacts with childhood trauma exposure to influence glucocorticoid-related gene expression and immune cell levels in trauma-exposed, Black women.

Methods: Black women (ages of 18 and 65 years) were recruited from the Women's Interagency HIV Study (WIHS) in Atlanta, GA and provided informed consent. All participants ($n = 89$, 29 without HIV, 60 women living with HIV; WLWH) completed a clinical interview conducted by a trained clinician to capture childhood trauma exposure via the Childhood Trauma Questionnaire (CTQ). Lifetime trauma history was determined by the 14-item Traumatic Events Inventory (TEI). Bloods samples were collected and later assayed for expression levels of NR3C1, FKBP4 and FKBP5 using a QIAseq UPX 3' Targeted RNAseq panel. Immune cell type proportions were estimated using a reference-based decomposition model that compares the bulk RNAseq results of the QIAseq panel to pre-quantified single-cell RNAseq data. The single-cell RNAseq reference profile was built from publically available expression datasets. ANOVAs controlling for income and HIV viral load (quantified by PCR) were used to assess the effects of HIV status, childhood trauma exposure and their interaction on glucocorticoid-related gene expression and immune cell types (CD4, CD8, CD14, CD16 and NK cells).

Results: Descriptive statistics showed that sociodemographic variables were not different based on HIV status, including age, education and employment (p's > 0.05). WLWH had significantly greater income levels compared to women without HIV ($p = 0.02$). Rates of adult and childhood trauma exposure were not significantly different between WLWH and those without HIV (p's > 0.05). ANOVA analyses controlling for education, income and HIV viral load showed a main effect of childhood trauma exposure on baseline FKBP4 gene expression. Women who experienced moderate-severe childhood trauma exposure had greater expression of FKBP4 at baseline than women with none-low childhood trauma exposure ($p = 0.038$). However, this effect of childhood trauma was not modified by HIV status ($p > 0.05$). Neither FKBP5 nor NR3C1 (GR) gene expression were impacted by HIV, childhood trauma, or their interaction (p's > 0.05). ANOVA analyses controlling for education, income and HIV viral load on cell type levels showed that women living without HIV with a history of childhood trauma had elevated CD16 ($p = 0.026$) and decreased CD4 ($p = 0.012$) compared to women without a childhood trauma. CD8, CD14, and NK cell type populations were not impacted by childhood trauma, HIV status, or their interaction (p's > 0.05).

Conclusions: Taken together, these findings suggest that childhood trauma exposure impacts FKBP4 expression in a manner that is not influenced by HIV status. Assessment of PBMCs as a proxy for genomic changes of environmental exposures is a common and important research tool that could be confounded by the cell type proportions. The method used here to assess cell-type proportions is an important new tool to improve interpretation of PBMC results without introducing cell isolation methods which could change expression of the targets of interest. Our data suggest that childhood trauma exposure may be a more salient factor than HIV and should be considered a critical variable in identification of treatment strategies.

Funding: MH110364, HD085850, AG062334

Keywords: Child Maltreatment, Adverse Childhood Events, HIV, FKBP5, Immune

Disclosure: Nothing to disclose.

P171. Functional Analysis and Targeted Pharmacological Screens in Zebrafish Mutants of Autism Risk Genes

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Background: At present, there are no pharmacological treatments that target the core deficits in autism spectrum disorders (ASD), which is due in large part to our incomplete understanding of the underlying neurobiology of these disorders. In recent years, gene discovery has led to important advances in our understanding of ASD biology, leading to a growing list of high confidence ASD risk genes and revealing common biological pathways, such as the regulation of gene expression and neuronal communication. However, despite this progress, we continue to face challenges in advancing from risk gene discovery to understanding the basic biological mechanisms underlying ASD, which is necessary for the development of novel, targeted pharmacotherapies. Our goal is to capitalize on the transparency, throughput, and ease of genetic manipulation in a zebrafish system to analyze in parallel the function of multiple ASD risk genes in the developing vertebrate brain and basic behavioral circuits.

Methods: We generated zebrafish mutants in 10 ASD risk genes, including: CHD8, CNTNAP2, CUL3, DYRK1A, GRIN2B, KATNAL2, KDM5B, POGZ, SCN2A, and TBR1, using CRISPR/Cas9, zinc finger nucleases, or TALENs. If genes are duplicated in zebrafish, both paralogs were targeted to generate double mutants. We hypothesized that these genes might converge on neural mechanisms controlling sensory processing and arousal behaviors, given that altered sensory sensitivity is a core feature of ASD. To test this, we performed automated, high-throughput assays of rest-wake activity and adapted an assay of visual-startle responses to lights-OFF and lights-ON stimuli by developing custom MATLAB software to quantify startle-related behavioral parameters. Next, we reasoned that we could leverage behavioral phenotypes identified in mutants to identify potential drug

candidates. To this end, we screened 775 compounds from the Enzo FDA-approved compound library in wild-type fish using the rest-wake and visual-startle assays and identified a unique behavioral "fingerprint" for each drug. Using this database, we identified compounds that strongly anti-correlate with each mutant behavioral phenotype. Finally, we performed whole-brain activity mapping using a custom computational pipeline to analyze differences in baseline brain activity across mutants.

Results: First, we identified a unique behavioral "fingerprint" for each ASD risk gene mutant and confirmed co-clustering of phenotypes in two independent lines per gene. We found that ASD risk gene mutants display both convergent and divergent phenotypes. For example, mutants of scn1lab, which is 77% and 79% identical to SCN1A and SCN2A, respectively, at the amino acid level, and double mutants of the two zebrafish paralogs of DYRK1A, both exhibits decreased daytime activity, yet they have increased and decreased responses to lights-ON and -OFF stimuli, respectively. Second, using our database of the behavioral responses of wild-type fish exposed to 775 FDA-approved compounds, we found that compounds with similar pharmacological mechanisms are more likely to cluster together. By mapping the behavioral phenotype of each ASD risk gene mutant onto the drug clustergram, we identified the top drugs that anti-correlate with each mutant behavioral profile and performed a targeted screen to identify suppressors of mutant behavioral phenotypes. Third, we found that ASD risk gene disruption leads to alterations in brain size and baseline brain activity. For example, dyrk1a double mutants display significantly decreased brain size, which is most prominent in the forebrain. In addition, consistent with our behavioral data, we found that ASD risk gene mutants display altered baseline brain activity affecting multiple regions.

Conclusions: Together, these studies highlight the strengths of in vivo functional analyses to identify correlations across ASD risk genes and identify potential pharmacological pathways for further investigation.

Keywords: Autism Spectrum Disorder and Related Syndromes, Human Genetics, Zebrafish

Disclosure: Nothing to disclose.

P172. Development of Valence Flexibility Across Emotional Tasks: An fMRI Study

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Background: Valence flexibility, the ability to switch between negative and positive emotions, may be critical for normative socio-emotional development. Task-switching studies have examined cognitive flexibility, the ability to switch between non-emotional attributes (e.g., shape, color) and affective flexibility, the ability to switch between cognitive (e.g., gender) and emotional attributes (e.g., emotion displayed). However, no studies have examined valence flexibility at any emotion processing level.

Methods: During fMRI acquisition, 85 9-20 year old individuals (57.6% female, 61.2% Hispanic, 24.7% non-Caucasian minority) participated in several task-switching paradigms involving emotion identification, self/other appraisal, or emotion evocation. In the emotion identification task, 62 healthy 9–20-year-olds ($M =$ 16.6 years, SD = 3.2 years) viewed happy-angry or happy-sad face pairs in separate runs. Individuals located the face matching a word cue appearing in between the faces. In the appraisal task, 73 9-20-year-olds ($M = 15.8$, SD = 3.4 years) indicated whether positive or negative statements generally described themselves (i.e., self-appraisal). Additionally, participants judged statements about a close friend (i.e., other appraisal) and completed a mixed run that included both appraisals. In the emotion evocation task, 78 healthy 9–20-year-olds ($M = 15.94$, SD = 3.60) viewed and identified the valence of positive and negative IAPS images. On successive trials of all tasks, the valence was repeated or switched. Reaction times (RT) and neural activation in emotional processing regions (e.g., amygdala, striatum, ventromedial prefrontal cortex) and regions of the central-executive, default mode and salience networks were measured. Significant interactions between previous trial-valence (i.e., positive or negative), trial type (switch vs. repeat) and age were interrogated using $p < 0.05$ corrected thresholds.

Results: In the emotion identification task, across age repetitive negative thinking (RNT) increasingly exacerbates switch cost differentially in happy-angry pairs ($F[1,231] = 5.71$, $p = .02$). Middle adolescents and young adults, but not early adolescents, tended to exhibit a positive correlation between RNT and switch cost for only angry-to-happy trials (i.e., angry-to-happy RT - angry repeat RT) ($F[1,154] = 3.66$, $p = .057$). Interactions were not detected in happy-sad blocks ($F[1,77] = 1.73$, $p = .19$). This result highlights the emergence of developmental differences in valence flexibility and that both valence combination and direction of the valence switch matters. Whole-brain analyses did not detect linear developmental differences in valence flexibility; however, a significant previous valence x condition interaction was detected in precuneus [(-4, -56, 9), k = 289, F = 20.0], bilateral caudate [left: (-11,1,14), k = 48, F = 27.4, right: (16, 1, 16), k = 82, F = 26.1], bilateral dorsal anterior cingulate cortex [left: (-6,21,40), k = 57, F = 20.2, right: (6, 29, 31, k = 32, F = 19.7; (4,9,44), k = 64, F = 19.7], right posterior cingulate cortex [(6,-44, 14), k = 52, F = 21.6], and right thalamus [(6, -19, 16), k = 29, F = 22.5], indicating that the regions are differentially responsive to consecutive emotional events.

In the appraisal task, individuals endorsed more positive compared to negative attributes and this difference was greater during self-evaluation than other runs [both $p < 0.001$]. Switch cost, collapsed across conditions, positively correlated with age [$r(73) = 0.24$, $p < 0.036$]. A significant 4-way interaction between age, run (i.e., self, other, mixed), previous trial-valence (i.e., positive or negative), and trial type (switch vs. repeat) was detected in the dorsal anterior cingulate cortex [(1,19,30), k = 41, $p < 0.005$, k = 41, F = 10.4]. In addition, ventromedial prefrontal cortex [(1,31,14), $p < 0.001$, k = 615, F = 28.6] and amygdala [(21,-6, -21), $p < 0.001$, k = 33, F = 21] respond differently depending on the relationship between consecutive trials, indicating that effects of switch vs. repeat trials depends on the valence.

In the emotion evocation task, contrary to our hypotheses that emotional flexibility would improve with age, young adults were slower to switch from identifying positive to negative emotions relative to identifying consecutive positive emotions [$F(1, 76) = 3.205$, $p = 0.07$]. This switch cost may reflect that negative pictures distracted young adults, yielding a longer reaction time. A significant 3-way interaction among previous trial valence, trial type and age was detected in the right amygdala (19, -6, -11), $p < 0.005$, k = 32, F = 19.9, which survives multiple comparison correction. Switching from negative to positive pictures yielded more amygdala activation than repeating negative pictures, but less activation was detected when switching from positive to negative compared to repeating positive pictures in children. These effects were absent in adolescents and young adults.

Conclusions: Developmental patterns of valence flexibility in behavior and neural patterns differ based on the emotional processing (e.g., emotion identification, socio-emotional appraisal, emotion evocation). Understanding the development of flexibility between negative and positive emotions has important clinical implications. These results may provide insight into a developmental mechanism which may be related to the heightened prevalence of mood and anxiety disorders in adolescence and young adulthood.

Keywords: Developmental, Executive Function, Affective Neuroscience

Disclosure: Nothing to disclose.

P173. Pilot Investigation of Fragile X Protein Level: Implications for Clinical Presentation and Small Molecule Target Engagement

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Background: Fragile X Syndrome (FXS) is the most common single cause of autism spectrum disorder (ASD) and most common inherited cause of intellectual disability impacting 1 in 4,000 males and 1 in 6-8,000 females worldwide. FXS results from CGG triplet repeat expansion in the promotor region of the FMR1 gene located on the long arm of the X chromosome. Despite commonalities in the presentation of FXS, significant variation does exist within FXS. Inherently, females with FXS are obligate mosaics with two X chromosomes resulting in a highly variable phenotype in girls and women ranging from no appreciable development impairment to risk for significant development delay. Even in males, phenotypic developmental variability is represented by functioning levels from severe to mild or even borderline intellectual/cognitive impairment. Prior work has evaluated fragile X protein (FXP) expression in human blood using various methodologies. In particular, recent work has measured FXP as a continuous variable in peripheral blood using a Luminex based assay (15). In this report, the lower limit of FXP detection was above zero indicating a challenge differentiating true zero FXP expression from potential low or trace level FXP levels. In this report we seek to improve upon the detection of FXP in peripheral blood to best discern potential molecular variation in FXS. We believe this will be important to new treatment development as FXP express likely varies extensively in FXS despite the single gene/single protein nature of the disorder. In appreciating molecular variation we aim to in the future use this understanding as a future means to biologically sub group persons with FXS when evaluating clinical presentation, outcome, and response to potential therapeutics. We now report on our initial work to optimize FXP detection in human blood with a focus on improving the lower limit of detection involving FXP assay in broad subgroups of individuals with emphasis on populations of males and females with full mutation FXS.

Methods: We adapted a Luminex-based assay to evaluate FXP in human blood in 187 across several human subject categories: males with FXS, females with FXS, fragile X premutation carriers, and typically developing control subjects.

Results: We optimized the assay conditions to decrease the overall background signal of the assay resulting in a consistently reliable lower limit of detection to 0.07 pM which is significantly lower than previous published limits of detection. This allows for a more accurate and quantifiable measure for patients with low levels of FXP which had been extrapolated, not quantified, using previous methods. We measured intra-assay variability, inter-plate variability, inter-draw variability, and inter-card variability to determine an acceptable standard of variation. Our overall assay performance statistics were highly acceptable with %CV rates of 10.1 intra-assay to 9.4 inter-plate to 6.0 inter-blood draw to 2.8 inter-card showing very good overall test-retest and within test reliability of the assay method. We first evaluated the expression of FXP between the diagnostic categories ($N = 187$ total participants). FXP levels are significantly reduced in individuals with FXS when compared with premutation carriers and typically developing control subjects (TDCs) respectively. There was no significant difference in protein concentration between premutation carriers and TDCs. We then analyzed the effects of sex on FXP. There was no significant difference between sex within the premutation carrier category nor within the TDCs (data not shown). There was a significant reduction in FXP in males with FXS in comparison to females with FXS (Mann-Whitney $U = 20$, $n1 = 70$ $n2 = 33$, $p < 0.0001$ two-tailed). We compared males that express the fully methylated (FM) FM to their mosaic (size and/or methylation mosaic) male counterparts; here, mosaicism is a grouped category where individuals with either repeat or methylation mosaicism were analyzed as the mosaic group. As expected, FM FM males have significantly lower FXP than mosaic males. Interestingly, we made a novel discovery that there are some FM FM males that consistently express low amounts of FXP less than the average mosaic male FXP level. Finally, we evaluated FXP blood concentration in the context of a drug versus placebo EEG-focused target engagement pilot single-dose challenge study of 30mg racemic baclofen (RBAC) in 16 adolescents and adults with full mutation FXS. In this analysis, there was an association between FXP level and drug-associated resting state high frequency gamma band activity. Lower subject FXP levels were associated with greater reduction in gamma activity. Gamma band activity is elevated at rest in humans with FXS.

Conclusions: FXP can be reliably and reproducibly assay in peripheral blood in humans. Variance in FXP was expected noted between males and females with FXS and between groups of persons with FXS versus PMC and non-FX impacted control groups. Clinical associations between peripheral FXP expression and cognition were noted consistent with prior work in this field. We have discovered a cohort of males with FXS clinically characterized at having a FXS full mutation fully methylated FMR1 allele who are expressing FXP in their blood. Future work is necessary to understand both the clinical relevance and molecular mechanisms of trace FXP expression in a subpopulation of males with FXS. FXP level as measured in blood may be a potential future predictor of brain target engagement in FXS clinical trials.

Keywords: Fragile X Syndrome, Baclofen, Molecular Neuroscience

Disclosure: Stalicla, Impel Neuropharma, Forge: Consultant (Self)

P175. A Role for Anterior Cingulate Cortex ZnT3-Positive Neurons in Drug-Seeking Behaviors

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Background: The anterior cingulate cortex (ACC) is a core component of the neural circuitry that drives reward, and a key target through which drugs of abuse modulate behavior. Previous studies demonstrated that ACC glutamatergic neurons modulate reward seeking behaviors via control of the striatum. In addition, recent studies suggest that ACC glutamatergic neurons regulate the positive and negative components of cocaine experience. The PFC glutamatergic neurons integrate inputs from multiple brain regions that are implicated in drug addiction. Within a subset of glutamatergic neurons (zincergic), $Zn2+$ is co-released with glutamate. These zincergic neurons that release $Zn2+$ exclusively express the $Zn2+$ transporter 3 (ZnT3), a protein essential for $Zn2+$ transport into synaptic vesicles and necessary for synaptic $Zn2+$ release. Previous research shows that synaptic $Zn2+$ acts as a neuromodulator of both excitatory and inhibitory synaptic transmission to influence synaptic plasticity and regulate cognition, memory and affective processing. Our group recently showed that cocaine increases synaptic $Zn2+$ neurotransmission in the striatum. In addition, ZnT3 global knockout mice show reduced effects of cocaine on dopamine

neurotransmission, locomotor sensitization, conditioned place preference, and cocaine self-administration. These data suggest that synaptic Zn2+ regulates dopamine neurotransmission and may play a role in development of cocaine use disorders. The goal of this study was to define the role of ACC zincergic neurons on drug seeking behavior.

Methods: C57BL/6J mice were used for fluorescent in situ hybridization (FISH) studies. FISH was performed on brain tissue using probes for ZnT3, VGLUT1, VGLUT2, VGAT, somatostatin (SOM), parvalbumin (PV), and vasoactive intestinal polypeptide (VIP). To further characterize zincergic neurons, we developed the Cre-ZnT3/DreO transgenic mouse which allows for both cre-mediated recombination of genetically targeted constructs within ZnT3-positive neurons and DreO-mediated conditional substitution (knock-out) of the ZnT3 gene with an mCherry reporter. Glutamatergic neurons from the ACC are known to project to different subcortical structures that participate in drug seeking behavior. To determine the different regions that are targeted by ACC zincergic neurons, we injected Cre-ZnT3/DreO transgenic mice with an cre-dependent AAV-DIO-EGFP:synaptophysin-mRuby into the ACC. This approach enabled us to distinguish and localize the projections and putative release sites from passing fibers of defined zincergic neurons. To examine the contribution of ACC zincergic neurons on cocaine seeking behavior, first we injected Cre-ZnT3/DreO transgenic mice ($n = 8$) and wild-type mice ($n = 8$) with an AAV-DreO into the ACC. This strategy allowed us to ablate ZnT3 in ACC glutamatergic neurons. We then examined drug seeking using the cocaine-induced conditioned place preference (CPP) with 5 mg/kg cocaine dose.

Results: We found that in the neocortex ZnT3 mRNA was expressed in 55% of glutamatergic (VGLUT1) neurons and 60% of GABAergic (VGAT) neurons. Then, we determined which GABAergic neuron population expressed ZnT3, and we found that ZnT3 mRNA was present in 55% of parvalbumin neurons and 57% of somatostatin neurons but absent in VIP neurons. We also quantified the average proportions of all cortical neurons. We found that ZnT3 neurons represent 38% of the neuronal population in the neocortex. The vast majority of ZnT3 neurons consisted of glutamatergic neurons (16%) and GABAergic neurons (4%). Notably, within the interneuron population, ZnT3 was expressed in 2% of PV and 2% SOM neurons, and not detected in VIP neurons. Using neuronal tracing techniques, we found that ACC zincergic neurons strongly innervate medium spiny neurons in the nucleus accumbens. However, despite the AAC zincergic innervation into the nucleus accumbens, our study showed no difference in cocaine CPP between control and ZnT3 knockout mice at the specific dose tested.

Conclusions: Previous neuroanatomical studies showed that ZnT3 was mainly expressed in glutamatergic neurons. Here, we demonstrate that half of glutamatergic and gabaergic neuron neurons express ZnT3 in the neocortex. In addition, within the gabaergic neurons, ZnT3 neurons is localized in parvalbumin and somatostatin neurons. Our findings suggest that zincergic neurons from the ACC do not mediate cocaine reward as assessed via the CPP procedure.

Sponsored by Dr. Michael Lewis.

Keywords: Cocaine, Zinc, Anterior Cingulate Cortex (ACC)

Disclosure: Nothing to disclose.

P176. Altered Neurochemical Ratio in the Prefrontal Cortex is Associated With Pain in Fibromyalgia Syndrome

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Background: The central mechanisms underlying Fibromyalgia syndrome remain undetermined; however, there is increasing evidence to suggest that neurochemical imbalances may play a critical role in the pathophysiology of the condition. The primary objective of this study was to establish whether brain excitatory and inhibitory (E/I; Glutamate/GABA) neurochemical concentrations, measured by magnetic resonance spectroscopy (MRS), are altered in top-down pain processing circuitry in fibromyalgia syndrome (FMS) compared to healthy controls – specifically within the left dorsolateral prefrontal cortex (L-DLPFC). Subdividing the FMS group, we aimed to determine whether neurochemical concentrations were altered with and without depression. Secondly, we aimed to determine the relationship between E/I concentrations and acute thermal pain, and clinical pain sensitivity, in participants with FMS. We hypothesized that the Excitatory/Inhibitory (E/I) ratio within the L-DLPFC would be altered in participants with FMS compared to controls and, that E/I ratio would be associated with pain sensitivity metrics.

Methods: This study was conducted ancillary to a preregistered clinical trial: ClinicalTrials.gov NCT02969707. A total of 67 participants with neuroimaging and behavioral data were analyzed for this study ($n = 51$ FMS; $n = 16$ healthy controls). Behavioral questionnaires including the mini neuropsychiatric interview (MINI) and brief pain inventory (BPI) were assessed at enrollment/screening and used to binarily classify depression and assess clinical pain respectively. Acute thermal pain sensitivity (threshold and tolerance) was evaluated using an ascending method of limits protocol by applying a computer-controlled Peltier probe (30x30mm) to the left forearm. Five trials of pain sensitivity and three trials of pain threshold were evaluated and averaged. Magnetic resonance imaging (MRI) consisted of the following acquisitions: 1) a 3D T1-weighted structural scan; 2) an ~8.5 minute eyes open resting scan; 3) a MEGA-PRESS spectroscopy scan prescribed within the L-DLPFC. MRS data was analyzed in using a standard Gannet Software pipeline. Functional imaging data was preprocessed with fMRIPrep and L-DLPFC to dorsal anterior cingulate cortex (dACC) connectivity values were extracted. Statistical analyses of neuroimaging and behavioral measures were analyzed in R software.

Results: E/I ratios in were significantly higher in participants with FMS ($n = 51$) than in healthy controls ($n = 16$), in relation to both water ($\Delta M = .084$, $t(18.307) = 2.219$, $p = .039$) and cr ($\Delta M = .085$, $t(18.303) = 2.241$, $p = .038$). Controlling for age, the analysis of covariance (ANCOVA) demonstrated a significant effect of diagnosis (i.e. FMS + depression vs FMS without depression) on E/I ratios in Cr ($F(1, 48) = 4.962$, $p = .031$, $\eta^2 = .094$), water ($F(1, 48) = 5.084$, $p = .029$, $\eta^2 = .096$). In participants with FMS, E/I ratios in relation to both water and Cr significantly predicted thermal pain tolerance ($R^2 = .101$, $F(1,49) = 5.530$, $\beta = .318$, $p = .023$ and $R^2 = .103$, $F(1,49) = 5.632$, $\beta = .321$, $p = .022$, respectively). Similarly to pain tolerance, the models significantly predict thermal pain threshold (water: $R^2 = .081$, $F(1,49) = 4.315$, $\beta = .284$, $p = .043$; Cr: $R^2 = .083$, $F(1,49) = 4.425$, $\beta = .288$, $p = .041$). In the FMS cohort, a significant positive relationship was identified between E/I ratio and the composite Brief Pain Inventory Scale.

Conclusions: We provide the first evidence of excitatory/inhibitory imbalance within the DLPFC in FMS, which we demonstrated to be positively associated with acute/clinical pain measures and the degree of resting-state functional connectivity to affective pain circuitry (dACC). Together these results suggest a dysregulation of excitation and inhibition in top-down pain modulatory networks - influenced in part by co-morbid depression diagnoses. Although the cross-sectional nature of this study does not enable the determination of causality, metabolic and functional dysfunction may have potential pathophysiological implications that lend to altered pain processing classically observed in FMS. Furthermore, this evidence provides potential behavioral, pharmacological, and neuromodulatory therapeutic targets for the treatment of FMS.

Keywords: Magnetic Resonance Spectroscopy, Pain, Depression, Fibromyalgia

Disclosure: Nothing to disclose.

P177. Selective Control of Anxiety- But Not Depression-Like Behaviors by the Midbrain Projection to Basolateral Amygdala

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Background: More than 93% of Medicare dollars are spent on patients suffering from comorbidities within the United States. The high co-occurrence of anxiety and depression (>60%) is associated with greater chronicity and psychological disability. This is further evidenced by 4 times higher suicide attempt rates in patients with anxiety/depression comorbidity. However, due to the restrictive single disease framework used in the field, current treatment options are limited to alleviate comorbid conditions. Here, we use a unique anxiety/depression comorbid model to investigate the dopaminergic subcircuit mechanisms that underlie anxiety but not depressive-like behaviors.

Methods: The chronic social defeat stress (CSDS) paradigm models singular or combined anxiety- and depressive-like behaviors. We assess social behavior, anhedonia and preference for natural reward as well as approach/avoidance behaviors with the purpose to segregate mice resilient to the depressive behavioral outcomes of the CSDS paradigm and developing solely anxiety-like behaviors—A mice—from mice susceptible to both depression and anxiety—AD mice. We then combine neural circuit-probing techniques with electrophysiological recordings to determine the characteristic of ventral tegmental area (VTA)-basolateral amygdala (BLA) neurons in control (stress naïve), AD and A mice. Further, we perform fiber photometry recordings in freely behaving mice to determine the role of VTA-BLA neurons during the expression of anxiety- or depressive-like behaviors. Additionally, we perform in vivo photo-tagging electrophysiological recordings from VTA-BLA neurons to define the optical stimulation patterns necessary to optogenetically establish a causal link between VTA-BLA neuronal activity and behavioral outcomes.

Results: We previously established that alteration of the firing activity of VTA dopamine neurons projecting to medial prefrontal cortex and nucleus accumbens induces the depressive-like behaviors selectively occurring in AD mice. Here, interestingly, we observe that the firing rate activity and excitability of VTA-BLA neurons are dramatically decreased in both A and AD mice after CSDS (ANOVAs, Firing rate: $F(2, 104) = 6.750$, $P < 0.01$, $n = 35$-45; Rheobase: $F(2, 29) = 5.110$, $P < 0.05$, $n = 10$-13). Additionally, we show that VTA-BLA firing activity is negatively correlated selectively with anxiety-like behaviors (Pearson $R2 = 0.398$, $P < 0.01$, $n = 23$) but not depressive-like behaviors (Pearson $R2 = 0.013$, $P > 0.05$, $n = 23$). Then, using in vivo fiber photometry, we determine, in real time, that the expression of anxiety-like behavior but not depressive-like behavior is associated with altered VTA-BLA circuit dynamics (Anxiety-like: ANOVA $F2/146 = 8.072$ $P < 0.05$, $n = 34$-62 epochs; depressive-like: *t*-test $t = 0.42$ $P > 0.05$ $n = 33$-45 epochs; 15 mice). Our optogenetic studies bi-directionally establish the causal link between VTA-BLA subcircuit activity and anxiety-like behavior: 1) VTA-BLA optogenetic inhibition induces anxiety-like behavior (*t*-tests, $t = 2.419$, $P < 0.05$, $n = 10$-15 mice), whereas 2) VTA-BLA optogenetic activation rescues anxiety-like behavior in CSDS-treated mice (*t*-tests, $t = 2.906$, $P < 0.05$, $n = 15$-17 mice). Finally, these optogenetic manipulations selectively affected anxiety- but not depressive-like behaviors.

Conclusions: A fundamental challenge for novel anxiolytic and antidepressant therapeutics is to achieve therapeutic efficacy while maintaining other healthy brain functions without off-target effects. Our studies unravel a novel functional role for VTA-BLA dopamine neurons in encoding anxiety-like behaviors in both anxiety-alone and anxious-depressive comorbid subjects. Our data provide the distinct mechanisms underlying anxiety- and depressive-related behaviors in a multi-disease framework that will contribute and assist in optimizing treatment for anxiety/depression comorbidity.

Keywords: Anxiety and Depression, Psychiatric Comorbidity, Dopamine, Cell- and Circuit-Selectivity, Neurophysiology

Disclosure: Nothing to disclose.

P178. Inflammatory Effects of COVID-19 Exposure in Paired Plasma and Cerebrospinal Fluid (CSF) Samples in a Cohort of Pregnant Women

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Background: Almost 200 million people have been infected by SARS-CoV-2 to date and this number is still on the rise. The subacute and long-term effects of this virus remain largely unknown, despite evidence of significant and lasting effects on the inflammatory system which can lead to adverse neuropsychiatric sequelae (e.g. the development of mood and psychotic disorders and cognitive impairment). Pregnant women are a particularly vulnerable population, as it has been shown that outcomes of SARS-CoV-2 infection are worse during pregnancy. Previous research has linked changes in the immune system to postpartum psychopathology. As part of an ongoing study that aims to examine the long-term effects of SARS-CoV-2 infection on psychiatric symptoms and cognition in a sample of pregnant women, we measured inflammatory biomarkers and SARS-CoV-2 antibodies in paired plasma and cerebrospinal fluid (CSF) samples. These samples were collected during neuraxial pain management procedures administered for labor and delivery. This method allows for the investigation of SAR-CoV-2 exposure effects on central and peripheral inflammatory markers in a vulnerable population of pregnant women.

Methods: Paired plasma and CSF samples were collected from 23 women at the time of delivery at the Mount Sinai hospital, New York City. Presence of IgG against the SARS-CoV-2 spike (S) protein was measured using a serologic enzyme-linked immunosorbent assay (ELISA) developed at the Icahn School of Medicine at Mount Sinai. Levels of 14 cytokines (GM-CSF, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, IL-23, and TNFα) were measured using a high sensitivity multiplex assay. Individual cytokine levels (pg/ml) were compared between the paired plasma and CSF samples using a Mann Whitney U test. Correlations were assessed using Spearman's rho. In addition, a hierarchical clustering analysis was performed to assess which cytokines show clustering in both the plasma and CSF samples.

Results: Out of 23 women, 9 showed IgG (S) positive plasma samples, up to 11 months after infection. None of the women showed an IgG (S) positive paired CSF sample. GM-CSF, IFN-γ, IL1-B, IL-2, IL-4, IL-10, IL-12p70, IL-13, IL-17A, IL-23, and TNFα levels are significantly higher in the plasma samples compared to the paired CSF samples. IL-8 is significantly higher in CSF than in plasma samples. IL-2, IL-5 and IL-6 show a statistically significant positive correlation between the paired plasma and CSF samples (*r* ranging between 0.12 - 0.77). The hierarchical clustering analysis revealed different clustering patterns between the paired plasma and CSF samples. There were no significant differences in inflammatory

markers among women exposed to SARS-CoV2 and those not exposed.

Conclusions: These results show that SARS-CoV-2 antibodies are present in peripheral blood for extended periods of time after infection. Consistent with previous studies, the correlation between central (CSF) and peripheral (blood) inflammatory markers is poor, and only 3 inflammatory biomarkers (IL-2, IL-5 and IL-6) were significantly positively correlated in paired plasma and CSF samples. This suggests that peripheral blood may not be an optimal proxy for central (CSF) immune markers. This preliminary exploration of central and peripheral immune markers of SARS-CoV-2 exposure provides a window of opportunity to understand the effect of COVID-19 infection on the inflammatory system and possible downstream outcomes related to psychopathology and cognition in an especially vulnerable population of pregnant women.

Keywords: COVID-19, Pregnancy, Neuroimmune Mechanisms, CSF, Cytokines

Disclosures: Neurocrine Biosciences, Inc: Advisory Board (Self)
AI Cure, Takeda: Grant (Self)
American Foundation for Suicide Prevention: Consultant (Self)

P179. Effects of Extended Cannabis Abstinence on Clinical and Cognitive Outcomes in Patients with Co-Occurring Major Depression and Cannabis Use Disorder

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Background: Cannabis use disorder (CUD) is a significant problem among individuals with major depressive disorder (MDD), with 15% of patients experiencing this comorbidity in comparison to ~3% of the general population. This comorbidity is associated with more severe symptomology, psychosocial impairments, and poorer treatment response. Most studies attempting to characterize the effects of cannabis in MDD have employed cross-sectional designs, preventing clear conclusions concerning the causal effects of cannabis use. The objective of this study is to determine whether a contingency reinforcement intervention to maintain 28-day cannabis abstinence will lead to improvements in depressive symptomology and cognitive functioning in these patients.

Methods: Using data from a previous open-label design ($N = 11$) and preliminary data from an ongoing, randomized control trial ($N = 5$), patients with comorbid diagnoses of CUD and MDD underwent 28-days of monitored cannabis abstinence. Participants in the ongoing trial were randomized to either a contingency reinforcement (CR) or non-contingency reinforcement (NCR) group. Clinical symptoms were assessed at baseline and then weekly, while cognitive functioning was assessed at baseline and Day 28. Abstinence and attendance were promoted by administering weekly behavioral support sessions. If abstinence was biochemically achieved at Day 28, participants in the CR group were entitled to a $300 bonus. Twice weekly urine toxicology was employed to confirm abstinence.

Results: In the open-label study, abstinence rates of 72.7% was observed (8/11). Further, reductions in cannabis use were found to be significantly associated with improvements in depressive symptoms and anhedonia at Day 28, as well as in improvements in selected cognitive domains (e.g., working memory, psychomotor processing). Preliminary feasibility data from the ongoing controlled study will be presented at the meeting.

Conclusions: Our preliminary findings are promising and highlight the feasibility and effectiveness of implementing a CM intervention in patients with MDD to investigate the direct effects of cannabis use on depression and cognitive outcomes in these patients.

Keywords: Major Depressive Disorder (MDD), Cannabis Use Disorder, Contingency Management

Disclosure: Nothing to disclose.

P180. Paclitaxel Chemotherapy Disrupts Behavioral and Molecular Circadian Clocks in Mice

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Background: Breast cancer patients and survivors experience debilitating behavioral symptoms (e.g., anxiety, depression, fatigue) during chemotherapy treatment that can continue for years into remission and result in reduced quality of life and increased mortality. Additional symptoms include disrupted sleep/wake activity and hormone (i.e., cortisol) patterns. Notably, these biological and behavioral processes exhibit 24-h circadian rhythms in humans and mice and their disruptions are correlated in cancer patients. However, the extent to which cancer treatments (e.g., chemotherapy) drive disruptions in 24-h rhythms has not yet been established.

Methods: In the present study, we examined the extent to which paclitaxel, a common chemotherapy drug, altered entrained and free-running circadian rhythms in wheel running behavior, circulating corticosterone, and circadian clock gene expression in the brain and adrenal glands of tumor-free mice. Master oscillator (suprachiasmatic nucleus; SCN) and adrenal clock genes were assessed ex vivo using transgenic clock reporter mice treated with chemotherapy in vivo. All experimental procedures were performed with prior approval from the Ohio State University Institutional Animal Care and Use Committee and based on standards listed in the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Results: Paclitaxel injections delayed voluntary wheel running activity onset in a light-dark cycle (LD) and lengthened the free-running period of locomotion in constant darkness (DD), indicating an effect on inherent SCN pacemaker activity. Paclitaxel attenuated clock gene rhythms in multiple brain regions in LD and DD. Furthermore, paclitaxel disrupted circulating corticosterone rhythms in DD by elevating its levels across a 24-hour cycle, which correlated with blunted amplitudes of Arntl, Nr1d1, Per1, and Star rhythms in the adrenal glands. Paclitaxel also shortened SCN slice rhythms, increased the amplitude of adrenal gland oscillations in PER2::luciferase cultures, and increased the concentration of pro-inflammatory cytokines and chemokines released from the SCN.

Conclusions: These findings indicate that paclitaxel chemotherapy disrupts molecular, physiological, and behavioral circadian rhythms driven by the SCN, which were likely due to chemotherapy-induced systemic inflammation. Together, this preclinical work demonstrates that chemotherapy disrupts both central and peripheral circadian rhythms and supports the possibility that targeted circadian realignment therapies may be a novel and non-invasive way to improve patient outcomes after chemotherapy.

Keywords: Circadian Rhythm, Neuroinflammation, Breast Cancer Chemotherapy, Corticosterone, Suprachiasmatic Nucleus

Disclosure: Nothing to disclose.

P181. Psychedelic Mushrooms in the USA: Knowledge, Patterns of Use and Association With Mental Health Outcomes

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Background: Psychedelics (serotonergic hallucinogens) have powerful and largely predictable, psychoactive effects, influencing perception, mood and cognition. In comparison with opioids, alcohol and tobacco, psychedelics have low addictive potential and benign toxicity profiles. There is a paucity of research describing the demographics and types of psychedelics use in the USA. The paradigmatic natural psychedelic is the psilocybin or "magic" mushroom (PM) which is relatively easy to cultivate on a small scale and increasingly accessible in a dried form. There is a growing body of evidence of the therapeutic potential of psilocybin in major depressive disorders. In a rapidly changing context that includes media reports of medical breakthroughs associated with psychedelics in PTSD and depression and successful decriminalization and legalization initiatives in a number of states and cities, the purpose of this research was to ascertain levels and patterns of PM use among American adults via a large, nationally representative population-based survey. We also aimed to explore the links between PM use and psychiatric morbidity and establish the extent to which PMs are used for self-medication.

Methods: A cross-sectional, nationwide survey of adults in the US was conducted between November 2020–March 2021. Participants self-reported knowledge and use of psychedelics in the past 12 months. Responses were weighted by region, gender and age to be representative of the US Census. Weighted tests were performed using Taylor Series Linearization method for estimating population characteristics from complex sample survey data. General linear models and chi-squares were conducted to examine PM use and various measures of health status, health related quality of life and self-reported mental health outcomes. Logistic regression models controlling for demographic and socioeconomic characteristics and comorbid conditions were carried out to estimate predictors of psychedelic mushroom use.

Results: The study response rate of 83.8% resulted in 7,139 respondents. Psychedelics use (all commonly used psychedelics, both natural and synthetic) was reported by 7.1% (CI: 6.5-7.7) of the population, and of psychedelics users, 49.2% (CI: 44.7-53.6) reported PM use only. PM users were more likely to be male (68.3 [CI: 59.3-76.1] vs 47.2 (CI: 45.9-48.5; $p < 0.001$), and younger (38.1 [SD 10.8] years vs 48.6 [SD 16.6]; $p < 0.001$), relative to psychedelics users. PM users had significantly lower mental health scores (39.5 [SD 11.3] vs 45.5 [12.4]; $p < 0.001$) and physical health scores (43.5 [SD 9.2] vs 45.28 [SD 10. 5]; $p < 0.05$), higher anxiety (9.6 [SD 5.8] vs 5.9 [SD 5.8]; $p < 0.001$) and depression (11.2 [SD 7.0] vs 6.8 [SD 6.8]; $p < 0.001$), and significantly more healthcare resource utilization for urgent care visits (20.8 [CI: 14.3-29.3] vs 9.9 [CI: 9.2-10.7]; $p < 0.001$) and hospitalizations (9.2 [CI: 5.2-15.8] vs 3.9 [CI: 3.4-4.4]; $p < 0.01$) than non-PM users. Significantly more PM users reported hearing positive information about psychedelics use in the past 6 months than non-PM users (2.06 [SD 1.07] vs 3.56 [SD 1.20]; $p < 0.001$). The most reported reason for PM use was for general mental health and well-being (63.6%). Factors predictive of PM use included being male [OR = 1.53 (1.09-2.15)] and reporting worse health [OR = 1.42 (1.22-1.65)]. Those with health insurance [OR = 0.50 (0.35-0.72)], or younger age [OR = 0.92 (0.90-0.93)], and relative to those living in the west US census region, and those living in the northeast [OR = 0.27 (0.15-0.50)], midwest [OR = 0.34 (0.20-0.56)], and south [OR = 0.38 (0.26-0.55)] were less likely to use PM.

Conclusions: This study demonstrates the utility of a population-based understanding of PM use. The data show a disturbing association between PM use and negative mental health outcomes. When compared with opioids, alcohol and tobacco, psychedelics have low addictive potential and benign toxicity profiles and it is therefore likely that PMs are being used as "folk medicine" for a range of mental health conditions. The absence of health insurance or access to psychiatric care may drive younger users, who have been exposed to some positive information about psychedelics, to use PMs for self-medication. While the extent to which PM uptake is influenced by emerging scientific evidence versus anecdotal or pseudoscientific knowledge requires further research, PMs are indeed firmly entrenched as health and wellness options in the US and these findings should inform future regulatory decision making.

Keywords: Psychedelics, Self-Medication with Psychedelics, Mental Health Disorders, Psilocybin

Disclosure: Back of the Yards Algae Sciences: Owner (Self)

P182. Dopaminergic Dysfunction Contributing to Motivational Deficits in Chronic Pain

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Background: A hallmark of substance use disorders is the inability to inhibit drug intake in the face of negative consequences. In humans and mice, most individuals can use addictive substances recreationally, while only a subset (~20-30%) transition to compulsive drug use and addiction, and understanding the neural substrates underlying this individual variability will provide insight into the etiology and pathology of punishment-resistant drug intake. The ventral pallidum (VP) has been extensively implicated in drug-seeking behavior; however how self-administration of opioids induces plasticity within the VP, and how this plasticity might contribute to compulsive drug seeking is known. VP-Glu neurons constrain reward seeking in the face of aversive consequences, and also express the mu-opioid receptor, which is an inhibitory g-protein-coupled receptor and is potently activated by opioids such as oxycodone. We hypothesized that self-administration of the prescription opioid oxycodone (OXY) would decrease the excitability and synaptic output of VP-Glu neurons, and that this plasticity would lead to compulsive drug seeking.

Methods: Mice (males and females, $n = 120$) self-administered oxycodone for 15 days, after which progressively increasing footshocks were introduced to dissociate mice into punishment-sensitive (stopped self-administration with footshock introduced, ~75% of mice) or punishment-resistant (did not reduce their self-administration with footshock; ~25% of mice). After classification of mice, we used patch clamp electrophysiology to record intrinsic excitability of VP-Glu neurons ($n = 25$ cells/8 mice). We transfected VPGlu neurons with channelrhodopsin, and used patch clamp electrophysiology to record synaptic output of these glutamatergic ventral pallidal neurons to the rostromedial tegmental nucleus and lateral habenula. In both experiments, we applied the mu-opioid-receptor agonist DAMGO (1 uM) to determine the opioid sensitivity of the intrinsic excitability and synaptic output. Data were analyzed with a mixed model ANOVA, with mouse and litter as random effects and sex as a fixed effect.

Results: Intrinsic Excitability: There was no difference in resting membrane potential (CTRL: -67.2 + /- 2.4 mV, OXY: -65.1 + /- 2.8 mV) or spontaneous firing (CTRL: 0.82 + /- 0.37 Hz, OXY: 0.7 + /- 0.26 Hz) of VP-Glu neurons following oxycodone self-administration. The maximum firing rate (CTRL: 27.1 + /- 2.5 Hz, OXY: 16.6 + /- 2.3 Hz) was significantly lower in mice that had undergone oxycodone self-administration, as was the area under the input-output curve.

Synaptic Output: We determined the paired-pulse ratio of optically-evoked excitatory currents between glutamatergic ventral pallidal neurons and the lateral habenula and rostromedial tegmental nucleus. At both sites, the release probability was

significantly reduced following oxycodone self-administration. We then recorded asynchronous optically-evoked excitatory events and determined that the frequency of these events was significantly lower following oxycodone-self administration relative to controls.

Oxycodone self-administration: When mild (0.1mA) footshocks are paired with oxycodone self-administration, the majority of mice will significantly reduce their oxycodone consumption (IC50 Controls: 40.0%), genetic ablation rendered mice punishment-resistant (IC50 caspase ablation: 73.8%, $F = 13.75$, $p < 0.001$. $n =$ 18/group).

Conclusions: Self-administration of prescription opioids decreases the intrinsic excitability of gluatmatergic ventral pallidal neurons and decreases their synaptic output to the lateral habenula and rostromedial tegmental nucleus. Inactivation of glutamatergic ventral pallidal neurons is sufficient to induce punishment-resistant oxycodone seeking. Therefore, we propose that cellular and synaptic adaptations in glutamatergic ventral pallidal neurons contributes to the punishment-resistant drug seeking phenotype observed in a subset of mice.

Keywords: Prescription Opioids, Mesolimbic Reward Circuitry, Electrophysiology, Synaptic Plasticity, Addiction Phenotypes

Disclosure: Nothing to disclose.

P183. Antidepressant Use and Risk of Intubation or Death in Hospitalized Patients With COVID-19: A Retrospective Cohort Study of Clinical Effectiveness

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Background: Growing evidence indicates that serotonergic antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), possess anti-inflammatory and antiviral properties – suggesting that SSRIs might represent potential treatments for the novel coronavirus disease (COVID-19). A recent randomized, placebo-controlled trial of fluvoxamine in symptomatic outpatients with COVID-19 demonstrated a significant reduction in clinical deterioration, and larger trials of SSRIs are underway. Given the urgency to develop novel COVID-19 treatments, additional observational studies would be valuable, particularly to assess the effectiveness of serotonergic antidepressants in clinical settings.

In the most comprehensive observational study to date, Hoertel and colleagues (Molecular Psychiatry 2021) found that among hospitalized patients with COVID-19, those receiving serotonergic antidepressants at admission showed a reduced risk of intubation or death compared to patients receiving no antidepressants. We attempted to replicate this finding using similar methods.

Methods: Using a retrospective cohort design, we searched electronic medical records of all patients hospitalized in the MassGeneral Brigham system (Massachusetts, USA) whose first (index) admission with a diagnosis of COVID-19 occurred between February 1, 2020 and March 3, 2021. The exposed group (antidepressant group; $N = 516$) represented all patients receiving treatment at the index admission with any of a set of antidepressants (SSRIs, norepinephrine-serotonin reuptake inhibitors, mirtazapine) found by Hoertel and colleagues to be associated with reduced risk of intubation or death. The unexposed group (non-antidepressant group; $N = 578$) represented a random sample of patients frequency matched for age, sex, and race/ethnicity to patients in the antidepressant group, but who were not receiving treatment with any type of antidepressant at the index admission.

The observation period for all patients started with the first day of the index admission and continued through the discharge date of the last hospital admission in the record. The primary outcome was the composite endpoint occurrence of either intubation or death (i.e., intubation without death, intubation followed by death, or death without intubation), and the secondary outcome was death alone. The primary measure of effect was the estimated hazard ratio from a proportional hazards model, and the secondary measure was the risk ratio, with both measures adjusted for age, sex, race/ethnicity, and eight comorbid diagnostic categories based on the index admission note. These diagnostic categories were: neoplasm; disorders of blood and immune system; obesity; type 1 or type 2 diabetes; diseases of the circulatory system; diseases of the respiratory system; mood and anxiety disorders; and other psychiatric disorders.

Results: The total sample ($N = 1094$) had a median age [interquartertile range] of 69 [59, 81] years, and was 54.2% female. The median observation time was 7 [4, 15] days for the antidepressant group and 7 [4, 16] days for the non-antidepressant group. Intubation or death occurred in 125 (24.2%) of the patients in the antidepressant group, and 119 (20.6 %) of patients in the non-antidepressant group, with a hazard ratio [95% confidence interval] of 1.1 (0.82, 1.4). Death occurred in 102 (19.8%) of the antidepressant group, and 87 (15.1%) of the non-antidepressant group, with a hazard ratio of 1.2 (0.87, 1.6). In further sensitivity analyses, individual antidepressant medications or classes of medications showed no evidence for differential effects.

Conclusions: We failed to replicate the results of a previous observational study which found a markedly protective effect of certain serotonergic antidepressants on treatment outcomes in patients hospitalized with COVID-19. The reasons for these contradictory findings are unclear. Two broad possibilities include: 1) both study results are internally valid, and the underlying populations receiving antidepressants in the two settings differed; and 2) one or both of the studies is not internally valid due to bias – most likely in the form of confounding by indication.

Further studies, particularly those utilizing other large healthcare databases, would be useful to explore the clinical effectiveness of antidepressants in individuals with COVID-19. Even if antidepressants were found to be ineffective in subsequent studies of hospitalized COVID-19 patients, additional studies of antidepressants in milder or early-stage COVID-19 should certainly be pursued.

Keywords: COVID-19, Antidepressants, Drug Repurposing

Disclosure: Nothing to disclose.

P184. Genomic and Neurocognitive Influences on Suicide Attempts Among Individuals With Alcohol Dependence

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Background: Recent genome-wide association studies (GWAS) have started to identify genomic and neurocognitive markers associated with suicide attempts among individuals with psychiatric illness (i.e., schizophrenia, bipolar disorder, depression). However, this has yet to be examined among those with alcohol dependence (AD) despite the high rates of suicide attempt among those with AD. In this study, we conducted a GWAS of suicide attempts among individuals with AD in the Collaborative Study on

the Genetics of Alcoholism (COGA). We also examined differences in neurocognitive functioning, given prior evidence of differences observed among individuals with psychiatric conditions who attempt suicide.

Methods: Within 4,068 alcohol dependent (DSM-IV AD) individuals, a GWAS compared 930 individuals reporting lifetime suicide attempts (53% female; 17% African ancestry; mean age: 38) with 3,138 participants who did not attempt suicide in their lifetime (32% female; 21% African ancestry; mean age: 40). We also compared neural functional connectivity (EEG coherence), planning and problem-solving skills (Tower of London), and visual working memory and attention span (Visual Span Task) among a subset of these groups (neurocognitive subsample: $N = 1,822$). All analyses were conducted separately by ancestry and adjusted for sex, age, further ancestral variation, genotype array type, and familial relatedness.

Results: One gene-based finding emerged -- RFX3 (Regulatory Factor X, located on 9p24.2) was associated with suicide attempts among those of European ancestry with AD and replicated in a prior study of attempted suicide. MPC2 (Mitochondrial Pyruvate Carrier 2, located on 1q24.2) was associated with suicide attempts in those of African ancestry, but did not replicate. Decreased right hemispheric frontal-parietal theta (3-7 Hz @ F8-F4--P8-P4) and decreased interhemispheric temporal-parietal (7-12 Hz @ T8-P8--T7-P7) alpha EEG resting-state coherences, and poorer problem solving, short-term memory and attention spans were observed among a subset of AD participants who had attempted suicide.

Conclusions: This study supports the role of RFX3 in the etiology of suicide attempts in those with AD, and neurocognitive functioning differences between individuals with AD who did and did not attempt suicide. RFX3 is a transcription factor involved in development of brain white matter tracts (including corpus callosum and thalamocortical tract), has previously been implicated in GWAS of depression, contains a variant that is an eQTL for depression risk gene CARM1P1, and is differentially expressed in brains of individuals with depression who died by suicide. This study also documented neurocognitive differences among adults with AD who have attempted suicide, replicating and extending prior research conducted among individuals with depression.

Keywords: Suicide Attempt, Alcohol Dependence, GWAS, Neural Connectivity

Disclosure: Nothing to disclose.

P185. Orexin Modulation of Threat Sensitivity in Humans

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Background: Anxiety disorders (AD) and alcohol use disorder (AUD) are highly prevalent and commonly co-occur. Available medications to treat these disorders are only modestly effective. There is an urgent need to develop new and more efficacious pharmacotherapies for AD + AUD. In order to accelerate the pace of drug discovery, a recent emphasis in medication development is the use of biologically-plausible and valid human laboratory measures of AD + AUD pathophysiology to screen promising compounds and test target engagement to inform the go/no-go decision to move to a clinical trial. Our lab has developed a reliable assay of stress reactivity that is robustly associated with AD and AUD, and substantiates the negative reinforcement model of AD and AUD comorbidity. Across several samples, we have shown that exaggerated behavioral (startle) reactivity to threats/stressors that are temporally unpredictable (U-threat) characterizes AD and AUD, and tracks symptom severity and motives for coping-oriented alcohol use. Emerging, exciting evidence from preclinical studies suggests that the hypocretin/orexin (ORX) hypothalamic neuropeptide system is a potential means for disrupting the negative reinforcement cycle of AD + AUD. Orexins play a role in the regulation of wakefulness and arousal, and are increasingly believed to have roles in motivated behavior. Preclinical studies demonstrate that ORX antagonism blocks reactivity during stress challenge and decreases alcohol consumption. The ORX system is therefore involved in the functional interactions between stress/anxiety and alcohol use, and is posited to target and modulate our laboratory paradigm reflecting stress-motivated alcohol use.

Methods: The current study was a proof-of-concept pathophysiological probe of the ORX system to test the hypothesis that ORX antagonism modulates reactivity to U-threat in human volunteers. Suvorexant (SUV) is an existing dual receptor ORX antagonist that is FDA-approved for the treatment of insomnia. We therefore examined whether an acute, one-time administration of a low dose of SUV could modulate our validated psychophysiological index of U-threat reactivity using a double-blind placebo-controlled within-subjects crossover design. Participants included adult volunteers ($n = 21$; M age $= 21.5 \pm 2.3$; 12 female; 71.4% Caucasian) from the community, with or without anxiety and alcohol use problems. Participants completed two laboratory sessions, approximately 2 to 7 days apart, during acute administration of 10mg SUV or placebo (PBO). During both laboratory sessions, we administered our well-validated threat-of-shock task designed to probe responses to U-threat and predictable threat (*P*-threat) while startle eyeblink potentiation was collected as an index of aversive responding. We also administered standardized questionnaires to assess mood states and subjective drug effects throughout the sessions.

Results: Results indicated the low dose of SUV was well-tolerated, with no adverse reactions. At 90-mins post capsule ingestion, SUV was associated with increased reports of feeling drowsy ($t[20] = 3.99$, $p = .009$) and tired ($t[20] = 2.89$, $p = .010$) relative to PBO. There were no session differences in other mood states including feelings of being calm, anxious, depressed, or agitated (ps > .19). With regard to study hypotheses, a within-subjects repeated measures ANOVA revealed a significant session (PBO vs. SUV) x threat condition (No-threat vs. *P*-threat vs. U-threat) interaction ($F[2, 40] = 12.99$, $p < .001$). There were no differences in startle magnitude between the two sessions for No-threat ($t[20] = 0.16$, $p = .874$) or *P*-threat ($t[20] = 0.72$, $p = .478$). Startle magnitude for U-threat was significantly lower during ORX administration relative to PBO ($t[20] = 4.09$, $p = .001$). On average, there was a 44.6% decrease in startle magnitude to U-threat during ORX compared with PBO.

Conclusions: Results indicate that a single dose of 10mg SUV selectively and effectively reduces startle reactivity to U-threat. SUV had no impact on baseline (No-threat) startle nor startle reactivity to threats that are predictable. ORX antagonism therefore targets and modifies our laboratory measure of AUD + AUD and may be a promising strategy for disrupting stress-related alcohol use. The current findings serve as a preliminary 'go' signal to pursue ORX antagonism as a potential novel pharmacological intervention for AD + AUD.

Keywords: Dual Orexin Receptor Antagonist, Sustained Threat of Shock, Fear-Potentiated Startle

Disclosure: Nothing to disclose.

P186. Cortical Thickness and Surface Area in Adolescent Females With Low-Weight Eating Disorders - Interactions With BMI and Puberty

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Background: Low-weight eating disorders (LWED) represent a heterogeneous class of disorders and include anorexia nervosa,

atypical anorexia nervosa, and avoidant/restrictive food intake disorder. While the motivation for restriction and degree of weight loss differentiates these disorders, all LWEDs are associated with substantial medical co-morbidity, increased mortality, and require cost- and time-intensive treatments. The psychological effects of LWED, paired with the impact of associated malnutrition on the brain during critical periods of brain development and refinement, remains unknown. Cerebral morphology, including cortical thickness (CT) and surface area (SA), are shaped by independent neurobiological events, with unique peaks of development between ages 3 and 10 years old, followed by steep refinement processes during the second and third decades of life (e.g., post-puberty). Eating disorder development typically occurs following peak periods of CT and SA development, however, the extreme dietary restriction and consequential nutritional deficiencies accompanying LWED may impact normative refinement that should occur during the second and third decades of life. The current study first examined differences in cortical morphology (CT/SA) among females with LWED and age-matched healthy controls. Next, we investigated if CT and SA were mediated by pubertal-status and body mass index (BMI) within LWED and HC groups. Based on previous findings in LWED, we hypothesized that adolescents with LWED would show evidence of widespread cortical thinning (lower CT/SA). Further, CT and SA would be mediated by pubertal status and BMI, such that the greatest reductions in CT and SA would be present among older patients with lowest BMI.

Methods: T1-weighted scans from 102 females (aged 10-23 years, $= 18.0 \pm 3.1$ years) diagnosed with a LWED ($N = 71$) and age-matched HC ($N = 31$) were processed with an internal pipeline, which included visual quality control steps, outlier detection, and masking using multi-atlas brain segmentation. Masked images were then processed using FreeSurfer7 and mean volumes for the bilateral occipital, frontal, parietal, and temporal lobes, and frontocingulate area were extracted. First, we assessed between-group differences (LWED vs. HC) in bilateral lobes using multiple linear regression in R. Next, we predicted CT and SA variation within LWED and HCs using multiple linear regression with (1) pubertal status (Tanner staging), (2) BMI z-scores, and (3) the interaction of pubertal status-by-BMI in R. In lobes with significant group differences, we extracted cortical sulci and gyri within each lobe to identify specific regions with each lobe. All models were corrected using FDR and included head size as a covariate.

Results: We found a significant main effect of group on the right temporal lobe ($F(1,100) = 4.001$, $p = 0.04$, $R2adjusted = 0.02$), such that individuals with LWED had reduced CT compared to HC. Within the right temporal lobe, individuals with LWED showed decreased CT in the superior temporal gyrus, banks of the superior temporal sulcus, and transverse temporal gyrus compared to HC (all $p < 0.005$). In HC, we observed a significant main effect of pubertal stage on the left frontal CT ($F(1,30) = -0.34$, $p = 0.01$, rostral middle frontal gyrus, left paracentral gyrus, and left frontal pole; $p < 0.005$), such that individuals in later puberty had greater reductions in CT. Pubertal status alone was not a significant predictor of CT in LWED. Instead, in LWED, we observed a significant main effect of BMI z-score, such that individuals with higher BMI z-scores had lower CT in the left occipital lobe ($F(1,70) = 0.15$, $p = 0.04$, left lingual gyrus and cuneus; $p < 0.05$), and right parietal lobe ($F(1,70) = 0.-19$, $p < 0.04$, superior parietal lobule, inferior parietal lobule; $p < 0.05$). Further, in those with a LWED, we found a significant interaction between BMI z-score and pubertal status, such that those at lower BMI and in later puberty had lower CT in the left occipital lobe ($F(6,70) = -0.19$, $p < 0.03$) (left cuneus) and right parietal lobe ($F(6,70)4.39$, $p < 0.03$) (superior parietal lobule, inferior parietal lobule, $p < 0.05$). In the inferior parietal lobe, pubertal status had a significant main effect such that individuals in later pubertal development had lower CT. There were no SA differences observed among the LWED group and HC.

Conclusions: In this study, we found widespread thinning of the cortical surface in adolescents with LWED relative to HC. Further, we found that normal neurodevelopmental patterns in LWED may be disrupted in the occipital and parietal lobes in a pubertal and BMI dependent manner. Individuals with LWED in later puberty and at a lower BMI showed the greatest reduction in CT in the left occipital lobe and right parietal lobe. Both the occipital and parietal lobe are actively maturing into the second decade of life in healthy individuals. Our data suggests that the malnutrition that takes place during periods of restriction in LWEDs may have a negative impact on the maturation of these cortical areas. Future studies will capitalize on the longitudinal nature of the current dataset to understand if pubertal and weight dependent changes reflect underlying biology or state-dependent alterations in LWED and how they may be related to clinical pathology across LWED.

Keywords: Neurodevelopment, Eating Disorders, Cortical Thickness, Body Mass Index, Puberty

Disclosure: Nothing to disclose.

P187. Early Visual Neural Activity Related to Body Perception in Adolescents With Anorexia Nervosa: A Pilot Study

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Background: Self-perceived weight or shape disturbance is one of three core symptoms of Anorexia Nervosa (AN), with high therapeutic and prognostic relevance. Characteristic disturbances of body perception in AN include the overestimation of body size and shape. Few studies have examined the electrophysiology of body processing in AN using EEG. In this study, we investigate the P1 and N1 event-related potential (ERP) signals which are involved in the visual processing of bodies, linked to extrastriate body area (EBA) and early configural processing. Both have been found to be abnormal in those with eating disorders and associated with eating disorder symptoms. This study examined P1 and N1 signals and their relationships to body shape concerns, in the interest of exploring them as potential neural biomarkers of abnormal visual processing of bodies in AN.

Methods: 16 females with AN and 7 non-clinical female controls with mild anxiety aged 10 to 19 were recruited for the study. Participants met DSM-5 criteria for Anorexia Nervosa, Restricting Type, within the previous six months. Twelve AN were medicated with SSRIs or SNRIS and 4 were unmedicated. Non-clinical females scored at least one half a standard deviation higher than population norms on the Depression Anxiety Stress Scale (DASS-21) anxiety subscale, and were unmedicated.

Participants performed a two-choice matching task consisting of blocks of images of others' bodies, houses, and shapes (ovals, circles, squares, or rectangles). Each trial consisted of a 500 ms crosshair and an image duration of 2s. EEG was recorded with 128-channel Geodesic Hydrocel Sensor Net at a 500 Hz sampling rate. Data processing was done using EEGLAB 2021.0.

The data were downsampled to 250 Hz, with a high pass filter at 0.2 Hz and a low pass filter at 100 Hz. Flatline and noisy channels were removed and interpolated. Additional muscle and blink artifacts were removed using AMICA. Data were epoched -500 ms before the stimulus and 2000 ms after. Epoched data were removed if a burst of noise or an eye blink appeared within the first 1000 ms of stimulus presentation. Baseline correction was

performed using the first 200 ms prior to stimulus onset. For ERP analysis, data were filtered at 30 Hz and epochs reduced to -100 ms prior and 500 after stimulus onset. The time windows 72-128 ms and 140-230 ms were selected to analyze P1 and N170/N190 components, respectively. Mean amplitudes and eating disorder severity (EDE) shape concern scores were included in the analysis.

Results: ANOVA showed significant group differences in the mean amplitude of P1 across all conditions ($F = 5.032$, $p = 0.0284$). No group-by-condition interaction was found. There was a significant relationship between EDE shape concern scores and P1 amplitude, higher in AN than in controls (Spearman's rho = 0.262, $p = 0.0294$). Linear regression controlling for medication status revealed that medication status, but not P1, significantly contributed to explaining the variance in EDE shape concern scores. Further, P1 amplitude means were similar between unmedicated AN and controls. No clinical symptom associations and no group differences were found for N170/N190.

Conclusions: Medication status has a significant effect on the mean amplitude of P1. It is unclear whether P1 has a relationship with body perception as measured by the EDE shape concern subscale. Chronic SSRIs have been reported to have an effect of enhancing the P1 signal. The significant relationship between shape concerns and medication could be because those with more severe symptoms were likely to be medicated; yet the medications do not appear to have resulted in reducing these symptoms. Study limitations include overall sample size and sample size of controls, as this was a pilot study.

Keywords: Anorexia Nervosa, Body Perception, Event-Related Potentials

Disclosure: Nothing to disclose.

P188. Activational Differences Within the Paraventricular Nucleus of the Thalamus in Binge Eating Prone and Binge Eating Resistant Rats

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Background: Binge eating is characterized by the excessive consumption of food in a limited period that exceeds the amount that would typically be eaten during that time. Previous data suggests that the paraventricular nucleus of the thalamus (PVT) may play a role in binge eating behavior. Since the PVT is innervated by the orexin system and orexin peptides are linked to feeding, it is possible that targeting the orexin system can impact neuronal activation within the PVT. The purpose of this study is to determine activational differences in posterior PVT and anterior PVT of binge eating prone (BEP) and binge eating resistant (BER) rats after orexin receptor-1 antagonism (SB-334867).

Methods: Female Sprague Dawley rats ($n = 7$-8/group, 250-300g) underwent nine feeding tests, to characterize feeding phenotypes as BEP or BER based on their consumption of high fat, sugar pellets (45% fat, 35% carb). After the phenotypes were identified, animals were administered SB-334867 (5, 10, 20mg/kg in vehicle, ip) or vehicle alone (2% DMSO and 10% 2-hydroxypropyl-β-cyclodextrin in sterile water) prior to additional feeding tests. Brain sections from the PVT were processed for c-Fos immunoreactivity.

Results: Consumption of the high fat, sugar pellets was significantly reduced after SB-334867 administration in BEP rats. Specifically, the 10mg/kg ($p < 0.05$) and 20mg/kg ($p < 0.005$) SB-334867 doses significantly reduced the amount of PF consumed in BEP rats. Although a reduction in high fat, sugar intake was observed in BER rats after SB-334867, the reduction was not significant. Quantification of c-Fos immunoreactivity within the PVT demonstrated that neurons within this region are activated after exposure to high fat, high sugar pellets. Administration of SB-334867 reduced the number of c-Fos cells in both BEP and BER rats. However, data from BEP rats indicate a significant reduction in Fos activation of pPVT neurons after orexin antagonism ($p < 0.005$). There was no similar observation in aPVT neurons of BEP or BER rats.

Conclusions: Activation of PVT neurons after palatable food consumption may indicate an involvement of these neurons in binge eating behavior. The significant reduction in Fos expression of pPVT neurons after orexin receptor-1 antagonism may also indicate that the pPVT is a target for pharmacological treatment to reduce binge eating behavior.

Keywords: Binge Eating, Orexin Receptor Antagonist, Immunohistochemistry

Disclosure: Nothing to disclose.

P189. Meal Intake Induced Oxylipin Aberration and Normalized Soluble Epoxide Hydrolase Level in Anorexia Nervosa

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Background: Oxylipins are bioactive lipid mediators formed by the oxygenation of polyunsaturated fatty acids in enzymatic pathways such as the lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP) pathways. Oxylipins have shown to be altered in various psychiatric disorders including major depressive disorder and anorexia nervosa (AN). CYP-derived oxylipins named epoxy fatty acids (epoxides) undergo catalytic conversion to dihydroxy fatty acids (diols) by soluble epoxide hydrolase (sEH). We have previously reported the risk of AN was associated with the sEH-encoding gene, Epoxide Hydrolase 2 (EPHX2). This study characterized the effects a standardized meal has on oxylipins and sEH to examine mechanisms underlying EPHX2-AN associations.

Methods: Fasting and postprandial levels of 59 individual oxylipins and 13 diol/epoxide ratios (as proxy markers for sEH in vivo activity) were assayed in 45 women with AN and 45 age-matched control women using LC-MS/MS. sEH protein expression and enzymatic activity were quantified in 70 women with AN and 96 control women. Blood samples were collected in the fasting state and 2h after consumption of a high-fat study meal. Individual oxylipins and oxylipin ratios were compared between AN and control groups using two-sample *t*-tests, whereas sEH protein expression and enzyme activity were compared between groups using ANCOVA adjusted for age, BMI, and sEH assay batch.

Results: In the fasting state, the concentrations of 25 (17 CYP, 8 LOX) of 59 oxylipins were 18% to 82% lower in AN compared to controls (p-values < 0.05). At the postprandial timepoint, five oxylipins (two CYP, three LOX) were 49% to 79% lower whereas four CYP oxylipins were 74% to 142% higher in AN (p-values < 0.05). Postprandial percent changes of oxylipin levels were also significantly different between AN and controls in 18 oxylipins (15 CYP, one LOX, and two non-enzymatic) (p-values < 0.05). Surprisingly, 14 out of 18 oxylipins were increased in AN whereas 17 out of 18 were decreased in controls two hours after the meal. At the fasting timepoint, AN displayed 16% higher sEH protein expression (adjusted p-value $= 0.043$) and 22% higher sEH enzyme activity (adjusted p-value $= 0.007$) compared to controls. However, no significant differences remained in either sEH protein expression or enzyme activity between AN and controls two hours after the meal (adjusted p-values > 0.05). Of the 13 diol/epoxide ratios representing sEH in vivo activity, six were elevated by 61%

to 178% in AN in the fasting state (p-values < 0.05) demonstrating higher in vivo sEH. Unexpectedly, eight oxylipin ratios became 46% to 78% lower in AN compared to controls in the postprandial state (p-values < 0.05).

Conclusions: Molecular mechanisms underlying genetic susceptibility in AN and other psychiatric disorders remain elusive, hindering the progress of developing new and more effective treatments. This study leveraged a meal exposure study design and identified significant and differential postprandial changes in bioactive oxylipins and sEH levels in women with AN. Our data revealed a molecular link between EPHX2 association and dysregulated lipid metabolism in AN, further highlighting the importance of additional research to better understand biological consequences of gene and diet interactions in AN.

Keywords: Anorexia Nervosa, Metabolomics, Lipids

Disclosure: Nothing to disclose.

P190. Role of Nucleus Accumbens MSNs in High-Fat Intake

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Background: Abundant epidemiological evidence supports the idea that the availability of calorically-dense, highly palatable foods is a leading cause promoting our nations ongoing obesity epidemic. There is a paucity of data exploring how intake of these foods alter the brains reward circuitry, ultimately resulting in an inability to abstain from overeating and relapse following successful abstinence. Therefore, an enhanced understanding of genetically and anatomically defined cell types regulating hedonic feeding may isolate the circuit mechanisms responsible for compulsive overeating.

My recent publication "Input-specific modulation of murine nucleus accumbens differentially regulates hedonic feeding" demonstrates that prolonged high fat intake leads to distinct cell type-specific changes in synaptic strength of two nucleus accumbens (NAc) excitatory inputs, the prefrontal cortex and anterior paraventricular thalamus. Modifying synaptic strength in vivo via plasticity protocols, either in an input-specific optogenetic or non-specific electrical manner, causes sustained changes in high fat intake. These results demonstrate that input-specific NAc circuit adaptations occur with repeated exposure to a potent natural reward and suggest that neuromodulatory interventions may be therapeutically useful for individuals with pathologic feeding.

GABAergic medium spiny neurons (MSNs) are the predominant NAc cell type, expressing dopamine receptor 1 or 2 (D1 or D2 MSNs, respectively). Neuronal activity adaptations in these subtypes, partially due to synaptic plasticity, regulate appetitive and aversive behaviors. Many studies implicate the NAc as a critical regulator of feeding behavior, yet a detailed understanding of which cell types and inputs modulate the motivation to feed is lacking. To address this gap, I am employing anatomical mapping, calcium imaging, slice physiology and optogenetics in sated mice to repeatedly exposed to high-fat food for 1-hour daily.

Methods: High fat intake: Mice were singly housed 1 week prior to the onset of high fat intake and had ad libitum access to chow and water. High fat chow was administered as previously described9. In brief, weight matched mice were randomly assigned to each experimental condition. A single, pre-weighed high fat pellet (60% fat, 20% protein, 20% carbohydrate; 5.24 kcal/g) was provided to the mice in their home cage daily for 1 hour at the same time each day for a given experiment. Intake of the high fat diet within that 1 h period was measured. For optogenetic behavioral experiments, mice were exposed to high fat for 20 min, followed by 3 days of 20 min exposure to high fat with optogenetic or chemogenetic stimulation. All mice with appropriate expression and targeting were included in data presentation and analyses.

Stereotaxic injections were performed two weeks prior to behavioral assays. For optogenetic experiments, DIO-ChR2 or -eYFP control was injected bilaterally into the NAc of D1-Cre mice. Chronically implantable optic fibers positioned above the NAc (0.2 mm above injection site). For chemogenetic experiments, DIO-hM3D or -mCHerry control was injected bilaterally into the NAc of A2a-Cre mice. NAc bregma coordinates: angle 10°, anteroposterior 1.6, mediolateral ±1.5, dorsoventral −4.4)

Optogenetic stimulation: Ferrules were connected to a 473 nm laser diode (OEM Laser Systems or Laserglow Technologies) through a FC/PC adapter and a fiber optic rotary joint (Doric Lenses). Laser output was controlled using a Master-8 pulse stimulator (A.M.*P*.I.). Animals received blue light (473 nm, 20 Hz, 5 ms pulse) for the entire duration of high fat exposure.

Chemogenetic stimulation: Mice received CNO injections (1 mg/kg, Tocris) or equal volume of saline vehicle intraperitoneally ~30 min prior to the start of a limited-access exposure. All mice were habituated with a saline injection in the morning for the 2 days prior to experimental manipulations.

Results: To test the effects of D1 activation on high fat intake, I stimulated these neurons at two frequencies: 1) 5 Hz, to mimick the firing rate of MSNs just prior to intake as we previously showed, and 2) 20 Hz a standard frequency used throughout the literature. Strikingly, 5Hz stimulation resulted in a significant increase high fat intake, whereas 20Hz stimulation had the opposite effect ($n = 9,11$ mice/group; 20 Hz: $F3,54 = 3.39$, $P < 0.05$; 5 Hz stimulation: $F1,18 = 4.93$, $P < 0.05$,). The decrease in intake observed with 20 Hz stimulation appears to be the result of increased locomotion ($F6,84 = 3.21$, $P < 0.05$,) and velocity ($F6,84 = 3.44$, $P < 0.05$).

To assess the effects of D2 MSN activity on high fat intake, I utilized a chemogenetic approach to allow for incorporation of endogenous input activity while increasing the probability of neuronal firing. Surprisingly, activation of D2 MSNs increased high fat intake similar to 5 Hz activation of D1 MSNs, without affecting locomotor activity.

Conclusions: These findings reveal the importance of assessing different patterns of stimulation and provide insight not only into how these neurons affect intake, but other behaviors as well. Indeed, the effect of 20Hz D1 stimulation resembles the anorectic affects observed with administration of stimulants such as cocaine.

Keywords: Mesolimbic Reward Circuitry, Maladaptive Feeding, Nucleus Accumbens, Hedonic Ingestion, Medium Spiny Neurons

Disclosure: Nothing to disclose.

P191. Downregulation of Striatal Dopamine D2-Receptor is Associated With Changes in Striatal Insulin Receptor Levels and Weight Gain in Mice

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Background: Understanding the neuronal circuitry underlying feeding behaviors is necessary with estimates suggesting that ~40% of adults, globally, are overweight. The central nervous system plays a critical role in overeating and excessive weight gain. While the neuronal circuitry underlying food intake is traditionally studied in the context of maintaining homeostatic control of energy balance, amassing evidence supports the idea that control of caloric intake also involves calculations of hedonic value, reward and motivation. The later aspect of feeding has been under studied, and for this reason, our current research focuses on

the role of the striatum, a brain area implicated in reward and motivation, in regulating feeding behaviors.

Methods: In both humans and rodents, some cases of obesity are associated with low levels of striatal dopamine D2 receptor (D2R) availability. However, the association is controversial in the clinical literature, and it is still unclear if low D2Rs are the cause or result of obesity. We implemented transgenic mice lacking the dopamine D2 receptor in the striatum projection cells to determine the effects on weight gain and metabolic factors.

Results: Using this preclinical rodent model, we show that selective down regulation of D2Rs on striatal projection neurons leads to excessive weight gain in male mice, even when maintained on a standard rodent chow. These mice show an up-regulation in insulin receptors in the striatum, where they modulate dopamine release. As previously shown, we use in vitro fast-scan cyclic voltammetry to demonstrate that insulin can increase dopamine release in the striatum. We then go on to show that mice with low levels of striatal D2Rs show exaggerated striatal dopamine release in response to insulin, compared to littermate controls. These mice also show an increased sensitivity in locomotor response to insulin.

Conclusions: Taken together these data indicate that central changes in striatal D2R levels are sufficient to induce an obesity-like state, which is underscored by increased striatal insulin receptor levels and associated changes in dopamine release.

Keywords: Dopamine, Obesity, Insulin, Striatum

Disclosure: Nothing to disclose.

P192. Behavioral Indices of Serotonin Syndrome are Enhanced Among Rats Eating a High Fat Diet

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Background: Drugs that act on serotonin (5-HT) systems are important for the treatment of many conditions, including anxiety, depression, and obesity. One potential adverse effect of these drugs is the development of 5-HT syndrome. Animal models of 5-HT syndrome include lower lip retraction, flat body posture, and forepaw treading in rats. Diet (e.g., type and amount of food consumed) has been shown to directly impact sensitivity of rats to the behavioral effects of drugs that act on monoamine systems, including drugs that act on 5-HT. The purpose of this study was to determine if eating a diet that was high in fat would impact sensitivity of rats to 5-HT syndrome behaviors induced by 5-HT receptor agonists.

Methods: To test the hypothesis that eating a high fat diet enhances the sensitivity of rats to 5-HT syndrome, male ($n = 16$) and female ($n = 16$) rats eating high fat (60% kcal from fat) or standard (17% kcal from fat) laboratory chow were tested once weekly with cumulative doses of 5-HT receptor agonists, including 8-OH-DPAT (0.01-1.0 mg/kg, s.c.) which has high affinity at 5-HT1A receptors, and lorcaserin (1.0-32.0 mg/kg, i.p.) and WAY 163909 (1.0-32.0 mg/kg, i.p.) which have high affinity at 5-HT2C receptors. Average forepaw treading, lower lip retraction and flat body posture scores were analyzed using three-way mixed model ANOVAs with diet, sex and dose as factors, and Bonferroni post hoc comparisons where appropriate.

Results: All three 5-HT receptor agonists induced forepaw treading in male and female rats; however, only 8-OH-DPAT induced lower lip retraction and flat body posture. Eating a high fat diet enhanced forepaw treading in male and female rats, regardless if this behavior was induced by 8-OH-DPAT, lorcaserin or WAY 163909. There were also some general sex differences in frequency of 5-HT syndrome behaviors regardless of diet. For example, 8-OH-DPAT induced more lower lip retraction and more flat body posture among males than females. In contrast, WAY 163909 induced more forepaw treading in females than males; while no sex differences were observed for forepaw treading induced by 8-OH-DPAT.

Conclusions: These results suggest that despite general sex differences that might occur with regard to 5-HT syndrome, dietary history could influence sensitivity of individuals to the adverse effects of serotonergic drugs, such as 5-HT syndrome.

Keywords: Serotonin, Serotonin 5-HT2C Receptor, Serotonin 1A Receptors, High Fat Diet, Rats

Disclosure: Nothing to disclose.

P193. Neural Incentive Processing of Monetary Reward in Women With and Without Binge Eating

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Background: Binge eating is a transdiagnostic eating disorder behavior that is characterized by consuming an objectively large amount of food in a discrete time period while experiencing a sense of loss of control overeating. The incentive-sensitization theory posits that increased "wanting" – more so than "liking" – underlies consummatory psychopathology, like binge eating. To date, researchers have mostly used food-related paradigms during neuroimaging protocols to test the incentive-sensitization theory in persons with binge eating. This research has documented altered activation of reward circuitry during anticipation ("wanting") of food reward, though findings have been mixed with respect to the direction of alteration (hypoactivation vs. hyperactivation). Few studies have tested whether persons with binge eating demonstrate alterations in reward circuitry during anticipation of generalized (i.e., non-food) reward, such as money.

Methods: 59 women (aged 18 to 35 years) with binge eating ($n = 41$) and without binge eating ($n = 18$) participated in this study. All participants completed the Eating Disorder Examination (to assess binge eating frequency and determine eating disorder diagnosis) and provided anthropometric measurements to calculate body mass index (BMI < 18.5 was exclusionary). Women with and without binge eating did not differ on BMI and age (ps > .05). Women with binge eating reported an average of 2.63 (SD = 1.67) weekly binge eating episodes. All women with binge eating met criteria for a DSM-5 eating disorder ($n = 18$ bulimia nervosa; $n = 15$ binge eating disorder; $n = 8$ low-frequency bulimia nervosa or binge-eating disorder). Participants underwent a task-based functional magnetic resonance imaging (fMRI) scan, during which they completed the Monetary Incentive Delay (MID) task. The MID is a commonly used task that, when administered during fMRI, measures neural activation in response to anticipation ("wanting") and receipt ("liking") of monetary outcomes. fMRI data were preprocessed with FMRIPrep. Binge-eating and non-binge-eating groups were compared using voxel-wise whole-brain analysis (Z > 3.1, FWE cluster significance threshold of $p = .05$) in FSL. Additionally, region of interest (ROI) analysis was conducted in FSL using functional 5mm spheres of the left and right nucleus accumbens created from MNI coordinates reported by previous study that used the MID (left nucleus accumbens: -12, 10, 2; right nucleus accumbens: 10, 8, 2). Mean percent signal change was extracted from these ROIs during anticipation of monetary gain (versus non-gain). Mean percent signal change was compared between binge-eating and non-binge-eating groups and correlated with weekly binge eating frequency.

Results: Voxel-wise whole-brain analyses yielded no group differences in neural activation during the MID. However, women

with binge eating exhibited decreased mean percent signal change in the left and right nucleus accumbens [left: $t(57) = -2.328$, $p = .023$; right: $t(57) = -2.874$, $p = .006$] relative to women without binge eating during anticipation of monetary gain (versus non-gain). Percent signal change in the right nucleus accumbens during anticipation of monetary gain (versus non-gain) was correlated with average number of weekly binge eating episodes (Spearman's rho = -.304, $p = .019$), but percent signal change in the left nucleus accumbens was not (Spearman's rho = -.233, $p = .076$).

Conclusions: Counter to the incentive-sensitization theory, results suggest decreased liking of general (monetary) reward in women with binge eating compared to women without binge eating. Results may refine extant transdiagnostic theories of binge eating and inform future investigations that directly test liking of food-specific versus generalized rewards. Such studies may ultimately inform pharmacological treatments for binge eating.

Keywords: Binge Eating, Binge-Eating Disorder, Bulimia Nervosa, fMRI, Monetary Incentive Delay Task

Disclosure: Nothing to disclose.

P194. Habenular Foraging Circuits Link Environmental Threats to Food Valuation and Drive Compulsive Eating in Obesity

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Background: Hunger increases the subjective value of food, lowers preference for palatable food, decreases aversion of novel food (hyponeophagia), and increases risk-taking behaviors that may yield food rewards. These behavioral adaptations are critical for survival when energy reserves are low or resources scarce, but increase the likelihood of predation, violent encounters with competitors, or consuming food low in energy or containing spoiled or even poisonous components. Consequently, foraging reverts to risk-averse strategies when satiety has been achieved and energy reserves replenished. Paradoxically, energy-replete obese humans and animals demonstrate high-risk foraging behaviors to obtain palatable food. Little is known about the neural mechanisms that link energy status to risk tolerance when foraging or whether abnormalities in this process contributes to obesity. Neural activity in lateral habenula (LHb) codes for negative reward prediction errors that support reinforcement learning and guide decision-making processes. LHb receives dense innervation from lateral hypothalamus (LH), a brain site that integrates information related to food 'value', including current energy status and adiposity levels. Nevertheless, the precise nature of this LH-derived food-relevant information is unclear. Here, we investigated the role of LH-LHb interactions in guiding foraging behaviors and their relevance to obesity.

Methods: Adenoviruses (AAVs) expressing DREADD receptors, opsins, GcAMP6m, diphtheria toxin A or codon-optimized flippase (FLPo) were delivered by stereotaxic injections into targeted brain sites of rats or mice. Fiber photometry coupled to GcAMP6m-derived fluorescence was used to monitor in vivo neural activity. Cell type-specific transgene expression was accomplished using vGlut2-cre, vGat-Cre and GAD2-Cre mice. The Chromium 10x platform was used for single cell RNA sequencing (scRNAseq), and the data analyzed using the ScanPy toolkit. Whole-cell recordings were performed using standard procedures. Whole-brain synaptophysin mapping was accomplished using iDISCO+ brain clearing, light-sheet microscopy, and the ClearMap Python package. Single cell projection mapping was accomplished using Multiplexed Analysis of Projections by Sequencing (MAPseq). All experiments were designed and powered for full factorial parametric statistical analyses.

Results: Neural activity in LHb was decreased in mice when food rewards were encountered in the environment, as measured by in vivo calcium imaging. The magnitude of this response depended on the caloric content of the food item, current energy status, and environmental threat level. Weight gain reconfigured LHb signaling such that standard chow no longer decreased LHb activity in obese mice, even when hungry. Instead, palatable energy-dense food induced starvation-like decreases in LHb activity in obese mice, even when fully sated. These maladaptive LHb signals coincided with the emergence of high-risk foraging behaviors in obese animals, reflected by their willingness to retrieve and consume palatable food but not chow in threatening environments. Chemogenetic stimulation of LH neurons that project to LHb (LH- > LHb) induced hunger-like behaviors in rats, including increased operant responding for standard chow pellets, increased chow consumption and concomitant weight gain, and decreased preference for highly palatable food. Conversely, lesioning LH- > LHb neurons induced obesity-like behaviors, including rejection of standard chow, increased preference for palatable food, and high-risk foraging behaviors for palatable food. Using slice physiology recordings, we confirmed that LH glutamatergic (LHGlu) and LH GABAergic (LHGABA) neurons provide synaptic input to LHb. scRNAseq revealed robust obesity-induced transcriptional plasticity in LH, particularly in LHGlu neurons. Consistent with this finding, whole-brain synaptophysin mapping revealed decreased connectivity of LHGlu neurons with brain reward/aversion sites including LHb and dorsal raphe nucleus (DRn), but unexpectedly increased connectivity with brain sensory sites including gustatory and somatosensory cortex. Moreover, LHGlu->LHb but not LHGABA- > LHb neurons were hyperpolarized in obese animals, and LHGlu-derived excitatory but not LHGABA-derived inhibitory transmission in LHb neurons was diminished in obese animals. We used a novel intersectional genetics approach to lesion only LHGlu-LHb neurons, which induced obesity-like risky foraging for palatable food but not chow. Chemogenetic inhibition of LHb similarly induced obesity-like foraging. Finally, we used a novel RNA sequencing-based brain mapping procedure with single cell resolution (MAPseq) to characterize the 'connectome' of individual LH- > LHb neurons. We identified a subpopulation of LH- > LHb neurons that project to DRn, which was highly sensitive to obesity-induced remodeling. Selectively lesioning neurons in LHb or DRn that receive synaptic inputs from LHb also precipitated high-risk foraging behaviors for palatable food.

Conclusions: Our findings identify a habenula-regulated network of brain reward/aversion sites that filters information from the LH to signal food value and guide foraging strategies. Weight gain induces abnormalities in LH communication with this habenula-regulated brain network, which increases risk tolerance during foraging for palatable food items and facilitates the emergence of obesity.

Keywords: Compulsivity, Obesity, Lateral Hypothalamus, Lateral Habenula, Dorsal Raphe

Disclosure: Nothing to disclose.

P195. Selective Deletion of the Melanocortin-4 Receptor in the Mouse Prefrontal Cortex Alters Feeding and Cognitive Behavior

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Background: Mutations of the melanocortin 4 receptor (MC4R) are strongly linked to obesity in humans and mice. MC4R is strongly expressed in the hypothalamus, but deletion of MC4R

from this region does not recapitulate the obesity induced by global brain knockout, suggesting MC4R in other regions are involved. The MC4R is highly expressed in the medial prefrontal cortex (mPFC), which is implicated in human feeding behavior, obesity, and eating disorders. We hypothesized that manipulation of the MC4R in the mPFC (mPFCMC4R) would affect feeding and cognitive behavior.

Methods: We examined how pharmacologic manipulation of the MC4R affects neuronal dynamics in the mPFC using MC4R-2a-cre mice. We also used viral-cre manipulation in IL-mPFC of male MC4Rlox/lox mice to selectively delete mPFCMC4R. We examined metabolic and behavioral changes including food intake, cognitive flexibility, decision making, and interference control using simple food-related behavior tasks.

Results: MC4R agonism depolarized the membrane and increased excitability of mPFCMC4R neurons. Selective deletion of mPFCMC4R increased food consumption and induced weight gain. This manipulation did not affect baseline exploratory behavior or cognitive rigidity in response to learned associations, but did influence decision making and interference control in male mice in the food restricted state.

Conclusions: Our data highlight a novel population of MC4R-expressing neurons in the medial prefrontal cortex that regulates food intake and other feeding-related behaviors. These findings contribute to our understanding of the mechanisms that govern feeding behavior, especially in the context of executive function, which is aberrant in individuals with eating disorders.

Keywords: Melanocortin, Medial Prefrontal Cortex, Executive Function, Feeding Behavior

Disclosure: Nothing to disclose.

P196. Behavioral and Neural Mechanisms of Food Choice Among Adolescents With Anorexia Nervosa

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Background: Anorexia nervosa (AN) is a serious illness, too often chronic or fatal, that commonly begins during adolescence. The central behavioral disturbance is restriction of caloric intake below the body's needs, with a specific restriction of calories from fat. This often begins as dieting during adolescence, and may be initially rewarding, leading to repetition of behavior and then to the persistent and maladaptive restriction in AN. This behavior has been shown to have behavioral and neural features of habits, with high habit strength, cue-dependence, and reliance on dorsal striatal neural systems. Our fMRI studies using a Food Choice Task have repeatedly shown that adults with AN, but not healthy controls (HC), engage the dorsal striatum during food choice – with no group differences in the ventral striatum. In a longitudinal study of neural circuits in adolescents with AN (R01 MH110445), we hypothesize that earlier in illness course, food choice will be associated with activation of the ventral reward system, and as illness persists, this will shift to dorsal striatal circuits. Here we examined, for the first time, the neural mechanisms of food choice among adolescents with AN as compared with HC in the baseline timepoint from the longitudinal study.

Methods: 80 adolescent females with AN and 40 female HC, ages 12-18 years, enroll in a two-year study with annual administration of the Food Choice Task with fMRI scanning. Pre-scan intake is standardized, and all scans occur two hours after lunch on a GE 3T MR750 scanner. The task consists of 3 blocks: Healthiness, Tastiness, and Choice. 76 food items are presented in each block, half defined as "high-fat" with a percent fat greater than 30%. After completion of Healthiness and Tastiness rating scales, an individualized neutral reference item is selected and the Choice block consists of rating preference for the neutral versus trial-specific items. After the scan, participants receive an actual snack based on trial selections. Proportion of high-fat choices on the Food Choice Task has been validated as associated with actual caloric and fat intake among patients with AN and HC. Study sample size yields a minimum detectable effect size of $d = 0.54$, with 80% power, and prior studies have shown a large effect size ($d = 1.3$), indicating adequate power. At this time, study enrollment includes 80 AN and 35 HC, with enrollment and baseline analyses to be completed in September. Mixed-effects logistic regression assessed whether food choices differed between groups. Contrast maps reflecting correlations between fMRI signal and food choice behavior from the first-level analysis are the dependent variable for group level analysis, and linear regressions test group differences, with ROIs in mesolimbic reward circuits (bilateral NAcc, ventral tegmental area, and OFC) and dorsal frontostriatal habit circuits (bilateral dlPFC, dACC, and dorsal striatum). Mixed effects linear regression test whether correlations between fMRI signal and food choice behavior are greater within ventral versus dorsal striatal ROIs amongst AN.

Results: Across 79 patients enrolled in the study, mean duration of illness is 0.71 ± 0.91 years. To date, behavioral Food Choice Task analyses include 75 AN and 33 HC and preliminary fMRI analyses include 42 AN and 19 HC. Relative to HC, adolescents with AN were more likely to: limit selection of high-fat foods ($b = -0.45$, $p < 0.001$), make choices that were influenced by healthiness ($b = 0.71$, $p < 0.001$); and rate healthier items as tastier ($b = 0.12$, $p < 0.001$). Preliminary analyses from the subsample of fMRI indicate that during the Choice block, dorsal striatum (caudate) engagement does not differ between groups ($b = 0.03$, 95% CI: -0.24, 0.30, $p = 0.83$). Ventral striatum also does not differ between groups ($b = 0.19$, 95% CI: -0.07, 0.45, $p = 0.17$). Among AN, ventral striatum engagement is greater than dorsal striatum engagement, though the difference is not statistically significant in this small sample ($b = 0.08$, 95% CI: -0.02, 0.18, $p = 0.10$).

Conclusions: Our overarching hypothesis is that there is a shift in the neural systems guiding behavior with progression of AN such that early in the course of illness, the ventral reward system underlies food choice, and that as the illness becomes persistent, decisions about what to eat come to be mediated by dorsal striatal circuits. Adolescents with AN manifest similar food choices patterns as adults with AN. Among adults with AN, the dorsal striatum and associated circuits guide food choices. Preliminary analyses of teens suggests that this effect may be attenuated earlier in illness. Findings from these baseline analyses will clarify whether neural mechanisms of maladaptive eating behavior are different early in the course of illness.

Keywords: Anorexia Nervosa, Decision Making, Adolescence, Eating Behavior, Cognitive Neuroscience

Disclosure: Nothing to disclose.

P197. Laparoscopic Sleeve Gastrectomy Alters Brain Structural Connectivity Between Medio-Dorsal-Thalamus/Habenular and Regions Involved With Homeostatic and Hedonic Processing in Obese Patients

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Background: Laparoscopic sleeve gastrectomy (LSG), one of the most effective procedures for treating obesity, produces sustained weight-loss and reduces reward and craving for high-calorie food

after surgery. Neuroimaging evidence suggests that improvements in eating behaviors were associated with brain functional alterations in circuits involved with homeostatic and hedonic processing. Our recent study showed that LSG significantly enhanced brain resting-state activity in the medio-dorsal thalamus (MDT) implicated in cognitive, learning and memory processing and habenula (Hb) implicated in negative reward processing. We also observed a novel link between the homeostatic and hedonic pathways in regulating eating behaviors and functional connectivities between MDT and Hb, as well as between MDT and posterior cingulate cortex/precuneus. In addition, brain imaging studies have shown that LSG promotes acute neuroplastic structural recovery including gray/white matter volumes and cortical morphometry in obese patients after surgery. However, whether LSG induces alterations in structural connectivity (SC) between these seed and hedonic processing regions, as well as their association with eating behaviors is unknown. We therefore employed diffusion tensor imaging (DTI) with probabilistic tractography to perform SC analysis between these regions testing for associations with eating behaviors.

Methods: Thirty patients with obesity who underwent LSG and 30 age- and sex-matched normal weight participants (NW) underwent whole-brain scan using 3T MRI. LSG group was tested before (PreLSG) and twelve-months (PostLSG12) after LSG. Preprocessing of DTI data was performed with the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). Bilateral ROIs, including hippocampus (HIPP), caudate (CAU), amygdala (AMY), medial-prefrontal cortex (MFC), hypothalamus (Hy), orbito-frontal cortices (OFC), ventral tegmental area (VTA), nucleus accumbens (NAc), anterior cingulate cortex (ACC), MDT and Hb, were extracted from the automated anatomical labeling (AAL) map or generated from the Harvard-Oxford cortical and subcortical structural atlas in standard space. Due to the small size of Hb and Hy, we combined right and left regions for subsequent analysis. Probabilistic tractography between these ROIs was conducted, and fiber tracts were visualized using FSLeyes (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLeyes). The values of the mean fractional anisotropy (FA) of the fiber tracts connecting each pair of ROIs were calculated. Statistical analyses were performed using IBM SPSS (Statis-tical Package for Social Sciences, Release 22.0, Chicago: SPSS, IL). In the LSG group, we assessed time effects (PreLSG, PostLSG12) on SC between ROIs using a paired t-test. In addition, we used two-sample t-tests to compare NW with PreLSG and PostLSG12.

Results: There were significant time effects on SC between MDT and several regions including bilateral HIPP, right CAU, left MFC, and Hy. Paired t-test showed significantly increased SC at PostLSG12, which on average was equivalent to that in NW at PostLSG12. SC of the right MDT-HIPP was negatively correlated with Yale Food Addiction Scale (YFAS) at PostLSG12 ($r = -0.53$, $p = 0.003$). Reward and craving for high-calorie food cues were negatively correlated with SC of the left MDT-HIPP ($r = -0.55$, $p = 0.002$; $r = -0.53$, $p = 0.003$), right MDT-CAU at PostLSG12 ($r = -0.58$, $p = 0.001$; $r = -0.54$, $p = 0.002$), and with SC of the left MDT-MFC at PreLSG ($r = -0.55$, $p = 0.002$; $r = -0.55$, $p = 0.001$). Disinhibition measured with the Three Factor Eating Questionnaire (TFEQ-disinhibition) was also negatively correlated with SC of the left MDT-MFC at PreLSG ($r = -0.60$, $p = 0.003$). SC of the right MDT-Hy was positively correlated with TFEQ-cognitive control at PreLSG ($r = 0.59$, $p = 0.003$). In addition, probabilistic tractography identified increased SC between the Hb and numerous regions including left lOFC, left mOFC, Hy, and bilateral MDT which were on average equivalent to that in NW at PostLSG12. SC of the Hb-left lOFC was negatively correlated with percentage excess body mass index loss (%EBMIL) at PreLSG ($r = -0.50$, $p = 0.005$). LSG-related increases in SC in the Hb-left lOFC also showed a negative correlation with reduction in BMI ($r = -0.56$, $p = 0.001$), and positive correlation with changes in %EBMIL at PostLSG12 ($r = 0.56$, $p = 0.001$). Reward and craving for high-calorie food cues were negatively correlated with SC of the Hb-left mOFC at PostLSG12 ($r = -0.52$, $p = 0.004$; $r = -0.60$, $p < 0.001$), SC of the Hb-Hy was negatively correlated with TFEQ-hunger at PostLSG12 ($r = -0.54$, $p = 0.008$). LSG-related increases in SC in the Hb-Hy were negatively correlated with reduction in depression ($r = -0.53$, $p = 0.003$) and external eating measured with Dutch Eating Behavior Questionnaire (DEBQ-external eating) at PostLSG12 ($r = -0.58$, $p = 0.004$). SC of Hb-bilateral MDT had a significant negative correlation with TFEQ-disinhibition at PreLSG ($r = -0.56$, $p = 0.006$).

Conclusions: These findings show that LSG increased SC between MDT/Hb and regions implicated in homeostatic/hedonic processing one year after surgery, highlighting the critical role of LSG-induced SC changes in maintaining long-term weight-loss and improving eating behaviors.

Keywords: Obesity, Diffusion Tensor Imaging (DTI), Bariatric Surgery, Structural Connectivity

Disclosure: Nothing to disclose.

P198. Neural Oscillation Biomarkers of Intervention Induced Change in Impulsive Decision-Making

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Background: Impulsive decision-making (IDM) is linked to poor outcomes in many psychiatric conditions and is a significant risk factor for suicide, violence, and risky substance use. Current clinical interventions to improve IDM have shown potential, but treatment effects are inconsistent across individuals and diagnoses. Across individuals, dysfunction can manifest within different brain regions that collectively, at a systems-level, lead to maladaptive levels of IDM. We theorize that this individual variation in the neural underpinnings of IDM precludes a one-size-fits-all treatment. We hypothesize that a systems-level activity measure (neural oscillations), recorded from brain regions known to regulate IDM, contains information that machine learning approaches could use to predict the effect of future interventions, and potentially identify new systems-level treatment targets. Therefore, we evaluated oscillation-based biomarkers using a rodent model with similar individual heterogeneity in IDM and response to pharmacologic and brain stimulation interventions as has been reported in patients. We used the well-established delay discounting task (DDT - choosing between small immediate rewards versus larger rewards associated with a delay cost) as a behavioral measure of IDM. We used machine learning to determine if: 1) oscillations can predict future intervention outcomes (predictive biomarker); and 2) changes in oscillations induced by interventions are predictive of intervention outcomes (monitoring biomarker).

Methods: Male and female Sprague-Dawley rats ($N = 10$, 12) were trained in the DDT and then implanted bilaterally with electrodes targeting the nucleus accumbens (NAc) shell and core as well as the infralimbic (IL) and orbitofrontal cortex (OFC). Local field potential (LFP) oscillations paired with video and operant behavioral events (MedPC) were recorded (Plexon) during DDT sessions. Once DDT performance was stable, interventions were tested (brain stimulation [7 sessions] targeted to the IL, NAc core or pharmacological manipulation [3 sessions] with 3 mg/kg of methylphenidate). Custom code written in Matlab was used to extract LFP features of power and coherence (connectivity between brain regions) across 6 established frequency bands (delta, theta, alpha, beta, low gamma, and high gamma). The 216 LFP features were then used as predictors in machine learning (lasso) models to classify intervention outcomes (increase, decrease [>2 SD change] or no change in DDT performance).

Models were either tested on randomly left out data (80% train: 20% test) or left out individuals (LOO) and model performance was determined using the area under the receiver operator characteristic curve (AUROC) with (± 95%) confidence intervals from 100 iterations of train:test data sets. If models built from all LFP features outperformed models estimating chance (AUROC = ~0.5), then an exhaustive evaluation of each LFP feature (simple regression) was carried out to determine the relative information attributable to each LFP feature.

Results: Intervention sessions with stimulation of the NAc core or methylphenidate produced either no significant change in DDT performance or a reduction in impulsivity (binomial outcomes). IL stimulation caused DDT performance changes in either direction or no change depending on the individual (multinomial outcomes). Models built from neural oscillations recorded during pre-intervention DDT sessions were able to classify (binomial) rats that decreased impulsivity from those with no change with NAc core stimulation (80:20 AUROC = 0.98 ± 0.01 and LOO AUROC = 0.7 ± 0.08) but models classifying methylphenidate outcomes were not able to outperform estimates of chance prediction likely related to a low sample size of non-responders ($N = 4$). Neural oscillations could classify the multinomial IL stimulation outcomes (80:20 AUROC = 0.86 ± 0.04 and LOO AUROC = 0.6 ± 0.04). Binomial models were then used to classify interventions sessions with and without significant reductions in impulsivity both within individuals and across all individuals (generalized) for each interventions type. NAc outcomes (generalized - AUROC = 0.93 ± 0.001 and individualized AUROC = 0.63-0.94), IL (generalized - AUROC = 0.97 ± 0.01 and individualized AUROC = 0.76-0.95), MPH (generalized - AUROC = 0.94 ± 0.004 and individualized AUROC = 0.91-0.95). Further, when data from all intervention types was pooled, changes in neural oscillations induced by interventions were able classify any intervention session outcome (AUROC = 0.68 ± 0.02). Thus, common intervention-induced changes in LFPs predicted reduced impulsivity on the DDT across intervention types.

Conclusions: Rodent frontal-striatal oscillations contain information that predicts the effect of a variety of translational interventions on impulsive decision-making (predictive biomarker). Further, intervention induced changes in oscillations predict changes in IDM (monitoring biomarker) and common feature changes across intervention types were identified that could lead to new treatment targets for IDM. These results support the development of neural oscillations as biomarkers in a trans-diagnostic population that could be used to align individuals with effective treatments for IDM, guide the optimization of those interventions through time and possibly identify novel systems-level treatment targets.

Keywords: Neural Oscillations, Neurostimulation, Machine Learning Classification, Delay Discounting, Stimulants

Disclosure: Nothing to disclose.

P199. Impulsivity-Related Behaviors are Associated With Novel Genetic Loci in a Population of Diversity Outbred Mice

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Background: Impulsivity and impulsive behaviors are heritable traits that are predictive of risk for the development of a substance use disorder. Past studies from our laboratories using the BXD and hybrid mouse diversity panels (HMDP) have shown that behavioral indicators of impulsivity measured in a reversal learning task are heritable and are genetically correlated with intravenous cocaine self-administration. Genome wide linkage studies in the BXD panel revealed a large quantitative trait locus (QTL) on chromosome 10, but the specific genes affecting this trait remain elusive. To achieve greater precision in our mapping efforts, we have turned to Collaborative Cross (CC) and Diversity Outbred (DO) mice.

Methods: A total of 332 adult DO mice (131 males, 201 females) were phenotyped using the same reversal learning test utilized in our BXD and HMDP studies (Laughlin et al. Biol Psychiatry. 2011 Jun 1;69(11):1109-16). Genotyping was conducted using the GigaMouse Universal Genotyping Array (GigaMUGA), a 143,446 SNP Illumina Infinium array. QTL were computed as previously described (Logan et al. Genes Brain Behav. 2013 Jun;12(4):424-37).

Results: One measure of impulsive responding isolates the relative difficulty mice have with reaching performance criteria under reversal conditions; this reversal learning difference score maps to a genome wide significant QTL on chromosome 7 (max LOD score = 8.73, $p < 0.05$) and a suggestive peak on Chr 14. The liberally defined 1.5 LOD drop-off region surrounding the peak Chr 7 SNP contains 24 protein-coding genes, 11 long non-coding RNAs and a small number of other predicted genes. One gene, Wdr73 – which encodes the WD Repeat Domain 73 protein – was selected as the lead candidate gene expressed from this QTL. In DO striatum, Wdr73 exhibits a strong cis-eQTL (LOD score of 17.5). Additionally, the reversal learning difference score is genetically correlated with expression of Wdr73 in the striatum of cocaine-naïve CC mice ($r = 0.41$, $p = 0.017$) and cocaine-sensitized CC mice ($r = 0.37$, $p = 0.033$). These data support the hypothesis that variants within the Wdr73 gene locus (there are 27 SNPs and 1 structural variant in the Wdr73 locus in the CC/DO populations) affect Wdr73 expression and the behavioral trait.

A measure of premature responding akin to that implemented in the 5-choice serial reaction time task yielded a suggestive QTL on chromosome 17 (max LOD score = 9.14, $p < 0.1$, peak = 65.68 Mbp). The 1.5 LOD drop interval of this QTL spans 64.84 to 66.34 Mbp, harboring 41 positional candidate genes, including 12 protein-coding genes (lncRNA:8, miRNA:1, pseudogene:15, snoRNA:1, snRNA:1, unclassified:3). Of the protein-coding genes expressed from the 1.5 LOD drop-off region, Rab31 is of interest. This gene exhibits a cis-eQTL (LOD score of 9.4), and its expression in cocaine-naïve and cocaine-sensitized CC mouse striatum is genetically correlated with the premature responding trait ($r = 0.29$, $p = 0.09$ and $r = 0.39$, $p = 0.03$, respectively).

Conclusions: These findings demonstrate the ability to map addiction-relevant traits in DO mice and to detect novel QTL not identified in other populations. In turn, they reveal new insights into the neurogenetic mechanisms that influence impulsivity.

Keywords: Impulsivity, Addiction Phenotypes, Genetic Variation

Disclosure: Nothing to disclose.

P200. Behavioral Approach/Inhibition Across Impulsive Aggression and Mood Latent Profiles of Youth in Community and Medical Center Outpatient Mental Health Clinics

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Background: Aggression is a common presenting problem in children's mental health agency and is associated with significant impairment and cost to children and their families, and to society 1,2 Yet, aggression is not well characterized in psychiatric diagnostic systems. Prior research indicates that impulsive aggression (IA) is distinct from other common childhood problems; analyses identified five principal components including IA, rule breaking, mania, depression, self-harm.3 Component scores served as indicators in a latent profile analysis, which

identified 8 distinct profiles.4 The primary objective of the current analyses was to examine behavioral approach and inhibition systems across these empirically defined profiles of impulsive aggression (IA), mood, and other behavioral symptoms in youth.

Methods: Data were derived from parent-reported measures among 634 youth (aged 5-18 years) in the ABACAB study. Parents and youth reported on youths' motivation to avoid negative outcomes (behavioral inhibition system/BIS) or move toward a goal (behavioral approach system/BAS, including Drive, Reward Responsiveness, and Fun Seeking subscales) on the BIS/BAS scale.5 Univariate ANOVAs examined associations between scores on the eight latent profiles and parent- and youth self-reported BIS/BAS scores. Similarly, correlations examined associations between the five previously derived component scores and BIS/BAS scores.

Results: Parent-reported BIS/BAS scores significantly differed across latent profiles, while youth-reported BIS/BAS did not. Specifically, a profile characterized by depression was associated with greater parent-reported BIS than profiles characterized by high levels of ADHD + IA, moderate mania + IA, and IA + self-harm (ps < .01). Further, youth with moderate mania + IA exhibited lower BIS than youth with mild symptoms ($p = .002$) or mixed bipolar (BP) symptoms + low self-harm ($p = .039$). The mild symptom profile was associated with lower BAS scores than ADHD + IA, moderate mania + IA, and mixed BP + IA + self-harm (ps < .05) profiles. Both ADHD + IA and moderate mania + IA had higher BAS than the depressed profile (ps < .05). Correlations identified positive associations between parent-reported BIS and depression and self-harm component scores, and a negative association with IA (ps < .05). BAS was positively associated with mania and IA and negatively associated with rule breaking (ps < .001).

Conclusions: IA (with or without mood features) was associated with less behavioral inhibition and greater approach than depression and mild presentations. These analyses provide additional support for IA as distinct from mood problems and may inform interventions targeting IA.

Keywords: Irritability/Aggression, RDoC, Behavioral Activation System, Behavioral Inhibition System

Disclosures: Signant Health: Consultant (Self)
American Psychological Association: Honoraria (Self)
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P201. Translating a Salience Network Node Within the Ventrolateral Prefrontal Cortex: A Cross-Modalities and Cross-Species Study

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Background: Salience detection is an essential attentional process for survival. It is responsible for identifying elements that stand out from neighbor events. Human neuroimaging studies report the existence of a salience network (SN) cortically anchored by the dorsal anterior cingulate cortex (dACC) and the anterior insular cortex (AIC). One open question is the involvement of the right ventrolateral prefrontal cortex (vlPFC) in this network. Some authors consider the vlPFC activation in imaging studies as a result of signal bleeding from the AIC. These studies combine the vlPFC and AIC into one SN node: the fronto-insular cortex (FIC). Other authors consider the vlPFC as independently activated during salience detection tasks. The goal of the present study is to address the controversy of whether the vlPFC is a separate node in the SN by applying an innovative cross-modalities and cross-species design. Our results demonstrate that a region within the caudal vlPFC should be considered as a separate SN node.

Methods: First, following injections of bidirectional tracers in the right vlPFC of macaque monkeys (area 47/12 = 4 sites, area 45 = 2 sites, area 44 = 1 site), we quantified the number of labeled cells in 22 regions of the frontal cortex and six of the insular cortex. The connectivity strength between each cortical area and the vlPFC sublocation was measured as the ratio between the number of cells in this area by the total number of labeled cells. To ensure that our results are different from chance, we performed one million permutations of random labeling of cells in each injection. We statistically compared the connectivity strength reported in the real labeling with the distribution of strengths from the random labels.

Second, we evaluated the consistency of our findings across modalities by using a seed-based resting-state functional connectivity (rsFC) analysis in macaques. We systematically placed seven seeds virtually at the same locations as the tracer injections in the vlPFC and created masks over the clusters of cells mapped in the dACC and AIC. The rsFC strength between each vlPFC seed and the voxels in each mask was computed using Pearson's correlation. To ensure that our results are different from chance, we performed one million permutations of voxels across the brain. After z-transforming our results, we statistically compared the real strength with the distribution of strengths from the permuted voxels.

Third, we investigated if our results are translatable to humans by using cross-species comparisons. We placed eleven seeds across the human vlPFC: six in area 47/12, three in area 45 and two in area 44. The rsFC computation and the permutation analysis followed the same pipeline as in the macaque data.

Results: The anatomic results showed that the injection site located in caudal area 47/12 stood apart from the rest of the vlPFC with respect to inputs from the two well-established SN nodes (AIC and dACC). Both AIC and dACC areas had connectivity strength to the caudal 47/12 higher than expected by chance ($p < 0.01$). Importantly, dACC projections to caudal 47/12 were twice as stronger than connections to any other vlPFC sublocations. Caudal 47/12 also showed dense axonal projections to subcortical SN nodes, including the dorsomedial thalamus, hypothalamus, sublenticular extended amygdala, and periaqueductal gray. Consistent with the anatomic data, the macaque imaging analysis showed the caudal 47/12 rsFC strength higher than the expected by chance ($p < 0.01$). This region presented the strongest rsFC with the dACC and AIC SN nodes compared to other vlPFC subregions. Area 44 also showed strong rsFC with the dACC and AIC, but still weaker than the caudal area 47/12. The partial overlapping between seeds in area 44 and caudal 47/12 is a possible explanation for such results. In humans, the caudal-most seed in area 47/12 also showed the strongest projections with both SN nodes in dACC and AIC.

Conclusions: The involvement of the vlPFC in the SN has not been clear due to methodological limitations from resting-state fMRI, such as echoplanar distortions. Here, we identified that the caudal area 47/12, is structurally and functionally linked to the two central nodes of the SN. These results were successfully translated from the macaque anatomy to human imaging data. Thus, this is the first study to formally identify a portion of the vlPFC that is a potential node of the SN. This is an important discovery for our understanding of the vlPFC involvement in attentional processes. Recent evidence shows the involvement of the vlPFC in other large-scale attention networks: the dorsal attention network (DAN - areas 44 and 45) and the ventral attention network (VAN - mid-caudal area 47/12). While the SN, VAN and DAN vlPFC nodes are located in different parts of the vlPFC, there is considerable intra-connectivity within its different subregions, despite their diverse functional roles. This places the vlPFC in a central position to

facilitate interactions between the three attention networks, which, together, are critical for cognitive and behavioral flexibility.

Keywords: Salience Network, vlPFC, Neuroanatomy, Human Neuroimaging, Nonhuman Primates

Disclosure: Nothing to disclose.

P202. Associations Between Aggression - Impulsive and Reactive Type (AIR) and Impulsivity, Callous/Unemotional, and Narcissistic Symptoms

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Background: The primary aim is to describe the associations between parent-reported symptoms of aggression with impulsivity and reactivity (AIR) and facets of antisocial behavior. The secondary aim is to examine relationships between antisocial behavior facets and empirically identified profiles of psychopathology marked by high AIR.

Methods: Parents of youth from the ABACAB sample ($N = 636$) completed questionnaires including the Antisocial Process Screening Device (APSD)1 and the measures needed to score the five indicators used previously to define profiles of psychopathology (AIR, depression, mania, self-harm, rule-breaking)2. The APSD has three subscales: Impulsivity, Narcissism, and Callous-Unemotional. Bivariate correlations explored links between these ASPD scales and AIR factor score. Benjamini-Hochberg corrections adjusted for multiple comparisons and Steiger tests examined significant differences in correlations. Profile-centered analyses used ANOVA to explore mean differences in APSD scores across psychopathology profiles marked by different levels of AIR.

Results: AIR was most strongly related to Impulsivity out of the three APSD scales (rAIR.Imp = .54, $p < .0001$), significantly more than it was with Callous-Unemotional (rAIR.CU¬ = .38, $p < .0001$; pdifference < .0001). Surprisingly, AIR and Impulsivity were not significantly more correlated than AIR and Narcissism (rAIR.Narc = .50, $p < .0001$; pdifference = .2). Analyses of mean APSD scores across empirical profiles of psychopathology also showed significant differences that survived post-hoc correction.

Conclusions: AIR symptoms are associated with symptoms of impulsivity and narcissistic traits, significantly more than callous/unemotional traits. This is consistent with AIR being characterized by impulsive, rather than premeditated, aggressive behavior. Further work should explore the connection between narcissism and AIR.

Keywords: Irritability/Aggression, Callous/Unemotional, Narcissistic Traits

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

P203. Childhood Adversity and Resiliency Mediate Motor Inhibition and Attentional Control

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Background: Childhood adversity represents a prevalent public health problem and a major risk factor for the development of drug use disorders and other health risk behaviors. However, childhood adversity is not deterministic, as marked individual differences exist in neurodevelopmental outcomes including resilience, or the adaptive ability to avoid trauma-related psychopathology. While early life stress is associated with risk of poorer inhibitory control (frequently measured with the Stop Signal motor task), the extent to which early life stress diminishes attentional control (as measured by the Stroop task using cognitive and emotional distractors) is less clear. Likewise, it is unknown if these influences of childhood adversity on inhibitory and/or attentional control persist among resilient individuals.

Methods: We conducted an fMRI neuroimaging study to evaluate if resilience mediated the relationship between childhood adversity and inhibitory and/or attentional control. We recruited 40 adult women ages 18-40 [mean(sd) = 27(6.2)] with or without self-reported history of childhood adversity but no current or lifetime history of drug abuse or dependence (assessed via SCID-IV). Participants completed questionnaires including the Childhood Trauma Questionnaire (CTQ) and Connor-Davidson Resilience Scale (CD-RISC). Participants also underwent a MRI session including the Stop-Signal task (225 Go trials and 75 Stop trials; 17 minute duration) and Counting Stroop task (360 trials with 40% neutral, 20% number congruent, 20% number incongruent, and 20% negatively valent words; 16 minute duration). Stop-signal reaction times (SSRT) and post-error slowing (PES) were calculated for the SST as previously described. Linear mixed effect (LME) regression estimated Stroop RT differences between Incongruent vs. Congruent trials (cognitive conflict) and Emotional vs. Neutral words (emotional conflict). LME also assessed the influence of CTQ and CD-RISC upon SST and Stroop behaviors.

Results: For SST, SSRT and percent PES both significantly differed from zero (two-tailed one-sample t-test, $p < 0.001$). For Stroop, Incongruent trials had slower RT than Congruent trials (two-tailed paired t-test, $p < 0.001$). Although emotional and neutral word RTs did not significantly differ; individuals' SSRT correlated with emotional Stroop conflict (emotional vs. neutral; $p < 0.027$) and not cognitive conflict (incongruent vs. congruent). CTQ and CD-RISC had a significant interaction effect when predicting SSRT (two-tailed t-test, $p = 0.03$). Among individuals with low resilience, higher CTQ predicted higher SSRT; but among resilient individuals, CTQ had no relationship with SSRT. CTQ and CD-RISC did not individually or collectively predict either cognitive nor emotional Stroop conflict.

Conclusions: Our primary finding is that resilience mediates the detrimental influence of childhood adversity on motor impulsivity. Future work will evaluate group differences in functional networks subserving these behaviors (i.e., frontocingulate networks) as putative adaptive neural mechanisms for conferring a resilient phenotype.

Keywords: Impulsivity, Counting Stroop Functional MRI (fMRI), Stop-Signal, Attentional Bias

Disclosure: Nothing to disclose.

P204. The Clinical Course of Antisocial Behaviors in Three Racial Groups

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Background: The criteria for DSM-IV and DSM-5 Antisocial Personality Disorder (ASPD) includes behaviors such as crimes that are grounds for arrest, repeatedly engaging in fights or assaults, lying and use of aliases, failure to sustain work, disregard for the safety of oneself and others, and mistreatment of others. It occurs in 2-4% of men and .5-1% of women in the U.S. ASPD as defined by DSM IV and 5, requires a history of childhood conduct disorder (CD), and if the behavioral problems persist into adulthood the diagnosis is then changed to ASPD. While not part

of the DSM, some clinicians label adults who meet adult criteria for ASPD but have no history of childhood CD as adult antisocial behavioral syndrome (AABS). Recent large-scale epidemiological studies suggest that AABS may be 4-5 times more common than ASPD. The present study aimed to determine if the clinical course and symptom profile of CD/ ASPD and AABS differ on sex, clinical subtype, and racial background. This is important because if the clinical course differs by race/sex or clinical label, then knowing those differences and may help to guide diagnosis and treatment strategies. However, if some symptoms are more likely to be diagnosed in some racial groups because of cultural "bias", then "labeling" individuals with a diagnosis of disease may over-estimate disease prevalence and lead to stigmatization of individuals, racial groups, and communities.

Methods: Using questions from a validated semi-structured interview, the Semi-Structured Assessment for the collaboration on the Genetics of Alcoholism (SSAGA), data were gathered from American Indians (AI), Euro-Americans (EA), and African Americans (AA) ($n = 7171$) who self-reported race and antisocial symptoms.

Results: Within this population 1148 (16%) individuals met ASPD criteria, 1932 (27%) met adult ASPD but not CD (e.g.AABS), 212 (3%) had CD only. Subsequent analyses focused on the clinical course of ASPD and AASB ($n = 3080$), as defined by the occurrence and age-related sequence of CD/ adult antisocial symptoms. Data showed that the first symptoms to appear were temper tantrums (age 7) with the symptoms of bullying, defiance, fire setting, and cruelty to animals, occurring in the 10-11 age range, and fights, school expulsion, running away from home and school, telling lies and stealing occurring in the 11-15 age range. Between age 15 and 20 multiple aggressive acts such as fighting, stealing, robbery, use of force, injuring people, and using a weapon occurred. From age 20-30 yrs. evidence of role failure in participants as documented by them endorsing: forging checks, failed financial responsibilities, homelessness, failed family responsibilities, as well as arrests, convicted felonies and time spent in jail. The clinical course of the 21 antisocial behaviors, with ages of onset, was determined comparing the mean age of each symptom using Spearman's rho and comparing the results based on race, diagnostic label, and sex. The clinical course was found to be highly significantly similar between the three races, the two sexes and the two diagnostic labels (rho = 0.925-0.978, $p < 0.001$). However individual symptom counts were significantly different across the groups when they were compared using logistic regression, covaried for significant demographic variables. Women reported fewer symptoms, were less likely to report fights, school expulsions, arrests or jail time, but more likely than males to run away from home. Those with ASPD had more symptoms overall than those with AABS including being less likely to experience remorse. African Americans, American Indians and those with ASPD were more likely to be expelled from school and arrested.

Conclusions: In these select populations, the order and sequence of antisocial behaviors did not differ by race, diagnostic label, or sex, however individual symptom endorsement did, with men (vs. women), those with ASPD (vs. AABS), AI and AA (vs. EA) reporting more expulsions from school and arrests. Previous research has shown that African American students are more likely to be referred for school-based disciplinary action and were more likely to be punished for the same offence, and more likely to be suspended or expelled than whites. While fewer studies have evaluated American Indians, in one large dataset, the findings indicated that disparities in discipline referrals and in "violation -to-action" were higher in American Indians and on par with those seen in African Americans as compared to EuroAmericans. These differences/disparities in school discipline suggest racial bias and are especially concerning as they can also associated with negative long-term outcomes such as involvement in the criminal justice system. In the present study men (vs.women), those with an ASPD diagnosis (vs. AABS) and AA and AI (vs. EA) were also more likely to have been expelled from school and arrested, supporting the construct that early school expulsions may increase risk for involvement in the criminal justice system especially for boys and AA and AI. Taken together these studies suggest that the diagnostic label of AABS should be considered in the DSM, however, sex and racial/demographic factors that may influence symptomatology and potentially be susceptible to bias, and should be a consideration when assigning diagnostic labels (supported by U10AA008401, AA027316).

Keywords: Antisocial Personality Disorder, Conduct Disorder, Adult Antisocial Behavioral Syndrome

Disclosure: Nothing to disclose.

P205. Effects of Fibroblast Growth Factor Two (FGF2) and Antagonist of FGF2 Receptor One (FGF2R1) on the Excitability of Dopamine Neurons in Rats

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Background: It was previously reported that the recombinant FGF2 increases (Even-Chen et al J Neurosci 37:8742, 2017), whereas an antagonist of FGFR1 (PD173074) decreases alcohol consumption in rodents (Even-Chen et al J Neurosci 39:7947, 2019). It can be therefore hypothesized that the FGF2-FGFR1 complex is involved in alcohol use disorder, via a mechanism involving modulation of excitability of dopamine-secreting neurons in the lateral ventral tegmental area (VTA) and medial substantia nigra (SN). This study aimed to test this hypothesis, using in vivo electrophysiology.

Methods: Adult male Wistar rats were used in experiments. In first experiment, rats were randomly divided into two groups. The first group received subcutaneous (s.c.) injection of FGF2 (80 μg/kg); the second group received vehicle. One hour after FGF2 or vehicle injecting, rats were anesthetized with chloral hydrate (0.4 g/kg, intraperitoneally: i.p.) and fixed in a stereotaxic frame. The electrode was lowered through the VTA and SN, nine times through each structure. Dopamine neurons were identified, using the privily described criteria (Csatlosova et al Eur Neuropsychopharmacol 43:82, 2021), and their activity was recorded. In a second experiment, the rats were divided into two groups again, and received no pre-treatment. In the first group, the electrode was inserted to the VTA, in the second-to the LC. After a spontaneously active dopamine neuron was recognized//identified? and its basal activity recorded, PD173074 was intravenously (i.v.) injected (via catheter placed in the femoral vein), in cumulative doses of 6,9,12 and 15 mg/kg.

Results: Rats pre-treated with the FGF2 had significantly higher excitability of dopamine neurons in the VTA (5.98 ± 0.54 Hz, $p = 0.03$, data from 78 neurons from 6 rats, two-tailed Student's t-test) and SN (4.94 ± 0.46 Hz, $p = 0.04$, data from 71 neurons from 5 rats, two-tailed Student's t-test) than vehicle-treated controls (VTA: 3.95 ± 0.45 Hz, data from 49 neurons from 5 rats; SN: 3.46 ± 0.43 Hz, data from 37 neurons from 5 rats). PD173074 dose-dependently inhibited the firing activity of dopamine neurons of the VTA ($F[4,21] = 6.76$, $p = 0.004$, analysis of variance for repeated measured: RM ANOVA; data from 5 neurons from 5 animals) and SN ($F[4,27] = 5.88$, $p = 0.003$, RM ANOVA; data from 6 neurons from 5 animals). Bonferroni post-hoc test conformed a significant difference between basal firing activity of dopamine neurons and firing activity of dopamine neurons the administration of 15 mg/kg of PD173074 (VTA: 5 ± 4 % of baseline, $p = 0.002$; SN: 28 ± 9 % of baseline, $p = 0.005$).

Conclusions: FGF2 has a stimulatory effect on dopamine neuronal firing. Since PD173074 has an opposite effect on the

excitability of dopamine neurons, it is likely that the stimulatory effect of FGF2 is mediated via FGFR1. It is therefore possible that increased alcohol drinking observed by FGF2-FGFR1activation is mediated by their effect on dopamine transmission. Therefore, this pathway might be targeted for the future drugs designated to treat addiction. This study was supported by the Slovak Research and Development Agency (grant APVV-20-0202), Israel Science Foundation (grant ISF 508/20), and German Science Foundation (grant DFG 857/29-1).

Keywords: Alcohol and Substance Use Disorders, Dopamine, Electrophysiology

Disclosure: Nothing to disclose.

P206. The Role of Family Dynamics in the Outcomes of Court-Involved Youth

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Background: The United States juvenile court system provided dispositions to approximately 700,000 youths under the age of 18 in 2019. Within this population, there is an over-representation of racial and ethnic minorities and children from families with limited economic resources. Overall, there has been a trend towards utilizing interventions that divert court-involved youth to mental health treatment, rather than incarceration, in order to prevent recidivism. Previous research has demonstrated that family functioning, parental mental health, and parenting practices, such as parental monitoring, can have a a significant effect on youth behavior. However, the specific impact of these family dynamics on recidivism at baseline has yet to be examined. Therefore, our objective was to explore the impact of family functioning and parental monitoring on the frequency and severity of delinquent acts in court-involved youth at the start of their court-mandated mental health treatment. We hypothesized that these family dynamics would significantly predict baseline youth delinquent behaviors.

Methods: We provided surveys to 163 adolescent-parent dyads recruited from 2 eastern U.S. cities during their court-mandated mental health treatment. Youth completed the Symptom Checklist-90-Revised/Global Severity Index (GSI), National Youth Survey of Self-Reported Delinquency (NYS), Customary Drinking and Drug Use Record (CDDR), Parental Monitoring Questionnaire (PMQ), and Family Assessment Device (FAD). Using the NYS responses, youth were divided into three delinquency severity categories (serious, moderate, and minor) and the frequency of delinquent acts was calculated. Youth were between the ages of 11 and 17 ($X = 15.19$) and had an open petition with the partnering Family Court at time of referral. Data was analyzed using bivariate comparisons and then with stepwise linear regression and multiple logistic regression.

Results: The sample was mostly male (58.3%) and 37.4% self-identified as ethnic and racial minorities. Approximately one-third of participants were placed into each delinquency category (36.2% serious, 31.3% moderate, and 32.5% minor). Participants also endorsed recent use of cannabis (38.7%) and alcohol (32.5%). Analyses using t tests showed that females reported worse psychiatric symptoms ($p < .001$) and family functioning ($p = .015$). ANOVAs demonstrated that delinquency severity was associated with age ($p = .038$), psychiatric symptoms ($p = .013$), family functioning ($p = .026$), parental monitoring ($p < .001$), cannabis use ($p = .014$), and delinquency frequency ($p < .001$). Multiple logistic regression indicated that psychiatric symptoms ($p = .041$), parental monitoring ($p = .003$), and cannabis use ($p = .008$) predicted delinquency severity. Delinquency frequency was correlated with age ($p = .05$). psychiatric symptoms ($p = .01$), family functioning ($p = .01$), and parental monitoring ($p = .01$). Linear regression showed that psychiatric symptoms ($p < .001$), parental monitoring ($p < .001$), and cannabis use ($p = .003$) significantly predicted delinquency frequency. Family functioning was not a significant predictor in either regression ($p = .680$, $p = .907$, respectively).

Conclusions: This study demonstrates that psychiatric symptoms and substance use alone do not predict youth delinquent behaviors and that parental practices at baseline play a significant role. Contrary to our original hypothesis, parental monitoring was the only significant family-related variable that predicted youth delinquency at baseline. Therefore, clinical interventions are needed that specifically target parental monitoring in addition to mental health symptoms and substance use. The next steps for this research include examining the role of these family dynamics on delinquency at the end of mental health treatment. In addition, through future research we plan to improve our understanding of the biopsychosocial barriers faced by these youth and their families and develop relevant and scalable interventions to target these risk factors.

Keywords: Adolescence, Court-Involved Youth, Health Disparities, Parent - Child Dyads, Clinical Interventions

Disclosure: Nothing to disclose.

P207. Dopamine D2 Receptors in Nucleus Accumbens Cholinergic Interneurons Increase the Cholinergic Pause and Impair Inhibitory Learning

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Background: Cholinergic interneurons (CINs) of the nucleus accumbens (NAc) have emerged as key regulators of striatal function by modulating striatal plasticity and regulating local dopamine (DA) release. While CINs express DA D2 receptors (D2Rs), little is known regarding the consequences of DA signaling in modulating CIN function and mediating reward-related behaviors. In response to presentation of reward-related stimuli, CINs exhibit transient changes in firing patterns, including a DA-dependent "pause" in firing which is thought to be important for associative learning. Ex vivo studies have also implicated D2Rs as mediators of the DA-dependent CIN pause. Yet, the specific role of D2Rs in shaping the pause response in NAc CINs and the roles of the native pause in behavior remain unclear. To this end, we used a combination of slice electrophysiology, in vivo fiber photometry and behavioral analysis in mice.

Methods: To determine the role of CIN D2Rs in CIN function, we first examined whether virus-mediated overexpression of D2R alters CIN firing in response to DA. We prepared acute NAc slices from ChAT-Cre x DAT-Cre mice expressing either D2Rs or EGFP in NAc CINs and channelrhodospin-2 in midbrain DA neurons. Using cell-attached recordings, we measured CIN firing in response to 20-Hz optogenetic stimulation of DA terminals. Next, we sought to determine if CIN D2R upregulation would alter CIN function in vivo. We expressed a genetically encoded GPCR activation-based acetylcholine (ACh) sensor (GACh3.0) in NAc to measure ACh levels using fiber photometry during a continuous reinforcement (CRF) schedule. To determine the behavioral consequences of CIN D2R upregulation, mice were tested on several NAc and DA-dependent operant tasks. We used Pavlovian conditioning and Pavlovian-to-instrumental transfer (PIT) tasks to examine associative learning and the motivational influence of cues on reward-

seeking behavior. Furthermore, using a go/no-go task, we examined whether CIN D2R upregulation alters the ability to withhold a response when a no-go stimulus is presented. Finally, to determine whether CIN D2R upregulation alters go/no-go responding by altering NAc ACh dynamics, we used fiber photometry to measure GACh3.0 signals during go and no-go trials of this task. Mice of both sexes were used for all experiments.

Results: Following DA terminal stimulation, NAc CINs expressing EGFP showed a brief reduction in tonic firing. This "pause" in firing was significantly longer in D2R-overexpressing CINs (EGFP: 0.81 ± 0.096 s, $n = 24$; D2R: 2.3 ± 0.25 s, $n = 25$). Baseline firing and other intrinsic membrane properties were not altered. Blocking D2Rs with sulpiride abolished the pause in both conditions, indicating that D2Rs are necessary for the DA-induced pause in NAc CINs. In vivo, following lever presentation in the CRF task, we observed a pause-like decrease in NAc ACh levels. This "pause" developed over several training days but appeared earlier and was of significantly greater amplitude and duration following CIN D2R upregulation. We found that D2R upregulation did not alter performance on either Pavlovian conditioning or PIT tasks. However, in the go/no-go task, D2R upregulation significantly delayed learning to suppress responding under no-go conditions. GACh3.0 signals aligned to cue onset during the go and no-go trials revealed a triphasic response comprised of a brief increase, followed by a dip and a rebound, in ACh levels. D2R upregulation increased the amplitude of the initial peak and the amplitude and duration of the ACh dip in go trials. In no-go trials, D2R upregulation was associated with a blunted ACh rebound relative to control mice. Furthermore, we performed within-group comparisons of ACh3.0 signals in go and no-go trials. While control mice initially showed comparable ACh responses to either trial type, these responses diverged with training. In contrast, in D2R-overexpressing mice, the ACh responses to go and no-go cues remained comparable throughout training.

Conclusions: These findings indicate that D2R upregulation increases the magnitude of the cholinergic pause in response to phasic dopamine and in response to reward-associated cues. In addition, D2R upregulation delays learning to inhibit responding in a go/no-go task. In this task, cues that signal opposing actions evoke distinct phasic ACh responses. However, the contrast between these ACh signals is reduced by D2R upregulation, which may impair the ability to distinguish between both trial types. Together, these results suggest that DA signaling via D2Rs expressed in NAc CINs shapes inhibitory learning by modulating cue-related ACh signals.

Keywords: Cholinergic Interneuron, Nucleus Accumbens, Genetically Encoded Sensor, D2 Dopamine Receptor, GoNoGo

Disclosure: Nothing to disclose.

P208. Post-Error Adaptation of Attentional, but Not Impulsive, Behavior in Mice

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Background: Cognitive control is the ability to evaluate previous behaviors and adapt to similar situations and suppress impulsive responses. Recently, it was reported that mice showed post-error adaptation of attentional behavior in the 5-choice serial reaction time task (5CSRTT), a visual attention task. In the present study, we aim to replicate the previous finding at our institute and investigate effects of atomoxetine, a noradrenaline reuptake inhibitor, on post-error behavioral adaptation.

Methods: We used a touchscreen-based 5CSRTT, which requires mice to sustain and divide attention across five response windows during a 5 sec delay in anticipation of the random presentation of brief stimulus at one of the five locations, to assess attention performance, response speed, and response control in male C57BL/6J mice ($n = 35$ total). To evaluate effects of atomoxetine (0.3 or 1 mg/kg, i.p.) on 5CSRTT performance, we injected mice with it 30 min before the test.

Results: Accuracy rate was improved following incorrect trials ($p < 0.01$) compared with correct trials. Incorrect response rate was decreased after incorrect trials ($p < 0.01$ vs. correct trials) and omission ($p < 0.01$ vs. correct trials), and correct response rate was not changed, indicating the post-error improvement in accuracy is ascribed to the decrease in incorrect responses. Omission rate was increased after omission ($p < 0.01$ vs. correct trials), but not incorrect, trials, demonstrating a previous omission increased the probability of an omission on the current trial. Neither correct response latency nor premature response rate was affected after errors (incorrect response and omission). Our preliminary results indicated that atomoxetine decreased premature response rate with somewhat better suppression after correct ($p < 0.05$ vs. vehicle) and omission trials ($p < 0.05$ vs. vehicle).

Conclusions: Post-error behavioral adaptation was observed in the 5CSRTT. Our finding suggests that mice integrated outcome-related feedback during error and next trials and adapted their decision making accordingly. We found that atomoxetine suppressed impulsive behavior somewhat preferentially after correct and omission trials. Given that prefrontal cortex (PFC) subserves cognitive control, increase in extracellular noradrenaline and dopamine in the PFC may contribute to the pretrial outcome-related effects of atmoxetine on impulsive behavior.

Keywords: Cognitive Control, Attention, Impulsivity, Atomoxetine

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

P209. Single Doses of a Highly Selective Inhibitor of Phosphodiesterase 1 (Lenrispodun) in Healthy Volunteers: A Randomized Pharmaco-fMRI Clinical Trial

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Background: Lenrispodun is a potent and highly selective inhibitor of phosphodiesterase (PDE) type 1, which is thought to prolong intracellular second messenger signaling within cortical and subcortical dopaminergic brain regions. This is the first study of a PDE1 inhibitor in healthy volunteers using both behavioral and neuroimaging approaches to examine its effects on neural targets. A pharmacological-fMRI approach evaluated the neural effects of the acute administration of lenrispodun on cognitive and affective processing. The stop signal task was utilized as a probe of cognitive processing, with an emphasis placed on activity within the inferior frontal gyrus (IFG) during the exertion of inhibitory cognitive control. A fear conditioning task was selected as a probe of affective processing, with an emphasis placed on activity within the insular cortex during the extinction phase of the task. The primary objectives were to determine whether lenrispodun induces changes in BOLD-fMRI signals in the inferior frontal gyrus (IFG) during the stop signal task, and the dorsal anterior insula (dAI) during fear extinction.

Methods: Using a double-blind, placebo-controlled, within-subjects design, 26 healthy individuals (18 completers) received in random order a single oral dose of placebo, lenrispodun 1.0 milligram (mg) or lenrispodun 10.0 mg and completed several tasks in the scanner including the stop signal task and fear conditioning task. Pre-specified region-of-interest analyses for the IFG and dAI were computed using linear mixed models.

Results: Lenrispodun induced increases in IFG activity during the stop signal task ($n = 24$) at 1.0mg (Cohen's $d = .63$) but not 10.0 mg (Cohen's $d = .07$) versus saline. Lenrispodun did not induce changes in dAI activity during fear extinction ($n = 22$) at the 1.0 mg (Cohen's $d = -0.052$) or 10.0 mg (Cohen's $d = 0.242$) doses. Lenrispodun administration was well-tolerated. Lenrispodun and three metabolites were present in blood samples taken 45 and 210 minutes after administration (drug, time, and drug*time interaction, all p's < 0.001), and post-hoc tests confirmed a dose-dependent response at each timepoint after administration.

Conclusions: A low dose (1.0 mg) of lenrispodun increased BOLD fMRI signals in the IFG during the stop signal task consistent with improved neural inhibitory control. However, lenrispodun did not induce an attenuating effect on BOLD fMRI signals in the dAI during the extinction phase of a fear conditioning task. Collectively, these results support the hypothesis that PDE 1 inhibition affects neural inhibitory control. Future investigations should determine whether lenrispodun improves neural inhibitory control in target populations such as individuals with attention deficit hyperactivity disorder.

Keywords: Pharmacology, Neuropharmacology, pharmaco-BOLD, Cognitive Control, Fear Conditioning and Extinction

Disclosure: Nothing to disclose.

P210. Impulsive Aggression: Serotonergic Neural Pathways and Neural Targets of the Anti-Aggressive Effects of Fluoxetine

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Background: Impulsive aggression (IA) is an unplanned intense aggressive reaction to a psychosocial precipitant. Recurrent acts of impulsive aggression are often seen in borderline personality disorder (BPD), intermittent explosive disorder (IED) and posttraumatic stress disorder (PTSD). The serotonergic system has been implicated in IA, but its neural mechanisms have not been well characterized.

Methods: We will report on our findings from a PET study comparing the regional binding of the 5-HTT ligand, [11C]DASB, in a group of 18 subjects with IED, who have current impulsive aggression to 11 healthy controls. Following baseline PET scans, IED subjects received 12 weeks of treatment with fluoxetine.

Results: While there were no significant differences in regional [11C]DASB binding between groups, in the IED group, trait aggression was positively associated with [11C]DASB binding in the anterior cingulate (ACC) ($r = 0.64$, $p = .01$)and ventral striatum (VST) ($r = .68$, $p = .005$). Greater state aggression was associated with greater [11C]DASB binding in the ACC ($r = 0.724$, $p = .002$). Furthermore, greater [11C]DASB binding in the VST predicted a greater decrease in state aggression with fluoxetine treatment ($p = .0007$, uncorrected). .

Conclusions: Binding of the serotonin transporter ligand in the anterior cingulate cortex ACC) is associated with state aggression and binding in the ACC and ventral striatum is associated with trait aggression. Teh anti-aggressive effects of fluoxetine appear to be mediated by serotonergic activity in the ventral striatum.

Keywords: Aggression, Serotonin Transporter, PET Imaging

Disclosure: Nothing to disclose.

P211. Markers of Oxidative Stress, Cell-Free Mitochondrial DNA and F2-Isoprostanes, are Elevated With Ongoing Caregiving Stress, Perceived Stress, and With Depressive Symptoms

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Background: Oxidative stress is increased in psychiatric disorders and psychological stress. Two reliable markers of oxidative stress are cell-free mitochondrial DNA (mtDNA) and F2-isoprostanes. Previous studies of these markers in depression have been limited in sample size and lack longitudinal findings. Further, relations between F2-isoprostanes and psychological or chronic stress is unknown. This study aimed to examine the association of cell-free mtDNA and F2-isoprostanes with stress and depressive symptoms over time.

Methods: One-hundred and eighty-three community- and clinic-recruited women with chronic caregiving stress ($N = 92$) or low-stress controls ($N = 91$) were included in this longitudinal case-control study. High-stress maternal caregivers had at least one child diagnosed with autism spectrum disorder and reported a score of ≥13 on the Perceived Stress Scale (PSS), while low-stress maternal control subjects were characterized as caring for a neurologically typical child and reported a PSS score of ≤19 at baseline (in line with national norms). Exclusion criteria included current psychiatric conditions, major chronic diseases, and regular use of steroid prescription medications. Active major depressive disorder or antidepressant use at baseline was an additional exclusion criterion for control participants only. Participants reported depressive symptoms (Inventory of Depressive Symptomatology), perceived stress (PSS), and provided a fasting morning blood sample at baseline, 9, 18, and 24 months. Cell-free mtDNA and F2-isoprostane levels were measured from plasma. Plasma cell-free mtDNA was determined using quantitative real time polymerase chain reaction; F2-isoprostanes were measured by gas chromatography-mass spectrometry.

Results: The average age was 42 + /-5.1; 76% identified as White, 92.3% as non-Hispanic. In a repeated measure mixed regression model, there was a significant effect of caregiver group on cell-free mtDNA ($F(1,590) = 4.20$, $p = .041$) and F2-isoprostane levels ($F(1,441) = 5.70$, $p = .017$), with caregivers having significantly higher levels of oxidative stress. Perceived stress ($F(1,560) = 5.35$, $p = .021$) and depressive symptoms ($F(1,578) = 8.96$, $p = .003$) were significantly associated with cell-free mtDNA regardless of caregiving group. In subjects with low perceived stress, cell-free mtDNA was significantly higher in subjects that were depressed compared to those without depression ($p = .050$), whereas cell-free mtDNA levels did not stratify by depressive symptoms in subjects with high perceived stress.

Conclusions: These longitudinal data reveal that both stress and depression are associated with durable increases in oxidative stress. Understanding the mechanisms by which depression, stress, and oxidative stress are related may help elucidate new biomarkers and treatment targets for depressive disorders.

Keywords: Circulating Cell-Free Mitochondrial DNA, Prostaglandin, Oxidative Stress, Depression, Perceived Stress

Disclosure: Nothing to disclose.

P212. Neural Substrates Underlying Stress-Induced Changes in Female Infant-Directed Behavior

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Background: Decades of research have focused on the neurobiology of maternal behavior, revealing common mechanisms and

pathways involved in infant caregiving behavior across a variety of species. However, less is known about the circuits that drive anti-parental behavior. We have recently described a neural population that is critical for expression of infant-directed neglect and aggression in both male and female mice, the urocortin-3 expressing neurons of the perifornical area of hypothalamus.

This cell population has previously been implicated in the physiological response to stress and involvement in expression of anxiety-related behavior. Stress is a risk factor for development of Postpartum mental illnesses including Postpartum Depression, Postpartum Anxiety, and other disorders. In the United States, these disorders can affect up to 20% of mothers and 10% of fathers annually. Preclinical research has demonstrated that stress also reduced maternal behavior in animal models. However, few studies have linked neural substrates to stress-induced deficits in maternal behavior. We hypothesized that stress would negatively affect infant-directed behavior in females and this behavior disruption is dependent on perifornical area urocortin-3 neuron (PeFAUcn3) activity.

Methods: To inhibit the activity of perifornical area urocortin-3 neurons, we used Ucn3::Cre transgenic female mice and stereotaxically injected AAV1-eF1alpha-DIO-HM4Di-mCherry or as a control, AAV1-eF1alpha-FLEX-mCherry (Addgene, 200nL AP -0.6 ML ± 0.3 DV -4.2), bilaterally. Infant-directed behavior was assayed at least two weeks after recovery with an injection of saline or CNO (0.3 mg/kg) 2-3 hours prior to behavioral testing. Brain tissue was collected and post-hoc histology performed to ensure appropriate viral expression. For chronic restraint stress experiments (virgin female C57 or lactating female C57s), we restrained mice in a perforated 50mL conical tube for 1 hour a day for 14-20 days or daily handling and weighing for the control group. Thirty minutes after behavior, trunk blood and fresh frozen brain tissue was collected. Brains were sectioned on a cryostat and fluorescence in situ hybridization was performed to probe for corticotropin releasing factor, urocortin-3, and c-fos. ELISA was performed on serum separated from trunk blood to assess corticosterone levels.

Results: We found that chemogenetic inhibition of PeFAUcn3 neurons in virgin females improved pup retrieval latency ($n = 11$ Cre-; $n = 10$ Cre +). Next, we observed that chronically stressed virgin females displayed reduced maternal behavior and increased activation of PeFAUcn3 neurons ($n = 9$ nonstressed; $n = 9$ stressed). We attempted to replicate this reduction in infant-directed behavior in lactating females, but we did not observe a significant impact of chronic restraint stress on parenting behavior ($n = 13$ non-stressed; $n = 12$ stressed). Finally, we show that inhibition of PeFAUcn3 neurons in stressed virgin females reverses stress-induced deficits in infant-directed behavior ($n = 7$ mCherry non-stressed; $n = 7$ DREADD stressed).

Conclusions: We show evidence for a critical role of PeFAUcn3 neuron activity in the expression of infant-directed behavior in both stressed and non-stressed female mice.

Keywords: Hypothalamus, Chronic Stress, Social Behavior, Neuropeptides, Chemogenetics

Disclosure: Nothing to disclose.

P213. Effects of Chronic Stress on Effort-Based Decision Making and Corticostriatal Circuit Activity

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

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

Results: Mice show sensitivity to reward and effort conditions as measured by averaged baseline-subtracted anticipatory and consummatory lick responses ($N = 25$; $F_{3,496} = 83.17$; $p < 0.0001$; $F_{3,500} = 128.90$; $p < 0.0001$) with no significant sex difference in behavior. Neural activity data ($N = 6$; ~500 cells) indicate that corticostriatal neurons exhibit diverse responses to task features. High-dimensional coding mechanisms were used to examine encoding of reward-predictive cues, as evidenced by accurate cue decoding from population activity (>70%). Stress exposure biased behavioral responding towards low-effort reward-seeking in susceptible mice (Wilcoxon Signed-rank test; $p < 0.001$), while a subset showed no change in behavior. There was no significant correlation with social interaction behavior ($r = -0.305$, $p = 0.129$) or anxiety-like behavior ($r = -0.4574$, $p = 0.1001$). Furthermore, stress increased sensitivity to previous trial effort condition (Mixed effects model; $p = 0.03$) and reduced the accuracy of decoding rewarded trials from population activity, specifically during the anticipatory and consummatory periods.

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

Keywords: Medial Prefrontal Cortex, Stress, Reward

Disclosure: Nothing to disclose.

P214. Mobile Footprinting: Linking Individual Distinctiveness in Mobility Patterns to Mood, Sleep, and Brain Functional Connectivity

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Background: Mapping individual differences in behavior is fundamental to personalized neuroscience. However, advances in have lagged in large part due to the challenge of quantifying human behavior. While mobility patterns captured by smartphones have increasingly been linked to a range of psychiatric symptoms, existing research has not specifically examined whether individuals have person-specific mobility patterns and how they relate to other aspects of behavior such as mood and sleep.

Methods: We collected about 3,000 person-days of GPS geolocation and accelerometer data – approximately 3 months of mobility data per individual from a clinical sample of 41 adolescents and young adults (age 17-30 years, 28 female), enriched with affective instability. Next, we extracted summary mobility metrics and used the covariance of these features to identify individuals, akin to mobile footprints. Across the sample, we calculated the individual identification accuracy, which we call "footprint distinctiveness". As psychomotor changes are commonly linked to sleep and mood disorders, we tested associations of footprint distinctiveness and subjects' circadian patterns and mood instability. Finally, using nested cross-validation, we examined multivariate patterns of brain functional connectivity that could predict individual footprint distinctiveness.

Results: Here, we establish that statistical patterns of smartphone-based mobility features represent unique "footprints" that allow individual identification ($p < 0.001$). Critically, mobility footprints exhibit varying levels of person-specific distinctiveness and are associated with individual differences in affective instability, circadian irregularity, and brain functional connectivity.

Conclusions: Together, this work suggests that real-world mobility patterns may provide an individual-specific signature linking brain, behavior, and mood.

Keywords: Digital Phenotyping, GPS, Resting State Functional Connectivity, Individual Differences, Smartphone

Disclosure: Nothing to disclose.

P215. Impact of Active and Sham Bifrontal rTMS on Cholinergic System in Treatment-Resistant Depression and Connection to Treatment Response: A Preliminary Study

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Background: Short-latency afferent inhibition (SAI) is a neurophysiological protocol measuring cholinergic activity likely mediated by the GABAA receptor subtype bearing the α1-subunit. It integrates afferent information from a peripheral nerve and modulates motor cortical excitability by inhibiting motor responses. It is measured by combining peripheral electrical nerve stimulation followed by transcranial magnetic stimulation (TMS) of the contralateral primary motor cortex. The cholinergic system regulates several central nervous system functions, and dysfunction of the cholinergic system may contribute to the development of depression. This study evaluated how repetitive TMS (rTMS) impacts SAI in treatment-resistant major depression (TRD) and how SAI and treatment response are related.

Methods: Twenty-two patients with TRD (age: 20-55 years, 12 females, 19 right-handed) were randomized to receive either active or sham rTMS. Active rTMS included 10 patients (6 females, 3 with psychotic depression) and sham rTMS 12 patients (6 females, 2 with psychotic depression).

Altogether 30 treatment sessions were applied bifrontally: 10 Hz rTMS was targeted on the left dorsolateral prefrontal cortex (DLPFC) and 1 Hz rTMS on the right DLPFC. Before and after the treatment course, the patients participated in a SAI measurement which included three conditions: 1) baseline, i.e., TMS-evoked motor evoked potentials (MEPs) without preceding electrical stimulation, 2) combined electrical stimulation and TMS, the time interval between the stimulations was subject-specific somatosensory evoked potential N20 latency + 3ms and 3) combined electrical stimulation and TMS, the time interval between stimulations was N20 latency + 10ms (control condition, no SAI phenomenon expected based on previous literature on healthy subjects). Each SAI condition included 120 trials. To confirm the SAI phenomenon, conditions 2 and 3 were compared to condition 1 with a Wilcoxon Signed Ranks Test. In addition, SAI strength was assessed as a percentage decrease in MEP amplitude in conditions 2 and 3 from the baseline MEP. The severity of depression was evaluated with the Hamilton Rating Scale for Depression (HAMD) before and after the treatment course. Response to treatment was defined as a HAMD decrement of 50% or more from the baseline. The differences in SAI between treatment responders and non-responders within a treatment group were assessed with a Mann-Whitney U Test.

Results: In the active rTMS group, the SAI phenomenon appeared as previously described in healthy subjects, i.e., SAI significantly appeared before ($p = 0.013$) and after ($p = 0.005$) treatment only in condition 2. In the sham group, before the treatment, SAI appeared only in condition 2 ($p = 0.004$), whereas after treatment, SAI did not appear anymore in condition 2 ($p = 0.071$). However, instead of inhibition, condition 3 experienced a facilitatory phenomenon ($p = 0.015$).

In the active treatment group, there were 6 responders and 4 non-responders, whereas, in the sham group, there were 8 responders and 3 non-responders. In one individual in the sham group, the response could not be evaluated due to missing after treatment HAMD. In the active treatment group, the responders had a significantly larger average SAI strength before the treatment than the non-responders (condition 2: $p = 0.038$, SAI% (responder) = 74%, SAI% (non-responder) = 21%; condition 3: $p = 0.010$, SAI% (responder) = 22%, SAI% (non-responder) = -45%). In the sham group, SAI strength between responders and non-responders did not differ before or after the treatment.

Conclusions: These preliminary results imply that SAI measured before the treatment could potentially predict treatment responders and non-responders in the active rTMS group. Active rTMS does not, however, change SAI behavior, whereas sham rTMS does. The SAI changes associated with sham are not connected to treatment response, and the underlying cause remains unknown.

Keywords: Repetitive Transcranial Magnetic Stimulation (rTMS), Major Depression, Neurophysiology, Treatment-Response

Disclosure: Nothing to disclose.

P216. Double Dissociation Between the VTA Population Activity Underlying Acute Stress Induced Impairments in Wanting and Liking

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Background: Stressful experiences frequently precede depressive episodes, however, the mechanism by which stress leads to depression remains unknown. Disrupted reward processing, is a core symptom of depression that is present in most depressed patients. In

both humans and rodents, stress also disrupts reward processing. Reward processing can be divided into wanting and liking. We recently demonstrated that acute stress impairs reward anticipation via ventral tegmental area (VTA) GABA neurons projecting to the nucleus accumbens (NAc), but until now there has been little evidence of the effect of stress on reward consumption. Thus, it remains whether stress impacts these different aspects of reward processing via a shared neural mechanism. Here, we conducted experiments to disentangle the contributions of ventral tegmental area (VTA) dopamine (DA) and GABA neurons to stress-induced disruptions of reward anticipation vs consumption.

Methods: We trained male and 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. After reaching criterion, mice were either stressed (30 minutes of restraint) or unstressed (30 minutes in a familiar environment). To determine the effect of acute stress on the VTA-NAc circuit, we simultaneously recorded single unit and local field potential (LFP) activity in the VTA and LFP activity in the NAc of mice during restraint, familiar environment, and subsequent reward processing. We expressed opsins (channelrhodopsin and halorhodopsin) by injecting AAV vectors into the VTA of VGAT-cre and DAT-cre mice. We analyzed the data using custom MATLAB scripts.

Results: We found that stress reduced lick rates during reward consumption independent of its effects on reward anticipation ($N = 13$ mice, $p < 0.01$). Surprisingly, while we recently demonstrated that restraint-induced 4 Hz NAc LFP oscillation strength correlates with reward anticipation deficits, this oscillation did not correlate with the effect of restraint stress on reward consumption. In addition, while optogenetically stimulating NAc-projecting VTA GABA neurons impairs reward anticipation, it spares reward consumption ($N = 5$ mice, $p = 0.47$). Finally, we found that restraint impairs the firing of putative VTA DA neurons during reward consumption (nFamiliar = 80 neurons, nRestraint = 80 neurons, $p < 0.05$) but had no effect on putative VTA GABA neurons during reward consumption (nFamiliar =29 neurons, nRestraint = 22 neurons, $p > 0.5$).

Conclusions: Together, these data suggest that stress impairs reward consumption via altered VTA DA activity, while stress impairs reward anticipation via altered VTA GABA activity.

Keywords: optogenetics, reward neural circuitry, electrophysiology

Disclosure: genetika + : Advisory Board (Self)

P217. A Non-Linear Relation Between Levels of Adult Hippocampal Neurogenesis and Expression of the Immature Neuron Marker Doublecortin

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Background: Recent reports have questioned whether adult hippocampal neurogenesis (AHN) occurs in the adult human hippocampus and to what extent(1,2). However, most of these studies rely primarily on doublecortin (DCX) expression to quantify levels of neurogenesis, which as we just discovered can be problematic. Thus, we investigated whether DCX expression in the mouse dentate gyrus (DG) can be regulated independently from levels of AHN under various conditions including antidepressant treatment or inflammation.

Methods: AHN, including DCX expression, was first evaluated using a chronic antidepressant treatment (fluoxetine, 18 mg/kg/day) in a mouse model of depression based on elevation of glucocorticoids in sham or irradiated animals (CORT model, $n = 12/15$ per group). Because of the importance of beta-arrestin 2 (Barr 2) for the effects of antidepressants(3), we also studied the neurogenic consequences of its deletion (Barr 2 KO) in comparison to wild-type treated animals ($n = 3/5$ per group). Then to provide further evidences that DCX is regulated independently from AHN, a dorsal injection of a pro-inflammatory lipopolysaccharide (LPS, 1mg/ul) on one side of the hippocampus were applied in male C57BL/6JRj mice, 24 hours, 3 days or 7 days before sacrifice ($n = 12/15$ per group). Finally, in order to investigate mechanisms that may contribute to the regulation of expression of DCX using RT-PCR, we also analyzed the expression of a number of microRNA (miR, miR-128, miR-18a5, miR-22a3, miR-22a5, miR411-5p, miR-409-5p) that had been implicated in stress or the modulation of neurogenesis(4) in the mouse CORT model and in Barr 2 KO mice and their littermates.

For all experiments, unpaired t-test, one-way ANOVA with repeated measures or two-way ANOVAs were applied to the data as appropriate. Significant main effects and/or interactions were followed by Fisher's PLSD post-hoc analysis. Statistical significance was set at $p < 0.05$.

Results: After confirming our earlier report that the signaling molecule beta2-arrestin is required for the antidepressant-like effects of fluoxetine(3), we found that the effects of fluoxetine on proliferation of neural progenitors and on survival of adult-born granule cells are absent in the B2-Arr KO mice. To our surprise fluoxetine induced a dramatic upregulation of DCX in the B2-Arr KO mice, indicating that DCX expression can be increased even though AHN is not. We discovered two other conditions where DCX expression is regulated non linearly compared to levels of AHN: in the CORT model where DCX is upregulated and an inflammation model where DCX is down regulated. We also showed that fluoxetine in the CORT model -upregulated levels of DCX mRNA in the hippocampus is also associated with changes in miR expression (18a5, 22a3, 34a3, 128), suggesting that these mIRs may be responsible at least in part for the regulation of DCX that we observe in our models.

Conclusions: In summary, we have shown that DCX expression can be modulated non linearly compared to levels of AHN. Although the functional significance of this regulation remains unknown, we hope that our study will serve as a cautionary note for those interested in quantifying neurogenesis particularly in humans and will emphasize the need for multiple markers to be able to assess the various stages of the neurogenesis process.

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Keywords: adult hippocampal neurogenesis, mood disorders, Doublecortin, miRNA

Disclosure: Scientific Advisory: Board Member (Spouse)

P218. Increased Dynamic Functional Network Reconfiguration With Frequent Antidepressant Use

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Background: Depressive and anxiety disorders are highly prevalent and belong to the leading causes of disability

worldwide. A dynamic functional brain network that continuously reconfigures itself is essential to adequately perform cognitive tasks and respond to an often challenging environment. However, these critical brain dynamics might be reduced in individuals with depression or anxiety phenotypes. It is currently unknown how these subnetworks are dynamically reconfigured in patients with depression or anxiety, nor the effects of pharmacotherapeutic treatment strategies on network dynamics in these patients. This study aims to identify (1) how functional brain networks are dynamically reconfigured in patients with a diagnosis of depression and/or anxiety disorder, and (2) how antidepressant medication affects reconfiguration dynamics.

Methods: Resting-state functional MRI (rs-fMRI) data from a large sample of adults ($n = 207$) was acquired as part of the Netherlands Study of Depression and Anxiety (NESDA) cohort. A sliding-window approach was used to investigate how patterns of connectivity change over time, assessed for eight well-known brain networks. These networks were characterized in each time window based on the connectivity pattern within that window, and how each brain region switched between networks was described using promiscuity (number of networks switched to) and flexibility (number of switches between networks). These measures were compared using an ANCOVA corrected for age, gender, and education level.

Results: The sample contained four groups: participants with no disorder ($n = 57$), depression ($n = 49$), anxiety ($n = 42$), or both disorders ($n = 59$). In the entire sample, 23% frequently used antidepressants (mostly selective serotonin reuptake inhibitors; $n = 38$), 27% infrequently used psychotropic medication other than antidepressants and 51% did not use psychotropic medication at all. No significant differences in dynamic network reconfiguration parameters were found between the four groups. Antidepressant use was related to significantly increased promiscuity ($p < 0.001$) and flexibility ($p = 0.001$) across the whole brain. Controlling for symptom severity or the use of other psychotropic medication did not alter this relationship, suggesting that these effects were specific for antidepressants. Antidepressant-related increased promiscuity and flexibility was most pronounced for the visual ($p = 0.004$ for promiscuity and $p = 0.003$ for flexibility) and sensorimotor networks ($p = 0.002$ for promiscuity and $p = 0.003$ for flexibility).

Conclusions: Dynamic reconfiguration of brain networks was markedly increased in patients who used antidepressant medication. In particular, patients who used antidepressant medication reconfigure brain regions across networks more often (i.e. more flexibility) and the reconfigurations were are widely distributed across the brain (i.e. more promiscuity). These results could indicate that antidepressants induce a compensatory process to ensure integration of information across the brain in these patients, or might alternatively be reflecting adaptive processes related to antidepressant-related changes in serotonin receptor density.

Keywords: Resting-state fMRI, Major Depressive Disorder (MDD), Antidepressant

Disclosure: Nothing to disclose.

P220. Massively Parallel, in Vivo Profiling of MDD SNP Effects on Transcription Across Age, Sex, and Cell Type

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Background: The majority of linkage regions associated with neuropsychiatric disorders such as major depressive disorder (MDD) are noncoding sequences, hypothesized to alter transcriptional regulatory function, ultimately disrupting molecular systems of the nervous system. Like many psychiatric disorders, MDD shows a female bias in incidence. We sought to investigate whether there are sex-differentiated effects of MDD risk variants by directly assaying SNP effects on transcription in the living mouse brain. Given the role of development in establishing aspects of sex-differentiated features in the molecular brain, we profiled SNP effects between sexes in early postnatal and adult brain. Finally, we examined cell type-specific sex differences in SNP effects in excitatory (Vglut2-expressing) adult mouse hippocampus.

Methods: We constructed a massively parallel reporter assay (MPRA) library containing over 1,400 psychiatric disorder-associated SNPs (virtually all from MDD GWAS loci). Marginal LD partners ($R2 > 0.1$) of 36 GWAS tag SNPs were selected for inclusion based on overlap with ≥1 human brain eQTL, plus at least one additional epigenomic annotation (in vitro human neural Hi-C, postmortem brain chromatin marks, etc.). SNPs from loci near two genes we have previously identified as sex-differentially expressed in the locus coeruleus of mice were included regardless of annotation at a more stringent LD threshold ($R2 > 0.65$). ~125bp human genomic sequences, centered around each variant, were cloned into an AAV-compatible plasmid upstream of a reporter gene (dsRed) with a minimal promoter (Hsp68 derived), with paired 3'UTR barcodes enabling RNA-based readout. The library was packaged into AAV9 for intracranial delivery into mice. For postnatal MPRA, the AAV9-packaged library was delivered intracerebroventricularly in utero at E12.5. For adult mice, lox-stop-lox Rpl10a•GFP mice were crossed to Vglut2-Cre recombinase mice, enabling cell type-specific Translating Ribosome Affinity Purification (TRAP) for excitatory neuronal RNA capture from dissected hippocampi. Targeted sequencing of RNA and virus were used to calculate RNA/DNA ratios (expression). Minimum n for each age point and cell type (postnatal whole brain or adult hippocampus TRAP fractions and total RNA) was $n = 5$ for each sex.

Results: We detected dozens of variants with sex-differentiated effects across our analyses. Epigenomic data supported our cell type-specific approach: for example, rs9937936 and rs61778711--SNPs from separate loci with female-specific adult effects in hippocampal excitatory neurons--were found in Hi-C contacts in human dentate granule cells, but not astrocytes or or cortical neuron cultures. Another striking case included female-specific effects of rs1413892 in adult hippocampal excitatory neurons, consistent with identification of this SNP's LD region in an all-female MDD GWAS (CONVERGE).

Conclusions: Our results indicate that understanding the molecular effects of common genetic risk variants in psychiatric disease will require incorporation of sex, age, and cell type to ascertain variant effects. We identify novel sets of SNPs associated with major depression whose transcriptional impact occurs in a developmentally- or sex-influenced manner, which provide a groundwork for investigating the neurodevelopmental and sex-differential molecular pathways leading to MDD. Broadly, we demonstrate that MPRAs provide a novel platform for discerning not only the transcriptional effects of SNPs, but the myriad contextual factors in the living brain that may impact them, including sex, development, and cell type and can do so at a reasonable scale. Future studies could address the vexing issue of genotype-by-environment analysis by leveraging this same ability of MPRAs to further assess the roles of, for example, stress or sex-by-stress on transcriptional function of GWAS variants.

Keywords: Genetics of Depression, SNP, Brain Transcription, Functional Variants, Sex Difference

Disclosure: Nothing to disclose.

P221. Role of Histone 3.3 Lysine 27 Methylation and SUZ-12 in Conferring Enduring Stress Susceptibility

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Background: Depression is a prevalent psychiatric syndrome characterized by symptoms such as feelings of sadness, lack of interest or pleasure, and suicidal ideation. Many of these symptoms can last a lifetime and remain even after several courses of antidepressant treatments. Vulnerability to depression is associated with long-lasting changes in the transcriptional signatures of the nucleus accumbens (NAc), a brain region involved in reward and mood regulation, however, the molecular mechanisms underlying these persisting alterations are not fully understood.

Methods: Here, we characterized the enduring changes in histone modifications in the NAc of mice exposed to chronic social defeat stress (CSDS), a validated model for the study of depression-like behaviors that separate mouse populations into susceptible (SUS) and resilient (RES) based on a social interaction test (SIT), which is highly predictive of numerous other behavioral abnormalities. Tissue from the NAc of control (CON), SUS, and RES mice was collected either 24 hr or 4 weeks after the SIT ($n = 6$, per group and timepoint) and processed for histone profiling via mass spectrometry. In parallel, we mapped the genome-wide enrichment of the most changed histone modifications using Cleavage Under Targets and Release Using Nuclease (CUT and RUN) and assessed for chromatin accessibility in D1-type or D2-type medium spiny neurons (MSNs) of the NAc using Assay for Transposase-Accessible Chromatin using sequencing (ATAC-Seq).

Results: We found that CSDS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3—the predominant form of H3 present in adult brain neurons. Specifically, we observed an increase in the abundance of H3.3K27me1 (one-way ANOVA: $F(2,14) = 13.11$; $p < 0.001$; Tukey test: $p < 0.01$, SUS different from CON and RES) and a decrease in the abundance of H3.3K27me2 (one-way ANOVA: $F(2,14) = 12.33$; $p < 0.001$; Tukey test: $p < 0.01$, SUS different from CON, and $p < 0.05$, SUS different from RES) in the NAc of SUS mice. Our preliminary data indicate that H3.3K27me1 increase in SUS mice is selective for D1-type MSNs in comparison to CON ($t(6) = 2.061$; $p = 0.08$). Genomic distribution shows that H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, suggesting its crucial role in determining stress-induced transcriptional profiles. In contrast, H3.3K27me2 is weakly deposited across intergenic regions. We are using advanced bioinformatics to identify changes in chromatin accessibility and functional regulatory elements that coincide with H3.3K27me1 enrichment in D1-type MSNs. In addition, reciprocal changes in H3.3K27me1 and H3.3K27me2 are associated with increased expression of SUZ-12, a protein that controls H3K27 methylation in cultured cells by guiding the polycomb repressive complex 2 to precise genomic sites. We are currently manipulating SUZ-12 expression, and several mutant forms of the protein, in the NAc in a cell-type-specific manner to assess their impact on H3.3K27 methylation and on CSDS-induced persistent behavioral alterations.

Conclusions: Together, our results suggest that H3.3K27me1 and H3.3K27me2 are important "chromatin scars" that mediate enduring susceptibility to stress in the NAc. Understanding the molecular basis of these adaptations, including a possible role for SUZ-12, and identifying the genomic regions affected will shed new light on persisting forms of stress-induced pathology.

Keywords: Histone Methylation, Chronic Social Defeat, Nucleus Accumbens, Depression

Disclosure: Nothing to disclose.

P222. Improvement in Symptoms of Depression and Anxiety With Zuranolone Treatment in Patients With Major Depressive Disorder: HAM-A Analysis From the Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Waterfall Study

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Background: Zuranolone is an investigational, oral neuroactive steroid and γ-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for major depressive disorder (MDD) as part of the LANDSCAPE program, a broad and flexible clinical development program in patient populations with unmet needs. The WATERFALL Study (NCT04442490), a Phase 3, randomized, double-blind, placebo-controlled trial, evaluated the efficacy, safety, and tolerability of zuranolone 50 mg (ZRN50) compared with placebo in patients with MDD. This study met its primary endpoint; patients who received ZRN50 showed a statistically significant improvement in depressive symptoms compared with those who received placebo as assessed by the change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 (primary endpoint: least squares mean [LSM] CFB [SE] − 14.1 [0.51] vs −12.3 [0.50]; treatment difference −1.7 points; $p = 0.0141$). In addition to core depressive symptoms, symptoms of anxiety are also highly present in patients with MDD. In this analysis, the impact of ZRN50 on symptoms of anxiety in the WATERFALL study were assessed.

Methods: Zuranolone is an investigational, oral neuroactive steroid and γ-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for major depressive disorder (MDD) as part of the LANDSCAPE program, a broad and flexible clinical development program in patient populations with unmet needs. The WATERFALL Study (NCT04442490), a Phase 3, randomized, double-blind, placebo-controlled trial, evaluated the efficacy, safety, and tolerability of zuranolone 50 mg (ZRN50) compared with placebo in patients with MDD. This study met its primary endpoint; patients who received ZRN50 showed a statistically significant improvement in depressive symptoms compared with those who received placebo as assessed by the change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 (primary endpoint: least squares mean [LSM] CFB [SE] − 14.1 [0.51] vs −12.3 [0.50]; treatment difference −1.7 points; $p = 0.0141$). In addition to core depressive symptoms, symptoms of anxiety are also highly present in patients with MDD. In this analysis, the impact of ZRN50 on symptoms of anxiety in the WATERFALL study were assessed.

Results: Patients ($N = 543$) were randomized 1:1 to receive ZRN50 ($n = 271$) or placebo ($n = 272$). Overall, 242 (90.3%) patients in the ZRN50 group and 235 (87.4%) in the placebo group completed the 42-day study. Demographic and baseline characteristics were generally well balanced between treatment groups; mean (SD) age: 39.4 (12.3) vs 40.1 (12.6); female patients: 69.4% vs 61.7%; White patients: 63.1% vs 76.6%; patients on pre-existing antidepressant therapy: 29.5% vs 30.1%; and mean (SD) HAMD-17: 26.8 (2.6) vs 26.9 (2.7), for the ZRN50 vs placebo groups, respectively. The CFB in HAM-A showed numerical improvements in symptoms of anxiety compared with placebo at all measured timepoints, with statistical significance at Day 8 (LSM treatment

difference −1.7, $p = 0.0011$) and Day 15 (LSM treatment difference −1.4, $p = 0.0199$). The HAM-A results over time showed a trend similar to what was observed for HAMD-17. The ZRN50 group showed a numerical improvement in depressive symptoms compared with placebo assessed by the CFB in HAMD-17 at all measured timepoints through Day 42, with statistical significance at Days 3 (LSM treatment difference −3.0, $p < 0.0001$), 8 (LSM treatment difference −2.6, $p < 0.0001$), 12 (LSM treatment difference −2.5, $p = 0.0003$), and 15 (LSM treatment difference −1.7, $p = 0.0141$). The proportion of patients who reported a treatment emergent adverse event (TEAE) was 60.1% (161/268) in the ZRN50 group and 44.6% (120/269) in the placebo group. The majority (153/161 [95.0%] vs 117/120 [97.5%]) of the TEAEs were mild to moderate, with 8/268 (3.0%) and 3/269 (1.1%) patients having severe events in the ZRN50 and placebo groups, respectively. Two patients (0.7%), one in each treatment group, experienced SAEs during the on-treatment period. The most common TEAEs (≥5% in any treatment group) included somnolence (15.3% vs 3.0%), dizziness (13.8% vs 2.2%), headache (10.8% vs 7.8%), sedation (7.5% vs 0.4%), and diarrhea (3.0% vs 5.2%) in the ZRN50 and placebo groups, respectively. No AEs of loss of consciousness, weight gain, sexual dysfunction, or euphoria were reported in either treatment group.

Conclusions: Patients receiving ZRN50 demonstrated rapid improvements in depressive symptoms and anxiety, as early as the first post-baseline assessment (Day 3 for HAMD-17 and Day 8 for HAM-A), with numerical improvements maintained through the end of the study (Day 42). ZRN50 was generally well-tolerated by patients and had a safety profile consistent with previous clinical studies. Taken together with other available clinical data to date, improvements in both depressive symptoms and anxiety have been observed in patients treated with zuranolone across doses.

Keywords: Zuranolone, Major Depressive Disorder (MDD), Neuroactive Steroid, GABA, Anxiety

Disclosure: Sage Therapeutics, Inc.: Employee, Stock/Equity (Self)

P223. Improvement in Severity and Symptoms of Major Depressive Disorder With Zuranolone Assessed by MADRS: Results From the Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Waterfall Study

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Background: There is a significant unmet need for an alternative, innovative treatment of depression that offers a rapid yet durable response and a generally well-tolerated safety profile without the need for chronic treatment. Treatment responses to standard of care (oral daily) antidepressants, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants, remain suboptimal in many patients (e.g., extended time to response, low remission rates, residual symptoms, and acute and long-term adverse events [AEs]). Despite these limitations, they are prescribed to approximately 75% of patients with major depressive disorder (MDD). Zuranolone is an investigational oral neuroactive steroid and γ-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for MDD as part of the LANDSCAPE Program, a broad and flexible clinical development program in patient populations with unmet needs. WATERFALL (NCT04442490), a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of zuranolone 50 mg (ZRN50) compared with placebo in patients with MDD, met its primary endpoint with patients who received ZRN50 demonstrating statistically significant and clinically relevant improvement in depressive symptoms compared with placebo as assessed by change from baseline (CFB) in 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 (least squares mean [LSM] standard error [SE] of −14.1 [0.51]) compared with placebo (−12.3 [0.50]; treatment difference −1.7 points; $p = 0.0141$). The Montgomery-Åsberg Depression Rating Scale total score (MADRS) addresses core mood symptoms such as sadness, tension, lassitude, and pessimistic and suicidal thoughts. Here, we report results from WATERFALL as assessed using MADRS.

Methods: Adult patients aged 18 to 64 years with MDD and a HAMD-17 of ≥24 at screening and Day 1 (prior to dosing) were randomized 1:1 to receive ZRN50 or placebo once daily (Days 1 to 14) in the evening. Use of a stable dose, preexisting antidepressant was permitted. CFB in MADRS at each measured timepoint (Days 8, 15, 28, and 42) was assessed. Safety and tolerability were evaluated by AEs, serious adverse events (SAEs), CFB in clinical laboratory evaluations, vital signs, and electrocardiograms. Endpoints (excluding the primary endpoint) were not adjusted for multiplicity; *p*-values reported here are nominal.

Results: Patients ($N = 543$) were randomized 1:1 to receive ZRN50 ($n = 271$) or placebo ($n = 272$). Overall, 242 (90.3%) patients in the ZRN50 group and 235 (87.4%) in the placebo group completed the study. Demographic and baseline characteristics were generally well-balanced between the ZRN50 and placebo groups and comprised mean (SD) age, 39.4 (12.3) vs 40.1 (12.6); patients on pre-existing antidepressant therapy, 29.5% vs 30.1%; mean (SD) HAMD-17, 26.8 (2.6) vs 26.9 (2.7); and mean (SD) MADRS: 35.2 (4.8) vs 35.0 (4.7). Patients receiving ZRN50 showed improvement in depressive symptoms compared with placebo as assessed by CFB in MADRS (LSM [SE] ZRN50 vs placebo) at Day 8, −14.6 (0.69) vs −11.2 (0.68); Day 15, −17.5 (0.77) vs −15.1 (0.76); Day 28, −16.4 (0.80) vs −14.9 (0.80); and Day 42, −17.5 (0.83) vs −16.2 (0.82). The LSM treatment difference (ZRN50 vs placebo) in CFB in MADRS was measured on Day 8 (−3.4, $p = 0.0003$), Day 15 (−2.4, $p = 0.0238$), Day 28 (−1.5, $p = 0.1777$), and Day 42 (−1.3, $p = 0.2676$). The proportion of patients who reported treatment emergent adverse events (TEAEs) was 60.1% (161/268) and 44.6% (120/269) in the ZRN50 vs placebo groups, respectively. The majority of TEAEs (153/161 [95.0%] vs 117/120 [97.5%]) were mild to moderate in intensity, with 8/268 (3.0%) and 3/269 (1.1%) patients experiencing severe events in the ZRN50 and placebo groups, respectively. Two patients (0.7%), one in each treatment group, experienced SAEs during the on-treatment period. The most common TEAEs (≥5% in either group; ZRN50 vs placebo) were somnolence (15.3% vs 3.0%), dizziness (13.8% vs 2.2%), headache (10.8% vs 7.8%), sedation (7.5% vs 0.4%), and diarrhea (3.0% vs 5.2%). No AEs of loss of consciousness, weight gain, sexual dysfunction, or euphoria were reported in either group. Of patients who received treatment, 3.4% (9/268) receiving ZRN50 vs 1.5% (4/269) receiving placebo discontinued study drug due to TEAEs.

Conclusions: Patients receiving ZRN50 showed improvement in depressive symptoms compared with placebo as assessed by CFB in MADRS. Patients receiving ZRN50 showed rapid improvements in core mood symptoms of depression as early as Day 8 (first assessment on treatment), with benefits sustained through the follow-up period. ZRN50 was generally well-tolerated, with a safety profile that was consistent with those shown in previous clinical trials.

Keywords: Zuranolone, Major Depressive Disorder (MDD), Neuroactive Steroid, GABA, MADRS

Disclosure: Sage Therapeutics, Inc.: Employee, Stock/Equity (Self)

P224. Zuranolone in Major Depressive Disorder: Safety and Tolerability Results From the Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Waterfall Study

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Background: Treatment responses to standard of care (oral daily) antidepressants remain suboptimal in many patients with major depressive disorder (MDD; e.g., extended time to response; high rate of discontinuations due to adverse events [AEs]; residual symptoms; and acute and long-term AEs, including suicidal ideation, associated with chronic use). Zuranolone is an investigational, oral neuroactive steroid and γ-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for MDD as part of the LANDSCAPE program, a broad and flexible clinical development program in patient populations with unmet needs. The WATERFALL (NCT04442490) Phase 3, randomized, double-blind, placebo-controlled trial evaluated the efficacy, safety, and tolerability of zuranolone 50 mg (ZRN50) compared with placebo in patients with MDD. The study met its primary endpoint, with patients who received ZRN50 showing a statistically significant improvement in depressive symptoms compared with those who received placebo as assessed by the change from baseline in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 (least squares mean [LSM] difference −1.7 points; $p = 0.0141$). These findings are consistent with previous clinical studies, in which patients treated with ZRN across both MDD and postpartum depression have demonstrated similar improvement in depressive symptoms. As safety is also critical to advancing the standard of care for MDD patients and there exists a concern with current standard of care therapies, detailed safety information from the WATERALL study is presented here.

Methods: Adult patients (aged 18 to 64 years) with MDD and a HAMD-17 ≥ 24 at screening and Day 1 (prior to dosing; $N = 543$) were randomized 1:1 to receive ZRN50 or placebo once-daily in the evening for 2 weeks. Safety and tolerability were evaluated by AEs, clinical laboratory evaluations, vital signs, and electrocardiograms. Suicidality was monitored by the Columbia Suicide Severity Rating Scale (C-SSRS). The 20-item Physician Withdrawal Checklist (PWC-20) total score was used to monitor for the presence of potential withdrawal symptoms following discontinuation of ZRN50.

Results: Patients ($N = 543$) were randomized 1:1 to receive ZRN50 ($n = 271$) or placebo ($n = 272$). The Safety Set included all patients who received at least one dose of ZRN50 ($n = 268$) or placebo ($n = 269$). Overall, 242 (90.3%) patients in the ZRN50 group and 235 (87.4%) in the placebo group completed the 42-day study. Demographic and baseline characteristics were generally well balanced between ZRN50 and placebo groups, respectively; mean (SD) age: 39.4 (12.3) vs 40.1 (12.6); female patients: 69.4% vs 61.7%; White patients: 63.1% vs 76.6%; patients on pre-existing antidepressant therapy at baseline: 29.5% vs 30.1%; and mean (SD) HAMD-17: 26.8 (2.6) vs 26.9 (2.7). The proportion of patients who reported a treatment emergent adverse event (TEAE) was 60.1% (161/268) in the ZRN50 group and 44.6% (120/269) in the placebo group. The majority (153/161 [95.0%] vs 117/120 [97.5%]) of the TEAEs were mild to moderate, with 8/268 (3.0%) and 3/269 (1.1%) patients having severe events in the ZRN50 and placebo groups, respectively. The most common TEAEs (≥5% in either treatment group) included somnolence (15.3% vs 3.0%), dizziness (13.8% vs 2.2%), headache (10.8% vs 7.8%), sedation (7.5% vs 0.4%), and diarrhea (3.0% vs 5.2%) in the ZRN50 and placebo groups, respectively. No AEs of loss of consciousness, weight gain, sexual dysfunction, or euphoria were reported. Of patients who received treatment and discontinued study drug due to a TEAE(s), 3.4% (9/268) were in the ZRN50 group and 1.5% (4/269) were in the placebo group. Two patients (0.7%), one in each treatment group, experienced serious adverse events (SAEs) during the on-treatment period. The one patient in the ZRN50 group who experienced SAEs of psychotic disorder and slow speech had a complicated medical history and symptoms of multiple underlying concomitant psychiatric diseases and behavior. The one patient with an SAE in the placebo group had elevated liver function levels. The C-SSRS rating scale showed 0% worsening in suicidal ideation or behavior for either ZRN50 or placebo groups at Day 15. The PWC-20 total score (SD) at Day 15 was 7.3 (6.47) vs 8.0 (6.57) for ZRN50 and placebo, respectively. The mean change (SD) from Day 15 in PWC-20 was −1.2 (4.32) vs −1.2 (4.32) at Day 18 and −0.3 (4.57) vs −0.5 (4.36) at Day 21, indicating no evidence of withdrawal symptoms after discontinuation of zuranolone. There were no clinically meaningful differences in the safety profile, as measured by TEAEs, for ZRN50 monotherapy compared with those receiving ZRN50 in combination with pre-existing antidepressant therapy.

Conclusions: In this Phase 3 study that met its primary efficacy endpoint, ZRN50 was generally well-tolerated, with a safety profile consistent with previous clinical studies. Few patients (3.4%) treated with ZRN50 discontinued the study due to a TEAE. Importantly, there were no signs of weight gain, sexual dysfunction, or euphoria in the study, suggesting improvement of depressive symptoms can be achieved without some of the AEs commonly reported with standard-of-care monoaminergic antidepressants. No evidence of withdrawal symptoms or increased suicidal ideation/behavior were identified.

Keywords: Zuranolone, Major Depressive Disorder (MDD), Neuroactive Steroid, Safety, Tolerability

Disclosure: Sage Therapeutics, Inc.; Employee, Stock/Equity (Self)

P225. Psychedelic Drugs in the Post-Approval World: Important Components of Risk Evaluation and Mitigations Strategy (REMS) Programs to Protect Public Health While Ensuring Widespread Access

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Background: Under the Food and Drug Administration Amendments Act of 2007, the FDA can require the use of risk evaluation and mitigation strategies (REMS) over and above professional labeling, to ensure that a drug's benefits outweigh its risks. As of August 2021, there were 314 listings on clinicaltrials.gov for interventional trials administering psychedelic/hallucinogenic compounds. Psychedelic drugs (e.g., MDMA, psilocybin, LSD, DMT, mescaline) are in development for myriad indications, including treatment of cluster headache, pain, substance use disorders, PTSD, and many other debilitating diseases. This unique group of drugs has demonstrated significant efficacy in many of these indications; yet, there are challenges inherent to their widespread use, including the psychedelic experience (which often includes auditory and visual hallucination, extreme emotional volatility), long-lasting acute drug effects, and questions about the durability of effect. These potential harms may be measured using a REMS post-approval to ensure a positive benefit/risk ratio.

Methods: A survey of key stakeholders including psychedelic drug researchers and medications developers was conducted in the summer of 2021. The results will be presented in detail in the poster, including expert opinions on best practices and metrics to

assess the safety of psychedelic drugs after approval within the context of a REMS as well as the most effective structure of these programs (i.e., individual or shared REMS programs). Based on the results of the survey and experience of the authors in FDA regulation and REMS, the poster will present what appear to be potential strategies and elements to assure safe use, that will likely be considered for drug labeling and REMS programs should any of these medications be approved by FDA.

Results: Preliminary examination of survey results indicates that the need for one or more psychedelic drug REMS programs is universally accepted, but there was significant divergence in opinion regarding the necessary components of those programs. Given the differences in treatment paradigms (number of doses; extent of associated psychotherapy, etc.) between psychedelic drugs in development, most—but not all—stakeholders agreed that individual REMS programs were more appropriate than a single shared REMS for all psychedelic drugs. Patient registries were supported by few, while prescriber and provider education requirements were generally supported by all experts in this area. A key consideration raised by many experts was that the REMS must not be overly restrictive so that these compounds may be accessed by all based on medical need and desire and will contribute to reducing—not increasing—health care disparities. We will present the plausible benefits and unintended consequences of potential REMS and labeling elements from the perspective of patients, medical practice based on results of the survey, and the experience of the authors in pharmaceutical development, regulation, and risk management—including REMS.

Conclusions: Although the FDA has not yet commented on any aspects of potentially required REMS, such discussions between pharmaceutical developers and FDA occur during late stages of development and during NDA review. It is nevertheless a topic of major discussion and concern to developers of potential psychedelic-based medicines. The requirements of any potentially required REMS program will need to balance the protection of public health with the need to ensure equitable access to these therapies so that the REMS programs are not furthering the already stark disparities in access to health care. It is important for analyses such as will be presented in this poster to be considered in future research and clinical trials because to the greatest extent possible, REMS and risk management-related labeling should be evidence-based.

Keywords: Psychedelics, Risk Evaluation and Mitigation Strategy (REMS), Drug Development

Disclosure: Nothing to disclose.

P226. Investigating Genetic Effects on Clinical Heterogeneity in Major Depression: Symptoms, Subtypes, and Cardiometabolic Traits

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Background: A diagnosis of Major Depression (MD) requires that at least 5 of 9 DSM accessory symptoms be present, although patients vary with respect to the particular combination of symptoms endorsed. These criteria do not appear to reflect a single underlying genetic factor and have been explained by multiple factors representing psychomotor/cognitive, mood, and neurovegetative dimensions of MD. In particular, vegetative and reversed vegetative symptoms, reflecting depression-related changes in weight, appetite, and sleep, seem to implicate energy balance and metabolism. Despite numerous associations between MD and relevant, comorbid medical conditions (e.g., obesity), there has been limited research on shared liability that addresses heterogeneity in a genetically informed framework.

Methods: Using detailed clinical information and molecular genetic data from the CONVERGE study of MD in Han Chinese women ($n = 10{,}640$), we consider the evidence in support of widespread pleiotropy between MD and a range of anthropometric traits and metabolic outcomes, and compare the polygenic profiles of MD cases reporting contrasting vegetative and reversed vegetative symptoms. Subsequent genome-wide association studies (GWAS) employ a 'case-only' approach to identify associations between single nucleotide polymorphisms (SNPs) and symptom dimensions (e.g., weight gain versus weight loss).

Results: Adverse metabolic outcomes such as obesity, coronary artery disease, and type 2 diabetes showed negative genetic correlations with MD, as did C-reactive protein levels. For sleep-related traits, we observed a positive genetic correlation between MD and insomnia. Within case GWAS identified symptom specific signals for weight gain/loss at intergenic SNPs downstream of SGK1 on 6q23.2 (rs55817816; $P = 2.37 \times 10\text{-}9$). SGK1 is a compelling candidate given an established role in stress response via glucocorticoid signaling and its effects on hippocampal functioning. An additional association was seen between a SNP in SORCS2 and increased/decreased appetite (rs4689156; $P = 1.87 \times 10\text{-}8$) on 4p16.1, lending additional support for hippocampal function and stress response as the encoded protein has been shown to facilitate BDNF-dependent synaptic plasticity in the hippocampus. For reversed/vegetative symptoms, we observed associations over an extended region of MHC on 6p22.1 (rs73387810; $P = 6.1 \times 10\text{-}9$).

Conclusions: We demonstrate that both specific genetic factors and aggregate genetic effects influence clinical heterogeneity in MD. Both the functional relevance of associated loci and robustness of polygenic effects highlight the importance of studies focusing on genetic risk factors for subtypes of MD. Our analyses of symptom dimensions revealed evidence of pleiotropic effects on the clinical presentation of MD, and implicated widely-studied biological mechanisms related to metabolism and stress response.

Keywords: Genetics of Depression, Major Depression, GWAS, Cardiometabolic Risk, Clinical Heterogeneity

Disclosure: Nothing to disclose.

P227. Accelerated Aging and Treatment Response in Late-Life Depression

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Background: Late-life depression (LLD) is the second most common psychiatric disorder in older adults and associates to increased risk of morbidity, mortality, and dementia. Considerable heterogeneity exists in clinical phenotypes among patients with LLD, likely reflective of differing psychobiological pathways to illness. Studies using leukocyte telomere length have produced mixed results in demonstrating accelerated aging in LLD. Age and mortality estimates derived from patterns of DNA methylation have shown considerable promise in measuring cellular aging. We hypothesize that accelerated aging may underlie treatment response in LLD.

Methods: Data were derived from a clinical trial of Tai Chi or health education in ($N = 120$) adults ≥ 60 years with moderate-severe depression unresponsive to current antidepressant or psychotherapy (NCT02460666). Whole blood samples were drawn prior to treatment and applied to Infinium HumanMethylation450 BeadChip arrays (Illumina, Inc., San Diego, CA, USA). Raw signal

intensity values were corrected using noob pre-processing. The pre-processed data were submitted to the DNAmAge website https://dnamage.genetics.ucla.edu. Two age acceleration measures were explored: AgeAccelerationResidual (Horvath) and AgeAccelGrim (GrimAge). To determine if an association exists between these measures and treatment response in this population, a logistic regression model was fit between post-treatment remission status and each measure, adjusting for sex, race, and education level. For the current analysis, remission was defined as a post-treatment Montgomery-Asberg Depression Rating Scale (MADRS) of $<= 10$.

Results: The overall sample possessed a mean age of 68.9 (SD: 6.4) years and 73% were female. Remitters and non-remitters did not differ in distribution of age, sex, race, years of education, number of prior episodes of depression, chronicity of current episode, or age of first depression. Baseline MADRS was higher in non-remitters than remitters (18.7 vs. 16.1, $p = 0.001$). Mean raw AgeAccelerationResidual was -1.2 (SD: 4.9) in non-remitters and 1.09 (SD: 4) in remitters ($p = 0.008$). Median raw AgeAccelerationResidual was -0.79 (SD: 3.2) in non-remitters and 0.1 (SD: 3.4) in remitters ($p = 0.06$). When adjusted for sociodemographic and technical covariates, AgeAccelerationResidual (OR 1.1, $p = 0.007$) and AgeAccelGrim (OR 1.2, $p = 0.017$) associated with remission.

Conclusions: The increased risk for age-related medical illness and mortality in LLD suggests an etiology of accelerated aging driven by genetic, epigenetic, environmental, and psycho-social moderators. In the current population of treatment-resistant adults with LLD, aging acceleration and increased mortality risk were positively associated with remission in response to Tai Chi or health education intervention. Differences in aging acceleration may underlie the phenotypic heterogeneity observed in LLD and deserve more extensive exploration.

Keywords: Late-life Depression, DNA Methylation, Treatment-Response

Disclosure: Nothing to disclose.

P228. Intensive Longitudinal Data Capture in Bipolar Disorder: Variation in Mood Over Time May Tell a Different Story Than Mood Measured at Study Visits

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Background: The prevalence of digital tools such as smartphones and smartwatches have made intensive longitudinal data collection possible. With relative ease and low cost, these tools can capture both active (e.g., self-reports of recent symptoms) and passive (e.g., daily movement from a device-based accelerometer) data between visits. This type of data is expected to revolutionize precision medicine and research insights by allowing far greater nuance in our understanding of disease experience than has historically been feasible to capture. To date, however, these methods have not been widely adopted in either research or clinical settings. In this set of analyses, we sought to explore the feasibility and value of intensive longitudinal data capture. We did so by evaluating participant compliance and correlates of missing data and then by exploring the degree to which intensive longitudinal data on depression severity painted a different picture than baseline mood severity ratings.

Methods: Findings reported here are preliminary as they are from a subset of participants ($N = 23$) recruited into a larger longitudinal observational study of bipolar disorder. The parent study involved a clinical interview and comprehensive battery of neuropsychological testing and self-report measures at baseline and again at 9, 18 and 27 months. All participants recruited into the parent study after November 2020 were offered the opportunity to participate. Participation involved 9 months of intensive longitudinal data collection via bi-weekly, digital self-report measures of severity of depressive symptoms (the Patient Health Questionnaire-8, PHQ-8) and severity of manic symptoms (Altman Self-Rating Mania Scale, ASRM) as well as passive sensor monitoring of biobehavioral signals with a Fitbit. Data collection is still ongoing, but here we report on a set of regression analyses conducted to determine the degree to which variability in mood ratings over time (defined as the range of PHQ-8 scores during the intensive monitoring period) was associated with select clinical and functional characteristics. We also evaluated whether these relationships were different than those observed between mood severity ratings at the baseline study visit (Hamilton Depression Rating Scale; Ham-D) and the same clinical and functional characteristics. In selecting baseline variables to explore these relationships, we chose one example of a clinical characteristic strongly associated with worse long-term outcomes (the Childhood Trauma Questionnaire, CTQ), one index of illness course (number of prior hospitalizations), and one measure of psychosocial functioning (the WHO Disability Assessment Scale; WHO-DAS). Our intention was to better understand feasibility and value of active intensive longitudinal data.

Results: Out of 27 participants recruited into the parent study during this timeframe, 23 (85.2%) agreed to participate in the intensive longitudinal data capture portion of the study. Average compliance with intensive longitudinal data collection for self-reports was 90%. Linear regression analysis did not identify any relationship between compliance with active data collection and participant age ($\beta = 0.27$, $p = 0.22$), education ($\beta = 0.05$, $p = 0.84$) or baseline depression severity (Ham-D; $\beta = 0.26$, $p = 0.25$). Linear regression analysis did, however, identify a relationship between compliance and baseline severity of manic symptoms (Young Mania Rating Scale; $\beta = 0.76$, $p < .001$).

Depression ratings from the in-person visit were not related to our outcomes of interest, but our more granular metrics from intensive longitudinal data capture provided additional information. Specifically, greater observed variability in depression severity scores was significantly associated with higher scores on the emotional abuse subscale of the Childhood Trauma Questionnaire ($\beta = 0.48$, $p = 0.03$) and greater number of hospitalizations ($\beta = 0.51$, $p = 0.01$). Observed variability in depression severity scores was not significantly associated with the overall WHODAS score ($\beta = 0.18$, $p = 0.45$).

Conclusions: Findings suggest that it is feasible to capture intensive longitudinal digital data, but compliance over time may be related to baseline clinical severity. This means that careful approaches to evaluating missing data and further investigation into how to encourage engagement for patients with more severe symptoms may be required. Additionally, findings suggest that intensive longitudinal data offers unique information when it comes to understanding disease experience in patients with bipolar disorder. For symptoms of depression, observed variability in mood severity scores was significantly associated with several key clinical characteristics that were not significantly associated with baseline depression severity. This finding builds upon evidence suggesting that intensive longitudinal monitoring of mood symptoms may offer data that materially enhance our understanding of disease experience beyond what can be captured in less frequent clinic or study visits. Replication and future evaluation in larger samples and other clinical populations (e.g., patients with major depressive disorder) will be essential to building a stronger understanding of the clinical and investigative utility of digital collection of intensive longitudinal data.

Keywords: Digital Psychiatry, Bipolar Disorder, Remote Assessment Solution

Disclosure: Nothing to disclose.

P229. Psilocybin Produces Long-Lasting Antidepressant-Like Effects in Drosophila Melanogaster

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Background: While there is no compelling evidence that Drosophila have emotions and suffer from complex psychiatric disorders like humans, yet fundamental mechanisms of CNS function governing behaviors are conserved to a remarkable degree between fly and human. As such, Drosophila has been utilized as a sophisticated genetic experimental system to study fundamental molecular mechanisms underlying behaviors relevant to human behavior and psychiatric disease such as learning and memory, social interaction, and drug abuse. In rodent experimental systems, a measure of passive coping strategy traditionally used to assess depressive-like behavior with high predictive validity for treatments having antidepressant activity is the Forced Swim Test (FST). Although the FST has been adapted for Drosophila, it has yet to be fully validated. Given the ease of use and low associated costs compared to rodents, a validated fly FST paradigm represents a potentially high-throughput screening platform for mechanistically evaluating the neurocircuitry involved in antidepressant effects of drugs. In this study, we pharmacologically validate fly FST using the psychostimulant methamphetamine (METH), the functional sedative DL-α-methyltyrosine, (αMT), and an SSRI antidepressant citalopram (CIT). As part of our validation, we also assessed the effects of psilocybin (PSI) in our paradigm, a drug that elicits long-lasting antidepressant effects in humans, and long-lasting antidepressant-like effects in our previously presented rodent models, after only a single treatment. PSI's active metabolite, psilocin, is an agonist at both 5-HT2A and 5-HT1A serotonin receptors, but with greater affinity for the 5-HT2A receptor. Importantly, Drosophila express functional homologs of both of these receptors.

Methods: Groups of one-day-old non-entrained male and female flies were fed for five days on 1% agarose, 10% sucrose medium containing METH (5.0 mM), αMT (3.0 mM), CIT (0.3, 1.0, or 2.5 mM), PSI (0.03 mM), WAY (1.0 mM), or KET (1.0 mM), or for one day (1x) on CIT (1.0 mM) or PSI (0.03 or 3.5 mM) then vehicle medium until testing. Control flies were fed vehicle medium for five days. As FST behaviors are measures of activity, overall locomotor activity was assessed to control for nonspecific stimulant or sedative effects. Locomotor activity was measured by photobeam break in the Drosophila activity monitoring system (DAMS) continually for at least six days, with the fifth day of activity compared ($n = 16$/group). Flies were assessed in FST trials for time spent immobile, latency to first immobility, and number of bouts of immobility ($n = 7(16)$/group) five days after first treatment. The FST apparatus was a four chamber well slide, with each chamber filled with 1.5 mL 0.08% SDS solution (to break surface tension). Flies were placed gently one per well into the apparatus and filmed for five minutes. After filming, flies were scooped out with a spatula and flicked gently onto a paper towel. Any fly unable to immediately get up and walk was excluded from analysis. Each FST data point is the mean of 16 consecutive flies.

Results: Males were less active than females in both assays. METH increased and αMT reduced DAMS activity in both sexes, but did not significantly affect FST behavior. Only CIT (2.5 mM) reduced DAMS activity, and only in females. For CIT (1.0 mM), only the 5 day feeding reduced immobility in the FST in males, and increased latency to first immobility and reduced bouts of immobility in both sexes. For PSI, feeding on 3.5 mM for only one day reduced DAMS activity in females, but increased DAMS activity in males. However, PSI feeding for five days on 0.03 mM had no effect in females and reduced DAMS activity in males. Significantly, feeding PSI (3.5 and 0.03 mM) for only the first day led to significantly reduced immobility and bouts of immobility, and increased latency to first immobility in males when measured on day 5.

Conclusions: We have successfully validated the FST assay for flies. Immobility and swimming behaviors are decoupled from overall locomotor activity and are serotonergically mediated. In males, both high and low concentrations of PSI, when fed for only the first day of the assay, elicit behaviors in the FST similar to CIT fed for the entire five day duration of the assay. Thus, as observed in both humans and rodent experimental systems, a single exposure to psilocybin has long lasting antidepressant-like effects in the fly. Further, overall locomotor activity, FST behaviors, and drug responses are sexually dimorphic in the fly. We propose the fly as a valid experimental system to study neuromolecular mechanisms underlying the antidepressant effects of psilocybin.

Keywords: Psychedelic Medicine, Drosophila, Depression, Serotonin, Psilocybin

Disclosure: Eleusis Therapeutics: Advisory Board, Grant (Self)
Palo Santo: Advisory Board (Self)

P230. Inflammation, Neural Reactivity to Reward and Resilience in a Racially Diverse Cohort of Depressed and Healthy Individuals

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Background: Recent evidence indicates that heightened pro-inflammatory markers are associated with reduced function of neural networks that mediate resilience in adolescents, particularly those exposed to community violence, which might disproportionately affect people of color (Miller et al., 2021). Heightened pro-inflammatory response to Lipopolysaccharide (LPS) stimulation of isolated peripheral blood mononuclear cells (PBMC) is also associated with reduced neural encoding of reward within the nucleus accumbens (NAc) across adults with Major Depressive Disorder (MDD) and healthy controls (Costi et al., 2021). Conversely, resilience has been associated with greater immune system sensitivity to the regulatory and anti-inflammatory cytokine, Interleukin (IL)-10 (Miller et al., 2021). However, the interaction between IL-10 reactivity to a stressor (LPS), NAc encoding of reward, and resilience has not been fully explored in a racially diverse sample of adult subjects with MDD.

Methods: In a diverse sample of patients with MDD ($n = 28$), and healthy subjects ($n = 20$), we examined relationships between IL-10 levels following PBMC stimulation with LPS, NAc reactivity to rewarding feedback measured from a modified monetary incentive delay task during functional MRI, and self-reported resilience (Connor-Davidson Resilience scale, CD-RISC).

Results: Higher IL10 levels were associated with higher NAc reactivity to reward across all subjects ($n = 48$, $R = 0.468$, $p = 0.001$) and in MDD subjects alone ($n = 28$, $R = 0.553$, $p = 0.003$) but IL-10 was not related to self-reported resilience (p's > 0.1). However, higher IL10 was associated with higher resilience only in people of color ($n = 22$, $R = 0.367$, $p = 0.046$) across groups. Interestingly, within the MDD group, people of color showed lower levels of IL10 ($n = 12/16$, $t = 2.36$, $p = 0.026$) and had lower NAc response to reward at trend level ($n = 12/16$, $t = 1.9$, $p = 0.068$) compared to white subjects.

Conclusions: These findings suggest that LPS-stimulated IL-10 levels are associated with neural reactivity to reward and resilience which might be differentially expressed in people of color. Future studies should examine the factors that influence these

differences, potentially starting with community-based stressors during adolescence and continuing with ongoing chronic stressors that negatively impact health (Williams et al., 2018).

Keywords: Immune Responses, Depression, Nucleus Accumbens

Disclosure: Nothing to disclose.

P231. Optimizing Outcomes of Treatment-Resistant Depression (TRD) in Older Adults (OPTIMUM): Measures of Effectiveness and Psychological Well-Being

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Background: The "Optimizing Antidepressants for Treatment-Resistant Depression in Older Adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized 621 depressed individuals aged 60 + with treatment-resistant depression (TRD), the largest pharmacological study of late-life depression. A key goal of this pragmatic trial was measuring outcomes of interest to patients, which in this trial included psychological wellbeing. This construct is closely tied to physical and psychological functioning and can be measured by self-report. OPTIMUM is one of the first studies to measure antidepressant effects on psychological wellbeing.

Methods: Participants were recruited and randomized if they were 60 years and older, met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Major Depressive Disorder, and had a score of 10 or higher on the Patient Health Questionnaire (PHQ-9), despite having been treated with at least two antidepressants with an adequate dosage and for at least four weeks (with previous antidepressants being different from the medications being tested in OPTIMUM). Upon study entry, participants were randomized into one of three strategies: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion. Treatment effectiveness was assessed using the Montgomery Asberg Rating Scale (MADRS) after ten weeks of treatment. Participants were also measured at the beginning and end of this 10-week step with the NIH Toolbox Psychological Well-being battery. Two wellbeing scales were measured: positive affect (34 items) and general life satisfaction (16 items). Positive affect is characterized as happiness, contentment, and interest in pleasurable or achievement–relevant activities. Each item administered has a 5-point scale with options ranging from "not at all" to "very much". Meanwhile, general life satisfaction is the cognitive evaluation of life experiences, and items assessing this concept are usually phrased in a general or global way rather than having a momentary or recent recall period. Items administered include those with both 5-point and 7-point scales, with options in each case ranging from "strongly disagree" to "strongly agree".

Results: Six hundred and twenty-one participants were included in the study of which 212 were randomized to augmentation with aripiprazole, 206 to augmentation with bupropion, and 203 to a switch to bupropion. The study found that augmentation with aripiprazole and augmentation with bupropion had similar effectiveness (remission rates of 34% per arm) and were more effective than switch to bupropion (remission rate of 24%). Participants randomized to either augmentation with aripiprazole or bupropion showed a statistically significant improvement in the general life satisfaction subscale estimated at the magnitude of 2.99 for aripiprazole ($p < 0.0001$) and 2.61 for bupropion ($p = 0.0001$) while those switched to bupropion did not. Participants in either of the two augmentation arms, aripiprazole or bupropion, also showed an improvement in positive affect estimated at the magnitude of 5.35 ($p < 0.0001$) for aripiprazole and 5.02 ($p < 0.0001$) for bupropion as compared to those in the switching to bupropion arm.

Conclusions: Augmentation with aripiprazole or bupropion led to higher remission rates and was associated with higher psychological well-being and positive affect compared to switching to bupropion.

Keywords: Treatment Resistant Depression, Older Adults, Psychological Wellbeing

Disclosure: Nothing to disclose.

P232. Accurate DLPFC Targeting Improves iTBS Response in Treatment Resistant Depression and Alters TMS-EEG Markers of Cortical Excitation

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Background: iTBS is a 3-minute form of repetitive transcranial magnetic stimulation (rTMS) with considerable therapeutic efficacy in TRD when applied daily for up to 4 weeks. The delivery of the stimulus is affected by the considerable inter-individual heterogeneity in head structure, DLPFC anatomy and conductivity. As rTMS physiological changes are inextricably linked to the induced E-fields, the ability to direct the E-field effectively to each patient's unique DLPFC architecture offers a personalized approach compared to standard neuronavigation targeting approaches based on group averages. We recently demonstrated that TRD is associated with abnormalities in TMS-EEG markers of cortical inhibition in the DLPFC and rTMS alters TMS-EEG markers of cortical inhibition in conjunction with clinical improvement, whereas iTBS alters TMS-EEG markers towards greater cortical excitation.

Methods: We utilized a novel E-field modeling pipeline (The Auxiliary Dipole Method (ADM)) to back-model the actual delivered E-fields in comparison to intended MNI group target for a subset of patients ($n = 17$) from a recent randomized controlled trial of iTBS in TRD. We then examined TMS-EEG results before and after the course of iTBS in 27 individuals from the same trial and compared the back-modeled delivered E-fields from the iTBS stimulation to the TMS-EEG markers and HRSD-17 scores.

Results: We found a mean shift of 13.86 □ 9.80mm. The shift was significantly greater in non-responders (17.73 + /-10.13mm) compared to responders (6.76 + /-2.93mm); ($t(12.713) = 3.343$, $p = 0.005$). Clinical response was correlated with a more accurately delivered iTBS pulse (i.e. closer to the intended group-based DLPFC MNI coordinates) ($r = 0.638$, $p = 0.006$). We examined 27 individuals from a recent trial investigating the efficacy of iTBS in TRD, and found that in responders, the GMFA-AUC amplitude, a TMS-EEG marker of cortical excitation, increases after a course of iTBS, where no change is seen in non-responders. In responders when the iTBS pulse was delivered closer to the intended DLPFC target, there was more cortical excitation (ie. larger GMFA-AUC change) ($r = 0.853$, $p = 0.003$). In non-responders, there was less accurate stimulus delivery and no change in GMFA-AUC ($r = 0.377$ p-0.461).

Conclusions: The mean distance found is considerable, as E-field strength depreciates by half with 5mm intervals. Thus, while iTBS is a significant improvement in efficiency, an important explanation for the high proportion of non-responders may relate to suboptimal targeting of the DLPFC using methods developed for the motor cortex. Further, TMS-EEG markers of cortical excitation (GMFA-AUC) hold important promise as biological markers of iTBS response.

Keywords: Non-Invasive Brain Stimulation, Repetitive Transcranial Magnetic Stimulation (rTMS), Theta-burst Stimulation, Electric Field Modeling, Cortical Excitation-Inhibition Balance

Disclosure: Nothing to disclose.

P233. Target Deconvolution Studies of (2R,6R)-Hydroxynorketamine: An Elusive Search

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Background: The off-label use of racemic ketamine and the FDA approval of its S-ketamine enantiomer represent promising developments for the treatment of depression. However, ketamine and S-ketamine are controlled substances with abuse potential and their use can have undesirable side effects. As such, research efforts have focused on identifying alternatives. One candidate currently in clinical trials is R-ketamine, which we recently showed exhibits a weaker abuse liability profile than S-ketamine. Another candidate also in clinical trials is (2R,6R)-hydroxynorketamine (HNK), a ketamine metabolite reported to lack the psychoactive properties of ketamine and its enantiomers while retaining antidepressant-like efficacy. In fact, metabolic conversion of ketamine to HNK has been proposed to mediate ketamine's antidepressant effects. Although ketamine acts as a non-competitive antagonist at N-methyl-D-aspartate receptors (NMDARs), it is not clear to what extent NMDARs are the mediators of the antidepressant effects of ketamine, since more selective NMDAR antagonists do not recapitulate ketamine's antidepressant profile. Moreover, R-ketamine, a weaker NMDAR antagonist than S-ketamine, exhibits greater antidepressant-like efficacy than S-ketamine in animal models of depression, and HNK exhibits negligible NMDAR affinity compared to ketamine and its enantiomers. We recently performed an in-depth pharmacological characterization of ketamine's enantiomers and reported that aside from their action at NMDARs, S-ketamine and R-ketamine differentially engage opioid and other receptors, but the pharmacological profile of HNK at these sites has not been previously reported. As such, the main goal of this study was to perform an in-depth pharmacological characterization of HNK at known ketamine targets, to use target deconvolution approaches to discover novel HNK targets, and to characterize the biodistribution and behavioral effects of HNK across several procedures related to depression and substance use disorders.

Methods: We assessed binding of HNK to ~100 receptors and enzymes including known targets of ketamine such as mu-opioid receptors (MOR, [3H]DAMGO]) and kappa-opioid receptors (KOR, [3H]U69,593]) via a competitive binding screen and via radioligand binding in brain tissue/cell lines. We also performed signaling assays in HEK293 cells transiently transfected with either delta-opioid receptors (DOR), MOR or KOR and evaluated HNK's ability to modulate G-protein activation in the rat brain using the [35S]GTPγS autoradiography assay. To increase the threshold of detection and expand the range of pharmacological targets, we radiolabeled HNK with tritium to use it as a direct probe. We tested [3H]HNK for binding to the high density HuProtTM (>16,000 human genes; ~81% of the human proteome) and Protoarray® microarrays (>9000 human proteins). We also leveraged RetrogenixTM target deconvolution technology to test [3H]HNK binding to >6000 cell surface and secreted human proteins transiently transfected in HEK-293 cells. In addition, a full yeast-3–hybrid screen was done with two modified HNK probes. For assessment of HNK biodistribution, we administered a trace dose of [3H]HNK (2 μCi/g, i.v.) in adult male and female rats ($n = 6$) followed by ex vivo autoradiography. We also tested HNK in its capacity to modulate brain metabolic activity via FDG-PET studies in mice and rats ($n = 6$ vehicle, $n = 6$ HNK). Finally, we profiled HNK using several behavioral procedures such locomotor activity and psychomotor sensitization (mice, $n = 12$), conditioned place preference (mice, $n = 12$), and intravenous self-administration (rats, $n = 12$).

Results: Unlike ketamine and its enantiomers, HNK did not displace binding of [3H]DAMGO to MOR, or [3H]U69,593 to KOR. HNK also did not affect binding of [3H]LY341495 to mGluR2/3 receptors, which have been previously implicated in its putative mechanism of action. HNK failed to induce any functional response in MOR, KOR or DOR up to concentrations of 1 mM. HNK did not increase [35S]GTPγS accumulation in the rat brain. Our competitive in vitro screening and target deconvolution experiments failed to identify any direct HNK-protein interactions, including estrogen receptor alpha (ERα) and Tropomyosin receptor B (TrkB), which were reported to bind HNK. Our [3H]HNK biodistribution studies revealed a fast clearance rate (~50% in serum in 30 min) with negligible brain uptake and regional enrichment and no specific binding in any organ other than the liver. HNK did not induce any metabolic effects in brain when injected IP in mice. In rats, a prolonged HNK IV infusion led to weak changes in regional brain metabolism which differed from the brain metabolic profiles induced by ketamine enantiomers. HNK was inert in all behavioral procedures investigated.

Conclusions: Our results indicate that HNK does not bind to nor does it activate any known ketamine targets at physiologically-relevant concentrations. Our extensive screening and target deconvolution experiments failed to identify any novel targets. Finally, while pharmacokinetic studies with [1H]HNK demonstrated reasonable brain permeability, ex vivo uptake studies using [3H]HNK in rodents indicated weak brain permeability and non-specific brain regional uptake and distribution. These findings indicate that HNK does not share any pharmacological profile similarities to ketamine and that it lacks high-affinity specific binding in the brain.

This poster was sponsored by Dr. Michael Lewis.

Keywords: Depression, Hydroxynorketamine, Ketamine

Disclosure: Nothing to disclose.

P234. Prenatal Stress Produces Aberrant PP1-HDAC4-MEF2 Pathway in Medial Prefrontal Cortex in Adult Offspring

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Background: Introduction: It has been shown that alcohol use disorder (AUD) is associated with a higher prevalence of psychiatric comorbidities, particularly anxiety disorders. However, effective treatments have not been well established because the underlying pathophysiology is poorly understood. Recent studies indicate that exposure to stress during pregnancy exerts profound effects on the behavior and neurodevelopment of offspring, predisposing them to psychiatric disorders including AUD later in life. Evidence from our animal research strongly supports this notion. We reported that offspring born from prenatally restraint stressed (PRS) dams exhibit increased alcohol intake and heightened anxiety-like behavior in adulthood compared to the offspring born from non-stressed (NS) dams. Of notable importance, PRS mice show significant defects in synaptic function and plasticity in the medial prefrontal cortex (mPFC), most likely via epigenetic reprogramming. Histone deacetylases (HDACs) play an important role in epigenetic programming, but their functional

regulation in pathophysiology after PRS is not fully explored. Here, we investigated phosphorylation/dephosphorylation of HDAC4 via protein phosphatase 1 catalytic subunit alpha (PP1) and the impact of this mechanism on the interaction between HDAC4 and transcription regulator, myocyte enhancer factor-2 (MEF2) in the mPFC of PRS mice.

Methods: Methods: Control dams (Swiss albino ND4) were left undisturbed throughout gestation, whereas stressed dams were subjected to repeated episodes of restraint stress. The stress procedure consisted of restraining the pregnant dam in a transparent tube (12×3 cm) under a bright light for 45 min three times per day from the seventh day of pregnancy until delivery. Biochemical measurements (gene and protein expressions, immunoprecipitations, and ChIP assays) were performed on postnatal day 70 (PND70) offspring. The significant differences between groups (PRS vs NS offspring mice, $n = 10$ per group) were assessed by Student's t-test.

Results: Results: Under normal physiological conditions, HDAC4 was predominantly cytoplasmic in neurons and its cytoplasmic retention required phosphorylation catalyzed by CaMKs. We observed significantly higher HDAC4 protein in nuclear extract than in cytoplasm in the mPFC of PRS mice compared to NS mice. Moreover, its phosphorylated form was significantly decreased in both cytoplasmic and nuclear extracts in PRS mice, suggesting an occurrence of dephosphorylation promoting its nuclear translocation. We also observed that dephosphorylation of HDAC4 was associated with increased levels of PPIA, as there was no significant change in CaMKIIa expression in either NS or PRS mice. Our immunoprecipitation assay showed a significant amount of PP1A bound to HDAC4 in PRS mice as compared with its NS counterparts. Further, immunoprecipitation results showed more HDAC4 bound to MEF2 in the nuclear extract of mPFC of PRS mice. The physical binding of HDAC4 may inhibit MEF2 translational activity, decreasing synaptic gene expression.

Conclusions: Conclusion: HDAC4, as a class IIa HDAC, has been associated with several neurodegenerative disorders. Under normal conditions, HDAC4 is phosphorylated by CaMKs, resulting in nuclear exit and cytoplasmic retention. These data provided evidence to suggest that prenatal stress drives HDAC4 translocation from cytoplasm to the nucleus through a dephosphorylation mechanism most likely mediated by PP1 not by CaMKIIa. In the nucleus, accumulated HDAC4 binds MEF2 and inhibits its transcriptional activity for synaptic genes. Thus, the abnormality in the transcription regulatory pathway of PP1-HDAC4-MEF2 likely acts as a significant pathological node that integrates synaptic events and anxiety-like and alcohol drinking behaviors observed in PRS mice. (Supported by NIH-NIAAA grant R21AA027848 to ED and P50AA022538, UO1AA019971 and by the VA Senior Research Career Scientist award to SCP)

Keywords: Prenatal Stress, Anxiety and Depression, HDAC4, MEF2C, Alcohol Epigenetic Marks

Disclosure: Nothing to disclose.

P235. PRAX-114, an Extrasynaptic-Preferring GABA-A Receptor Positive Allosteric Modulator: Multiple Dose Safety, Tolerability, Pharmacodynamics and Preliminary Efficacy in Major Depressive Disorder

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Background: Neuroactive steroid positive allosteric modulators of GABA-A receptors (GABA-AR PAMs) differ from benzodiazepines (BZ) by mediating both phasic and tonic inhibition through potentiation of synaptic and extrasynaptic receptors, respectively. This mechanism has demonstrated rapid efficacy in major depressive disorder (MDD), postpartum depression and essential tremor, but the therapeutic window has been limited by sedative effects related to BZ-like activity at synaptic GABA-AR.

PRAX-114 is a novel extrasynaptic GABA-A receptor-preferring PAM neuroactive steroid currently in development for treatment of MDD. We postulated this extrasynaptic preference to be the basis for preclinical findings in which we demonstrated wide (>20-fold) separation between doses associated with antidepressant- and sedative-like effects in rodents.

Many classes of GABA-AR PAMs have been shown to increase EEG β-frequency band power (β-power). We previously demonstrated 1.6-fold increases in β-power following PRAX-114 administration at doses associated with antidepressant-like effects in rodents. Therefore, we used β-power as a translational biomarker in a Phase 1 trial assessing PRAX-114 safety and tolerability in healthy participants. Results informed dose selection for a subsequent open-label Phase 2 trial assessing the safety and preliminary efficacy of PRAX-114 in MDD.

Methods: Phase 1 multiple-ascending dose (MAD) trial: PRAX-114 (15, 30, 60 mg, qAM fasted) was studied in 36 healthy participants ($n = 9$ PRAX-114 and $n = 3$ placebo per cohort) in a 14-day trial incorporating EEG β-power measurements (Days 1 and 14). This trial aimed to determine the safety, tolerability, and pharmacokinetics (PK) of PRAX-114, and to establish relationships between β-power, dose, plasma concentration, and incidence of adverse events (AEs) related to sedation.

Phase 2 MDD trial: This trial aimed to assess the safety, tolerability, and preliminary efficacy of PRAX-114 in an open-label MDD trial with 33 participants receiving 14-days PRAX-114 (45, 60, 80 mg) and a subsequently added cohort of 13 participants receiving 27 days PRAX-114 (60 mg), dosed qPM 4 h after a meal. Eligible participants (18-65 years) had a DSM-5 diagnosis of MDD with a minimum Hamilton Depression Rating Scale (HAM-D) score of 22. The 14-day cohorts had 7 days inpatient followed by 7 days outpatient treatment, and the 27-day cohort was outpatient; each cohort had a 14-day post-treatment follow-up. A key efficacy endpoint was HAM-D change from baseline at Day 15, analyzed using mixed model repeated measures including dose, timepoint and a dose-by-timepoint interaction as fixed effects and baseline total score as a covariate. Further efficacy endpoints included the Hamilton Anxiety Rating Scale (HAM-A) and the patient-reported Symptoms of Depression Questionnaire (SDQ), among others.

Results: Phase 1 MAD trial: PRAX-114 increased mean β-power from 1.6 (30 mg) to 2.7-fold (60 mg) compared to placebo, did not cause sedation, and was safe and well-tolerated at all doses tested. The most common treatment emergent AE was mild somnolence, the frequency of which appeared to be dose related. Based on the PK/PD relationship observed in this study, a dose of 45 mg was expected to result in most participants achieving a target β-power increase of ~1.6-fold as well as full MDD efficacy, informing the initial target dose for evaluation in the Phase 2 MDD trial.

Phase 2 MDD trial: Mean age of the 14-day cohort was 35 years, 55% were male, with a mean baseline HAM-D total score of 25 (range 20-33). Mean age of the 27-day cohort was 40 years, 31% were male, with mean baseline HAM-D total score of 25 (range 22-30). The majority of participants in both cohorts had demonstrated an inadequate response or loss of a prior response to an antidepressant in the current episode.

PRAX-114 was generally well-tolerated across the dose range tested. The AEs were mostly mild, with no serious AEs or discontinuations due to AEs. The most frequent AE was somnolence; this increased with dose, but was lower in frequency compared to somnolence rates observed with AM fasted dosing in the MAD trial for the 60 mg dose common to both trials. There were no AEs or safety findings of clinical concern, and no AEs in vital signs, ECG, or safety laboratory data.

PRAX-114 treatment led to marked improvement in HAM-D total scores at all dose levels in both cohorts, with improvement

still evident upon follow-up. The HAM-D least square mean change from baseline at Day 15 ranged from 11-16 points across all dose levels in both cohorts, and the Day 15 HAM-D change from baseline in the 27-day cohort was maintained through Day 28. Similar improvements were observed within each cohort in the additional efficacy endpoints, including the HAM-A, over the active treatment periods.

Conclusions: Based on combined findings from Phase 1 translational and Phase 2 clinical MDD efficacy trials, the preference of PRAX-114 for extrasynaptic GABA-AR appears to translate into separation of dose-limiting sedative-like side effects from efficacy and pharmacodynamic effects, highlighting the potentially wide therapeutic window for PRAX-114. The observed HAM-A improvement suggests that greater preference for extrasynaptic GABA-AR does not compromise anxiolytic efficacy. The promising preliminary MDD efficacy data at well-tolerated dose levels support further clinical development of PRAX-114 in a randomized controlled trial as a rapid-acting antidepressant with the potential to address unmet needs for patients with MDD.

Keywords: Neuroactive Steroid, Translational Biomarker Approaches to Drug Development, Extrasynaptic GABA Receptors, Rapid Antidepressant, GABA-A, Positive Allosteric Modulator, MDD

Disclosure: Praxis Precision Medicines, Inc.: Employee (Self)

P236. Association of Wnt7a Pathways in Distinct Human Amygdala Cell Populations and Affective Symptoms in Bipolar Disease

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Background: Emotion dysregulation, such as depression, anxiety, and decreased appetitive drive alternating with mania (appetitive drive for reward and pleasure) are the key features of bipolar disorder (BD). Emerging evidence from rodent studies indicates that distinct cell populations in the amygdala are predominantly involved in aversive ("FEAR-On" neurons) or appetitive ("APPT-On" neurons) behavior. These neuronal populations are characterized by distinct patterns of molecular expression, including selective expression of members of the Wnt pathways. Pilot data from our group show that such molecular signatures are partially conserved in the human amygdala, providing insight on their functions based on their rodent analogs. We postulated that a disruption of FEAR-On and APPT-On amygdala neurons, including dysregulation of neuron-specific Wnt pathways, may contribute to emotional dysregulation in BD. A disruption of Wnt pathways, including Wnt family members, β-catenin and GSK3β, is supported by several studies, Wnt7a has been identified as a risk gene for bipolar disorder in genome-wide association studies, and GSK3β is inhibited by Lithium, a mood-stabilizer regularly prescribed in this disorder.

Methods: Human post-mortem brain tissue blocks containing the amygdala, were obtained from the Harvard Brain and Tissue Resource Center. Single-nucleus RNA sequencing (snRNA-seq) was performed in 4 healthy donors. Western blotting analyses were carried out on cell lysates from the amygdala of donors with BD ($n = 16$) and healthy controls ($n = 17$), using antibodies raised against Wnt7a, GSK3β, R-spo2β, and DKK3. Several covariates, including age, sex, postmortem interval, and medication history were included in the analysis.

Results: Analyses from snRNA-seq identified 13 distinct glutamatergic populations and 22 populations of GABAergic neurons in human amygdala. As expected Wnt downstream pathways, such as β-catenin mRNA and GSK3β mRNA were expressed at similar levels in distinct cell populations. In contrast, several elements of the Wnt family, as well some Wnt receptors and receptor regulators were selectively expressed in distinct neuronal populations. For instance, Wnt7a mRNA was found to be expressed exclusively in subpopulations of GABAergic neurons. Notably, the highest Wnt7a signal was detected in a GABAergic neurons postulated to belong to the intercalated cell masses (ITCs) on the basis of their expression of FOXP2, OPRM1, and DRD1. These neurons are thought to mediate fear extinction under direct prefrontal cortex control. Other members of the Wnt pathways, including R-spo2 and DKK3 showed cell-specific expression.

Western blotting analysis in the amygdala show a marginally significant decrease of Wnt7a signal in BD donors ($p = 0.057$). Expression of GSK3β, R-spo2β, and DKK3 proteins were significantly increased compared to control donors (p-values 0.007, 0.057, and 0.001, respectively).

Conclusions: These findings show a disruption of Wnt pathways in the amygdala of donors with BD. Dysregulation of key mediators of Wnt receptor signaling, such as GSK3β, may impact neuronal functions within the amygdala, potentially responsive to lithium effects. The potential for neuron specific effects is supported by selective expression of Wnt modulators in neuronal populations putatively involved in aversive and appetitive behaviors. Speculatively, involvement of ITC neurons in BD may contribute to anxiety, a symptom pervasive in this disorder and often manifest both during depression and mania.

Keywords: Bipolar Disorder, Wnt Signaling, Amygdala, RNAseq

Disclosure: Nothing to disclose.

P237. Insular Volume Reductions Associated With Increased Severity of Suicidal Ideation in Youth With Mood Disorders

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Background: Mood disorders are associated with significant suicide risk, particularly during adolescence (Tondo et al., 2021). There is a critical need to better understand those factors which contribute to the increased risk in order to target prevention efforts. Abnormalities in the insular cortex have been reported in neuroimaging studies of suicide behavior (SB) and may play a role in the transition from suicidal ideation (SI) to attempts (SA) (Schmaal et al., 2020). Few studies have examined the involvement of the insula in SB and studies that included rigorous detailed assessment of SI are limited. The aim of the present study was to investigate the relationship between insular volume and suicide ideation youth with mood disorders compared to healthy youth.

Methods: One-hundred ninety youth (124 with a mood disorder and 66 healthy controls), ages 13 to 21, completed a structured diagnostic interview, clinical assessments, and also underwent 3T magnetic resonance imaging. Morphometric analysis of brain images was performed using FreeSurfer to evaluate differences in gray matter volume (GMV) in insular regions of interest (Desikan et al., 2006). Lifetime symptoms of suicidal thoughts and behaviors were assessed using the Columbia Suicide Severity Rating Scale (Posner et al., 2011). Analysis of covariance was used to evaluate whether there were differences in insular volume between mood disorder youth with SI and healthy controls, while controlling for age, sex, and total intracranial volume. Additionally, we examined the relationship between insular volume and SI severity and intensity (frequency,

duration, controllability) of the most severe SI or most commonly experienced SI using Pearson Correlation tests.

Results: All youth with a mood disorder reported a history of SI and 48 also reported a history of SA.

Between group analysis of covariance revealed a significant difference in volume in the right insula ($p = .034$, $\eta 2 = .024$) between mood disorder youth with SI and healthy controls.

In addition, right insula volume was negatively correlated with the intensity of most severe SI ($p = .036$), frequency of most severe SI ($p = .009$), and controllability of most common SI ($p = .031$). While there was not a significant difference between groups in left insula volume, there was a significant negative correlation between left insula volume and the intensity of most severe SI ($p = .038$), frequency of most severe SI ($p = .008$), and controllability of most common SI ($p = .017$).

Conclusions: These findings demonstrate a significant reduction in right insular GMV in youth with mood disorders that was negatively correlated with characteristics of SI. While the presence of mood disorders likely contributes to morphometric differences seen between the two groups, the results also demonstrated that both left and right reduced insular volume was associated with more severe SI, experiencing the most severe SI more frequently, and having less control of the most common SI suggesting a specific association between insular volume and suicide behavior. The insula plays an important role in self-awareness (Uddin et al., 2017) and interoceptive processing (Wang et al., 2019) and has been suggested to be involved with disconnection from body experiences that may lead to engagement in self-injury and SB (DeVille et al., 2020). These adolescent findings are consistent with results reported in studies of adults, and add to converging evidence that the insula is involved in SB.

Keywords: Mood Disorders, Suicidal Ideation, Insula

Disclosure: Nothing to disclose.

P238. Associations of Aggression With Impulsivity and Reactivity and Mood Symptoms With Parental Depression Symptoms and Family Risk for Mood Disorders

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Background: Previous research has identified intergenerational links for mood disorders. Findings point to both genetic and environmental influences, such as family conflict and low parental warmth, as contributors to shared generational risk for mood disorders. However, it is not known if aggression with impulsivity and reactivity (AIR) is also associated with a family history of mood disorders. This study described links that caregiver mood symptoms and family history of mood disorders have with child mood and AIR symptoms.

Methods: This study used the ABACAB dataset ($N = 634$) with a sample who were aged 5 to 18 years ($M = 11.1$, $SD = 3.3$), 39% female, 25% European-American, and had a median family income of $18,400. Prior analyses with parent-reported measures of focal child symptoms and behavior produced 5 principal components: mania, AIR, depression, self-harm, and rule-breaking (Young, Youngstrom, Findling et al., 2019). Using components as indicators in latent profile analyses, 8 distinct psychopathology profiles emerged. An adult close to the caregiver completed the Beck Depression Inventory and the Mood Disorders Questionnaire to assess caregiver depression and mood symptoms. History of mood disorders among biological family members was identified through the Family History–Research Diagnostic Criteria and positive mood disorder screens of biological parents on the Mini International Neuropsychiatric Interview. Univariate ANOVAs, correlations, chi-square, and t-tests were used to evaluate links caregiver mood symptoms and family history of mood disorders had with child profiles and component scores.

Results: ANOVAs showed that caregiver depression and mood symptoms were significantly different across profiles ($p < 0.001$) and were highest in the high mixed bipolar symptoms + self-harm, mixed bipolar symptoms + low self-harm, and mixed bipolar symptoms + AIR + self-harm profiles. Caregiver depression symptoms had significant, small to moderate correlations with the AIR ($r = 0.19$, $p < 0.001$), mania ($r = 0.27$, $p < 0.001$), depression ($r = 0.21$, $p < 0.001$), and self-harm components ($r = 0.12$, $p < 0.001$), but not rule-breaking ($r = 0.03$, $p = 0.47$). Similarly, caregiver mood symptoms were significantly related to AIR ($r = 0.22$, $p < 0.001$), mania ($r = 0.38$, $p < 0.001$), depression ($r = 0.27$, $p < 0.001$), and self-harm components ($r = 0.12$, $p = 0.007$), but not rule-breaking ($r = 0.05$, $p = 0.29$). Family history of mood disorders was significantly different across profiles ($\chi 2 = 20.3$, $p = 0.005$) with higher family history in the mixed bipolar symptoms + low self-harm (53%), moderate manic symptoms + AIR (43%), mixed bipolar symptoms + AIR + self-harm (39%), and mixed bipolar symptoms + self-harm profiles (30%). Children with family history had significantly higher mania (Cohen's $d = 0.52$), depression ($d = 0.21$), and AIR ($d = 0.18$) scores than those without it ($p < 0.01$).

Conclusions: Caregiver depression and mood symptoms as well as biological family history of mood disorders differentiate child profiles of mood and behavior and relate to mania, depression, and AIR symptoms. Results also suggest that AIR symptoms relate to caregiver mood symptoms and family psychiatry history is ways that are similar to mood symptoms. Future research should explore shared biological and environmental correlates between AIR and mood symptoms.

Keywords: Aggression, Depression, Bipolar Disorder, Latent Class Analysis

Disclosure: Nothing to disclose.

P239. Combined Administration of (R,S)-Ketamine and Prucalopride, a 5-HT4R Agonist, Has an Additive Effect of Decreasing Stress-Induced Anxiety-Like Behavior

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Background: Serotonin (5-HT) receptors and N-methyl-D-aspartate receptors (NMDARs) have both been implicated in the pathophysiology of depression as well as in mediating the prophylactic and antidepressant effects of (R,S)-ketamine. However, the high comorbidity rate of depression and anxiety disorders may necessitate the combinatorial targeting of multiple receptors to improve interventions to prevent and treat these psychiatric disorders. Here, we evaluated whether combined dosing of (R,S)-ketamine and prucalopride, a 5-HT type 4 receptor (5-HT4R) would have additive effects, resulting in improvements in stress-induced fear, behavioral despair, and anxiety-like behaviors.

Methods: A single injection of saline, (R,S)-ketamine (10 or 30 mg/kg), prucalopride (1.5, 3, or 10 mg/kg), or a combined dose of (R,S)-ketamine and prucalopride (10 + 1.5, 10 + 3, 30 + 1.5, or 30 + 3 mg/kg) was administered before or after contextual fear conditioning (CFC) stress in male and female 129S6/SvEv mice ($n = 6$-15 mice per group). Drug efficacy was assayed using a variety of behavioral tests, including the forced swim test (FST), elevated plus maze (EPM), open field (OF), and novelty-suppressed feeding (NSF) test. Immediate early gene (IEG) expression in the hippocampus was assayed using immunohistochemistry. Generally, the effect of Drug or Group was analyzed using an analysis of

variance (ANOVA), using repeated measures where appropriate. Post-hoc Dunnett, Sidak, or Tukey tests were used where appropriate.

Results: As previously shown, a single dose of (R,S)-ketamine (10 mg/kg in female mice and 30 mg/kg in male mice) attenuated learned fear in male mice ($p = 0.0057$) and reduced behavioral despair in both sexes ($p < 0.0001$, $p = 0.0235$). Similarly, a single dose of prucalopride (1.5 mg/kg in female mice and 3 mg/kg in male mice) reduced fear in male mice ($p = 0.0211$) and behavioral despair in both sexes ($p = 0.0382$, $p = 0.001$). Combined administration of (R,S)-ketamine and prucalopride ($10 + 1.5$ mg/kg in female mice and $10 + 3$ mg/kg in male mice) was effective at decreasing learned fear in male mice ($p = 0.006$) and immobility time in both sexes ($p = 0.0246$, $p < 0.0001$). Moreover, combined administration of (R,S)-ketamine and prucalopride was effective in reducing latency to feed in the NSF in both sexes ($p = 0.0250$, $p = 0.0059$), but not when administered separately. Combined (R,S)-ketamine and prucalopride administration significantly increased c-fos expression in all subregions of the hippocampus when compared with saline controls ($p < 0.0001$).

Conclusions: Our results indicate that combined administration of (R,S)-ketamine and prucalopride has additive benefits for reducing and preventing stress-induced pathophysiology, providing preliminary evidence that future clinical studies using this combined treatment may prove advantageous. Together, our data suggest that targeting multiple receptors through combinatorial drug administration may enhance the treatment and prevention of stress-induced psychiatric disorders.

Keywords: 5HT4R Agonist, NMDAR Antagonist, Depression, Anxiety, Fear

Disclosure: Nothing to disclose.

P240. Impact of Body Mass Index on Clinical Outcomes in Major Depressive Disorder – Results From the European GSRD Database

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Background: Overweight and obesity as measured with the body mass index (BMI) is associated with reduced health and elevated risks for premature death. Elevated BMI also results in worse outcomes of cardiovascular diseases, cancer, diabetes, or osteoporosis. Strikingly, BMI rates are increasing in industrialized countries with high caloric diets (1). Previous results on the impact of high BMI on mental health in non-depressed subjects indicate that that elevated BMI is associated with increased suicidal ideation and increased numbers of suicide attempts (2). Patients with major depressive disorder exhibit a bi-directorial risk for depression, with overweight subjects being at risk for developing depression and depressed patients susceptible for obesity (3). However, the impact of elevated BMI on core clinical outcomes such as suicidality and hospitalization in patients with major depressive disorder (MDD) are still unknown.

Methods: Data were analyzed in retrospect from the multicenter clinical database study by the European Group for the Study of Resistant Depression (GSRD). Patients with primary diagnosis MDD above 18 years were recruited between 2011 and 2020. Excluding diagnoses were bipolar and schizoaffective depression as well as were any severe substance abuse disorder or severe comorbid personality disorder as assessed with the MINI-Interview. All eligible patients underwent a standardized battery for including clinical rating scales for affective disorders, biometric evaluation, and psychosocial questions. In this study in accordance with international standards, we defined TRD as failure of response (=MADRS < 22) after 2 antidepressant trials of at least 4 weeks at an adequate dose. For statistical analyses, response and non-response, psychosocial variables as well as MADRS sub items were used with BMI as marker of obesity with ANOVAs, controlled for age, sex and risk of weight gain due to medication.

Results: Data were available from 892 patients (580 female, 50.5 + /-13.6 years) of whom 323 were categorized responder and 569 treatment resistant. In the overall sample 17% ($n = 152$) of all patients were obese having a BMI > 30. In addition, BMI was significantly positive associated with suicidality ($p = 0.002$), longer hospitalization time ($p = 0.006$) and an earlier onset of first episodes ($p = 0.011$). Treatment resistance was trend-wise associated with BMI ($p = 0.085$). Increases of BMI were also significantly positive associated with higher frequencies of comorbidities such as agoraphobia ($p = 0.006$), social phobia ($p = 0.035$) and PTSD ($p = 0.002$). Analyzing MADRS subitems, we found that appetite ($p < 0.001$) and concentration ($p < 0.001$) was significantly reduced with higher BMI irrespective of treatment response, while lassitude ($p = 0.02$) was only reduced at before antidepressant treatment.

Conclusions: In this study, we investigated the impact of BMI on clinical outcomes in depression and their contribution to treatment resistance. We found that patients with MDD and increases in BMI are susceptible for substantial disease complications such as suicidality or prolonged hospitalization. Well known pathophysiological links between weight gain and depression exist, which could potentially explain previously demonstrated relationships between MDD and obesity (4). Our clinical results add that patients with MDD and co-morbid obesity exhibit worse outcomes and require closer attention to achieve clinical improvements.

Keywords: Obesity, Depression, Suicidality, Patient Outcomes

Disclosures: Janssen, LivaNova: Honoraria (Self)

P241. Identifying Aberrant Reward Neurocircuit Mechanisms That Link Immune Dysregulation to Anhedonia: Findings From the EMBARC Study

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Background: Converging lines of evidence have implicated dysregulation within the immune system as a pathophysiological mechanism underpinning depression. Systematic reviews and meta-analyses have found elevated levels of immune biomarkers [especially interleukin 6 (or IL-6)] in individuals with major depressive disorder (MDD) versus healthy controls. Our previous work has shown that elevated levels of circulating inflammatory factors are associated with higher levels of anhedonia. However, the neurocircuit mechanisms that link systemic inflammation (as reflected in elevated levels of inflammatory factors in peripheral circulation) to symptoms of anhedonia remain poorly characterized.

Methods: Participants of Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study with available reward task functional magnetic resonance imaging scans and plasma samples for immune biomarker assays were included ($n = 127$). In the reward task, participants completed 24 trials of a game of chance. In 12 trials, money was lost for a wrong guess but not gained for a correct guess. In the other 12 trials, money was gained for a correct guess but not lost for a wrong guess. This allows measurement of a participant's differential brain activation to punishing vs. rewarding trials (reward expectancy, RE). RE contrasts were obtained for

121 regions of interest based on functional parcellation of the 7 major cortical networks [default mode (DMN), dorsal attention (DAN), executive control (ECN), limbic (LN), somatomotor (SMN), salience (SN), and visual (VN)], the striatum, amygdala, thalamus, and hippocampus. Levels of 40 immune markers (cytokines and chemokines) were assayed in plasma samples using the BioRad 40-pex chemokine panel. A canonical correlation analysis of regions that were correlated with symptoms of anhedonia (spearman's rho >0.10) and the 40 immune markers was used to identify shared variance among differential brain activation to punishing vs. rewarding trials and markers of immune response.

Results: The first two coefficients in the canonical correlation analysis were significant [first: coefficient = 0.992, $p = 0.0007$; second: coefficient = 0.986, $p = 0.028$). The first canonical factor was driven by immune factors that modulate inflammatory response (including IL-6, tumor necrosis factor alpha) and RE contrast within the striatal regions (especially, ventral striatum). In contrast, the second canonical factor was driven by cytokines that are produced by T lymphocytes (interferon gamma, interleukin 2, and interleukin 4). In ongoing analyses, we are using mass cytometry in a subgroup of patients with peripheral blood mononuclear cells (PBMCs) available to characterize the immunophenotype of individuals categorized based on the two canonical factors.

Conclusions: We identified latent constructs between brain's reward function and dysregulation within immune system in this unplanned secondary analysis of data from the EMBARC study. This work can help inform neurocircuit targets for developing immunomodulatory treatments (such as monoclonal antibodies against inflammatory cytokines) as novel antidepressants.

Keywords: Inflammation, Reward Functioning, Major Depressive Disorder, Functional MRI (fMRI)

Disclosure: Acadia Pharmaceuticals: Grant (Self)

Eleusis, Guidepoint Global: Consultant (Self)

North American Center for Continuing Medical Education, Global Medical Education: Honoraria (Self)

P242. The Unique Face of Anxious Depression: Exaggerated Threat but Preserved Valence Sensitivity

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Background: Comorbid Major Depressive Disorder and Anxiety Disorder (e.g. generalized anxiety disorder, social phobia, panic disorder, or simple phobia) are among the most common presentations for mental health providers. For example, between 42 and 78 percent of all depressed patients suffer from anxiety. Yet, the underlying brain and behavioral processes that contribute to this comorbidity and that characterizes anxious depression are still incompletely understood. Affective startle modulation (ASM) has been used extensively to examine the neural and physiological basis of affective processing and is thought to result from motivational priming of both appetitive and defensive systems. In healthy participants, congruent aversive motivational states prime the defensive system which potentiates the defensive startle response, whereas incongruent appetitive states do not. Deviations from the expected pattern of ASM are thought to reflect abnormal functioning of the underlying motivational system and thus ASM is an important target process that is altered transdiagnostically in individuals with mood and anxiety disorders. This study examined the hypothesis that individuals with comorbid depression and anxiety show a different pattern of ASM to those with pure depression and that anxiety and depression may interact in their effect on ASM.

Methods: Multi-level (symptom, behavior, physiology, circuitry, and genetic) data were collected from 236 participants (170 female) from the Tulsa 1000 study, including self-report measures of depression and anxiety, blood sampling for genetic testing and an emotional reactivity task during eyeblink electromyography (EMG). Participants viewed appetitive, neutral, and aversive images from the International Affective picture series (IAPS) for 6 s. Noise probes (95 dB) were presented between 2500 and 4500 ms after picture onset to elicit startle blink responses during 24 of these image presentations (8 per valence). To reduce the bias due to confounding variables 124 participants with comorbid depression and anxiety disorders (Dep+Anx) were propensity matched with 62 participants with depression only (Dep). Startle magnitudes were analyzed using mixed-effects linear regression in R.

Results: Mixed effects linear regression results showed a significant valence X group interaction (F(1,184) 6.362, $p = 0.01$). Planned contrasts showed that the Dep group had no modulation of startle response from valence (pairwise comparisons; all $p > 0.5$), whereas the Dep+Anx group showed negative potentiation (negative > positive) ($t(184) = 5.420$, $p < 0.001$) and positive attenuation (positive < neutral) ($t(549) = -4.732$, $p < 0.001$). The Dep+Anx group also had lower startle response during appetitive stimuli compared to the Dep group ($t(399) = -2.418$, $p = 0.02$). Dimensional analyses examined the effects of self-report anxiety sensitivity (ASI) and depression (PROMIS) on startle response during aversive stimuli using linear regression. There was a significant Anxiety Sensitivity X Depression interaction. This indicates that depression moderated the effect of anxiety sensitivity ($F(1,178 = 4.867$ $p = 0.03$), so that those in the top quartile of depression scores did not see the same pattern of anxiety sensitivity increasing startle response during aversive stimuli. Finally, exploratory analyses showed that polygenic risk for depression was associated with blunted startle response during aversive stimuli ($F(1,175 = 5.699$ $p = 0.02$).

Conclusions: These results are consistent with the hypothesis that individuals with comorbid anxiety and depression show different appetitive and aversive system responsivity compared to those with pure depression, who are blunted across valence. Dimensionally, increased anxiety sensitivity increases startle response, an effect which is reduced in severe depression. Exploratory findings suggest that polygenic risk for depression is also associated with blunting. In sum, these findings propose intact emotional reactivity in comorbid anxiety and depression as a unique phenotype that is not seen in pure depression. This suggests that treatment strategies targeting threat sensitivity or utilizing preserved positive valence reactivity may be useful in this treatment resistant sub-group.

Keywords: Startle, Depression and Anxiety, Polygenetic Risk Score

Disclosure: Nothing to disclose.

P243. Dysfunctional Self-Related Processing in Depression: Preliminary Results From the Mechanisms of Negative Affectivity Study

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Background: Negative self-evaluations are a core characteristic of depression, and continuing to evaluate oneself negatively after treatment is a cardinal risk marker for relapse. But we know strikingly little about the disruptions in information processing and brain function that lead depressed adults to make overly negative self-evaluations. When non-depressed adults make evaluations about themselves, they demonstrate a self-reference

effect whereby they are faster to make judgments about themselves than others. A series of studies in healthy adults has demonstrated that self-related judgments can be made accurately and rapidly, supported by processing in the medial prefrontal cortex (MPFC), without reliance on more effortful cognitive processes. In the current study, we hypothesized that depressed adults would show abnormalities in self-related processing and would: 1) engage a broader network of neural regions and 2) show a reduced self-reference effect when making self-related judgements compared to non-depressed adults.

Methods: The primary sample ($N = 58$, age = 18-25, 72% Female) consisted of $n = 35$ depressed (Quick Inventory of Depressive Symptoms, QIDS, > 6); and $n = 23$ non-depressed (no history of psychiatric illness and QIDS < 6) adults. During fMRI, participants rated the degree to which they believed positive and negative statements about themselves and famous others. Twenty trials of each type were presented.

Image preprocessing was performed using fMRIPrep and first-level models were constructed in SPM12. Parameter estimates were extracted from regions of interest identified in prior work: Bilateral dorsal anterior insula, MPFC, precuneus/posterior-cingulate cortex (PCC), ventro- and dorsolateral PFC (VLPFC, DLPFC), dorsal ACC, and the temporal-parietal junction (TPJ). Data were analyzed using mixed-effect repeated-measures models with separate terms for each condition (Target: self/other; Valence: positive/negative), implemented in SAS 9.4. False Discovery Rate corrections were used for multiple comparisons. Secondary analyses examined the impact of gender on observed effects.

Trial-by-trial reaction time data were examined using repeated measures models as above. A separate sample ($N = 35$, age: 18-40; $n = 12$ healthy, $n = 23$ with a DSM-IV diagnosis of major depressive disorder) provided behavioral data on the same task and was included as a preliminary replication sample for behavioral effects.

Results: We observed differences between the depressed and non-depressed groups in neural activity in regions of the default mode, salience, and cognitive control networks. In the default mode network, we observed group differences in MPFC ($F(1,85.9) = 5.93$, FDR $q = 0.02$) and the precuneus/PCC ($F(1,85.9) = 5.93$, FDR $q = 0.01$). Differences in the MPFC were driven by increased activity among the depressed group to negative self-related statements ($t(56) = 3.10$, $d = 0.83$, $p = 0.003$). Likewise, those with elevated depression failed to show the normative de-activation in the precuneus/PCC to processing self- compared to other-related information ($F(1,56) = 5.30$, $d = 0.63$, $p = 0.03$). In the salience network, we observed differences between groups in the left dorsal anterior insula ($F(1,94.2) = 7.11$ FDR $q = 0.009$), and the dorsal ACC ($F(1,94.9) = 11.13$, FDR $q = 0.004$). Both effects were driven by increased activity to negative self-related statements for those in the depressed group (insula: $t(56) = 2.29$, $d = 0.62$, $p = 0.03$; dACC: $t(56) = 3.86$, $d = 1.04$, $p = <0.001$). Finally, we observed group differences in the left VLPFC ($F(1,90.8) = 5.31$, FDR $q = 0.02$). Again, the depressed group displayed abnormally increased activity during negative self-related statements ($t(56) = 2.22$, $d = 0.60$, $p = 0.03$). Secondary analyses revealed no evidence that gender moderated the effects reported above (all $Fs(1,54)<2.60$, $ps>0.11$).

Regarding differences in behavior, across the Primary and Replication samples we observed a group-by-target (self/other) interaction for reaction times (Primary: $F(1,56) = 9.63$, $p = 0.003$, Replication: $F(1,33) = 20.9$, $p < .001$). This effect was not moderated by gender (Primary: $F(1,54)<0.01$, $p = 0.98$, Replication: $F(1,31) = 0.07$, $p = 0.80$). The non-depressed group were quicker when making evaluations of themselves than others (Primary: $t(56) = 3.27$, $p = 0.002$, Replication: $t(33) = 6.37$, $p < 0.001$); the depressed group was not (Primary: $t(56) = -0.89$ $p = 0.38$, Replication: $t(33) = 1.02$, $p = 0.32$). Critically, this effect was not due to general slowing as the two groups did not differ in response time when making evaluations of others (Primary: $t(56) = 0.67$, $p = 0.50$; Replication: $t(33) = 0.34$, $p = 0.74$).

Conclusions: Findings suggest that depressed adults process information about themselves differently than do non-depressed adults. Behaviorally, they appeared to lose the benefit in processing speed that non-depressed adults displayed when evaluating themselves. Regarding neural function, depressed adults showed abnormally increased activity during self-related processing, particularly to negative stimuli, across regions of the salience, default mode, and cognitive control networks. It is possible that these patterns reflect abnormal bottom-up processing of self-related information resulting from abnormal initial salience processing. If confirmed, these findings could point to new treatment targets in the salience network for producing more enduring changes in self-evaluation for adults with depression.

Keywords: Depression, Self-Referential Processing, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

P244. Ketamine and Acetyl-L-Carnitine: Mechanisms of the Rapid Regulation of Ventral Hippocampal Plasticity

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Background: In patients with major depressive disorders (MDD), including treatment resistant depression, the levels of acetyl-L-carnitine (LAC) are decreased as compared to age- and sex-matched controls. In rodent models of chronic stress (a major risk factor for depression), administration of LAC leads to a rapid antidepressant response by up-regulation of a chronic stress-induced decrease in expression of the metabotropic glutamate receptor mGlu2 in ventral hippocampus. Similarly, in rodent models of stress, the glutamatergic agent ketamine leads to a rapid antidepressant response. Yet, the circuit level mechanisms underlying the rapid antidepressant-like responses of LAC remains to be determined.

Methods: Here, we used a chemogenetic, behavioral and pharmacological approach to test the role of the ventral hippocampal circuit in the responses to LAC as compared to ketamine at the chronic restraint stress (CRS) in mice of both sexes. Specifically, we used Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) approaches to suppress neuronal firing of the ventral hippocampal circuit in transgenic mice expressing Cre recombinase under the control of the mouse calcium/calmodulin-dependent protein kinase II alpha (Camk2a) promoter (Camk2a-Cre+ mice). Ketamine and LAC were administered at the following doses: ketamine, 10 mg/kg, i.p. injection; LAC, 100 mg/kg, i.p. injection. Two-tailed t-tests, 2-way ANOVA followed by Tukey test were used as appropriate to specific analyses.

Results: Preliminary data showed that single injection of LAC leads to an antidepressant-like response that is as fast as that of ketamine at the CRS paradigm, with sex-specific effects on specific behavioral domains. By using the DREADD approach described above, we show that silencing of neuronal firing of the ventral hippocampal circuit blunts the effects of LAC on the amelioration of CRS-induced behavioral deficits.

Conclusions: These findings support the role of the ventral hippocampus in rapid antidepressant action. Together with our prior findings of decreased LAC levels in subjects with MDD (including treatment resistant depression) our mechanistic framework suggests that further exploration of the link between the mitochondrial metabolite LAC and hippocampal plasticity will aim to develop novel personalized medicine strategies to treat MDD.

Keywords: Glutamate, Depression, Mitochondria
Disclosure: Nothing to disclose.

P245. Efficacy and Safety of AXS-05, an Oral NMDA Receptor Antagonist, in the Prevention of Relapse in Patients With Treatment-Resistant Depression: Results From MERIT, a Double-Blind, Placebo-Controlled Relapse Prevention Trial

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Background: Over 19 million U.S. adults experience at least one major depressive episode per year. Nearly two-thirds of patients with major depressive disorder (MDD) do not experience adequate response to first-line therapy, and most also fail second-line treatment. The goal of treatment is to rapidly achieve and maintain remission of depressive symptoms. Each successive trial of antidepressant therapy is associated with an increasing risk of relapse for those who attain remission, and also for those who partially respond but do not achieve remission. There is therefore an urgent need to rapidly control depressive symptoms to improve outcomes, including relapse risk, functioning, suicide risk and long-term clinical stability. Patients who have not responded to at least 2 different antidepressants in the current depressive episode are considered to have treatment-resistant depression (TRD). Patients with TRD experience relapse at an even higher rate than do those with treatment-responsive MDD.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. AXS-05 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and metabolic inhibition technology, to modulate the delivery of the components. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves primarily to increase the bioavailability of dextromethorphan.

Methods: The MERIT (or Mechanistic Evaluation of Response in TRD) is a randomized-withdrawal, double-blind, placebo-controlled, multi-center study to evaluate AXS-05 compared to placebo in delaying relapse of depressive symptoms in patients with TRD, who were in stable remission after treatment with AXS-05. Eligible subjects were patients with TRD who participated in the up to 12-month open-label study with AXS-05 (AXS-05-303) and had been in stable remission prior to randomization. The dose of AXS-05 was 45 mg dextromethorphan-105 mg bupropion twice daily. Stable remission was defined as at least two consecutive MADRS scores of ≤12, separated by at least 4 weeks. Subjects meeting these criteria were randomized (1:1) to either continue receiving treatment with AXS-05 or to switch to placebo treatment. Randomized subjects were continued on treatment and monitored for relapse of depressive symptoms over up to 52 weeks. The definition of relapse included a MADRS score ≥18 for two consecutive assessments separated by 7-21 days or a CGI-S score change from point of randomization of ≥2 (with a minimum CGI-S score of 4) for two consecutive assessments separated by 7-21 days. The primary objective of the study was the delay in relapse of depressive symptoms, for AXS-05 as compared to placebo, in subjects with TRD who are in stable remission.

Results: A total of 44 TRD patients who experienced a stable remission after up to 12 months of open-label treatment with AXS-05 were randomized to either remain on AXS-05 ($n = 22$) or switch to placebo ($n = 22$). AXS-05 met the primary endpoint by substantially and statistically significantly delaying the time to relapse of depressive symptoms as compared to placebo ($p = 0.002$), with no relapses observed with AXS-05 over at least 6 months of double-blind treatment. AXS-05 also met the key secondary endpoint of relapse prevention, based on the rates of relapse over the double-blind treatment period (0.0% of AXS-05 patients, 36.4% of patients switched from AXS-05 to placebo, $p = 0.004$).

AXS-05 was well tolerated in the trial. There were no treatment-emergent adverse events reported in >1 patient in the AXS-05 group. One subject in the AXS-05 group experienced two serious adverse events (gout and bacteremia) both of which were deemed not related to study medication.

Conclusions: Treatment with AXS-05 significantly delayed the time to relapse of depressive symptoms compared to placebo. AXS-05 is a novel oral NMDA receptor antagonist with multi-modal activity being developed for the treatment of CNS disorders, including TRD and MDD.

Keywords: NMDA Antagonists, AXS-05, Treatment-Resistant Depression, Major Depressive Disorder (MDD)
Disclosure: Axsome Therapeutics: Employee (Self)

P246. Rapid Antidepressant Effects and MADRS Core Symptom Improvements With AXS-05, an Oral NMDA Receptor Antagonist, in Major Depressive Disorder: Results From Two Randomized, Double-Blind, Controlled Trials

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Background: Over 19 million U.S. adults experience at least one major depressive episode per year. Nearly two-thirds of patients with major depressive disorder (MDD) do not experience adequate response to first-line therapy, and most also fail second-line treatment. With existing oral antidepressants, which act primarily via monoaminergic mechanisms, onset of clinically meaningful response can take 6-8 weeks. There is therefore an urgent need for faster-acting, more effective, and mechanistically novel treatments for MDD.

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. AXS-05 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and metabolic inhibition technology, to modulate the delivery of the components. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and sigma-1 receptor agonist, and the bupropion component serves primarily to increase the bioavailability of dextromethorphan.

Methods: AXS-05 was evaluated in two double-blind, randomized, controlled, 6-week trials. The GEMINI trial was placebo-controlled and the ASCEND trial used bupropion as the control. The primary efficacy variable in both was change in the MADRS total score. Here we focus on the efficacy in the first 2 weeks of treatment in both trials, and additionally present a pooled analysis of improvement in the symptom items of the MADRS (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts), for AXS-05 as compared to control.

Results: AXS-05 met the primary endpoint in both studies.

In the GEMINI trial ($N = 327$), starting at Week 1, AXS 05 was statistically significantly superior to placebo on: mean MADRS improvement (7.3 vs. 4.9; $p = 0.007$), MADRS response (≥50% improvement; 15% vs. 7%; $p = 0.035$), CGI-I (22% vs. 13%; $p = 0.035$), CGI-S (0.7 vs. 0.4; $p = 0.013$) and Q-LES-Q-SF (9.0% vs. 5.8%; $p = 0.031$). At Week 2, AXS-05 was statistically significantly

superior to placebo on MADRS remission (≤10; 17% vs. 8%; $p = 0.013$) and on the Sheehan Disability Scale (6.8 vs. 4.5; $p = 0.003$).

In the ASCEND trial ($N = 80$), starting at Week 1, AXS-05 was statistically significantly superior to bupropion on: CGI-I (18% vs. 3%; $p = 0.045$) and MADRS-6 response (≥50% improvement; 16% vs. 3%; $p = 0.044$). From Week 2, AXS-05 was statistically significantly superior to bupropion on: mean MADRS improvement (12.5 vs. 7.8; $p = 0.024$), MADRS remission (≤10; 26% vs. 3%; $p = 0.004$), and CGI-S (1.41 vs. 0.9; $p = 0.049$).

A pooled analysis of both studies found rapid therapeutic effects with AXS-05 on each item of the MADRS. As early as Week 1, treatment with AXS-05 resulted in statistically significantly greater improvements in reported sadness ($p = 0.009$), inner tension ($p = 0.014$), inability to feel ($p = 0.010$), pessimistic thoughts ($p = 0.005$), and suicidal thoughts ($p = 0.001$), as compared to control. At week 2, effects statistically significantly favored AXS-05 for improvements in apparent sadness ($p = 0.008$), reported sadness ($p < 0.001$), inner tension ($p = 0.003$), concentration difficulties ($p = 0.038$), inability to feel ($p = 0.028$), pessimistic thoughts ($p < 0.001$), and suicidal thoughts ($p < 0.001$). At Week 6, AXS-05 demonstrated improvements over control on all items of the MADRS, achieving statistically significance on all items, with the exception of reduced appetite.

Conclusions: AXS-05 demonstrated rapid and statistically significant improvements in symptoms of depression at Weeks 1 and 2 in both placebo- and active- controlled trials. In these studies, rapid remission from depressive symptoms was achieved by Week 2 and maintained over the 6-week treatment periods. These rapid clinical benefits in depression were also reflected on the individual items of the MADRS, including the suicidal thoughts, anxiety, and cognition items. The novel mechanisms of action of AXS-05 may contribute to these rapid therapeutic effects.

Keywords: NMDA Glutamate Receptors, Rapid Antidepressant Effects, Major Depressive Disorder (MDD)

Disclosure: Axsome Therapeutics: Employee (Self)

P247. Anti-Suicide Effect of Ketamine is Associated With Improvements in Effort-Based Anhedonia in Individuals With Comorbid PTSD and Depression

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Background: Evidence suggests intravenous ketamine has rapid effects on suicidal ideation, suggesting potential clinical utility for patients at high risk of suicide. Suicidal ideation is a common feature of severe depression and posttraumatic stress disorder, among other psychiatric diagnoses. Identification of clinical correlates of improvement in suicidal ideation may identify novel targets for the treatment of suicidal thoughts. Like suicidal ideation, anhedonia occurs across psychiatric diagnoses and has been associated with improvements following treatment with ketamine. This analysis sought to evaluate whether reductions in suicidal ideation following a course of repeated ketamine infusions was related to reduced levels of five anhedonia constructs (effort/motivation, interest, social interest, and positive/pleasurable feelings).

Methods: This post-hoc analysis included individuals with comorbid posttraumatic stress disorder and treatment-resistant major depressive disorder that underwent an open-label course of repeated ketamine infusions. Participants received six infusions of of 0.5 mg/kg ketamine on a Monday-Wednesday-Friday schedule over a 12-day period. The outcome of interest for this analysis was a composite index of suicidal ideation (comprised of scores from the Columbia Suicide Severity Rating Scale (CSSRS) and the Montgomery-Asberg Rating Scale (MADRS) suicidal ideation item). Anhedonia constructs were assessed using the MADRS items corresponding to motivation (item 7) and interest/pleasure (item 8), as well as Clinician Assessment of PTSD Symptoms for DSM-5 (CAPS-5) items for interest (item 12), social engagement (item 13), and positive emotions (item 14).

Results: Effort/motivation related anhedonia, as measured by MADRS item 7 was significantly associated with improvements in suicidal ideation after completion of the ketamine infusion series ($F(1,14) = 8.52$, $p < 0.05$). Improvement in effort/motivation-based anhedonia accounted for 39.6% of the variance in suicidal thought reduction All other anhedonia items were not significantly associated with improvements in suicidal ideation following the ketamine infusion series.

Conclusions: Suicidal thoughts may be related to symptoms of anhedonia that address effort/motivation constructs. These improvements are independent of other depression symptoms. These results provide preliminary evidence suggesting that ketamine's benefit for suicidal thoughts may be strongly related to changes in anhedonia as it relates to effort/motivation.

Keywords: IV- Ketamine, Anhedonia, Suicidal Ideation, Depression, PTSD

Disclosure: Nothing to disclose.

P248. Liquid Biopsy in Neuropsychiatry Disorders: Brain Derivate Extracellular Vesicles in Late-Life Depression and Alzheimer Dementia

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Background: Despite the prevalence and public health importance, the biological mechanisms related to neuropsychiatry disorders are not well-defined. Most studies evaluated the molecular abnormalities related to these disorders examined changes in peripheral tissues (e.g., blood or plasma/serum), looking for possible peripheral biomarkers. However, it is not clear to what extent such changes directly reflect the molecular changes in the CNS during these disorders. Following a stressful and depressive condition, there is an activation of the neurons and astrocytes, leading to subsequent changes in other systems such as immune and cardiovascular. A persistent or highly intense stress stimulus in these cells might lead to increased release of EVs, an important mechanism to intercellular communication leading to a different response in the periphery, including maladaptive immune response, ultimately inducing brain-cell death and behavioral changes such as anxiety and depression. Derived EVs from neurons (NDE) and astrocytes (ADE) can easily cross the blood-brain barrier and be identified in the periphery. Only a few papers are using preclinical data evaluating NDE and ADE in neurodegenerative disorders, especially AD. But none in depression and cognitive dysfunction in humans. Therefore, identifying circulating brain-derived EVs can provide invaluable information of ongoing molecular pathology in depressive episodes.

Methods: We recruited 47 LLD subjects, 19 AD patients, and 34 healthy elderly controls, matched by age and gender. After the psychiatric evaluation, the blood was collected, centrifuge to obtain the plasma-free platelet. The sample was collected and stored at -80°C. We used the kit vFC™ vesicle flow cytometry for counting and sizing vesicles.

Results: Individuals with LLD presented low levels of EV (652.5 ± 318.3) when compared to controls (854.2 ± 387.9). The opposite was demonstrate with EV from AD Patients, with a increased

number of EV (1083 ± 402.8). Regarding the origin of EV, we evaluated EV from innate immune cells, neurons, and astrocytes. The innate immune EVs in LLD is decreased compared to controls. However, there is no difference in neurons and astrocytes. For AD patients, there is no difference between innate and neuron EV. However, for astrocytes AD patients present 2 times more EV when compared to CT and LLD. Further, we stratify the EV population by size. The quantity of exosome from the neuron (170 ± 214 and 349 ± 219.7), astrocytes (104 ± 51.67 and 126 ± 34.93), and innate immune cells (349 ± 299 and 587.5 ± 300) are reduced in LLD compare to controls. For AD, the ADE population is responsible for the increase the circulating EV in AD.

Conclusions: The communication between the brain and the peripheral cells driving by the EVs is compromised for both disorder: LLD and AD, contributing to this disorder's pathophysiology but in a opposite direction. The exosomes from innate immune cells and astrocytes are the main population affected in LLD and AD, respectively. This showing the crosstalk between brain cells and periphery as a window to directly evaluate the molecular pathology of late-life mood disorder and AD.

Keywords: Extracellular Vesicles, Late-Life Depression, Neuron-Derived Exosomes (NDE), Astrocyte-Derived Exosomes (ADE)

Disclosure: Nothing to disclose.

P249. Long-Term Intermittent Exposure to Alcohol Alters Social Avoidance Behavior in Adult and Adolescent Male Mice Exposed to Emotional or Physical Stress

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Background: Emotional and/or physical stress have been shown to influence adult-onset psychopathology and increase the propensity for drug seeking. Animal models of chronic stress corroborate that exposure to physical stress results in long-term maladaptive behavior as seen in the social interaction test (SIT) and elevated plus maze (EPM), used to measure depression- and anxiety- like behavior, respectively. Furthermore, exposure to stress alters the rewarding properties of many drugs of abuse, including alcohol, which is commonly abused by both adults and adolescents. Previous work suggests that stress can promote increased alcohol intake and further influence depression-related behavior, however, little is known as to whether alcohol has the same effect across different types of stressors (i.e. emotional vs. physical). Additionally, chronic stress has been shown to breakdown the blood-brain barrier (BBB), specifically at the level of tight junction proteins and increase stress susceptibility. Interestingly, alcohol consumption itself has also been shown to alter BBB integrity thus suggesting that consumption after exposure to chronic stress can exacerbate already existing mood-related deficits. Using the vicarious social defeat stress (VSDS) model, we aimed to assess how stress, both indirect (emotional/psychological) and direct (physical), influence alcohol intake in adult and adolescent male mice and subsequent social-avoidance behavior. Further this work evaluated how stress-induced BBB- and inflammation-related changes may drive social avoidance behavior and how these deficits are influenced after alcohol consumption.

Methods: Adult and adolescent mice were subjected to ten days of VSDS and then given intermittent access to 20% alcohol. Briefly, the home cage of a male CD-1 retired breeder mouse was separated by a Plexiglas divider into two adjacent compartments. An adolescent male C57BL/6J mouse was introduced into the compartment territorialized by the CD-1 mouse where it was repeatedly overpowered (PS), demonstrating escape-like behaviors, vocalizations, and submissive posturing, while a second adolescent male C57BL/6J mouse witnessed (ES) the interaction from the adjacent compartment. After ten days, adult and adolescent ES and PS mice show avoidance of a social target in the social interaction test (SIT), indicative of a depressed-like phenotype. Next, all experimental conditions (i.e. CON, ES, PS) were exposure to intermittent access to 20% alcohol for eight weeks. Blood serum and nucleus accumbens tissue punches were collected from all groups to assess changes in peripheral inflammatory markers and BBB-related targets, respectively. Additionally, A separate group of mice were exposed to VSDS to see how endothelial tight-junction expression changed just after exposure to either ES or PS in both adult and adolescent mice.

Results: After two months of alcohol consumption, mice were re-exposed to the SIT, and then to the EPM. Adult ES and PS mice show differences in alcohol consumption a difference not observed in adolescent mice. However, after alcohol intake, adult and adolescent mice show differences in avoidance behavior, specifically, those exposed to ES, suggesting a developmental difference in stress x alcohol interactions.

Conclusions: Taken together these data suggest that adults and adolescents react differently to stress and that stress exposure differently drives alcohol consumption. This data may shed light on why people with mood disorders have a higher incidence of comorbid depression and substance use, while also highlighting that adolescents exposed to psychological stressors may be more susceptible to the maladaptive consequences of alcohol consumption. Future investigations into the mechanisms involved may provide further insight into the etiology of stress-and alcohol-related mood dysfunction.

Keywords: Social Defeat Stress, Alcohol, Adolescent

Disclosure: Nothing to disclose.

P250. Predicting Treatment Response to Transcranial Magnetic Stimulation Using an Exponential Decay Function

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Background: Recovery from major depressive disorder (MDD) has been shown to follow a nonlinear pattern of treatment response that can be modeled using an exponential decay function. This pattern of large reductions in depressive symptoms early in treatment followed by smaller but continued improvements has been demonstrated at the group level for multiple antidepressant medications. However, it is unclear if this exponential pattern of symptom response can be extrapolated to other depression treatment modalities, such as transcranial magnetic stimulation (TMS). The objective of this study was to apply this exponential decay model of treatment response to therapeutic TMS and investigate the utility of this model for predicting clinical outcomes based on early treatment response.

Methods: We collected symptom rating data from a naturalistic sample of 97 patients treated with left-sided, high-frequency, clinical TMS at the Providence VA Medical Center at baseline and after every five TMS treatment sessions using the Patient Health Questionnaire 9 (PHQ-9). We constructed a nonlinear mixed-effects model using the exponential decay function, $D(t) = A*e^{(-t/B)} + C$. In this model, symptom ratings (D) at treatment (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 patient level, and parameters A, B, and C were fit as fixed effects at the group level. We compared this nonlinear model to a

corresponding linear mixed-effects model in which the slope and intercept were treated as random effects by patient using the Akaike information criterion (AIC) and likelihood ratio test (LRT). We then assessed the predictive utility of this model using leave-one-out cross-validation (LOOCV) by estimating the time constant (B) on a subset of the sample and using this estimate to calculate the predicted symptom level at the end of treatment (C) for the left-out individual based on symptom rating scores at baseline and after five or ten sessions of TMS.

Results: The naturalistic sample of 97 patients receiving clinical TMS incorporated 562 observations with each individual contributing 2 to 9 (Median 6) longitudinal measurements of depressive symptoms as measured by PHQ-9. The pattern of treatment response to TMS was well modeled with the exponential decay function, yielding significant estimates for model parameters A, B, and C (all $p < 0.001$). On average, patients experienced a 5.8 point drop in PHQ-9 scores with a time constant (B) of 6.1 TMS treatments. When compared to a corresponding linear mixed-effects model, the exponential decay model displayed lower AIC values and a significant likelihood ratio (LRT = 63.2, $p < 0.001$), suggesting that the nonlinear model is a better fit. In subsets containing complete longitudinal data ($n = 82$-90), LOOCV yielded consistent estimates of the time constant B (mean 6.065, sd 0.12). By rearranging the exponential decay function using this time constant estimate (B) and symptom scores at baseline and after five ($n = 90$) or ten sessions ($n = 82$), we calculated predicted values of C for the left out patients. These predicted C values yielded significant correlations with the PHQ-9 scores at the end of treatment, accounting for 38% to 59% of the variance in final scores, using baseline and either scores after five or ten TMS sessions, respectively (all $p < 0.001$).

Conclusions: These results provide evidence that the antidepressant response to TMS demonstrates a nonlinear pattern of symptom improvement that follows an exponential decay function. This modeling suggests that the greatest improvements in symptom reduction occur early in the TMS treatment course. These methods provide a mathematical description of the relationship between early symptom changes and treatment trajectories that could be used to predict TMS outcomes and guide clinical treatment decisions.

Keywords: Transcranial Magnetic Stimulation, Statistical Methods, Predictive Models

Disclosure: Nothing to disclose.

P251. Alteration of Hypothalamus Functional Connectivity Related to Change in Cortisol and Ghrelin Following Psychosocial Stress in Major Depressive Disorder

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Background: Exposure to psychosocial stress activates the HPA-axis, induces changes in global brain networks, and is implicated in the development of psychiatric disorders, including Major Depressive Disorder (MDD). Stress can lead to changes in HPA-axis hormones (cortisol) which play key roles in the positive adaptation to stress; and recent data supported the novel involvement of ghrelin, a hypothalamic orexigenic peptide, in the adaptation to stress. The stress-related endocrine system is connected to the global brain network through the hypothalamus, which is part of the HPA axis. Previous studies suggested that acute stress induces time-dependent shifts in brain functional connectivity (FC) in the salience and executive control networks. However, relationships between endogenous hormones and brain functional connectivity in the aftermath of stress in MDD have not been well characterized. To fill this gap, we investigated the association between hypothalamus functional connectivity and individual differences in cortisol and ghrelin responses to psychosocial stress in MDD.

Methods: Sixty-nine individuals with current Major Depressive Disorder (MDD; 27.42 ± 5.94 years; 35 females) and 39 Healthy Controls (HC; 28.10 ± 5.94 years; 19 females) participated in this study. Subjects completed two study visits (Stress and Control), one involving a psychosocial stress task (Maastricht Acute Stress Test, MAST), the other a matched control task, each followed by a resting-state functional MRI (rs-fMRI) scan approximately 60 minutes post-stress/control task. Serial blood draws for assessment of cortisol and ghrelin were collected pre- (T0) and post-stress/control tasks (T20 min, T80 min, etc.). The area under the curve (AUC) between T0 to T80 for ghrelin and cortisol was calculated using the trapezoidal method. rs-fMRI data preprocessing and analysis were performed using CONN toolbox v19b with results threshold at $p < 0.05$, FWE-corrected. Differences in hypothalamus FC between the Control and Stress visits were compared between MDD and HC groups using seed-to-voxel analysis. Average hypothalamus FC values were extracted from significant clusters. Pearson correlations were used to assess relationships between hypothalamus FC and hormones with SPSS v24.

Results: There was a Group (MDD vs. HC) x Visit (Stress vs. Control) interaction in clusters spanning anterior and posterior cingulate gyrus (512 voxels, p-FWE = 0.001), superior frontal gyrus (SFG; 486 voxels, p-FWE = 0.002), middle frontal gyrus (MFG; 427 voxels, p-FWE = 0.006) and putamen (380 voxels, p-FWE = 0.014). Post-hoc analyses revealed that during the Stress Visit compared to the Control visit, hypothalamus FC to cingulate gyrus was increased in HC ($t = -6.43$, $p < 0.001$) but decreased in MDD ($t = 3.69$, $p < 0.001$). Additionally, HC showed decreased but MDD showed increased hypothalamus FC to SFG (HC: $t = 5.13$, $p < 0.001$; MDD: $t = -3.50$, $p = 0.001$), MFG (HC: $t = 3.92$, $p < 0.001$; MDD: $t = -4.01$, $p < 0.001$), and putamen (HC: $t = 3.82$, $p < 0.001$; MDD: $t = -5.58$, $p < 0.001$). For the Stress Visit, cortisol AUC was positively correlated with hypothalamus FC to putamen in HC ($r = 0.353$, $p = 0.028$), but not in MDD ($r = -0.12$, $p = 0.35$). In contrast, for the Control Visit, HC showed a negative correlation between cortisol AUC and hypothalamus FC to MFG ($r = -0.411$, $p = 0.009$); in MDD this relationship was not significant ($r = -0.02$, $p = 0.87$; fisher's test $z = -2.01$, $p = 0.044$). Across groups, for the Control Visit, there was a negative correlation between ghrelin AUC and hypothalamus FC to cingulate gyrus ($r = -0.223$, $p = 0.03$).

Conclusions: These findings indicate that, in the aftermath of stress, individuals with MDD exhibit differential hypothalamus FC to nodes of the default mode network (DMN) and frontal-parietal network (FPN), and to the putamen, relative to healthy controls. In response to stress, relative to the control task, HC showed increased hypothalamus FC to DMN, while those with MDD exhibited the opposite pattern: decreased hypothalamus FC to DMN. Previous studies have reported that, in the absence of a psychosocial stressor, MDD is characterized by hyperconnectivity within DMN nodes compared to HC. Current findings suggest that altered DMN functioning in MDD is further disrupted under stress, particularly in relation to connectivity with the hypothalamus. Increased stress-induced hypothalamus to FPN/putamen FC in HC is consistent with prior literature showing that acute stress induces increased salience network FC and decreased executive control network FC in HC. In addition, increased hypothalamus-putamen FC in MDD after acute stress aligns with evidence of increased putamen-subcortical connectivity in MDD. Relationships between cortisol and hypothalamic FC, which were present in HC but absent in MDD, point to dysregulation of the HPA-axis in response to stress in MDD. Finally, ghrelin AUC-hypothalamus-cingulate FC relationships across groups indicate ghrelin may be involved in maintaining coordinated co-activation of stress-regulation

(hypothalamus) and attention/emotion-regulation circuits in the absence of stress. In conclusion, results suggest differential interactions between the hypothalamus and default mode and executive control networks in response to psychosocial stress in MDD. These findings provide novel evidence of a dissociation between hypothalamus and default mode and executive network connectivity in MDD, highlighting new pathways to target for treatments of stress-related psychiatric conditions.

Keywords: Resting State Functional Connectivity, Acute Stress, Major Depressive Disorder (MDD), Ghrelin, Cortisol

Disclosure: Nothing to disclose.

P252. The Essential Role of CRF in Gating the Emergence of Depression

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Background: Major Depressive Disorder (MDD) is a debilitating mental disorder with a lifetime prevalence in the U.S. of 25%. Despite extensive research exploring the etiology of MDD, an urgent question remains as to what governs the exact moment of its emergence. The chronic social defeat stress (CSDS) paradigm is a well-vetted model of depression that produces resilient and depressive-like phenotypes. Using the strength of this model, we asked the question: At which point do we see the earliest emergence of what would become a durable depressive-like (DEP) phenotype in C57BL/6J mice? The oval nucleus of the bed nucleus of the stria terminalis (BNSTov) plays a pivotal role in stress-related psychopathology, aided in part by CRF neurons. Here we reveal surprising results that, in contrast to its well-studied role in promoting negative aversive states, CRF neurons play an unexpected beneficial role in promoting durable resiliency to depression.

Methods: Mice subjected to 10 days of CSDS were assessed via social interaction (SI) and sucrose-preference tests. To capture the neuronal changes associated with the emergence of depressive-like behavior selectively in BNSTovCRF neurons, we utilized cell-attached electrophysiology in Crf-Cre::TdTomato mice. To simultaneously manipulate and record the activity of BNSTovCRF neurons in vivo, Crf-Cre mice were injected with viral constructs (Cre-dependent DREADDs and gCAMP7f calcium-encoded indicator) and ferrule cannulae implanted. RNAScope was used to corroborate electrophysiological changes with molecular changes in the CRF neuronal system.

Results: We observed that depressive-like behavior emerges between 7 and 10 daily defeat episodes as indicated by the marked change in mean social interaction score (day 7: 1.96 vs day 10: 0.61, $N = 216$ mice, $p < 0.0001$, 2-way ANOVA) and sucrose preference test (80% vs 51%, $p < 0.005$, $N = 15$, One-way ANOVA). The depressive phenotype occurred exclusively after at least seven stress episodes of social defeat, directly related to a stress accumulation effect. A decrease in the spontaneous firing rate of BNSTovCRF neurons was observed selectively in mice subjected to 10 days of social defeat that expressed depressive-like behavior (DEP) compared to those that underwent only 7 defeat episodes (denoted STR mice) and had not yet gone on to develop a depressive-like phenotype (5.194 hz vs 1.210 hz; $p < 0.0001$, $N =$ 17-19 neurons per group, one-way ANOVA). However, in CRF-BNST neurons no significant difference were observed between the groups ($p > 0.05$, $N = 27$ neurons). DREADDs were used to test the causal role of BNSTovCRF neurons in gating the trajectory of STR mice becoming DEP mice. hM3Dq DREADDs resulted in (0/7 mice, 0%) of STR becoming DEP mice, compared with the hM4Di condition where (1/8 mice, 87.5%) and control-mCherry (9/13 mice, 70%) of STR became DEP mice respectively. Notably this effect occurred only when CNO was administered between the 7th and 10th social defeat stress exposure, not between equivalent 3-day intervals such as between the 4th-7th or 11th-13th episodes ($p > 0.05$, $N =$ 14-20 mice/group, 2-way ANOVA). To determine whether the emergence of depressive-like behaviors were reflected by changes in BNSTovCRF neuronal responses to social contexts, we used fiber photometry combined with DREADDs. We observed an increase in neuronal activity in response to a novel social context (z-Score increased from 0.29 to 3.1067 during -3 to +3s of social contact, $n = 5$, $p < 0.0001$) in hM3Dq/gCamp7f injected mice, compared to hM4Di/gCamp7f and mCherry/gCamp7f injected mice respectively (z score -1.46 to -1.916, $n = 5$, $p > 0.05$; -2.74 to -2.94, $n = 5$, $p > 0.05$). Using RNAscope, we uncovered that STR mice displayed a greater degree of crhr1 mRNA in CRF neurons relative to DEP mice (24.75% vs 2.63%; $F(3, 18) = 20.91$, $p < 0.0001$, $n =$ 4-6).

Conclusions: Altogether, these findings reveal that CRF-system plays a fundamental role in resiliency to developing depression states in the context of chronic stress adaptation. Interestingly, the findings showcase a novel role that CRF is both necessary and sufficient to gating the affective consequences of stress but in a dynamic and stress-dose dependent manner. This opens an exciting avenue for translationally-relevant treatments that takes into account the subject's stress history in providing crucial components to which drugs may work.

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Keywords: Depression, Social Stress, Corticotropin-Releasing Factor (CRF)

Disclosure: Nothing to disclose.

P253. Survivors of SARS-CoV-2 Infection Show Neuropsychiatric Sequelae Measured by Surveys, Neurocognitive Testing, and Magnetic Resonance Imaging: Preliminary Results

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Background: Following recovery from primary infection with SARS-CoV-2, the virus that causes COVID-19, 22%-44% of patients report neuropsychiatric symptoms, including depression, anxiety, and neurocognitive deficits. Furthermore, abnormalities in the olfactory bulb are the most common structural neuroimaging findings following COVID-19 infection. In this report, in the months following COVID-19 diagnosis, we aimed to 1) characterize the prevalence and severity of psychiatric symptoms and neurocognitive deficits; 2) assess the structure of the olfactory bulb and relate it to a common symptom of COVID-19, anosmia; and 3) identify neural circuit dysfunction.

Methods: As part of the Infection Recovery in SARS-CoV-2 (IRIS) Neurostudy cohort, we enrolled 100 participants who were diagnosed with COVID-19 due to symptoms and confirmed by PCR testing from a convenience sample of patients presenting to Stanford. During the initial study visit at ~3 months after COVID symptom onset, depression symptoms were captured using the Patient Health Questionnaire-9 (PHQ-9) and anxiety symptoms with the Generalized Anxiety Disorder 7-item (GAD-7). Clinically significant psychiatric symptoms were defined as PHQ-9 and/or GAD-7 > 10, corresponding to a least moderate depression and/or anxiety. A battery of neurocognitive assessments was also administered to assess

sustained attention, working memory, processing speed, executive function, selective attention, and recall memory. For neurocognitive tests, standardized means were calculated for each of the measures of interest using a normative sample and one sample t-tests were run comparing each mean to zero. k-means clustering was applied to the neurocognitive data to separate participants into groups. In a subset of participants ($n = 15$), a T1-weighted anatomical MRI image was collected and reviewed by a neuroradiologist to detect any structural abnormalities in the olfactory bulb. In this same subset, functional MRI (fMRI) assessments were also completed. Task residuals from three fMRI tasks were used to quantify pairwise intrinsic functional connectivity (FC) between key nodes in the attention circuit, default mode network (DMN), and the salience circuit after removing the task-related activity. Furthermore, we used the same data to quantify FC seeded in the ventromedial prefrontal cortex (vmPFC) given evidence that this region acts a central hub for reduced FC associated with increased inflammation in depression. For the cognitive control and negative and positive affect circuits, we examined brain-wide activation as elicited by the Go-NoGo and Viewing of Facial Emotion Tasks. We ran one sample t-tests comparing the mean of the IRIS Neurostudy participants standardized to a healthy control sample ($n = 50$) to a mean of zero. We report results at the voxel-level $p < 0.001$ (uncorrected) and cluster level $p < 0.05$ (FWE-corrected) for activation and seed-based FC results, and at the edge level $p < 0.01$ (uncorrected) and component level $p < 0.05$ (FWE-corrected) for pairwise FC results via the network-based statistic.

Results: 26% of participants had moderate to severe depression and/or anxiety symptoms, indicative of clinically significant psychiatric impairment. Participants showed a profile consistent with 'brain fog' characterized by significant impairment in domains of sustained attention, working memory, processing speed, and executive function when compared to standardized age, sex, and education matched healthy reference norms (adjusted p's < 0.001). k-means clustering yielded two clusters: 41.6% of the cohort was 'impaired' across all neurocognitive domains; the other cluster was relatively 'intact' with the exception of sustained attention, which was impaired in both clusters. Of the 15 clinical MRI reads, 8 (53.3%) were found to have small olfactory bulbs, all of whom reported anosmia - a partial or complete loss of sense of smell. We found that pairwise FC between the medial superior prefrontal cortex and the bilateral precuneus within the attention network was significantly lower for standardized IRIS subjects. Standardized IRIS subjects also showed hypoconnectivity between the vmPFC and its surrounding voxels, middle cingulate cortex, and bilateral ventral striatum. No brain-wide activation results survived multiple test correction.

Conclusions: With over 199 million patients diagnosed with COVID-19 to date worldwide, post-COVID sequelae are a major public health burden. To our knowledge, our study is the first to examine functional neuroimaging findings in post-COVID patients. We demonstrate that psychiatric symptoms, neurocognitive dysfunction, and olfactory bulb abnormalities are accompanied in some patients by dysfunction in the attention network and hypoconnectivity between the vmPFC and bilateral striatum. Notably, prior work in depressed subjects has demonstrated that inflammation is associated with decreased resting-state FC in the attention network and in corticostriatal neurocircuitry. Furthermore, olfactory bulb atrophy in combination with anosmia suggests the possibility that SARS-CoV-2 may enter the brain through the olfactory nerve, triggering neuroinflammation that effects other brain areas. A next step will be to assess the relationship between inflammatory markers and our symptom and neuroimaging data. Our work contributes to efforts to understand the mechanisms contributing to neuropsychiatric sequelae of COVID-19.

Keywords: COVID-19, fMRI, Neuro

Disclosure: Nothing to disclose.

P254. Multidimensional Brain-Body Predictors of Susceptibility and Resilience to Social Defeat Stress: Individual Trajectories of Mitochondrial Dysfunction

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Background: Why do some individuals succumb to stress and develop debilitating psychiatric disorders, whereas others adapt well in the face of adversity? Prior studies characterized susceptible and resilient phenotypes after exposure to stress; however, the mechanisms underlying individual differences predisposing to those phenotypes are less known. Here, we tested whether i) multidimensional biomarkers spanning systemic and brain domains predicted susceptibility or resilience to social defeat stress (SDS) in mice, and ii) how early life stress contributes to the development of these phenotypes.

Methods: We used computational, behavioral and pharmacological techniques to ascertain the emergence of the novel mitochondrial mediator of glutamatergic function acetyl-L-carnitine (LAC) in relation to brain imaging measures and previously described individual predictors of susceptibility to stress, including inflammatory markers and anxiety-like behavior. Before the beginning of the social defeat stress (SDS) paradigm, mice were screened at the light-dark test (LDT) as high anxious phenotype (HS) and less anxious phenotype (LS), as we previously reported (Nasca et al, Mol Psychiatry 2015); next submandibular blood was collected for assessment of i) LAC levels by liquid chromatography–mass spectrometry (LC-MS) as we previously described in Nasca et al, PNAS 2018, and ii) immunological assessment by flow cytometry and IL-6 measurements as we previously reported in Hodes et al, PNAS 2015. Prior to the beginning of 10 days of SDS, separate cohorts of HS and LS phenotypes were also subjected to magnetic resonance imaging (MRI) scans. After 10 days of SDS, HS and LS phenotypes were tested for social interactions (SI). RNAseq and bioinformatics analysis for the ventral dentate gyrus was performed as we previously described in Nasca et al, Neuron 2017. We also developed an algorithm in *R* to integrate multiple phenotypic measures for predicting a priori the individual trajectories of responses to SDS. Statistical analyses were performed using 1- or 2-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test, or 2-tailed unpaired Student's t tests, as appropriate. LDT screening ($n = 88$, $p < 0.001$); inflammatory and mitochondrial measures ($n = 25$, $p < 0.01$); hippocampal volume ($n = 8$, $p < 0.01$); RNAseq for vDG: 4 biological replicates per group (FC > 1.3, $p < 0.05$); social interaction test ($n = 45$, $F2,42 = 4$, $p = .0002$).

Results: Preliminary data showed decreased levels of the pivotal mitochondrial metabolite LAC in high-susceptible (HS) biobehavioral phenotypes as compared to low-susceptible (LS) phenotypes ($p < 0.01$). The HS phenotype is also characterized by co-presence of anxiety (i.e.: increased time spent in the dark box of the LDT, $p < 0.001$), decreased hippocampal volume ($p < 0.01$) and elevated systemic interleukin-6 levels ($p < 0.01$) prior to any applied stress. After 10 days of social defeat stress, only the HS phenotype showed social withdrawal ($p < 0.05$), while the LS remain resilient. Using an algorithm in *R* to integrate brain-body phenotypic measures, we developed a model that predict a priori whether a given animal developed SDS-induced social withdrawal, or remained resilient. In addition, our new data showed that that low maternal care is a risk factor for development of deficits in mitochondrial metabolism of LAC.

Conclusions: Our new findings suggest that specific aspects of mitochondrial dysfunction may be a molecular mechanism linking early life experience to the individual trajectories of responses to social defeat stress. Taken together, this study identifies integrated multidimensional biological networks and environmental factors for providing more detailed signatures to predict a priori susceptible or resilient phenotypes in the response to stress.

Keywords: Mitochondrial Dysfunction, Early Life Stress, Glutamate

Disclosure: Nothing to disclose.

P255. Increased Levels of Circulating Cell-Free mtDNA in Plasma Predicts Severity of Depressive Symptoms in Bipolar Disorder

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Background: Bipolar disorder (BD) is a severe and chronic psychiatric disorder that affects approximately 1-4% of the world population. The pathophysiological pathways responsible for BD remain elusive, likely due to multifactorial etiology involving the interaction between multiple genetic, neurochemical, and environmental factors. The mitochondrial dysfunction hypothesis has been corroborated by several studies showing that BD patients present an atypical mitochondrial metabolism, abnormal mitochondrial morphology and dynamics, and mitochondrial DNA (mtDNA) damage. The amount of mtDNA released by a cell is a marker of mitochondrial health. Circulating cell-free mitochondrial DNA (ccf-mtDNA) levels reflect dysregulation homeostasis in place of cellular stress, apoptosis, or bioenergetic compromise. Furthermore, a recent surge of investigators looking at ccf-mtDNA as a potential biomarker in psychiatric conditions has been increasingly growing in interest, mainly in the context of mitochondrial dysfunction. In this study, (1) we evaluated if the ccf-mtDNA levels were different between individuals with BD compared to healthy controls (HCs), and (2) we evaluated the association between BD symptomatology with peripheral ccf-mtDNA levels.

Methods: In this study, 122 subjects were enrolled at the Center of Excellence in Mood Disorders at UTHealth, including 73 BD type I (BD-I) and 49 HCs. All subjects underwent a comprehensive clinical interview and diagnosis of BD according to the DSM-IV-TR. Mood symptoms were assessed with the Montgomery Asberg Depression Scale (MADRS), Young Mania Rating Scale (YMRS), and psychomotor speed with the Brief Assessment of Cognition in Affective Disorders (BAC-A). Quantitative analysis of the plasma levels of ccf-mtDNA was performed using a real-time polymerase chain reaction (rtPCR).

Results: One-Way ANCOVA, after controlling for age, sex, body mass index, smoking status, and psychotropic treatment showed that BD-I subjects present higher levels of ccf-mtDNA when compared to HCs ($R2 = 0.032$, $p = 0.030$). Moreover, we found that ccf-mtDNA levels predicted the severity of depressive symptoms ($\beta = 0.199$, $p = 0.015$), while the YMRS scores were not associated with levels of ccf-mtDNA. Furthermore, ccf-mtDNA levels predicted a deficit in psychomotor speed ($\beta = -0.234$, $p = 0.021$).

Conclusions: These preliminary results indicate that elevated levels of ccf-mtDNA are observed in BD-I subjects compared to HCs. In addition, that levels of ccf-mtDNA are associated with the severity of depressive symptoms among BD-I subjects. Finally, ccf-mtDNA levels predicted a deficit in psychomotor speed. Thus, our results provide further evidence that mitochondrial dysfunction may be proximal to the pathogenesis of BD. Further studies are needed to investigate the potential role of bioenergetics in disease progression, prognosis, and response to treatment.

Keywords: Circulating Cell-Free Mitochondrial DNA, Bipolar Disorder, Mitochondria

Disclosure: Nothing to disclose.

P256. Appetitive and Aversive Stimuli Activate Two Distinct Populations of Ventral Pallidal Cholinergic Neurons

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Background: The ventral pallidum (VP) is a key brain region involved in encoding hedonic value of external stimuli and mediating motivated behaviors. Traditionally, these actions were believed to be accomplished largely via VP GABAergic and glutamatergic neurons, which bidirectionally modulate motivation. However, the VP also encompasses a population of cholinergic neurons. Although acetylcholine has a well-defined role in encoding emotionally salient memories, the functional role of cholinergic neurons in the VP remains unclear. We have previously found that exposure to innately threatening stimuli elicits defensive behaviors in mice, leading to a significant increase in the number of activated cholinergic neurons in the VP/substantia innominata. Whether this increase is specific to aversive stimuli, or if the same cholinergic neurons are also activated in response to appetitive stimuli remains unknown. This study defines the specific population(s) of cholinergic neurons in the VP that respond to innate appetitive vs. aversive stimuli.

Methods: To investigate whether cholinergic neurons are activated by both aversive and appetitive stimuli, transgenic mice (both male and female) which express a green fluorescent protein (GFP) under control of an immediate early gene (fos) were used. Behavioral responses to saline, an appetitive odor (2-phenylethanol) or an aversive odor (predator urine), were characterized in a single, ten-minute session in a Y-maze. Following behavioral testing, the VP was examined for activated cholinergic neurons by expression of IEG reporters (c-Fos). To test whether distinct subsets of VP cholinergic neurons are activated in response to appetitive vs. aversive odors, viral vectors that permanently label activated cells were injected in the VP and used in conjunction with immunohistochemistry and fluorescent microscopy. We used two viral vectors in these studies: 1. an activity- and cre-dependent viral vector (ADCD; (Rajebhosale, Ananth et al, 2021)) and 2. a robust activity marking system (RAM; (Sorensen et al, 2016)). Both viral vectors utilize a Tet-Off system, where, in the absence of a doxycycline (DOX) diet, activated neurons are permanently labeled with mCherry. With both viral vectors, cFos immunostaining can also be used to label activated neurons in two distinct contexts. Mice underwent behavioral testing across 3 days: Day 0 = habituation (DOX-on), Day 1 = appetitive odor (DOX-off), Day 2 = aversive odor (DOX-on). Following aversive odor exposure, brains were collected, and tissue was processed for immunohistochemistry.

Results: Behavioral results indicate that both appetitive and aversive odors elicit innate behavioral responses in mice. When given a choice between an arm containing a saline pad or an appetitive odor pad, mice spent significantly more time in the arm with the appetitive odor. In contrast, mice spent significantly less time in the arm containing the aversive odor. Furthermore, both odors significantly increased the number of activated cholinergic neurons in the VP. Utilizing ADCD and RAM, we examined if these activated cholinergic neurons in the VP were the same neurons following exposure to appetitive and aversive odors, or if each odor activated different subsets of VP cholinergic neurons. Our results are consistent with there being two distinct

subpopulations of VP cholinergic neurons: one population activated in response to an appetitive odor and a second, distinct population activated upon exposure to an aversive odor. Importantly, the results were replicable using either ADCD or RAM viral vectors, and consistent across order of odor presentation (i.e. if odor presentation was reversed).

Conclusions: The results from the present studies reveal that the VP contains two distinct and non-overlapping subpopulations of cholinergic neurons, which are uniquely engaged by either appetitive or aversive stimuli. These results contribute to our understanding of the diversity of basal forebrain cholinergic neurons. In ongoing studies, we are exploring how these subpopulations of VP cholinergic neurons differ, with a focus on mapping their projections and measuring their baseline electrical properties. In addition, we are directly assessing their contribution to innate approach/avoidance behaviors.

Keywords: Cholinergic System, Ventral Pallidum, Innate Behavior

Disclosure: Nothing to disclose.

P259. Serotonin Receptor mRNA Expression is Lower in Hippocampus of Untreated Depressed Subjects, Higher With Antidepressant Treatment, and Correlates With Number of Cells Expressing PSA-NCAM

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Background: The serotonin 1A receptor (5-HT1AR) is implicated in morphogenesis and survival of newly born neurons in the adult hippocampus. Treatment with the serotonin reuptake inhibitor (SSRI) fluoxetine increases neurogenesis and reduces depressive phenotype, yet neither effect is produced in 5-HT1AR knock-out mice. In response to stress, 5-HT1AR density and mRNA levels decrease via adrenal axis stimulation. We hypothesize that low 5-HT1AR mRNA density may be a hallmark of major depression (MDD) neuropathology, and that greater 5HT1AR mRNA density may be indicated in subjects treated with SSRIs. We also hypothesize that 5HT1AR mRNA density correlates with putative immature neurons expressing the neural migration marker, polysialylated neural cell adhesion molecule (PSA-NCAM).

Methods: Psychological autopsy identified 10 untreated MDD subjects, nine MDD subjects treated with antidepressants, and nine non-psychiatric controls, matched for age, sex and post-mortem interval. At autopsy, brain pH, neuropathology, and toxicology exams were performed. Frozen whole hippocampi were fixed and sectioned at 50 μm. We carried out 5-HT1AR in situ hybridization using an 35S-labeled 5-HT1AR riboprobe and quantified the density of mRNA in CA1, CA3, DG and white matter. PSA-NCAM was labeled by immunocytochemistry on sections at 2-mm intervals throughout the anterior, mid and posterior DG and their number was estimated by stereology.

Results: In untreated MDDs, 5-HT1AR mRNA density (μCi/g) in the anterior hippocampus is less than controls in the DG ($p = 0.014$) and CA1 ($p = 0.02$), but not CA3. In MDDs treated with selective serotonin reuptake inhibitors (SSRI), 5-HT1AR mRNA density in the anterior hippocampus is greater than untreated MDDs in the DG ($p = 0.023$), CA1 ($p = 0.010$), and CA3 ($p = 0.005$). In the anterior hippocampus, PSA-NCAM-IR cell number in the DG correlated with 5HT1AR mRNA density in the CA3 ($p = 0.009, r = 0.460$), which is the terminal field of the DG.

Conclusions: Enzymatic degradation of PSA-NCAM inhibits the anti-depressant effect of fluoxetine and reduces hippocampal neurogenesis. In rodents, the cells in the CA3 that project back to the DG have been shown to control neurogenesis in the DG. Chronic activation of post-synaptic 5-HT1A receptors has also been shown to stimulate dendrite outgrowth in the hippocampus (Huang and Herbert, 2005).

Keywords: Selective Serotonin Reuptake Inhibitors (SSRIs), MDD, Adult Hippocampal Neurogenesis, Serotonin 1A Receptors

Disclosure: Nothing to disclose.

P260. Dorsal Anterior Cingulate Cortex, Anteromedial Thalamus and Anterior Insula Effective Connectivity During Threat Anticipation in Individuals With Internalizing Psychopathology

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Background: Converging lines of evidence suggest that heightened responses to unpredictable threat (U-threat) may be an important neurobiological marker of internalizing psychopathology. Prior data also indicate that aversive responses to uncertainty may be mediated by hyperactivation of several brain regions within the frontolimbic circuitry, namely the anterior insula (AIC), anteromedial thalamus, and dorsal anterior cingulate cortex (dACC). The present study aimed to understand how these three regions of interest (ROIs) function as a network during U-threat and predictable threat (P-threat) anticipation in adults with internalizing psychopathologies.

Methods: Towards this goal, fMRI and dynamic causal modeling (DCM) were used to examine effective connectivity (EC) among these three nodes in 22 healthy controls and 49 patients with various comorbid mood (depression and anxiety) disorders. Both sexes were included in the study. During fMRI, participants completed a modified version of the well-validated No-Threat, Predictable Threat, Unpredictable Threat (NPU-threat) task. All ROI time series extractions were from the right hemisphere because of the stronger BOLD activation pattern (in terms of size and/or strength) on this side of the brain in the present study. Six hypothesized connectivity models, based on anatomic connections, were entered into Parametric Empirical Bayes (PEB) analysis to examine group-level differences in EC parameters between healthy controls and patients.

Results: During the P-threat trials, compared to the healthy controls, the modulatory EC change from dACC to the anteromedial thalamus in the patient group was decreased (-0.289Hz, posterior probability [PP] = 0.77). Similar, albeit smaller, effect was also observed during U-threat trials, such that modulation of EC change from dACC to the anteromedial thalamus was reduced in patients relative to healthy controls (-0.085Hz, PP = 0.77).

Conclusions: To our knowledge, this is the first study to examine EC during a threat sensitivity type task in individuals with mood disorders. Given the important role dACC and the anteromedial thalamus play in the detection and initial cognitive processing of external (and particularly aversive) events, our preliminary findings loosely suggest that the lower modulatory change in EC between these two key nodes in patients relative to controls may primarily index a cognitive control (i.e., "top-down") abnormality. Based on the cross-sectional design of this study, we cannot infer whether these observed abnormalities represent a predisposing risk factor or an individual's acquired propensity to

experience internalizing symptoms. Thus, further research efforts are needed to corroborate and expand the present findings.

Keywords: Anterior Insula, Anterior Cingulate Cortex (ACC), Thalamus, Dynamic Causal Modeling, Threat of Shock

Disclosure: Nothing to disclose.

P261. Predicting Mood Disorder Recurrence With Resting State Connectivity and Clinical Metrics

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Background: Mood disorders are often chronic and recurrent. Yet, for younger adults the probability of recurrence in the near future is approximately 50%, meaning that it would be particularly helpful if treatment providers and patients had information on how and in which contexts risk for recurrence might occur. Presently, current residual symptoms are a weak predictor of recurrence risk, and other clinical metrics are also uniformly weak in such prediction. Resting state connectivity may enable us to evaluate recovery of brain circuits, or even compensation processes that may facilitate sustained wellness.

Methods: We compared 128 individuals with currently remitted or euthymic mood disorder (Major Depressive Disorder $n = 114$ or Bipolar Disorder $n = 18$) with 65 healthy comparison participants, 18-30 years were included. All individuals were invited to complete longitudinal follow-up interviews at 12 months to evaluate if any recurrence of mood disorder had occurred. Baseline global assessment of functioning (GAF), number of prior depressive episodes, and Hamilton depression rating scale (HDRS) symptoms were used as clinical predictors. Reward responsiveness was measured with titrated monetary incentive delay task and inhibitory control was measured with Parametric Go/No-go test.

Results: There was good follow-up completion, at 79.8%. Amongst the mood disorder sample, those with mood disorder recurrence had more prior episodes ($B = .23$, $p = .006$), and lower baseline GAF scores ($B = -.41$, $p < .001$) relative to those with no recurrence (Adjusted $R2 = .21$, $p < .001$). Baseline GAF and HDRS scores were highly correlated ($r = -.44$, $p < .001$). After adjusting for these significant clinical regressors, prediction of recurrence included increased connectivity between left subgenual cingulate (LGSAC) and right premotor cortex (PMC) and right anterior middle frontal gyrus (LMFG, $p < .001$, $k > 75$). The added model of LSGAC-LMFG, LSGAC-LPMC resulted in adjusted R2 of .45, $p < .001$, 24% increase in R2). RDoC performance metrics for reward responsiveness ($B = .07$, $p = .50$) and inhibitory control ($B = -.04$, $p = .67$) were not significant.

Conclusions: Brain-based metrics could provide some critical added insight into likelihood of mood disorder recurrence. For young adults early on in the illness, developing integrated models with solid predictive ability could be critical toward securing and designing new interventions and applying existing person-centered interventions to reduce chances of recurrence.

Keywords: Depression, Resting State Intrinsic Connectivity, Magnetic Resonance Imaging, Depression Recurrence Risk

Disclosure: Secondary Triad, Inc: Board Member (Self)

P262. Neuronal Monoaminergic Antidepressant Response Signatures in the L1000 Database

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Background: Major depressive disorder (MDD) has a ~16% global lifetime prevalence and is associated with extensive morbidity and mortality. There is a critical need to understand the cellular and molecular targets of traditional antidepressant medications, including for future drug design/targeting and repurposing of existing medications. Global gene expression changes have been studied in preclinical/non-human models of depression and in peripheral tissue, e.g. blood, from MDD patients, but, to date, antidepressant response signatures have not been systemically studied in human neural tissue. In this study, using a bioinformatics approach, we sought to identify gene expression commonalities in monoaminergic antidepressant response.

Methods: The L1000 gene expression database is a publicly-accessible repository of high-throughput expression data released by the Library of Integrated Network-based Cellular Signatures (LINCS) consortium and downloadable from the Gene Expression Omnibus (GEO). Using available keyword queries, the database was filtered to "Antidepressant(s)" perturbagens. Five separate databases were concatenated into a single milieu with the open-source Juptyer Notebook, a web-based environment for cloud computing, and filtered by antidepressant class, i.e. tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), etc.; dose (10 mcM); length of exposure (24 hours); and cell line [limited to two neuronal-like lines, i.e. NEU, "a terminally differentiated neuronal cell line," and "NPC," fibroblast-derived human induced pluripotent stem cells (hiPSCs) induced along a neural lineage but not terminally differentiated]. In the L1000 database, gene expression data are reported as Z-scores, and, on first pass, we used a Z-score cut-off of ≥2 and ≤2 as significant up- and downregulation, respectively. Majority up- and downregulated genes were compiled, with functional correlation of lead targets.

Results: The preponderance of available data is from the NPC line (reported below by default unless otherwise indicated). To date, we have analyzed the following antidepressants within a given class: TCAs (9) – amitriptyline, amoxapine, clomipramine, desipramine, dibenzepin, doxepin (3 datasets), maprotiline, nortriptyline, and trimipramine; SSRIs (5) – escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline; serotonin norepinephrine reuptake inhibitors (SNRIs) (2) – duloxetine and venlafaxine; and monoamine oxidase inhibitors (MAOIs) (2) – bifemelane and isocarboxazid. 3 genes were upregulated (HLA-DMA, PAK6, and PIP42K), and 3 genes were downregulated (CRK, GJA1, and NUP86) by ≥5/9 TCAs (including multiple representations in the 3 doxepin datasets). For the NPC line, 10 genes were upregulated (including HLA-DMA), and 11 genes were downregulated by ≥3/5 available SSRIs. For the NEU line, 2 genes were upregulated (GRB10 and TSPAN8), and 5 genes were downregulated (CA2, CD40, EPHA3, PELI1, and RFC5) by both fluoxetine and fluvoxamine. Only one gene was upregulated (TSTA3) and downregulated (SSBP2) by the SNRIs duloxetine and venlafaxine. For the NPC line, only one gene was upregulated (PRKX) and downregulated (IGFBP) by the MAOIs bifemelane and isocarboxazid. On the other hand, in the NEU line, 9 and 8 genes were up- and downregulated, respectively, by both MAOIs.

Conclusions: Most of the gene expression profiles were non-overlapping across monoaminergic antidepressant classes. However, in the NPC line, HLA-DMA [major histocompatibility complex class II alpha chain, catalyzing the release of class II-associated invariant chain peptide (CLIP), thereby freeing the antigen binding site] was upregulated by 6 TCAs (including in all 3 doxepin datasets) and 3 SSRIs. Therefore, monoaminergic antidepressants may mediate host immune response by HLA-DMA induction. Potential next steps include the identification of gene expression signatures of other antidepressant "perturbagens" in the L100, including those with different mechanisms, e.g. bupropion, a norepinephrine-dopamine reuptake inhibitor and nicotine receptor antagonist. We also seek to validate and extend our findings to other antidepressants with alternative mechanisms of action, e.g. the *N*-methyl-D-aspartate receptor and glutamate modulator

(+/-)-ketamine and its bioactive metabolites, in hiPSC-derived organoid cultures, i.e. human cortical spheroids [Sloan et al. (2018) Nat Protoc 13(9):2062-2085, PMID: 30202107].

Keywords: Gene Expression, L1000, Tricyclics, Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitor

Disclosure: Nothing to disclose.

P263. Neurokinin-1 Receptors in the Nucleus Accumbens Shell Mediate Sensitivity to Social Defeat and Stress-Induced Alcohol Consumption

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Background: Chronic social defeat stress (SDS) is a widely used preclinical model of depression, and involves repeated exposure to physical defeats using a resident-intruder model. Exposure to SDS induces depressive-like phenotypes in mice including anhedonia, social withdrawal, and increased drug and alcohol consumption. In our prior work, we found that expression of the neurokinin-1 receptor (NK1R) is increased in the nucleus accumbens (NAC) of mice that are sensitive to this stressor. The NK1R is the endogenous receptor for the neuropeptide substance *P* (SP), and plays a prominent role in stress, anxiety, and addiction.

Methods: In the present study, we used genetic, pharmacological, and viral vector strategies to demonstrate a functional role of the NK1R in the NAC shell in sensitivity to SDS. Due to sex differences in territorial aggression, the SDS model only works effectively in male mice. Therefore, these studies used male C57BL6/J mice ($n = 4$-12/group).

Results: First, we exposed NK1R -/-, which have a genetic deletion of this receptor, to the SDS procedure and found that they had normal sensitivity to SDS, likely due to developmental compensatory adaptations in the neurokinin systems in these mice. To inhibit the NK1R without inducing developmental adaptations, we delivered the NK1R antagonist L703606 prior to each defeat exposure and found that this pretreatment decreased the sensitivity to SDS, attenuating the resulting social withdrawal. This effect was observed when the antagonist was delivered either systemically or directly into the NAC shell. Conversely, we then overexpressed the NK1R in the NAC shell using viral vector strategies and found that this increased the sensitivity to SDS and stress-induced alcohol consumption.

Conclusions: Together, these experiments provide evidence for a functional role of the NK1R in the NAC shell in the sensitivity to SDS and stress-induced alcohol consumption.

Keywords: Neurokinin, Alcohol, Stress and Depression, Neuropeptides

Disclosure: Nothing to disclose.

P264. Spatially Resolved Transcriptomes in Human Hippocampus

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Background: In mammals, adult hippocampal neurogenesis (AHN) is necessary for cognitive and emotional functions. We reported that the hippocampus neurogenic niche of psychiatrically and neurologically normal aging subjects with no cognitive impairment showed no age-associated decline in progenitor (SOX2/nestin +) cells and immature (doublecortin[DCX]/PSA-NCAM +) neurons into the eighth decade of life, despite a smaller multipotent (SOX2 +) progenitor pool in older subjects. Sustained AHN in human hippocampus has been replicated by other groups. Although, some studies failed to detect immature neuron markers in adult human dentate gyrus (DG), tissue quality and methodology employed may explain this failure. We have also confirmed DCX mRNA expression in human hippocampus, using RNAscope® technology (ACDBio) and RT-qPCR, providing further support for the presence of immature neurons in adult human brain. We do not know if AHN is lower in untreated subjects with major depressive disorder (MDD) compared with non-psychiatric controls.

The striking differences between human and lower mammal brains in terms of persistence of neurogenesis late into adult life need to be more fully characterized and understood. This will require using new technologies to investigate cellular lineages in the human HNN, and molecular regulators of progenitor cell proliferation, fate, differentiation, maturation, and survival. We report on progress in applying spatial omics to human brain in a pilot study of depressed and sudden death controls.

Methods: In homogenized DG-hilus tissue, we implemented single nuclei (sn) RNA sequencing (seq). In slide-mounted hippocampus tissue, we applied our custom-made slide-seq technology, using deterministic barcoding in tissue for spatial omics sequencing (DBiT-seq). These technologies provide complementary information on the human hippocampus neurogenic niche: they quantify single nuclei RNA expression (snRNA-seq), and provide anatomical co-mapping of cell-type specific differentially expressed genes on intact tissue sections (DBiT-seq), where whole cells and their connections are preserved.

To investigate human hippocampus neurogenic niche molecular features in controls and depressed suicides, we applied snRNA-seq and DBiT-seq to hippocampus postmortem tissue from five non-psychiatric, nonsuicide, sudden death controls and five suicide decedents with MDD, who had negative toxicology for psychotropic drugs and alcohol. Both groups were clinically characterized using psychological autopsy and neuropathology assessment, age 25-55 years, all males, with sudden death, short agonal state, postmortem interval<24 hrs., RNA integrity number (RIN) > 8, and brain tissue pH>6.

Results: The snRNA-seq and DBiT-seq data segregated human hippocampal cell populations based on gene expression. The cell clusters localized in known hippocampal subfields, including granule cell layer, subgranular zone, molecular layer, and Cornu Ammonis (CA) regions. Spatially resolved cell clusters expressed genes expected to be associated with the specific cell populations based on location, which supported the ability of DBiT-seq to correctly locate and identify cell clusters by snRNA-seq.

Differentially expressed genes in cells located in the DG neurogenic niche, or subgranular zone, included: PTPRT ($p =$ 6.44*E-95), involved in cell growth, differentiation, and mitotic cycle; GAD2 ($p = 1.50$*E-94), involved in production of gamma-aminobutyric acid; SOX1 ($p = 4.72$*E-11) involved in the regulation of embryonic development and in the determination of the cell fate; L1CAM ($p = 1.56$*E-05), which plays an important role in nervous system development, including neuronal migration and differentiation; RELN ($p = 1.38$*E-46), involved in cell migration and adhesion; CNR1 (2.76*E-24), involved in cannabinoid-dependent depolarization-induced suppression of inhibition; TAC1 ($p = 1.24$*E-89), which encodes four products of the tachykinin peptide hormone family, thought to function as neurotransmitters, excite neurons, and evoke behavioral responses; NRSN1($p = 1.73$*E-65), involved in neurite extension and memory consolidation.

In the DG granule cell layer, top differentially expressed genes included PROX1 ($p = 1.65$*E-149), transcription factor involved in

cell fate determination, embryonic development and neurogenesis; CALB1 ($p = 1.18$*E-52), calcium-binding protein thought to buffer entry of calcium upon stimulation of glutamate receptors, MAP2 ($p = 9.13$*E-30), neuron-specific cytoskeletal protein enriched in dentrites, with a role in determining and stabilizing dendritic shape during neuron development.

Conclusions: The advent of next-generation sequencing to measure transcriptome and other genomic features at single-cell/nucleus level has revolutionized our ability to identify cell types and state within the brain. However, these techniques disaggregate tissue, thereby losing spatial information, which is necessary for the capture of 3D cellular contents at tissue scale. Thus, proper taxonomy of cell type in the brain requires integration of single cell and spatial transcriptomic approaches. Here we demonstrate that DBiT-seq allows identifying, in human hippocampus tissue, cell clusters showing molecular features and anatomical distribution that reflect their phenotype and function, as well as discovering molecular markers that regulate cell activity and viability.

Keywords: Single-Nucleus RNA Sequencing, Spatial Transcriptomics, Postmortem Brain Tissue, Hippocampus, Major Depressive Disorder

Disclosure: Nothing to disclose.

P265. Parkinson's Disease-Linked LRRK2-G2019S Mutation Alters Behavioral Responses and Synaptic Properties Following Chronic Stress

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Background: Parkinson's disease (PD) is associated with often debilitating non-motor symptoms including cognitive and psychiatric symptoms that appear early, are initially independent of dopamine neuron loss and are poorly understood mechanistically. The G2019S mutation in LRRK2 is one of the most prevalent PD risk-gene mutations and has been found in both sporadic and familial late-onset PD. The risk for both PD and psychiatric symptoms is increased significantly by stress. In both humans and mice, excitatory circuitry of the NAc is implicated in depression, and imaging in PD patients shows abnormal corticostriatal connectivity.

Methods: To probe relationships between the PD mutation, stress, and neural circuit modifications, we subjected young adult wildtype (WT) and G2019S knockin mice to a well-established chronic stress paradigm followed by posthoc behavioral assays and whole-cell recordings to interrogate synaptic function in striatal projection neurons of the nucleus accumbens, an area enriched in LRRK2 and known to regulate stress and depression-like responses.

Results: We find that the G2019S mutation alters behavioral responses to chronic stress. Subsequent whole-cell recording from SPNs indicates changes in excitatory synaptic activity in SPNs from stressed G2019S mice. This would suggest that mice expressing G2019S mount entirely distinct behavioral and adaptive cellular plasticity responses to stress.

Conclusions: Ongoing experiments are further probing the underlying mechanisms leading to the altered excitatory drive following chronic stress. Ultimately the data may reveal novel targets for ameliorating mood-related and cognitive symptoms associated with PD.

Keywords: Parkinson's Disease, Chronic Stress, Synapses, Depression, Glutamate

Disclosure: Nothing to disclose.

P266. Coping With Stress Promotes Resilience Through Distinct Prefrontal Circuits

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Background: Coping processes are central to determining how an individual responds to adverse life events and represent an integral part of prevention efforts aimed at promoting resilience. Across species, behavioral control over stress - a key aspect of coping - not only blunts the impact of the stressor being experienced, but also buffers against the effects of future adversity. Prior work indicates that the medial prefrontal cortex (mPFC) plays a central role, but the circuitry through which it mediates the enduring and transsituational protective effects of behavioral control is incompletely understood.

Methods: For manipulation of controllability, adult Sprague-Dawley male rats were run in a triad design. One subject of each triad received escapable shock (ES), a second received yoked-inescapable shock (IS), and a third received no shock (HC). Across studies, we examined the role of select prefrontal projections in the production (EXP1: $n = 8$-10/group) and expression (EXP2: 8-10/group) of ES-induced resilience. In EXP1, pathway-specific silencing was achieved using a dual viral approach: a Cre-inducible Gi-coupled DREADD was delivered to mPFC and a retrograde viral vector encoding Cre recombinase to dorsal medial striatum (DMS) or dorsal raphe nucleus (DRN). CNO was given prior to ES/IS/HC (Time A) and then all groups received IS 7 days later (Time B). Behavioral testing (social exploration) was conducted 24 h after Time B. In EXP2, the above procedures were identical except silencing occurred prior to Time B. In EXP3, a viral-based Tet-Off system containing an activity-regulated promoter was delivered to the mPFC to determine if the same prefrontal ensembles participate in both the encoding (Time A) and later use of the control experience to regulate threat conditioning (Time B).

Results: In EXP1 chemogenetic silencing of either the PL-to-DMS and PL-to-DRN pathways during initial stress treatment (Time A) both prevented the stress-buffering effects of behavioral control against later uncontrollable stress (Time B). Social exploration times were significantly lower in hM4Di-treated controllable stress compared to no stress subjects. Interestingly, only PL-to-DRN silencing during subsequent uncontrollable stress (Time B) eliminated the protective effects of prior control (EXP2). In EXP3, hM4Di-mediated inhibition of IL neurons previously activated by the initial control experience (Time A) completely eliminated the fear-buffering effects of behavioral control at Time B.

EXP1: Chemogenetic silencing during stress treatment. mPFC-DMS ($n = 66$): social exploration, stress main effect $p < 0.0001$, stress X virus interaction $p = 0.0198$. mPFC-DRN ($n = 58$): social exploration, stress main effect $p = 0.0015$, stress X virus interaction $p = 0.0802$. Tukey's: mPFC-DMS and mPFC-DRN silencing during ES decreased social exploration following subsequent IS.

EXP2: Chemogenetic silencing subsequent challenge. mPFC-DMS ($n = 62$): social exploration, stress main effect $p < 0.0001$, no stress X virus interaction $p = 0.4750$. mPFC-DRN ($n = 52$): social exploration, stress main effect $p = 0.0029$, stress X virus interaction $p = 0.012$. Tukey's: mPFC-DRN, but not mPFC-DMS, silencing prevented ES-induced stress buffering.

EXP3: Pilot Tet-Off Activity Marking System. mPFC ($n = 16$): Increase in cued freezing in ES, student's t-test, $p < 0.01$. No differences in pre-tone freezing levels.

Conclusions: The data suggest that separate prefrontal cortex ensembles process separable features of behavioral control: a) a corticostriatal circuit that detects the contingency between the controlling response (action) and stressor termination (outcome) and b) a prefrontal-to-brainstem projection that subsequently uses control

information to inhibit stress-responsive structures. The above provides a circuit-level framework for testing how other resilience-inducing factors produce their effects and may identify candidate circuit elements for correcting deficits in emotion regulation.

Keywords: stress resilience, Corticostriatal circuit, coping

Disclosure: Nothing to disclose.

P267. A Neuropeptidergic Mechanism for Governing Valence Assignment

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Background: The ability to assign positive or negative valence to environmental cues is paramount for survival. Basolateral amygdala (BLA) circuits have been implicated in the acquisition of associative memories, and BLA projections to the nucleus accumbens (NAc) predominantly mediate positive valence (reward), while BLA projections to the centromedial nucleus (CeM) of the central amygdala (CeA) predominantly mediate negative valence (punishment). However, the neural mechanisms initially directing signals to the appropriate pathway during learning remain mysterious. We demonstrate that the neuropeptide neurotensin (NT) plays a critical role in valence assignment during the acquisition of learned associations.

Methods: Adult wild-type C57BL mice, NT::Cre mice, and NT::Cre mice crossed with the Ai14 reporter mice aged at least 2 months were used for experiments. For experiments involving gene manipulation and cranial implants, only male mice were used. Mice received stereotaxic injection of retrobeads in the NAc or CeM for labeling different BLA projectors, an injection of AAV encoding Cre-dependent ChR2 in the PVT and an optical fiber implantation in the BLA for optogenetic stimulation, an injection of AAV encoding Cre-dependent GCaMP6m in the PVT and an optical fiber implantation in the BLA for fiber photometry recordings, an injection of GRABNTS1.0 NT fluorescent sensor and an optical fiber implantation in the BLA for monitoring NT dynamics, injections of AAV encoding SpCas9 in the PVT and a retrograde AAV encoding guide RNAs targeting exon 1 and exon 3 of the NT gene in the BLA for CRISPR-mediated NT gene inactivation, and injections of AAV encoding Cre-dependent ChR2 in the BLA and a retrograde virus encoding Cre in the NAc or CeA for in vivo identification of BLA projectors. Mice were allowed 4-6 weeks of recovery before behavioral training. To assess associative learning, mice were trained with a Pavlovian conditioning paradigm, in which a 2 kHz or 20 kHz tone was paired with either a 10ul 30% sucrose delivery or 0.6mA footshock for reward and punishment learning paradigm, respectively. During the three-cued discrimination task, reward, shock, and neutral trials (which predicts no outcome) were chosen randomly at a 50%:25%:25% probability. In the experiments of photometry recordings, mice were head-fixed and received airpuff as a punishment instead.

Results: We found that BLA-NAc and BLA-CeM neurons express the neurotensin receptor 1 (NTSR1) at different levels (***$P = 0.0005$), and that NT dose-dependently altered glutamatergic transmission in an opposing manner for BLA-NAc (facilitation; *$P = 0.0425$) and BLA-CeM (suppression; **$P = 0.0039$) neurons. Among inputs providing NT innervation to the BLA, we identified the paraventricular thalamus (PVT) as a functional source of NT that mediates learning. Photostimulation of the PVT-BLA:NT projection enhanced reward learning (*$P = 0.018$) and impaired punishment learning (*$P = 0.0279$). However, we also found that PVT:NT neurons corelease glutamate into the BLA. To selectively isolate the contribution of NT, while leaving glutamate transmission unaffected, we used a CRISPR-Cas9 mediated Nt gene conditional knockout (cKO) and found an impairment in reward learning (**$P = 0.0052$), and an enhancement in punishment learning (*$P = 0.0396$). By developing, validating, and applying a genetically-encodable fluorescent NT sensor to isolate NT signaling from coreleased glutamate, we observed that NT concentration in the BLA increased during reward conditioning (*$P = 0.047$) and decreased during punishment conditioning (*$P = 0.003$). Finally, to reveal the impact of PVT-BLA:NT on the ensemble dynamics during valence processing in vivo, we recorded the activity of BLA neurons ($n = 683$) during a valence-discrimination task in mice with PVT-BLA:Nt CRISPR-cKO relative to scrambled guide controls. We found that Nt cKO blunted responses to both reward- and punishment-predictive cues, and that valence-coding properties of BLA-NAc and BLA-CeA were disrupted, even when controlling for behavioral states on a trial-by-trial basis.

Conclusions: Taken together, we have identified a neuropeptide that signals valence in the BLA, and show that NT is a critical modulator of valence processing, distinctly gating synaptic transmission and orchestrating ongoing activity of amygdala projection neurons mediating positive and negative valence.

Keywords: Valence, Paraventricular Nucleus of the Thalamus, Neurotensin, Amygdala

Disclosure: Nothing to disclose.

P268. Nucleus Reuniens Inactivation Reverses Stress-Induced Deficits in Dopamine System Activity and Hippocampal-Accumbens Synaptic Plasticity

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Background: The nucleus reuniens (RE) of the thalamus relays inputs from the PFC to the hippocampus, two brain regions dysregulated in depression, suggesting that the RE may be part of the neurocircuitry that underpins depression. Core depression symptoms, such as anhedonia, have been associated with blunted activity of the ventral tegmental area (VTA) dopamine (DA) system, which is also found in animal models for depression. It has been suggested that a decrease in to ventral subiculum of the hippocampus (vSub) to nucleus accumbens (NAc) pathway connectivity contributes to the reduction in VTA DA neuron activity. Here we investigated the impact of repeated stress exposure on VTA DA neuron activity and synaptic transmission in the vSub-NAc pathway, and whether the RE plays a role in the changes induced by stress.

Methods: Adult male Sprague-Dawley rats were subjected to a stress protocol that we found previously to cause a decrease in VTA DA system activity. The stress protocol consisted of a combination of daily footshock (25 footshocks of 1.0 mA/2s/session) during 10 days and three restraint stress sessions (1 h session) occurring on days 1, 2, and 10 immediately after the FS session. Naïve animals were left undisturbed in their home cages. One week after the end of the stress protocol, animals were tested in the forced swimming test (FST). The activity of VTA DA neurons was also evaluated using in vivo extracellular single-unit recordings. Three parameters of activity were measured: population activity, ie, the number of spontaneously active DA neurons per electrode track; average firing rate; and the percentage of action potentials occurring in bursts. Then, we evaluated whether the inactivation of the RE with tetrodotoxin (TTX; 1M in 0.5µL) would reverse the changes in behavior and VTA DA system activity induced by stress. TTX was locally infused 10 min before the

behavioral and electrophysiological tests. We also evaluate potential changes in synaptic transmission in the vSub-NAc pathway in stressed rats and if RE inactivation would reverse these changes. The hippocampal-evoked activity was assessed by recording neurons in the NAc shell responsive to fimbria stimulation before and after high-frequency stimulation (HFS; 20 Hz, 10s at suprathreshold) of the fimbria. All experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Pittsburgh and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Results: Stress exposure increased the time of immobility in the FST ($t22 = 2.25$, $p = 0.035$) and decreased the number of spontaneously active VTA DA neurons ($t12 = 4.36$, $p < 0.001$) resembling that observed in animal models for depression based on stress exposure, such as chronic mild stress and learned helplessness. No change was found in the average firing rate and burst activity of VTA DA neurons. Inactivation of the RE with TTX reversed the stress-induced changes in the FST (2-way ANOVA - stress: $F1,22 = 4.79$, $p < 0.039$; treatment: $F1,22 = 7.44$, $p = 0.012$; interaction: $F1,22 = 6.11$, $p = 0.021$) and restored VTA DA neuron population activity to what is observed in naïve animals (2-way ANOVA - stress: $F1,30 = 8.98$, $p < 0.001$; treatment: $F1,30 = 19.47$, $p = 0.005$; interaction: $F1,30 = 19.01$, $p < 0.001$). In addition, fimbria HFS induced long-term potentiation (LTP) in the vSub-NAc pathway of naive animals, whereas long-term depression (LTD) was induced in stressed rats. The baseline evoked-spike probability in saline-treated naïve animals was 0.45 ± 0.03 and increased to 0.81 ± 0.04 30 min post-HFS, whereas in saline-treated stressed animals the baseline spike probability was 0.54 ± 0.06 and decreased to 0.14 ± 0.06 30 min post-HFS. The latter is similar to that found in helpless rats. RE inactivation reversed stress-induced deficits in vSub-NAc synaptic plasticity (baseline evoked spike probability in TTX-treated stressed rats was 0.42 ± 0.06 and changed slightly to 0.43 ± 0.07 30 min post-HFS; 2-way ANOVA - stress: $F1,19 = 25.63$, $p < 0.001$; treatment: $F1,19 = 1.34$, $p > 0.05$; interaction: $F1,19 = 25.63$, $p < 0.001$), indicating that the RE may play a role in the disrupted vSub-NAc plasticity. The inactivation of the RE in naive rats did not induce any change in the FST and electrophysiology.

Conclusions: Our findings support the role of RE in the regulation of affective dysregulation and DA function induced by adult stress. Also, it points to the NAc and hippocampus as a potential neural circuit in which RE could modulate the behavioral and VTA DA neuron activity changes occurring after the stressors. Overall, our findings indicate that the RE may represent a key brain region involved in the neurobiology of amotivational states and may provide insights on circuit dysfunction and markers of the maladaptive stress response.

Keywords: Nucleus Reuniens, Depression, Dopamine, Stress Abnormalities

Disclosure: Nothing to disclose.

P269. Endocrine-Behavioral Profiling and Hippocampal Genomics in Male and Female Mice Maintained on Chronic Oral Corticosterone: Implication for Methylated 1F Exon of Glucocorticoid Receptor

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Background: Dorsal and ventral hippocampus (HPC) are functionally distinct brain structures due to differences in their respective neuroanatomical connectivity and in the biological processes that they encode. These two hippocampal circuits also show anatomical sex differences in response to stress and display region-specific patterns of genes both at baseline and after pharmacological or environmental stimuli. Gene networks identified using whole-genome-sequencing serve to dissect distinct brain circuits that respond to stress in unique fashion. We used RNA-sequencing to study differentially expressed genes (DEGs) in the dorsal (dHPC) and ventral HPC (vHPC) of male and female mice maintained on chronic oral corticosterone (CORT), a pharmacological model that induces a blunted endocrine response to acute stress.

Methods: Wild-type mice or heterozygous BDNF Val66Met (hMet) male and female mice were maintained on chronic oral CORT (25mg/l) or vehicle for six weeks. Prior to dissection of the ventral (vHPC) and dorsal hippocampus (dHPC), mice were tested for anxiety- and depression-like behavior using the light-dark box and splash test, respectively. Three biological replicates were used per experimental group, comprising of RNA pooled from hippocampi from two animals. The cDNA libraries were sequenced on Illumina NextSeq 500 using 75-bp single-end reads. Differential expression analysis was conducted using the limma-voom package. The effect size (Cohen's D) was calculated for each gene using the differential expression results and this was used as an input in a fixed effects meta-analysis model from which an estimate and associated p-value<0.05. Differences in integrated read density were visualized using the heat map tool Multi Experiment Viewer. The individual comparisons were also used as inputs to a rank-rank hypergeometric overlap (RRHO) algorithm, which overlaps any two sets of comparisons. Methyl–DNA–immunoprecipitation (MeDIP) assay was performed using the MagMeDIP kit. Primers were designed in order to amplify the region of the Nr3c1 loci.

Results: Oral CORT increased affective behavior in males but not in females, a difference that was more marked in the hMet genotype, in which females showed decreased affective behavior compared to controls. Analysis of DEGs ($p < 0.05$, $FC > 1.3$) revealed that CORT induced a greater number of DEGs in the vHPC than in the dHPC. After chronic CORT, WT males showed 184 DEGs in the vHPC and 119 DEGs in the dHPC. This difference was more marked in hMet male mice, that showed 493 DEGs in the vHPC and 178 DEGs in the dHPC. Overall CORT induced a lower number of DEGs in females than in males. Curiously, WT females showed more DEGs in the dHPC (151) than in the vHPC (54) when treated with CORT. However, CORT had only a mild effect on DEGs in hMet female mice, especially in the dHPC. We used stratified RRHOs to identify the patterns and weight of overlap of differentially DEGs across sex and genotype. We identified a robust overlap in the dHPC between genes downregulated in WT females and downregulated in hMet females after CORT. This major overlap across genotypes also occurred with the same treatment groups for male mice when considering the dHPC. In the vHPC, males showed a considerable overlap in genes downregulated in WT mice and downregulated in hMet mice, both under CORT treatment. A major overlap in the vHPC also occurred between genes downregulated in WT females and upregulated in hMet females after CORT. Heatmaps were generated to analyze the expression pattern of epigenetic modifiers and GR-binding genes across groups in the dHPC and vHPC. The cladogram in GR-binding genes and epigenetic modifiers in response to CORT suggested remarkable sex and genotypic differences in the vHPC as opposed to the dHPC. Total mRNA levels of the GR receptor, Nr3c1, in the vHPC was lower in WT females compared to males after CORT treatment. Differences in Nr3c1 expression were consistent with selective changes in the methylation of the promoter of the exon 1F, suggesting a major role of exon 1F in sex differences observed in response to oral CORT.

Conclusions: DEGs induced by CORT in both the ventral and dorsal hippocampus showed genomic differences in response to stress that are region-, sex-, and genotype-specific and that intersect with behavioral differences. When genes were grouped

according to their biological functions, there was a considerable epigenetic component specific to the vHPC. We found that CORT selectively targeted the expression of exon Nr3c1F in the vHPC, suggesting that sex- and region-specific epigenetic regulation of GR is one mechanism by which CORT induces distinct changes in the gene network.

Keywords: Corticosterone, Sex Differences, Dorsal Hippocampus, Ventral Hippocampus, Epigenomics

Disclosure: Nothing to disclose.

P270. Left Ventrolateral Prefrontal Cortex Structure and Reward-Expectancy Related Activity Predict Manic Symptom Changes One Year Later

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Background: Identification of biomarkers associated with development of manic symptoms over time is a significant challenge in the diagnosis of bipolar disorder (BD). Given the associations between mania and heightened reward sensitivity, regional blood oxygen level dependent (BOLD) signal during reward expectation (RE) is one such candidate neural marker. Prior work has focused on the left ventrolateral prefrontal cortex (L vlPFC), which is associated with evaluating and matching stimuli to outcomes. Left vlPFC BOLD during RE conditions may represent heightened sensitivity to potential reward. Indeed, we previously reported a relationship between RE-related L vlPFC activity and concurrent measures associated with BD risk. However, it is unclear if RE-related L vlPFC activity is a robust predictor of manic symptoms over time, and if the relationship is specific to functional activation or if it extends to structural metrics such as cortical thickness.

Methods: Forty-four right-handed young adults (36 female) ages 18-25 who were seeking treatment for psychological distress were recruited from the Pittsburgh, PA community. Participants completed the Mood Spectrum Scale (MOODS), which includes a Manic Domain. This self-report measure was repeated at a 12-month follow-up visit. At their baseline visit participants also completed a multimodal MRI scan with high resolution structural imaging. In the scanner, participants completed a card guessing task designed to assess BOLD activity during anticipation of reward. We calculated a parametric regressor, RE, that represents the 2-6 s period following the participant decision but prior to reveal of trial outcome. RE-related BOLD activity was extracted from a L vlPFC region of interest determined via meta-analysis. We used Freesurfer's automated pipeline for cortical surface reconstruction and to calculate mean cortical thickness in regions of interest that comprise the L vlPFC (the pars orbitalis, pars triangularis, and the pars opercularis of the inferior frontal gyrus, as well as the lateral orbitofrontal gyrus).

We performed a linear regression model with RE-related L vlPFC BOLD activity, baseline MOODS Manic Domain scores, gender, age, educational attainment, and framewise displacement. MOODS Manic Domain at 12-month follow-up was the dependent variable.

We then performed four parallel linear regression models with MOODS Manic Domain at 12-month follow-up as the dependent variable, each of the structural regions of interest as independent variables and covariates as above. Results were considered significant at $p < 0.0125$.

Results: RE-related L vlPFC BOLD activity was significantly associated with 12-month MOODS Manic Domain scores, controlling for baseline ($\beta = 7.46$, $t = 4.17$ $p = 0.041$). There was also a significant association with cortical thickness of the pars orbitalis ($\beta = 14.59$, $t = 11.75$ $p < 0.001$), but not the other three structural regions of interest (all ps>0.1).

Conclusions: These findings highlight the importance of RE-related L vlPFC BOLD activity and cortical thickness in predicting manic symptom changes over time. Future studies should assess if these markers can indeed predict conversion to BD and the potential for targeting the L vlPFC for therapeutic interventions.

Keywords: Impulsive Sensation Seeking, Bipolar Disorder, Reward Anticipation, Mania, Ventrolateral Prefrontal Cortex

Disclosure: Nothing to disclose.

P271. Zuranolone in the Treatment of Major Depressive Disorder in Patients ≥65 Years of Age: Outcomes From the Phase 3, Naturalistic SHORELINE Study

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Background: Zuranolone (ZRN) is an investigational, oral neuroactive steroid and γ-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator under clinical development as a once-daily, 2-week therapy for major depressive disorder (MDD) as part of the LANDSCAPE program, a broad and flexible clinical development program in patient populations with unmet needs. The SHORELINE Study (NCT03864614) is a Phase 3, naturalistic study evaluating the safety, tolerability, and need for repeat dosing with ZRN through 1 year in adults with MDD aged 18 to 75 years. Overall interim analysis (all ages, $N = 924$), including all patients receiving ZRN 30 mg (ZRN30), dose switch dose (patients receiving ZRN30 initially who received subsequent dose(s) of ZRN 50 mg [ZRN50]), or patients receiving ZRN50, has previously been presented. The least squares mean (LSM) change from baseline (CFB) in the 17-item Hamilton Rating Scale for Depression total score (HAMD-17) at Day 15 was −15.2 for the ZRN30 cohort, −15.5 for the dose switch cohort, and −16.0 for the ZRN50 cohort. Of patients who responded (≥50% improvement from baseline in HAMD-17) to the initial ZRN30 treatment course (ZRN30 and dose switch cohorts) and continued in the study, 60.4% (344/569) received ≥1 repeat dosing cycle (2-weeks of treatment) over the 1-year study period. As the population ages globally, additional data are needed to provide dosing recommendations and inform future clinical studies in geriatric patients with depression. Here, we present the results from a post hoc analysis of the subgroup of patients aged ≥65 years who were enrolled in the SHORELINE trial and received ZRN30 or ZRN50 for 2 weeks.

Methods: Patients with MDD, HAMD-17 ≥ 20, and a Montgomery-Åsberg Depression Rating Scale ≥28 were enrolled. The study comprised 3 cohorts; those receiving either ZRN30, dose switch, or ZRN50. The ZRN50 cohort has not yet completed the trial and data collection is still ongoing. Patients who achieved a HAMD-17 response at Day 15 were assessed every 2 weeks by HAMD-17 and the 9-item Patient Health Questionnaire to determine eligibility for repeat dosing (patients were followed for up to 48 weeks). The primary endpoint was safety and tolerability as assessed by adverse events (AEs) and clinical measures through 1 year (52 weeks). Secondary endpoints of HAMD-17 response and HAMD-17 remission (HAMD-17 ≤ 7) were assessed, and rates of repeat dosing were calculated in patients who responded after completing 1 treatment cycle. Descriptive statistics of CFB in HAMD-17 and HAMD-17 response and remission were calculated for each treatment cycle. A mixed effects model for repeated measures was used to plot the LSM

CFB in HAMD-17, and standard deviation (SD) was based on raw mean.

Results: Ninety-six patients (aged ≥65 years) were included in this analysis (ZRN30, $n = 68$; dose switch, $n = 8$; ZRN50, $n = 20$). Patient baseline demographics in this subgroup were consistent with the general study population: mean (SD) age of 68.4 (2.8) years, predominantly female (64.6%), and White (88.5%) with a mean (SD) HAMD-17 of 26.1 (4.2). The LSM (SE) CFB in HAMD-17 at Day 15 (following the first 2-week treatment course) was −15.9 (8.2) for the ZRN30 and dose switch cohorts and −13.8 (8.4) for the ZRN50 cohort. Overall ($n = 96$), HAMD-17 response and remission rates at Day 15 were 71.7% and 35.9%, respectively. Among 76 patients who received ZRN30 in the initial course of treatment, 52 (68.4%) achieved a response at Day 15; of those, 31 (59.6%) did not require repeat dosing (compared to 42.9% who did not require repeat dosing cycles in the overall ZRN30 cohort [all ages]). During the first treatment cycle, treatment-emergent adverse events (TEAEs) were similar in nature and frequency among the general study population receiving any dose and the subgroup of patients aged ≥65 years, with (66.9%) and 56.3% of patients reporting at least 1 AE, respectively. The most common (≥5%) TEAEs in patients aged ≥65 years included dizziness (13.5%), somnolence (10.4%), headache (8.3%), sedation (6.3%), and diarrhea (5.2%). The majority of TEAEs were reported to be mild or moderate (87.0% in patients aged ≥65 years and 90.3% in the general study population). During the initial treatment period, 7.3% of patients aged ≥65 years discontinued and 10.4% reduced their dose due to AEs. No AEs of loss of consciousness, weight gain, sexual dysfunction, or euphoria were reported to date.

Conclusions: ZRN was effective and generally well-tolerated in patients aged ≥65 years, showing similar efficacy to that of the general study population. When initially treated with the ZRN30 dose, more than half of patients aged ≥65 years did not require a second course of treatment within the follow-up year, similar to the need for repeat dosing cycles in the general study population. Data on the ZRN50 cohort are still being collected and will be reported when available. Overall, these data support further development of ZRN for potential use as an oral, as-needed treatment for patients with MDD, including those aged ≥65 years.

Keywords: Zuranolone, Major Depressive Disorder (MDD), Neuroactive Steroid, Geriatric Depression, GABA

Disclosures: AbbVie, Acadia, AiCure, Alfasigma, Alkermes, Allergan, Cognitive Research, Intra-Cellular Therapies, Janssen, Jazz Pharmaceuticals, Lundbeck, MedAvante-Prophase, Neurocrine, Noven, Otsuka, Sage Therapeutics, Sunovion, Supernus, Takea, Terran Biosciences, Teva: Consultant (Self)

P272. Impact of COVID-19 Pandemic of Seriously Mentally Ill (SMI) Subjects in Clinical Trials

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Background: Recent research on the COVID-19 pandemic suggests that individuals who suffer with serious mental illness (SMI) are at heightened risk of infection and have increased mortality, due to their illness or lack of access to health care. As a consequence, progress in developing new treatments for the SMI has been disrupted, with many interruptions and holds places on clinical trials in psychiatry due to concerns regarding the pandemic and its risks to SMI patients. Given these implications, we aimed to examine the impact of the COVID-19 pandemic on SMI patients, specifically in regards to psychiatric morbidity and their ability to cope with pandemic-related precautionary measures, restrictions, and disruptions to daily life. Additionally, we aimed to examine the effects of pandemic-induced stress across patient groups.

Methods: To investigate this further, we conducted, a multi-site cross-sectional, survey study of 287 male and female clinical trial patients, which included non-psychiatric controls ($n = 149$) and SMI patients ($n = 139$) with a diagnosis of bipolar disorder ($n = 23$), major depression ($n = 46$), or schizophrenia ($n = 69$), located in five geographically-distinct clinical trial sites across the United States (Maryland, Georgia, Florida, Utah, California) between April and July of 2021. Survey responses were collected on an electronic platform (i.e. Qualtrics) between April and July of 2021. The interviewer-administered survey collected information on demographics, mental health care and status, covid health service utilization, COVID knowledge and concerns, risk perceptions, use of precautionary measures, vaccination, and psychological distress, which was measured using the Kessler's Psychological Distress Scale (K10) (Kessler et al., 2003). A univariate analysis was performed to obtain general frequencies of the population distribution, and chi-squared tests were used to compare frequencies among groups. Unpaired t-tests were used to compare groups on numerical variables and ANOVA's were used to identify differences when comparing 3 or more categories. Post-hoc analyses were conducted as needed. For the K10 scale, low distress/ high distress dichotomization was obtained evaluated the median of the to K10 questionnaire through the whole population in the study.

Results: The results indicated that there are slight differences between SMI patients and controls in regards to disease management, with SMI patients having around 50% less COVID-19 exposure incidences ($p < 0.001$) and fewer numbers of confirmed infections ($p < 0.05$) than controls. SMI patients were also more likely to report wearing face masks, avoiding large gatherings, and endorse the use of precautionary measures despite receiving a COVID-19 vaccine ($p < 0.001$). In examining psychiatric morbidity, 70.3% ($n = 97$) of all SMI patients reported experiencing at least one episode of worsening, 48% reported experiencing suicidal ideation, and 66% reported a need for increased mental health care due to COVID-19 distress during the pandemic period. SMI patients also reported higher levels of stress in comparison to the controls, with MDD patients having the highest levels of stress ($p < 0.001$).

Conclusions: These findings suggest that SMI individuals are at greater risk for mortality from COVID-19 disease, despite their use of preventative measures and other positive coping behaviors (i.e. vaccination, testing, less exposure). It also suggests a need to account for pandemic-induced psychological stress in clinical trials design, subject selection, and symptoms ratings. On a site level, it raises the question of whether or not preventative disease management can be facilitated by clinical trial sites treating this patient population. Overall, further investigation using a longitudinal design and sub-groups of psychiatric patients (community-based, co-morbid medical/substance use, research settings) is warranted in order to delineate factors mitigating risk and better understand illness course in a pandemic.

Keywords: COVID-19, the COVID-19 Pandemic, CNS Clinical Trials, Clinical Psychiatry

Disclosure: Nothing to disclose.

P273. Clinical Data Analyses Using Model-Based Approach: The Relationship Between mTORC1 Activation Biomarkers and NV-5138/SPN 820 Concentration in the Human Plasma and CSF

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Background: NV-5138/SPN 820 is a novel, orally bioavailable small molecule that directly and transiently activates mTORC1, enhancing cellular metabolism in the brain. In animals, NV-5138 increases key synaptic proteins and synaptic remodeling in the prefrontal cortex and hippocampus, leading to sustained antidepressant behavioral responses. In adult subjects with treatment resistant depression (TRD), a single oral dose of NV-5138 2400 mg showed rapid and clinically meaningful benefits on the core symptoms of depression following single-dose administration, and was generally safe, well tolerated, and without dissociative effects. In healthy subjects, a single dose of NV-5138 2400 mg rapidly impacted brain metabolism of orotic acid, as well as N-acetyl methionine and N-formyl methionine, suggesting that these metabolites could be useful biomarkers to guide dose selection of NV-5138 in future antidepressant trials.

In this report, we present the effects of multiple doses of NV-5138 on biomarkers and plasma and cerebrospinal fluid (CSF) concentrations. Specifically, the present analysis evaluated the relationship between: a) NV-5138 plasma and CSF concentrations; b) NV-5138 plasma concentrations and CSF biomarkers of mTORC1 activation: orotic acid, N-acetylmethionine, and N-formyl methionine, and c) NV-5138 CSF concentration and CSF biomarkers.

Methods: These data were collected from a randomized, double-blind, placebo-controlled, safety and tolerability pharmacokinetic (PK) study of multiple ascending dosage levels of NV-5138 (400, 800, 1600, 2400 and 3000 mg) in healthy subjects ($N = 42$). Each randomized (3:1; NV-5138: placebo) subject received either NV-5138 or placebo once daily for 7 days. NV-5138 plasma PK samples were collected over 24 hours (pre-dose, 0.08, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours post dose) on days 1 and 7, and at pre-dose only on days 2 to 6 for all dose levels. NV-5138 CSF PK and CSF biomarker samples were collected on days 1 and 7 at pre-dose, 4, 8 and 12 hours post dose for all dose levels except the 3000 mg.

Effects of NV-5138 on orotic acid, N-acetyl methionine and N-formyl methionine were assessed across a range of NV-5138 plasma/CSF concentrations. Individual observed values were used in the analysis. An exploratory analysis was initially conducted to evaluate the distribution of the data and to inform the modeling approach to be implemented for characterizing the relationship between data. Based on these observations, a linear model was finally retained for characterizing the relationship between plasma and CSF concentrations of NV-5138 and biomarker concentrations.

Results: Twenty-six (54% male, 50% Hispanic and 54% white) healthy subjects with simultaneous measurements of NV-5138 (plasma and CSF) and CSF biomarker concentrations were included in this exploratory analysis (400 mg, $N = 8$; 800 mg, $N = 6$; 1600 mg, $N = 6$; 2400 mg, $N = 6$).

An increase in NV-5138 plasma concentrations was significantly correlated with an increase in NV-5138 CSF concentration ($p < 0.0001$) and an increase in CSF biomarkers: orotic acid ($p = 0.0804$, slope = 0.02), N-acetylmethionine ($p = 0.0002$, slope = 0.13), and N-formyl methionine ($p < 0.0001$, slope = 0.18). An increase in NV-5138 CSF concentration was also associated with an increase in CSF biomarkers: orotic acid ($p = 0.001$, slope = 0.21), N-acetylmethionine ($p = 0.0002$, slope = 0.67), and N-formyl methionine ($p < 0.0001$, slope = 0.92).

The safety analysis included all 42 subjects (57% female, 57% not Hispanic/Latino and 48% white) randomized in the study. The majority of adverse events (AEs) reported were mild in severity, with no severe, serious, unusual, or unexpected AEs, nor any dissociative effects. The most frequently reported AEs were lumbar puncture syndrome ($n = 15$ [47%] in NV-5138 vs. $n = 3$ [30%] in placebo) and back pain ($n = 5$ [16%] in NV-5138 vs. $n = 2$ [20%] in placebo). Overall, all doses of NV-5138 were well-tolerated and dose limiting toxicity was not found in doses up to 3000 mg/day.

Conclusions: NV-5138 plasma and CSF concentrations were significantly linearly correlated and therefore CSF concentrations can be robustly predicted from plasma concentrations in future studies. Increases in NV-5138 plasma and CSF concentrations were associated with increases in orotic acid, N-acetyl methionine, and N-formyl methionine CSF concentrations, indicating that plasma and CSF concentrations of NV-5138 are predictors of the CSF biomarker changes and activation of mTORC1. This NV-5138 CSF/biomarker correlation is consistent with results from the prior study of NV-5138 2400 mg conducted in healthy subjects. These data provide a robust characterization of dose-related effects of NV-5138 in healthy subjects and may inform dose selection in future trials. Administration of multiple doses of NV-5138 from 400 mg – 3000 mg were generally safe and well tolerated, and dose limiting toxicity was not detected.

Keywords: mTORC1, Pharmacokinetic and Pharmacodynamic, Treatment Resistant Depression

Disclosure: Supernus Pharmaceuticals: Employee (Self).

P275. Decreased Mitochondrial Health in Peripheral Blood Mononuclear Cells From Bipolar Disorder Patients

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Background: Bipolar disorder (BD) is a prevalent, debilitating condition, but its overall pathophysiology remains unknown. Although mitochondria dysfunction is known to play an important role in the pathophysiology of BD and cognitive impairment, little is known about the mechanism underlying the relationship between mitochondrial function and different clinical phenotypes, leading to a significant gap in understanding of why some patients present more adverse clinical outcomes and substantial cognitive and functional impairment than others. This study aimed to evaluate the composite MHI in peripheral blood mononuclear cells (PBMCs) of BD subjects and healthy controls. We also explored whether lower MIH will be related to higher levels of cell-free mtDNA (ccf-mtDNA) and poor clinical outcomes.

Methods: Fifteen patients with BD type I and 15 age- and sex-matched controls were enrolled for this study. PBMCs were separated using LeucoPREP brand cell separation tubes. PBMCs were used to measure the enzymatic activities of citrate synthase and complexes II and IV and mtDNA copy number. Further, MHI was calculated by mathematically integrating enzymatic activities and mtDNAcn. DNA was isolated from plasma samples from the same subjects, and ccf-mtDNA was evaluated by qPCR. Regression diagnostics were checked to ensure that the assumptions underlying the linear regression models were met. Analysis of covariance (ANCOVA) was performed to determine the relationship between groups and enzymatic activities, MHI and ccf-mtDNA with the addition of age, sex, ethnicity, BMI, smoking status (yes/no), and treatment (yes/no) as covariates. If an interaction was significant, Bonferroni corrected post hoc test was performed ($P < 0.05$, two-tailed). Correlations between variables were tested with either Pearson or Spearman tests, depending on their distribution.

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Results: To test the hypothesis that BD has lower mitochondrial health, we used standard analysis of covariance models, controlling for sex, age, BMI, and smoking status, to examine BD versus control group differences in the MHI. Our results showed that patients with BD present a decrease in the MHI compared to HCs ($R2 = 0175$, $p = 0.022$). Considering the association between mitochondrial dysfunction and brain dysfunction, we checked the correlation between the MHI and clinical measures. We found that MHI negatively correlated with depression (rho = -0.413, $p = 0.040$) and mania (rho = -0.417, $p = 0.038$) severity, and number of manic episodes (rho = -0.430, $p = 0.041$). Our findings also highlighted that subjects with worse functional status (as shown by lower GAF (rho = 0.514, $p = 0.009$) and higher FAST scores (rho = -0.412, $p = 0.041$) showed significantly lower MHI. Since a decrease in the mitochondrial health can ignites inflammation, we evaluated ccf-mtDNA levels and if MHI could be associate with ccf-mtDNA. Our preliminary data showed that BD patients had higher levels of ccf-mtDNA ($R2 = 0.070$, $p = 0.025$), which was negatively correlated with MHI (rho = -0.531, $p = 0.004$).

Conclusions: Taken together, our results suggest that an overall diminished mitochondrial respiratory capacity may characterize BD as a group. Moreover, our findings could suggest that alterations in the mitochondrial function may play a role in clinical and functional outcomes. In summary, the present findings corroborate previous studies and provide strong support to the notion that mitochondrial regulation and function are integral parts of the pathogenesis of BD.

Keywords: Bipolar Disorder, Poor Clinical Outcome, Functional Impairment, Mitochondria, Circulating Mitochondrial DNA

Disclosure: Nothing to disclose.