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M1. Lifespan Effects of Early Life Stress on Aging-Related Trajectory of Memory Decline

Benedetta Bigio, Danielle Zelli, Timothy Lau, Paolo de Angelis, Daniella Miller, Jonathan Lai, Anisha Kalidindi, Susan Harvey, Anjali Ferris, Aleksander Mathe, Francis Lee, Natalie Rasgon, Bruce McEwen, Carla Nasca*

Rockefeller University, New York, New York, United States

Background: Early life adversities (ELA), such as variations in maternal care of offspring, are critical factors underlying the individual likelihood to development of multiple psychiatric and medical disorders. For example, our new translation findings suggest a role of ELA in the form of childhood trauma on development of metabolic dysfunction, such as a deficiency in acetyl-L-carnitine (LAC) and insulin resistance (IR), in patients with major depression (MDD). Arising from the postulate of insulin resistance (IR) as a pathophysiological link in diabetes, depression and dementia ("the 3 D's"), we implemented a mating rodent model with high and low nurturing dams to study the lifespan effects of ELA on peripheral metabolic physiology, central glucocorticoid function and behavioral states.

Methods: We devised a computerized setup to record and assess the maternal care provided by wild-type or heterozygous BDNF val66met (hets) dams on offspring which were screened for individual anxiety-like behavior at the light dark, peripheral markers of IR and central glucocorticoid function in adulthood, and subsequently assessed for memory function in later age. Maternal care was assessed on the basis of previously employed ethological parameters by analyzing in and out of the nest caring and self-maintenance behaviors. Behavioral and molecular analyses in adulthood and midlife mice were performed as previously described by four observers who were blind to the sample conditions. Two-tailed t-tests and multiple regression were used as appropriate to specific analyses.

Results: We find that offspring receiving low quality maternal care in the early life show peripheral IR in adulthood as suggested by increased levels of insulin, glucose and tryglicerides in comparison with offspring that received high quality maternal care. This state of IR in adulthood is concomitant with increased expression of the mineralocorticoid receptors (MR) in hippocampus and corresponding anxiety-like behavior at the light-dark test in low nurtured offspring. Furthermore, low nurtured mice showed cognitive impairments in contextual memory at the Y maze in midlife, suggesting dementia-like symptoms, which were not apparent before.

Conclusions: These findings suggest a role for ELA in the form of poor maternal care in increasing the likelihood to development of peripheral IR, altered central glucocorticoid function and corresponding anxiety states in adulthood, and that these factors may encode lifelong susceptibility to pathophysiological aging. Given our earlier reported association between IR and a LAC deficiency, a candidate biomarker of major depression that is a risk factor for aging-associated memory decline, we are currently assessing LAC levels in this mechanistic framework. This model may provide endpoints for identification of early windows of opportunities for preemptive tailored interventions.

Keywords: Early Life Adversity, Glucocorticoids, Insulin Resistance, Glutamate, Memory Function

Disclosure: Nothing to disclose.

M2. Genetic Signatures of Response to Combination Escitalopram-Memantine Treatment for Geriatric Depression: A Randomized, Double-Blinded, Placebo-Controlled Pilot Study

Adrienne Grzenda, Helen Lavretsky, Prabha Siddarth, Natalie St. Cyr*

UCLA, Los Angeles, California, United States

Background: Geriatric depression is frequently associated with mild cognitive impairment (MCI), which responds poorly to antidepressant monotherapy. Furthermore, comorbid depression in patients with cognitive impairment appears to accelerate the neurodegenerative process, accelerating conversation to dementia. Our objective was to evaluate the efficacy of memantine augmentation of escitalopram treatment in elderly patients in improving clinical and cognitive outcome. Determine if unique gene signatures underlie escitalopram-memantine treatment response compared to escitalopram alone.

Methods: We conducted a 12-month double-blinded, placebo-controlled trial in older adults to assess the efficacy of combination memantine and escitalopram therapy compared to escitalopram and placebo for the treatment of depression (ClinicalTrials.gov NCT01902004). For the current study, we analyzed the first 37 participants to completed 6-month follow up. The primary outcome was remission of depressive symptoms, defined as Hamilton Depression Rating Scale (HAM-D) scores of 6 or less for 3 consecutive weeks following initiation of treatment. Secondary measures included apathy, quality of life, and cognition. Genome-wide transcriptional profiles were generated from peripheral blood leukocytes sampled at baseline and 3 months following initiation of treatment.

Results: Escitalopram daily doses ranged between 10-20 mg; memantine daily doses ranged between 10-20 mg. Both treatment groups demonstrated similar remission rates at 6-month follow-up with significant improvement in depression, anxiety, and overall clinical illness severity. Escitalopram with memantine treatment resulted in additional improvements in apathy, quality of life, and intermediate/delayed memory. There exists unique baseline and post-treatment gene signatures that predicted response to combination escitalopram-memantine compared to escitalopram-placebo treatment. Furthermore, bioinformatics analysis of differentially expressed gene targets indicates unique and synergistic mechanisms of action mediating antidepressant response in monotherapy and memantine augmentation.

Conclusions: Pilot data indicate that memantine augmentation of escitalopram treatment in geriatric depression results in an enhanced clinical response profile, including improvements in apathy, resilience, quality of life, and cognition. There was no difference in depression remission rates between the two groups. Remission of depression, however, was associated with unique gene signatures in each treatment group, which may direct selection of patients to receive combination therapy in future precision medicine initiatives. The current findings need to be replicated in a larger sample with additional time-course data to determine if additional differences exist between the treatments remission rate and overall degree of response.

Keywords: Geriatric Depression, Antidepressant Response, Neuroprotection, Escitalopram, Memantine

Disclosure: Nothing to disclose.

M3. Online Repetitive Transcranial Magnetic Stimulation Enhances Working Memory Performance in Younger and Older Adults

*Lysianne Beynel, Simon W. Davis, Susan Hilbig, Wesley Lim, Angel V. Peterchev, Roberto Cabeza, Greg Appelbaum, Sarah Lisanby, Bruce Luber**

National Institute of Mental Health, Bethesda, Maryland, United States

Background: Working memory (WM) is the ability to perform mental operations on information that is stored in a flexible, limited capacity buffer. Through the interface between long-term memories and moment-to-moment information available in the environment, WM allows humans to carry out successful goal-directed behaviors. As such, WM is widely involved in the achievement of complex tasks such as learning, decision making, and reasoning. Critically, decline in WM is a major factor in cognitive impairment that accompanies healthy aging. Therefore, many different approaches are being explored as possible interventions to enhance these abilities, including non-invasive brain stimulation methods such as repetitive transcranial magnetic stimulation (rTMS). Previously, we have shown 5 Hz rTMS to enhance WM performance in different groups of young and older healthy adults. However, these studies only examined only the maintenance component of WM, the process that sustains information in an activated state, rather than the ability to manipulate information in WM (the "working" part of WM), which is central to many aspects of human cognition. Further, compared to maintenance, manipulation is more dependent on dorsolateral prefrontal cortex (DLPFC) which is one of the brain regions shown to be most impaired by aging, although as of yet, no rTMS studies have tried to enhance WM manipulation by stimulating DLPFC. The current study tested the capacity to enhance working memory manipulation with online 5 Hz rTMS to DLPFC in healthy young and older adults.

Methods: Online high frequency rTMS was applied over the left DLPFC to test the hypothesis that active rTMS would lead to significant improvements in memory recall accuracy compared to sham stimulation, and that these effects would be most pronounced in WM manipulation conditions with the highest cognitive demand in both young and older healthy adults. rTMS was applied while participants performed a delayed response alphabetization task with three individually-titrated levels of difficulty. The TMS coil placement was optimized by integrating electric field modeling with individualized functional magnetic resonance imaging activation maps in left DLPFC based on the WM task and was implemented during the experiment using stereotactic neuronavigation with real-time robotic guidance, allowing accurate targeting during the stimulation. Participants were scheduled for 6 sessions. The first visit consisted of consenting, exclusionary screening, resting motor threshold (rMT) assessment and 6 blocks of practice with the behavioral task. Participants then returned for an MRI visit and four more rTMS sessions. On each rTMS visit, 25 pulses of 5 Hz rTMS were applied at rMT while subjects performed the WM task with the titrated 3 difficulty levels (Easy, Medium, and Hard), with accuracy feedback given at the end of each block. Ten blocks of the task were performed: a first block without stimulation, four blocks of active or sham stimulation, one block without stimulation, and four more blocks with the sham or active stimulation. The order of stimulation type (Active or Sham) was presented according to an ABBA schedule

Results: Twenty-nine young adults (17 females and 12 males; 22.9 ± 4.8 years old) and eighteen older adults (13 females and 5 males; age: 69.7 ± 4.8 years old) completed the full protocol. A significant interaction between Difficulty Level and Stimulation Type (Active or Sham rTMS) was found ($F(2, 88) = 8.49$, $p < .001$). The decomposition of this interaction with Bonferroni correction revealed a significant difference in the Hard condition, with active rTMS producing increased accuracy compared to sham rTMS ($F(1,44) = 17.15$, $p = .006$). Investigating this effect in both young and older groups separately, the one-way interaction between Difficulty and Stimulation Type, was found to be significant for both the young ($F(2, 54) = 4.11$, $p = .022$) and the older cohort ($F(2, 32) = 4.79$, $p = .015$). Thus, the results yielded two main findings. First, active 5 Hz rTMS delivered to individualized left DLPFC targets, identified with fMRI and electric field modeling, significantly enhanced WM manipulation abilities over the course of the intervention, but only in the most difficult condition of the task, namely the hardest difficulty level. Second, active versus sham rTMS produced similar effects in young and older adults, suggesting that rTMS enhancement was not modulated by age.

Conclusions: The current study showed that 5 Hz rTMS applied over the left dorsolateral prefrontal cortex can enhance WM manipulation abilities, but only in the most difficult condition, with no differences between young and older adults. This result points towards further investigation of rTMS for memory enhancement, focusing on high difficulty conditions as those most likely to exhibit benefits.

Keywords: TMS, Working Memory, Aging, Memory Enhancement, TMS Targeting

Disclosure: Nothing to disclose.

M4. Individualized Structural Connectome for Diagnostic and Prognostic Prediction for Alzheimer's Disease

Yun Wang, Chenxiao Xu, Ji-Hwan Park, Seonjoo Lee, Yaakov Stern, Shinjae Yoo, Hyoung Seop Kim, Jiook Cha*

Columbia University/New York State Psychiatric Institute, New York City, New York, United States

Background: There is an urgent, unmet need for clinically useful biomarkers for Alzheimer's disease (AD) based on non-invasive and affordable measures suited for screening for individuals with subthreshold symptoms. More Studies have been focusing on brain MRI-derived markers. Cortical thinning and reduced hippocampal volumes based on structural MRI are known for markers for Alzheimer's disease, but these structural estimates alone are insufficient for implementation at clinical settings because of insufficient accuracy and generalizability. Here we tested the utility of the white matter structural connectomes in predicting diagnosis, and disease trajectory.

Methods: We used data from 208 elderly patients who visited the dementia clinic at National Health Insurance Service Ilsan Hospital (NHIS-IH), Goyang, South Korea from 2010 to 2015. Participants included 110 with diagnosis of Alzheimer's disease (AD; median age = 82; interquartile intervals (Q3-Q1) = 85-77), 62 with mild cognitive impairment (MCI; median age = 73; Q3-Q1 = 77-66), and 37 subjective mild cognitive impairment (SMC; median age = 74; Q3-Q1 = 78-72). To test the generalizability of our approach, we also used ADNI-2 (Alzheimer's Disease Neuroimaging Initiative), of which structural and diffusion MRI was collected.

For both data, using multi-modal brain MRI (structural and diffusion MRI), we performed high-throughput brain phenotyping, including automated morphometry and white matter structural connectomics (probabilistic tractography) to generate large-scale multi-modal, multi-parameteric imaging-derived phenotypes used as features in machine learning. For structural MRI analysis, firstly, we estimated morphometrics measures using Freesurfer image analysis pipeline from T1 and T2-FLAIR images. Morphometric measures (N = 948 per subject) include volumes of the hippocampal subdivisions, and thickness, surface area, and volume of cortical/subcortical regions using two different atlases available in freesurfer. For diffusion MRI analysis, we used MRtrix 3. The connectome measures (N = 33,698 per subject) include counts of streamlines, a surrogate measure of structural connectivity, and mean length of streamlines given any two brain regions based on multiple atlases.

We built several machine learning models using the large-scale brain MRI-derived phenotypes to predict diagnosis of AD and MCI, respectively. We benchmarked three classifiers available at a python library for machine learning, scikit-learn (4): random forest, logistic regression (LR) with L2 regularization, and support vector machine (SVM) with linear kernel. Model training and validation was done using nested cross validation to avoid overfitting due to bias to training data (5, 6). For hyper-parameter optimization, we used the grid search method, varying C parameter for SVM and LR classifier, and varying the number of estimators and the minimum samples per leaf for random forest classifier. We used 3-fold cross validation with 10 iterations with stratification by target labels (repeated, stratified, nested 3-fold cross validation). We estimated accuracy, sensitivity, specificity, F1 score, and receiver operating characteristic (ROC) curve from repeated 3-fold cross-validation to evaluate the performance of our classifiers.

Results: In dataset1, for classification of AD vs. SMC, "morphometry + connectome" model showed optimal classification accuracy (accuracy = 0.99; RF. While "connectome" model showed similar accuracy (accuracy = 0.99; RF), "morphometry" model showed least significant accuracy (accuracy = 0.88; RF). In classification of MCI vs. SMC, "morphometry + connectome" models also showed best classification accuracy (accuracy = 0.90; RF), followed by "connectome" model (accuracy = 0.88; RF) and, "morphometry" model showed poor performance (accuracy = 0.86; RF). In classification of AD vs. MCI, "morphometry + connectome" models showed a best accuracy (accuracy = 0.99; RF), followed by "connectome" model (accuracy = 0.99; RF), and "morphometry" model (accuracy = 0.87; RF). Throughput all classifications, connectomes and morphometry showed greater diagnostic accuracies compared with the WMH benchmark. In dataset2, to compare the performance of our classifiers, we used models based on CSF biomarkers as a benchmark. In classifying diagnosis of AD and MCI, the combined connectome and morphometric model shows similar accuracy compared with the CSF benchmark model (0.63 vs 0.69). Of these samples, data from 60 elders with initial diagnosis of MCI who were followed at least two years were used to test prognosis. The same CSF benchmark was used. In predicting MCI-to-AD progression, all MRI-based models outperformed the CSF benchmark. However, in this case, the combined connectome and morphometric model underperformed either connectome or morphometric only model.

Conclusions: In this study, we showed that large-scale MRI-derived brain phenotypes could be used to accurately classify Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) and to predict disease progression to AD from MCI in multiple datasets with moderate sample sizes. These promising results show potential utility of white matter structural connectomes in addition to widely use morphometry as a proxy measure of neurodegeneration in AD pathology.

Keywords: Diffusion Tensor Imaging (DTI), machine learning classification, Alzheimer's Disease

Disclosure: Nothing to disclose.

M5. Sensitivity to Maternal Buffering of Fear in Infancy is Sex-Dependent

*Amanda White, Jacek Debiec**

University of Michigan, Ann Arbor, Michigan, United States

Background: Beginning in infancy, social cues play a crucial role in the regulation of emotional state and behavior. In addition to providing their child with nutrition, warmth, and safety, mothers can suppress amygdala activity, cortisol release, emotional distress, and fear learning in their child, an effect termed "maternal buffering." When infant rats undergo fear conditioning in the presence of a calm mother, they do not acquire the association between the neutral cue and mild foot shock. There is an emerging literature on sex differences in expression of fear and in the social regulation of fear in adults; however, sex differences in maternal buffering of fear have not received much attention. Here, we examined whether maternal presence differentially modulates fear in female and male rat pups.

Methods: All experiments were conducted using Sprague-Dawley rats. Rat mothers were anesthetized with 50 mg/kg ketamine and 5 mg/kg xylazine. Once dams were fully anesthetized, they were placed in a clean cage lined with an absorbent blue pad. Postnatal day 13 (P13) pups were then placed in the cage with the mother and given a 10-min adaptation period. Following the adaptation period, pups received 11 presentations of a 30-s peppermint odor (CS) and a 1-s, 0.5-mA tail shock unconditioned stimulus (US) (Lafayette scrambled shock generator), with an intertrial interval (ITI) of 4 min. Peppermint odor was delivered by a flow dilution olfactometer (2 L/min flow rate) at concentration of 1:10 peppermint vapor. Paired odor–shock pups received a shock overlapping with the last second of the 30-s odor presentation. On P18, pups were placed in clear plastic boxes and given a 3-min adaptation period. A 30-second CS odor was presented to the pups 3 times with an ITI of 2 minutes. Pup behavior was recorded via video camera. Neuronal activation and endocrine response will be examined in future experiments.

Results: In females, we found a significant main effect of maternal presence (p = 0.008); females that were conditioned in the presence of an anesthetized mother (n = 6) froze significantly less at test than females that were conditioned in the absence of

an anesthetized mother (n = 7). However, we did not observe significant differences between males that were conditioned in the presence of an anesthetized mother (n = 7) and males that were conditioned in the absence of an anesthetized mother (n = 5) (p = 0.75). In subsequent experiments we assessed corticosterone levels and neural activity in pups during maternal buffering of fear.

Conclusions: Our data demonstrate that female pups are more susceptible to maternal buffering of fear, and suggest that sex differences in social regulation of emotion emerge very early in life. Caregivers buffer their child's emotional response to stressful events and protect their child's developing brain from the deleterious effects of stress. A better understanding of the mechanisms underlying maternal buffering of fear may help clinicians improve treatment outcomes for children that have experienced trauma

Keywords: Fear Conditioning, Maternal Behavior, Infancy, Early Life Stress, Social Stress Buffering

Disclosure: Nothing to disclose.

M6. Tracing and Intersectional Optogenetic Approaches to Identify a Novel Serotonergic System That Projects to the Hypothalamus to Increase Arousal and Place Preference and Inhibit Panic

*Cristian Bernabe, Izabela Caliman, Zachary Rodd, Anantha Shekhar, Philip Johnson**

Indiana University School of Medicine, Indianapolis, Indiana, United States

Background: Although selective serotonin transporter reuptake inhibitors are the first line pharmacological treatment for severe anxiety disorders such as panic disorder (associated with recurrent panic attacks) and highly comorbid phobias, our understanding of how serotonin regulates panic and fear networks is poorly understood. Our preclinical work has identified that the perifornical hypothalamus (PeF) and local orexin (OX)/glutamate neurons play a critical role in animal models of adaptive and pathological panic, but little is known about how serotonin regulates this system in the context of panic and phobias. Based on previous immunohistochemistry (IHC) and electrophysiological studies showing that 5-HT1a and 5-HT2a receptors are respectively expressed on and inhibit and excite OX/glutamatergic and melanin concentrating hormone (MCH)/GABA neurons in the PeF and lateral hypothalamus (LH), we hypothesized that serotonin is inhibiting panic locally.

Methods: In experiment 1 we wanted to use optogenetics to confirm that the PeF/LH is pro panic/phobia. We bilaterally injected an adeno-associated viral construct (AAV) with a glutamatergic promoter into the PeF/LH to induce local expression of channelrhodopsin (ChR2) and a fluorescent reporter. Wireless LED implants were later implanted into the PeF/LH to excite ChR2 expressing glutamate neurons. In experiment 2, we injected the retrograde tracer cholera toxin B (CtB) conjugated to a flourophore into the PeF/LH of rats and immunostained for tryptophan hydroxylase to identify serotonergic neurons that project to the PeF/LH. In experiment 3, we next bilaterally injected a canine adenovirus (CAV) with a nonspecific neuronal promoter into the PeF/LH. The CAV is retrogradely transported and induces expression of Cre-recombinase (Cre-R) in all neurons that project to the PeF/LH. We then injected an AAV into the lwDRN and MRN with a nonspecific neuronal promoter to induce a double floxed inverted (DIO) sequence of ChR2 which in the presence of Cre-R is expressed. Wireless LED were later implanted into the lwDRN/MRN.

Results: In experiment 1 - LED excitation of glutamate neurons in the PeF/LH induced: 1) panic-associated flight/escape behaviors and robust cardioexcitation; 2) and also phobia associated unconditioned and conditioned place avoidance. Ex vivo IHC confirmed that the reporter (evidence of ChR2 expression) was expressed on all local OX neurons (n = 4-5/group). In experiment 2 – Retrograde tracing revealed that CtB expressing serotonergic neurons that project to the PeF/LH were concentrated in the lateral wings of the dorsal (lwDRN) raphe and also medial (MRN) raphe nucleus (n = ~7) and did not overlap with pro-fear amygdala projecting serotonergic neurons in the midline DRN (n = ~15). In experiment 3, LED excitation of ChR2 + lwDRN/MRN terminals in the PeF/LH: 1) increased non-agitated locomotion; 2) unconditioned and conditioned place preference and, 3) inhibited CO2 (a suffocation stimuli) induced panic (e.g., flight/escape behaviors and cardioexcitation). Ex vivo analyses revealed robust expression of the fluorescent reporter (evidence of ChR2 expression) in the lwDRN/MRN and the PeF/LH, but also in collateral fields associated with reward such as the ventral tegmental area and the nucleus accumbens (n = 9-10/group).

Conclusions: The data here support the hypothesis that serotonergic neurons in the lwDRN and MRN that project to the PeF/LH represents a panic-off circuit that also mobilizes arousal and motivated behaviors. Future studies will focus on elucidating this circuit's role in reward, addiction, and depression and if inhibition of this circuit induces pathological panic and or depression.

Keywords: Anxiety, Panic, Agoraphobia, Hypothalamus, Serotonin

Disclosure: Nothing to disclose.

M7. Adolescent Intermittent Alcohol Exposure Enhances Sensitivity to Future Stress Events That Promote Abnormal Fear-Related Behavior in Adulthood

Lawrence Chandler, Justin Gass*

Medical University of South Carolina, Charleston, South Carolina, United States

Background: Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are two of the most common mental disorders and are highly comorbid. Accumulating evidence indicates that the neuropathology of both of these conditions arise from engagement of aberrant learning and memory processes, and recent evidence further suggests that the neurocircuitry of alcohol addiction and the neurocircuitry of fear and anxiety disorders overlap and have many common characteristics. It is becoming increasing apparent that abuse of alcohol during adolescence has long lasting effects of brain and behavior in adulthood. Although the important relationship between PTSD and AUD is an increasing focus of research, the question of whether the abuse of alcohol during adolescence adversely impacts how an individual reacts to a traumatic stress event, as well as their resilience to subsequent stressors, has received little attention.

Methods: Adolescent Long Evans rats were subjected to repeated episodes of alcohol exposure by vapor inhalation followed by a single episode of acute restraint stress to simulate a traumatic event. Rats were subsequently tested for stress resilience using a fear conditioning and extinction procedure.

Results: We observed that adult rats that had been subjected to adolescent intermittent ethanol (AIE) acquired fear conditioning at a faster rate but exhibited a slower rate of extinction of the fear memory. AIE-exposed rats also exhibited increased freezing behavior during testing for both extinction recall and spontaneous recover. However, treatment with an mGluR5 positive allosteric

modulator during fear extinction training attenuated these deficits in extinction learning and retention. An especially interesting observation was that while extinction recall was not altered by stress alone, it had a synergist effect with AIE on extinction recall (e.g., deficits in the ability to retain the extinction memory).

Conclusions: These findings in rats provide support for the hypothesis that adults with a history of abuse of alcohol during adolescent who experience a traumatic stress event later in life have reduced stress resiliency and are at a significantly greater risk of developing PTSD and AUD and identify potential therapeutic targets for the treatment of these comorbid disorders.

Keywords: PTSD, Fear Conditioning, Adolescent Alcohol Exposure, Fear Extinction, Alcohol Use Disorder

Disclosure: Nothing to disclose.

M8. Prefrontal Regulation of the Extended Amygdala and Anxious Temperament in Young Nonhuman Primates

Margaux Kenwood, Jonathan A. Oler, Andrew S. Fox, Do P. Tromp, Rasmus M. Birn, Elisabeth A. Murray, Ned H. Kalin*

University of Wisconsin Madison, Madison, Wisconsin, United States

Background: Anxious temperament (AT) is an early-life risk factor for the later development of stress-related psychopathology. Using a well characterized nonhuman primate model of AT with FDG-PET in a large sample ($n = 592$), we identified the AT neural circuit. This circuit includes the bed nucleus of the stria terminalis (BST) and central nucleus of the amygdala (Ce), components of the central extended amygdala (EAc). Studies from our laboratory suggest that the EAc is regulated by the prefrontal cortex, as orbitofrontal cortex (OFC) lesions reduce BST metabolism. The connectivity between these structures is via fibers that are carried in the uncinate fasciculus (UF), a major white matter tract between the OFC and subcortical structures. Interestingly, decreased UF fractional anisotropy (FA) has been demonstrated in adults and children with anxiety disorders. Here, we used a selective lesioning strategy to assess the role of UF fibers in the expression of AT, and multimodal imaging to understand the neural circuit mechanisms underlying this effect.

Methods: With the intent of disrupting fibers of passage, we lesioned a narrow strip of the posterior OFC in 10 young female rhesus monkeys. 10 age- and sex-matched animals served as cage-mate controls. Before and after the lesions, animals were phenotyped for AT and assessed with multimodal brain imaging (DTI, fMRI, and FDG-PET). To assess lesion-induced alterations of white matter microstructure, deterministic tractography was used to create regions of interest (ROIs) of the UF and other major white matter tracts. Average FA was extracted from these ROIs and examined for lesion-induced changes. To assess changes in BST function resulting from the lesions, threat-related metabolic activity was extracted from the FDG-PET images using a bilateral BST seed. To assess changes in BST functional connectivity resulting from the lesions, fMRI signal was averaged across all voxels in the same BST seed, and voxelwise temporal correlations were computed using AFNI. The behavioral and imaging data were analyzed using a (LESION[post-pre] - CONTROL[post-pre]) design. Finally, to determine whether lesion-induced changes in BST fMRI connectivity occurred in regions that are functionally connected to the BST, intrinsic functional connectivity of the BST was assessed using the same seed in separate animals ($n = 378$).

Results: Lesioned animals demonstrated the predicted decrease in AT (Student's t-test, $t = 1.589$, $p = .06$, one-tailed). Extraction of average FA values demonstrated substantial lesion-induced alterations in white matter microstructure of the UF (Student's t-test, $t = 4.16$, $p = 0.0005$, two-tailed). Additionally, in the lesioned animals, the decrease in UF FA was associated with individual differences in the decrease in AT (Pearson's $r = 0.72$, $p = 0.029$). Notably, no other fiber tracts showed significant decreases in FA. Replicating previous findings, lesioned animals showed a significant decrease in BST metabolism (Student's t-test, $t = 3.98$, $p = 0.0009$). Finally, the lesioned animals demonstrated decreased functional coupling between the BST and regions of the left ventrolateral PFC (vlPFC, area 12/47), the upper bank of the rostral portion of the cingulate sulcus (ACC) and the right superior temporal sulcus ($p < 0.005$, uncorrected). Importantly, all three clusters demonstrating lesion-induced changes in BST functional connectivity overlapped with regions intrinsically coupled to the BST in the large sample ($n = 378$).

Conclusions: This study, combining causal manipulations with multimodal imaging in young nonhuman primates, provides insight into the importance of white matter fibers that connect prefrontal with subcortical structures in mediating the early risk to develop stress-related psychopathology. The findings from this study, along with those in children demonstrating altered UF FA in relation to anxiety, highlight the importance of the fibers passing nearby or through the OFC, particularly those of the UF, in mediating anxiety regulation. The results point to BST interactions with frontal cortex in mediating the adaptive and maladaptive regulation of anxiety. Furthermore, the functional connectivity data from the operated monkeys implicates not only OFC, but also the vlPFC and ACC in the regulation of BST function. Taken together, findings from this study demonstrate the value of a strategy that combines causal manipulations with multimodal imaging methods in NHPs to discover mechanisms underlying the early life risk to develop psychopathology.

Keywords: Extended Amygdala, Orbitofrontal Cortex (OFC), Rhesus

Disclosure: Nothing to disclose.

M9. Effect of Exogenous Hormones on Rodent Models of Fear Memory

Teniel Ramikie, Kerry Ressler*

McLean Hospital, Harvard Medical School, Belmont, Massachusetts, United States

Background: Posttraumatic Stress disorder (PTSD) affects approximately 7% of the US population in their lifetime (Kessler et al., 2005). Alarmingly, PTSD rates are 2-fold higher in women as compared to men and women experience greater PTSD symptom severity and longer symptom duration. Although women and men experience differences in trauma type exposure (e.g. women experience higher rates of sexual assault), PTSD-related sex differences persist even when controlling for trauma type and severity (Breslau et al., 1998). Collectively, these data suggest that increased PTSD vulnerability in women is, in part, shaped by sex differences in non-environmental factors. Notably, epidemiological studies have shown that PTSD-related sex differences rise following puberty onset and fall following menopause, highlighting the impact of fluctuating gonadal hormone levels on shaping PTSD vulnerability in women of reproductive age. In support of this, many studies now show that gonadal hormone status does influence PTSD symptom development in women (Milad et al., 2006; Glover et al., 2012, 2013). While this remains a critical area of study, most of these investigations have focused on endogenous gonadal hormones while only a few studies have examined the role of exogenous gonadal hormones in shaping PTSD outcomes in women of reproductive age. This is an important research area as hormone-based contraceptives (HC), have been used by women for over 50 years and are one of the

1st-lines of treatment for women after sexual assault. In addition to suppressing endogenous gonadal hormone levels and decreasing pregnancy risk, clinical evidence shows that peri-traumatic administration of exogenous hormones, via HC intake, impact memory related PTSD symptoms (Ferree et al., 2012)—suggesting that exogenous hormones also shape fear memory. The biological mechanisms through which exogenous gonadal hormones shape emotional memory remains unknown. Our study will begin to address this question by examining the impact of exogenous gonadal hormones on fear memory in mice.

Methods: All experiments were carried out using female C57/BL6J mice, 8-12 weeks of age. Each experimental group had 8-12 mice. Estrous cycle was examined using vaginal cytology and subsequent H&E staining. HC used for these experiments was administered orally, via drinking water. Either HC-containing or control drinking water was the only source of water available to experimental groups. An estradiol (E2) ELISA was used to confirm HC biological efficacy. Auditory fear conditioning and fear extinction behavioral experiments were performed to assess fear memory-related behaviors (% freezing), startle chambers were used to measure shock reactivity; open field (OF) and elevated plus maze (EPM) behavioral protocols were used to assess anxiety-like behaviors. Two-way ANOVA and Student's t-test were used to analyze group differences. Data analysis was performed using GraphPad Prism 7.

Results: Vaginal cytology and ELISAs were used to characterize the efficacy of sub-chronic and chronic HC intake at different concentrations. Results revealed that chronic HC intake effectively suppressed E2 levels (measured as a % of proestrus levels) in HC treated groups as compared to controls (sub-chronic HC intake $F(2,9) = 0.0505$, $p = 0.951$; chronic HC intake $F(2,7) = 65.13$ $p < 0.0001$). We assessed the effects of chronic HC use on basal measures of anxiety-like behaviors using OF and EPM. These results revealed that chronic HC did not affect measures of anxiety-like behaviors or locomotor measures (control vs. HC-treated groups, $p > 0.05$).

Next, we assessed the effects of peri-traumatic HC administration on fear memory. To do this, we assessed the following forms of peri-traumatic HC intake: 1) acute HC intake immediately following trauma, 2) chronic HC intake following trauma and 3) chronic HC intake prior to and after trauma. These HC intake protocols best reflected the HC administration methods used in clinical settings (Ferree et al., 2012). These experiments revealed that acute HC intake immediately following fear conditioning had no effect on fear learning or fear expression but significantly improved fear extinction memory in HC treated group as compared to controls (Drug effect: $F(1,22) = 4.611$, $p < 0.05$). In addition, chronic HC intake immediately following fear conditioning led to both decreased fear expression in HC-treated groups as compared to controls ($p < 0.05$) and enhanced fear extinction learning and retention in HC-treated groups as compared to controls (Drug effect: $F(1,22) = 7.811$, $p < 0.05$). Lastly, our subsequent experiments revealed that chronic HC intake prior to and after fear conditioning had no effect on fear learning ($p > 0.05$) but resulted in a relatively greater decrease in fear expression ($p < 0.01$) and also enhanced fear extinction memory in HC treated groups as compared to controls (Drug effect: $F(1,22) = 7.811$, $p < 0.01$). Given evidence of gonadal hormone effects on pain sensitivity, we also measured the pain sensitivity of our HC-treated animals and found no difference between our control and HC-treated groups ($p > 0.05$).

Conclusions: These results indicate that though HC-intake does not affect basal levels of anxiety-like behaviors or pain sensitivity, acute and chronic exogenous gonadal hormone intake, via HC, decrease fear conditioning recall and enhance fear extinction memory. Collectively, these experimental outcomes indicate that peri-traumatic exogenous hormone intake can positively modulate fear-related memory.

Keywords: Gonadal Hormones, Fear Memory, Sex Differences
Disclosure: Nothing to disclose.

M10. A Subpopulation of Extended Amygdala Neurons Drives Physiological Arousal and Anxiety States

Jose Rodriguez-Romaguera, Randall Ung, Hiroshi Nomura, James Otis, Marcus Basiri, Pengcheng Zhou, Hanna van den Munkhof, Vijay Namboodiri, Xueqi Zhu, J. Elliott Robinson, Jenna McHenry, Shanna Resendez, Louisa Eckman, Oksana Kosyk, Liam Paninski, Thomas Jhou, Thomas Kash, Michael Bruchas, Garret Stuber*

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

Background: Anxiety is a complex state consisting of cognitive, emotional and physiological arousal components. The bed nucleus of the stria terminalis (BNST, part of the extended amygdala) is a key region implicated in the regulation of anxiety. Due to the large genetic diversity in cell types within BNST, it is unclear whether specific components of anxiety, such as physiological arousal, are driven by precisely defined BNST subpopulations. Neuropeptide systems contribute to define BNST cell-types. BNST is enriched with the neuropeptide nociceptin/orphanin FQ (N/OFQ), and besides its role in pain sensitivity, recent studies suggest its involvement in positive and negative emotional states across many brain regions. Given that painful and emotional stimuli alter arousal, we hypothesized that neurons within BNST that selectively express the genetic precursor to N/OFQ-prepronociceptin (Pnoc-BNST) may contribute to physiological arousal and modulate anxiety-mediated behavior.

Methods: We characterized the anatomical and genetic identity of Pnoc-BNST neurons using histological ($n = 11$), electrophysiological ($n = 4$), and single-cell sequencing ($n = 24$) approaches. We then determined whether Pnoc-BNST neurons encode increases in physiological arousal, by visualizing the activity dynamics of individual Pnoc-BNST neurons in response to aversive (2,3,5-Trimethyl-3-thiazoline) and rewarding (peanut oil) odors in head-fixed mice. Furthermore, to assess anxiety-mediated behaviors, freely-moving mice were exposed to the elevated plus maze (EPM). We did so by using either head-fixed two-photon ($n = 1{,}180$ neurons, $n = 7$ mice) or freely-moving one-photon ($n = 258$ neurons, $n = 10$ mice) calcium imaging approaches. Lastly, we tested whether cell-specific optogenetic photoactivation of Pnoc-BNST neurons drive physiological arousal as measured by pupillary responses ($n = 8$) and promote anxiety-mediated behavior in the EPM ($n = 13$).

Results: Histological, electrophysiological, and single-cell sequencing data revealed that Pnoc-BNST neurons consists of a previously unstudied subset of GABAergic neurons that are interconnected and dispersed across BNST subnuclei. In vivo single-cell calcium imaging revealed that activity of Pnoc-BNST neurons correlates with increased pupillary responses in mice presented with aversive ($p < 0.0001$) or rewarding ($p < 0.0001$) odors. Similarly, exposure to open arms of the EPM increased Pnoc-BNST activity ($p < 0.001$). In addition, in vivo optogenetic photoactivation revealed these neurons increase physiological arousal ($p = 0.0398$) and anxiety-mediate avoidance ($p = 0.0037$).

Conclusions: Pnoc-BNST neurons show high correlations with increases in physiological arousal to salient stimuli and also signal anxiety-mediated states, suggesting a role of these neurons in driving the physiological arousal component of an anxiety state. Our data demonstrate that driving neurons that mediate physiological arousal in combination with exposure to an anxiogenic environment induces a hyperarousal-like state that produces excessive and aberrant anxiety-mediated behavior.

Moreover, our data strongly suggest that targeting these neurons may be effective for patients suffering from anxiety disorders.

Keywords: Anxiety Circuitry, Hyperarousal, In Vivo Calcium Imaging

Disclosure: Nothing to disclose.

M11. Corticostriatal Circuit Defects in Hoxb8 Mouse Model of Repetitive Behaviors

Abstract not included.

M12. Transcriptional Profiling of Primate Central Nucleus of the Amygdala Neurons to Understand the Molecular Underpinnings of Early Life Anxious Temperament

Rothem Kovner, Tade Souaiaia, Andrew Fox, Patrick Roseboom, Delores A. French, Jonathan A. Oler, James A. Knowles, Julie Fudge, Ned Kalin*

University of Wisconsin, Madison, Madison, Wisconsin, United States

Background: Children exhibiting stable and extreme anxious temperament (AT) are at an increased risk to develop anxiety and depression later in life. Numerous studies point to the importance of the amygdala in mediating adaptive responses to threat as well as stress-related psychopathology. Using a well validated non-human primate model with neuroimaging and lesions strategies, our laboratory identified the central nucleus of the amygdala (Ce) as a key component in the neural circuitry mediating AT. Our previous work assessing punch biopsies of the dorsal amygdala with microarray technology revealed alterations in neuroplasticity genes that were related to AT. To refine our understanding of the molecular alterations related to AT, we now focus on neurons within the lateral Ce (CeL) using laser capture microscopy (LCM) to selectively capture neurons combined with deep RNA sequencing (RNA-Seq).

Methods: Using LCM, approximately 600 CeL neurons were collected from each of 47 AT phenotyped young male and female rhesus monkeys and RNA-Seq was performed. Multiple regression analysis investigated the relationship between exonic transcripts and individual differences in AT. We focused on transcripts from genes known to be implicated in anxiety and also used a discovery approach to identify alterations in the function of new transcripts. Gene ontology was performed using Panther to determine biological processes related to AT. Transcripts predictive of AT were selected for further anatomical validation using triple-labeling immunofluorescence combined with confocal microscopy and stereological cell counting.

Results: RNA-Seq analysis demonstrated 600 transcripts to be associated with AT ($p < 0.05$, two-tailed uncorrected). Permutation testing was done for each of the 600 transcripts in relation to AT and 576 transcripts passed permutation testing ($p < 0.05$ out of 10,000 tests). Gene ontology analysis demonstrated a variety of biological processes that are associated with AT such as neuron development (GO:0048666, GO:0031175) and differentiation (GO:0030182) as well as enrichment in transcripts related to protein phosphorylation (GO:0006468). More specifically, we identified a number of transcripts related to epigenetic mechanisms (e.g. SS18, SMYD2, and DNMTA3) as well as transcripts predicted to be related to anxiety and psychopathology such as NPY2R and VMAT-2. Of particular interest was the discovery that protein kinase C type-delta (gene name: PRKCD, protein name: PKC-delta) was positively associated with AT ($R2, 0.15, t = 3.280, p = 0.017$). PKC-delta is an interesting candidate due to its demonstrated role in rodent CeL neurons involved in threat processing and conditioned fear learning. To understand the extent to which these rodent microcircuitry studies are translatable to primates, we characterized the distribution of PKC-delta and other neuropeptide expressing neurons such as somatostatin (SST) in the monkey CeL and compared this to the mouse CeL. The estimated percent of neurons that expressed PKC-delta was 59% in the monkey and 43% in the mouse. Surprisingly, there was a significant difference in the percent of SST expressing neurons with only 7% of neurons expressing SST in the monkey compared to 20% in the mouse ($p = 0.02, t = 3.6$).

Conclusions: Here, we demonstrate a method in non-human primates to identify alterations in gene function within neurons of the CeL that are relevant to early life pathological anxiety. The findings implicating PRKCD in CeL neurons are particularly exciting as they build on findings in rodents demonstrating an important functional role for PKC-delta CeL neurons in threat processing. In addition, the data point to other new molecular targets that could be used for circuit-based interventions aimed at modulating CeL microcircuit function. The use of viral vector-based methods to alter gene expression and manipulate circuits in the CeL of primates will allow for further translation of these findings. These studies in nonhuman primates have the potential to inform the development of new treatments for patients suffering from anxiety disorders.

Keywords: Central Nucleus of the Amygdala, Anxiety Circuitry, Gene Expression

Disclosure: Nothing to disclose.

M13. Mitochondrial Pathways Associated With Anxiety-Related Behavior in Mice and Panic Disorder Patients Through a Multi-Omics Analysis

*Zuzanna Misiewicz, Stella Iurato, Natalia Kulesskaya, Laura Salminen, Luis Rodrigues, Giuseppina Maccarrone, Jade Martins, Darina Czamara, Mikaela Laine, Ewa Sokolowska, Kalevi Trontti, Ingrid Balcells, Christiane Rewerts, Suvi Saarnio, Bozo Novak, Dong Ik Park, Angelika Erhardt, Christoph W. Turck, Iiris Hovatta**

University of Helsinki, Helsinki, Finland

Background: Anxiety disorders are influenced by genetic and environmental factors and an interaction between them, which is largely undefined. The chronic social defeat stress (CSDS) mouse model allows identification of factors underlying resilience and susceptibility to chronic psychosocial stress-induced anxiety-like behavior, in a controlled manner not possible in human settings. We have taken a cross-species approach to identify biological pathways associated with anxiety through integrative analyses of omics data from the bed nucleus of the stria terminalis (BNST), a part of the extended amygdala involved in stress response, and blood cells from mice and from panic disorder patients who experienced exposure-induced panic attacks.

Methods: To induce an anxiety-like response in mice, we subjected two inbred strains, innately non-anxious C57BL/6NCrl (B6) and anxious DBA/2NCrl (D2), to CSDS. Following CSDS, we carried out the social avoidance test, to divide the mice into those susceptible and resilient to the behavioral effects of stress. We analyzed the BNST for differences in gene (RNA-seq) and protein (liquid chromatography-tandem mass spectrometry) expression between the stress-resilient, susceptible and control mice. In addition, we carried out RNA-seq from blood cells of stressed mice and performed microarray gene expression profiling of blood samples from panic disorder patients, collected directly and 24 h after exposure-induced panic attacks.

Results: The two mouse strains had distinct response to CSDS as 87% of D2, but only 30% of B6 mice showed social avoidance behavior. To assess the active and passive stress-coping response

following CSDS, we performed the forced swim test and measured the latency to immobility. We observed a high correlation between active coping strategy and resilience to psychosocial stress in the CSDS-subjected D2 mice ($r = 0.920$, $P = 0.009$), but not the B6 mice ($r = 0.026$, $P = 0.852$). In the BNST, mitochondria-related pathways and gene sets were down-regulated in the D2 (both on mRNA and protein levels) and up-regulated in the B6 strain (on mRNA level). We also found up-regulation of cytochrome c (CYCS), a key molecule of the mitochondrial electron transport chain involved in energy production and initiation of apoptosis, in the B6 resilient and susceptible mice versus controls, which we validated by western blot analysis ($P = 0.015$ and $P = 0.027$, respectively). We next conducted gene set enrichment analyses of the mouse and panic disorder patient blood cell transcriptomic data. In the blood cells, mitochondria-related gene sets were significantly up-regulated (FDR < 0.05) in both the stressed B6 mice and panic disorder patients after exposure-induced panic attack. Mitochondria-related gene sets were not differentially expressed in the blood cells of D2 mice. To investigate if CSDS leads to changes in mitochondrial number or morphology, we carried out electron microscopy in the BNST. We observed that susceptible B6 mice had a larger number of pre-synaptic mitochondrial cross-sections than B6 resilient mice ($P < 0.05$), but that the mitochondria were smaller than those of B6 control mice by 8.4% ($P < 0.01$). We did not observe differences in the mitochondria size or number between stressed and control D2 mice, but D2 susceptible mice had more total mitochondrial cross-sections in comparison to the B6 susceptible mice ($P = 0.013$).

Conclusions: We found a global evolutionarily conserved response of mitochondrial pathways in anxiety-related behaviors. Identification of the underlying mechanisms will provide much needed insight into the molecular basis of anxiety, a critical step in developing targeted therapy.

Keywords: Anxiety, Panic Attacks, Gene Expression, Proteomics, Mouse Model

Disclosure: Nothing to disclose.

M14. In Vivo Evidence for mGluR5 Dysregulation as a Biomarker of Suicidality in PTSD, but Not MDD

Margaret Davis, Ansel Hillmer, Sophie Holmes, Nicole DellaGioia, Robert Pietrzak, Nabeel Nabulsi, David Matuskey, Gustavo Angarita-Africano, Richard Carson, Steven Southwick, John Krystal, Irina Esterlis*

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Posttraumatic stress disorder (PTSD) is associated with high risk for both suicide attempt and mortality. Unfortunately, few available pharmacological interventions have demonstrated efficacy in reducing suicide risk in this population. Exploration of the molecular underpinnings of suicidal behavior in PTSD is essential to targeted treatment development. Recent in vivo, genetic, and postmortem evidence suggest dysregulation of the metabotropic glutamate receptor type 5 (mGluR5) may play a role in the pathophysiology of PTSD and suicidal behavior. Using positron emission tomography (PET) and [18 F]FPEB, we aimed to quantify mGluR5 availability in frontal and limbic areas implicated in the pathophysiology of both PTSD and suicidal ideation.

Methods: Participants ($n = 29$ PTSD, 14 with reported scan-day suicidal ideation (SI; based on scan-day self-report); $n = 29$ with major depressive disorder (MDD), 15 with SI; $n = 29$ healthy control (HC)) were recruited and matched for age, gender, and smoking status. All participants participated in 1 MRI scan and 1 PET scan with 18F-FPEB and as well as psychiatric and cognitive assessments. Volume of distribution (VT: the ratio of activity in tissue relative to that in blood) was computed using a venous input function. The radiotracer was injected as bolus plus constant infusion and subjects were scanned during steady state (90-120 mins post-injection). Primary analyses focused on a cortico-limbic circuit comprised of 5 brain regions: dorsolateral prefrontal cortex (dlPFC); orbitofrontal cortex (OFC); ventromedial prefrontal cortex (vmPFC); amygdala; hippocampus.

Results: We observed higher mGluR5 availability in PTSD compared to HC individuals in all regions of interest (15%-20% difference, p's = .001-.01), and compared to MDD individuals in the OFC (15%, $p = .0007$), dlPFC (17%, $p = .007$), and hippocampus (15%, $p = .007$). mGluR5 availability was not significantly different between MDD and HC individuals ($p = 0.17$). When examining the relationship between suicidality and diagnosis, we observed higher mGluR5 availability in the PTSD-SI group compared to PTSD-non ($F7,16 = 4.03$, $p = .01$), but not between the MDD groups. Post hoc analyses indicated PTSD individuals with reported SI had significantly higher mGluR5 availability in all regions of interest (average 24% difference, p's = .001-.007). Exploratory analyses revealed that mGluR5 availability was positively correlated with avoidance (vmPFC $r = .57$, $p = .007$), and measures of tension (vmPFC, $r = .53$, $p = .007$) and anxiety (vmPFC $r = .47$, $p = .008$) in individuals with PTSD. Interestingly, the opposite was observed among individuals with MDD; mGluR5 availability was inversely correlated with measures of tension (e.g., dlPFC = r = -.52, $p = .01$) and anxiety (e.g. OFC, $r = -.38$, $p = .01$).

Conclusions: Individuals with PTSD had higher mGluR5 availability in frontal and limbic brain regions relative to both MDD and HC. Further, highest mGluR5 availability was observed in those reporting scan-day SI relative to those without SI in the PTSD group only, implicating mGluR5 as a possible marker of SI specific to individuals with PTSD. The variability in the directionality between mGluR5 and psychological measures further proposes differential role for mGluR5 in PTSD versus MDD. Findings underscore the importance of continued investigation of the glutamatergic system, and mGluR5 specifically, as a target for intervention and risk management in PTSD.

Keywords: MDD, PTSD, Suicidal Ideation, PET, mGluR5

Disclosure: Nothing to disclose.

M15. Applying Computational Modeling for Quantifying Fear Conditioning and Extinction Learning Processes Across Anxiety and Age

Rany Abend, Andrea Gold, Jennifer Britton, Bruno Averbeck, Ellen Leibenluft, Daniel Pine*

National Institute of Mental Health, Bethesda, Maryland, United States

Background: Fear conditioning and extinction are complementary learning processes by which one flexibly acquires, and extinguishes, associations between neutral and harmful stimuli in the environment. Translational research proposes that these processes may play key roles in the etiology and maintenance of anxiety disorders, but several important gaps remain. First, while prior research provides indirect evidence for stronger fear conditioning in anxious individuals, no study formally tests the acquired associative strength between neutral and aversive stimuli as a function of anxiety. Second, some research suggests that fear conditioning and extinction learning may be influenced by age, with developmental differences potentially contributing to the emergence of anxiety disorders. However, extant developmental findings are mixed, limiting insights into the etiology and maintenance of anxiety. Third, findings on the neural correlates of

fear conditioning and extinction learning in humans are also limited and mixed, limiting our understanding of underlying mechanisms. Such gaps in knowledge may arise from several reasons, including insufficient sample sizes, variability in study paradigms and parameters, and challenges in quantifying associative learning indices.

Here, in a novel approach, we leverage computational modeling to directly quantify associative learning strength between neutral and aversive stimuli during a fear conditioning and extinction paradigm, in a large sample (N = 349) of clinically-anxious and healthy youths and adults. Learning indices were then used to investigate three questions: 1) Does associative learning strength during conditioning or extinction differ as a function of anxiety? 2) Does learning strength differ as a function of age? 3) Does learning strength relate to brain morphometry? Insights may link aberrations in fear conditioning and extinction process to anxiety and brain structure across development and may bear implications for treatment of anxiety disorders.

Methods: Clinically anxious (n = 155) and non-anxious (n = 194) youths and adults (ages 8-50 years; 196 females) completed an established fear conditioning and extinction paradigm. During conditioning, a conditioned stimulus (CS +) is repeatedly followed by an aversive unconditioned stimulus (UCS). A non-conditioned stimulus (CS-) is never reinforced. Next, during extinction, each CS repeatedly appears, never reinforced. Skin conductance responses (SCR), an index of physiological fear response, were continuously recorded. Reinforcement learning models were fitted to individual trial-by-trial SCR to the CS + during the conditioning and extinction phases. The models yield one associative learning parameter per phase, αCOND and αEXT, indicating how strongly one learns to associate the CS + with the UCS or its absence, respectively. Linear regression models predicted these parameters based on anxiety group and age.

High-resolution structural brain imaging (T1-weighted) data were available for a subsample of 92 youths. Standard FreeSurfer procedures were used for processing, including cortical thickness estimation and subcortical volume segmentation. We tested for associations between learning indices and cortical thickness and subcortical gray matter volume (GMV) in regions previously implicated in fear conditioning and extinction.

Results: Across the sample, fear conditioning and extinction learning parameters were significantly greater than 0 (αCOND: M = 0.26, αEXT: M = 0.17, ps < 0.001). A linear regression analysis predicting αCOND indicated a significant effect of anxiety group, α = 0.12, t = 2.23, p = 0.027, with stronger associative learning during conditioning among anxious participants. Additionally, diminished learning during conditioning was noted with age, α = -0.20, t = 3.89, p < 0.001. Anxiety and age did not significantly interact. αEXT was not significantly predicted by anxiety group and age, p = 0.11.

Associations emerged between αCOND and GMV in right caudate (r = 0.23, p = 0.03), left putamen (r = -0.21, p = 0.05), and right putamen (r = -0.22, p = 0.04), but these did not survive Bonferroni corrections. No other significant associations emerged. Of note, structural data for 149 additional youth and adult participants are currently analyzed and will be ready for the meeting and are expected to increase statistical power to detect effects.

Conclusions: The current study applied computational modeling to quantify associative learning during fear conditioning and extinction. Anxiety was associated with stronger learning during fear conditioning, whereas age was related to diminished learning. Preliminary imaging data suggest potential associations between conditioning learning strength and subcortical regions previously implicated in learning. These findings reveal novel evidence for associations between fear conditioning processes in anxiety and across age.

Keywords: Adolescent Anxiety, computational modeling, brain structure

Disclosure: Nothing to disclose.

M16. Neural Correlates of Provoked Aggression and PTSD: Preliminary Findings

Jennifer Fanning, Lauren Pasetes, Victoria Okuneye, Jamie Wren-Jarvis, Sarah Keedy*

University of Chicago, Chicago, Illinois, United States

Background: Exposure to psychological trauma contributes significantly to the public health burden of aggressive behavior, and this association is mediated in part by the development of posttraumatic stress disorder (PTSD). A rich literature associates PTSD symptoms with increased anger, hostility, and aggressive behavior. Neurobiological models of PTSD and pathological aggression implicate hyper-activity in limbic regions that mediate threat detection and response (e.g., amygdala) and hypo-activity in regions that support emotion regulation (e.g., orbitofrontal cortex). However, we know little about how patterns of neural activity may account for the relationship between PTSD and aggressive behavior. The purpose of this study is to address this question using fMRI neuroimaging in a sample of adults with and without exposure to trauma who vary in PTSD symptom severity.

Methods: Adult women and men recruited from the community were studied as part of an ongoing investigation of the effects of interpersonal trauma on brain function and behavior. The overall study uses an RDoC approach to study the neural correlates of interpersonal provocation and retaliation in healthy non-trauma exposed subjects (HC) and trauma-exposed subjects (TE) who vary in PTSD symptom severity, as assessed in preliminary analyses using the PTSD Checklist for DSM-5 (PCL-5). Participants completed a social interaction in task in the scanner against a confederate who was actually fictitious. The task was adapted for the scanner from a well-validated social psychology task with extensive data to support its validity as a measure of provoked aggressive behavior. While in the scanner, the participant and opponent engaged in a competitive cover task, during which the participant was provoked by the opponent with threatened electric shocks to the fingertips. On losing trials the participant received the selected shock. The level of interpersonal threat (i.e., shock intensity) was manipulated on a trial-by-trial basis, and the participant had the opportunity to retaliate on each trial by setting a shock for the opponent, of the intensity of their choice. The task included sensorimotor control trials in which no shocks were delivered. Scans were acquired on a Philips Achieva Quasar 3 T scanner. Structural MRI images were acquired using a T1-weighted 3D Turbo Field Echo (MP-RAGE) anatomical scan. To reduce signal dropout in the orbitofrontal cortex (OFC), a volume-selective z-shim technique was implemented in four slices covering the OFC. Data were pre-processed and analyzed in SPM12 software. First-level statistical models were specified and estimated for the time series per voxel per subject with motion parameters included as regressors. Trial events were modeled using box-car functions convolved with the canonical hemodynamic response function. A first-level general linear model (GLM) with regressors for the opponent's provocation and the subject's retaliation was used to model the BOLD signal for the contrast of decision > control. The decision regressor was associated temporally with the subject's button press response during retaliation. The data were analyzed using a priori region of interest analysis (combined ROI, including prefrontal, limbic, striatal, and parietal regions and motor cortex) and whole-brain analysis. PTSD symptom severity was analyzed as a covariate of the contrast.

Results: The current sample includes 26 women and 9 men with a mean age of 30 (SD = 7), including 9 HC subjects and 26 TE subjects. The current ratio of women to men participants precludes analysis of sex differences at the present time. Subjects varied in PTSD symptom severity (mean PCL-5 = 16.5, SD = 18.7). Over the course of 48 trials, participants most frequently matched the level of provocation by their opponent (40%) or set a lower intensity (38%). Participants escalated on 22% of trials on average. During the decision phase, whole brain analysis revealed significant activity in the supplementary motor area (SMA) and nucleus accumbens (p-uncorrected < .001, FWE < .05). PTSD symptom severity did not correlate with aggression on the task (r = .18, p = .32) but did correlate with self-reported aggression (Buss Perry physical aggression: r = .40, p = .023; anger: r = .57, p < .001) as expected. PTSD symptom severity was associated with significant activity in the periaqueductal gray (PAG) region (p-uncorrected < .005, FWE < .05).

Conclusions: Preliminary data from this ongoing study suggests that PTSD symptom severity is associated with heightened activity in the PAG region during retaliation against a provocative confederate. The PAG is implicated in defensive responding to imminent threat and animal models of defensive behavior suggest that subregions of PAG differentially relate to the topography of defensive behavior with respect to freezing, escaping, and attacking. Human neuroimaging studies are suggestive of similar functional specificity within the PAG. The current study points to a potential important role of the PAG in PTSD-related aggressive behavior.

Keywords: Posttraumatic Stress Disorder, Aggression, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

M17. Striatal Activation to Social Reward Anticipation Predicts Symptoms of Social Anxiety Disorder in Adolescent Girls Varying in Level of Risk for Anxiety Disorders

Cecile Ladouceur, Neil Jones, Jennifer Silk*

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Social anxiety disorder (SAD) is characterized by impairing fear of social situations, such as being negatively evaluated by others (Kessler et al., 2005). SAD typically onsets during early adolescence and there is evidence suggesting that shyness represents a risk factor for SAD, particularly among girls (Tsui et al., 2017). Recent studies have reported striatal hyperactivation to reward anticipation in youth at-risk for (Guyer et al., 2006) and diagnosed with SAD (Guyer et al., 2012). It remains unclear how variability in the functioning of cortico-striatal regions during anticipation of social reward could representation a marker of risk for the development of SAD symptoms. Here, we examined neural activation to social reward cues in girls at risk for anxiety disorders and tested whether such activation levels predicted levels of SAD symptoms at follow-up.

Methods: Consistent with the NIMH RDoC framework, adolescent girls (n = 59; mean age = 12.6 (SD = .95) were recruited varying in level of risk for anxiety disorders (41 high; 18 low) based on scores being 0.75 SD above or below the mean on the Fearfulness and Shyness subscales of the Early Adolescent Temperament Questionnaire-Revised. Participants completed a modified version of the Social Incentive Delay (SID) task (Spreckelmeyer et al., 2009) to be used with adolescents during fMRI acquisition. This task was adapted from the original MID task to examine neural activation to anticipation and receipt of social feedback from a virtual peer (i.e., virtual peer facial expression) based on the participants' task performance. An ROI mask was constructed by combining meta-analytic maps for the terms social (z > 3.30, FDR p < .05), reward (z > 8.84, FDR p < .05), and punishment (z > 4.45, FDR p < .05) from Neurosynth.org. Four separate voxelwise analyses were conducted for the: reward anticipation vs. neutral anticipation; punishment anticipation vs. neutral anticipation, reward outcome vs. neutral outcome, punishment outcome vs. neutral outcome contrasts masking activation using the ROI mask defined above. Analyses were conducted using AFNI's 3dttest with the -Clustsim option, which uses a nonparametic approach to cluster-size thresholding with a cluster forming threshold of p < .001, extent threshold ~ 23 voxels. Linear regression analyses focused on neural activation to social reward anticipation and SAD symptoms, measured using the SAD subscale of the SCARED at 12 and 18 months following the scan and controlling for age and baseline SAD symptoms. Bonferonni correction was used to correct for type-I error as needed.

Results: Analyses focusing on task-related activation indicated greater activation in the caudate and medial frontal gyrus (MFG) to reward (vs neutral) anticipation; no significant clusters were found for punishment anticipation. There was greater activation in a number of subcortical (amygdala, striatum) and prefrontal cortical (e.g., VMPFC, VLPFC) regions as well as the superior temporal gyrus (STG) to reward (vs. neutral) outcome. Similar regions were activated to punishment (vs. neutral) outcome in addition to activation in the posterior cingulate gyrus (PCG). Regression analyses revealed that greater activation in the caudate to social reward anticipation predicted higher levels of SAD symptoms at 18 months, (R2 = .48, Beta = .63, t = 3.18, p = .008).

Conclusions: Findings suggest that the adapted version of the SID task recruited expected regions implicated in processing social (e.g., STG, PCG), reward (e.g., caudate, putamen, VMPFC), and punishment (e.g., amygdala) information. Our findings of greater caudate activation to anticipation of social reward predicting later symptoms of SAD in these at-risk girls is consistent with previous findings in youth with early-life behavioral inhibition (Guyer et al., 2014). They also support a neurodevelopmental model of SAD suggesting that aberrant information processing of social reward cues may escalate the risk for SAD at a time when increased sensitivity to rewarding experiences such as peer acceptance typically occurs (Caouette and Guyer, 2014). Future analyses, including a follow-up scan with a larger sample, will deepen our understanding of neurodevelopmental pathways of SAD in at-risk girls.

Keywords: Risk for Social Anxiety Disorder, Early Adolescence, Social Reward, Functional Neuroimaging

Disclosure: Nothing to disclose.

M18. Dissecting the Genetically Regulated Transcriptomic, and Phenotypic Complexity of PTSD Across 9400 Trauma-Exposed Individuals and 30 Million Observations With Bayesian Machine Learning

*Yue Li, Vasiliki Michopoulos, Adriana Lori, Abigail Lott, Bekh Bradley, Tanja Jovanovic, Kerry Ressler, Manolis Kellis, Nikolaos Daskalakis**

McLean Hospital, Harvard Medical School, Belmont, Massachusetts, United States

Background: Post traumatic stress disorder (PTSD) is a severe mental disorder occurring in some trauma-exposed individuals, but its molecular basis remains uncharacterized. Transcriptomic imputation models (e.g., PrediXcan) leverage large expression quantitative trait loci reference panels to translate genome-wide genotype data into more biologically meaningful measures. Previously, we have associated genetically regulated gene

expression in the brain and peripheral tissues with PTSD which were validated by translational findings in mice and humans (Huckins…Daskalakis, In Preparation Manuscript by Psychiatric Genomic Consortium for PTSD). Here, we study the relationship between genetically-regulated transcriptional variation, and phenotypic variation in PTSD, in a cohort of 9400 inner-city, low-socioeconomic-status, primarily-African-American patients of the Grady Memorial Hospital.

Methods: Each individual was ascertained phenotypically using interview-based assessments and self-report questionnaires including childhood trauma history and PTSD diagnosis, and 12 lab tests including endocrine, metabolic and immune markers (e.g., cortisol, cholesterol, IL-6). In addition, we imputed expression for ~5000 genes across 48 tissues using Genotype-Tissue Expression (GTEx) project's expression quantitative trait loci (v7 data release) and selecting the top 200 most variable and tissue-specific genes.

To study the comorbidity patterns of tissue-specific gene expression and phenotypic information across individuals, we used MixEHR, a Bayesian unsupervised learning method for phenotype correlation and imputation analysis (Li & Kellis, 2018), which explicitly deals with the non-missing-at-random nature of phenotypic information and lab tests. We applied MixEHR systematically and found several noteworthy disease topics of high probability of PTSD diagnosis that were concordant with PTSD symptom severity, depression symptom severity and childhood trauma levels, thereby recapitulating the PTSD clinical presentation.

Results: We found enrichments for well-studied genes and tissues in specific disease topics across multiple tissues. For example, a human-lineage-specific gene, NBPF3, which is implicated in neurodevelopmental disorders, showed high probability for PTSD across multiple brain tissues. Similarly, the top tissues with the highest marginal PTSD associations are basal ganglia, amygdala, substantia nigra, and pituitary, which have been associated with emotion regulation and PTSD. We also constructed a ranked list of PTSD genes by calculating the marginal probabilities of each gene with respect to PTSD across multiple disease topics. The top genes were: MXRA8, the top gene, is important in the maturation and maintenance of blood-brain barrier; ATP6AP1L, ranked #2, is implicated in the glucocorticoid receptor pathway and neural responses to stress; and AP3S2, ranked #3, is essential for vesicles delivery into neurites and nerve terminals.

Conclusions: By combining transcription imputation across the brain and the rest of the body with Bayesian machine learning in a trauma-exposed sample, we discovered genes that yield new biological insights into the genetic and phenotypic architecture of PTSD.

Keywords: Bayesian Modeling, PTSD, Childhood trauma, transcription imputation, Genetic variability

Disclosure: Nothing to disclose.

M19. Amygdala Subregions Volumes are Associated With PTSD

Rajendra Morey, Emily Clarke, Rachel Phillips, Courtney Haswell, Kevin LaBar*

Duke University, Durham, North Carolina, United States

Background: The amygdala is perhaps the most strongly implicated brain structure in the pathophysiology of posttraumatic stress disorder (PTSD). The amygdala is a subcortical structure involved in emotion processing and associative fear learning. Prevalent models of anxiety have focused on an amygdalocentric neurocircuitry that is critical in fear response, conditioning, generalization, and facilitates the response to stressful experiences. Functional magnetic resonance imaging (MRI) studies have shown that individuals with PTSD have an exaggerated amygdala response to emotional stimuli when compared with control subjects. Animal studies have demonstrated changes in amygdala morphology with chronic stress, evident primarily in the growth of dendritic spines. Experimental studies of amygdala volume in mice and humans have shown an association among smaller amygdala volumes, increased levels of fear conditioning, and an exaggerated glucocorticoid response to stress. However, efforts to find evidence of an association between amygdala volume and PTSD in humans have produced equivocal results. These studies point to specialized roles of basolateral (BLA) and centromedial amygdala (CMA) complexes in associative fear learning. However, this level of investigation has been largely absent in human studies, despite the critical role of individual amygdala complexes predicted in PTSD.

Methods: The study assessed US military veterans ($N = 346$) with lifetime PTSD ($N = 141$) and trauma-exposed non-PTSD controls ($N = 206$), who served since 9/11 (2001). Participants completed clinical and neuroimaging assessments that included the Structured Clinical Interview for DSM-IV Disorders (PTSD), Alcohol Use Disorders Identification Test, Combat Exposure Scale, Trauma Life Events Questionnaire to assess childhood trauma exposure, Beck Depression Inventory, and Drug Abuse Screening Test. High resolution T1-weighted anatomical scans optimized for tissue contrast were acquired on a 3 T GE MR750 scanner. Automated segmentation of amygdala subregions was completed using FreeSurfer (version 6.0) on nine nuclei or subregions per hemisphere including basal, lateral, accessory basal, anterior amygdaloid, central, medial, cortical, corticoamygdaloid transition area, and paralaminar. The FreeSurfer 6.0 tool is based on a probabilistic atlas of hippocampal anatomy created upon manually segmented ultra-high-resolution (0.13-mm isotropic) ex vivo MRI scans from 15 post-mortem samples and manual segmentations of nearby structures performed on 1-mm resolution isotropic in vivo T1 images. The subregion volumes obtained from FreeSurfer were the dependent variable in an ordinary least square (OLS) regression model run separately for each subfield. Bonferroni correction for multiple testing was applied to the volumetric analyses given that nine regions from two hemispheres were assessed (p-corrected $= 0.05/18 = 0.003$). Covariates for age, gender, ipsilateral whole amygdala volume, alcohol use, depressive symptom score, childhood trauma exposure, combat exposure, and use of psychotropic medications were modeled.

Results: We found that lifetime PTSD was associated with larger volume of left medial nucleus ($p = 0.005$; Cohen's $d = 0.35$; Bonferroni corrected), left cortical nucleus ($p = 0.007$; Cohen's $d = 0.26$; Bonferroni corrected), right accessory basal nucleus ($p = 0.01$; Cohen's $d = 0.07$; Bonferroni corrected), and right central nucleus ($p = 0.02$; Cohen's $d = 0.18$; Bonferroni corrected). Right accessory basal nucleus volume was affected by alcohol use ($p = 0.04$) and marginally affected by age ($p = 0.06$) and childhood trauma ($p = 0.06$). Right central nucleus volume was affected by gender ($p = 0.02$). Left medial nucleus volume was marginally affected by alcohol use ($p = 0.09$).

Conclusions: The present results highlight that PTSD is associated with larger volumes in amygdala subregions strongly implicated in fear processing that include the medial nucleus, central nucleus, and the accessory basal nucleus. Our results are consistent with rodent models that demonstrate chronic threat and stress lead to corticosterone-mediated spinogenesis and dendritic arborization.

Keywords: Combat PTSD, Amygdala, Central Nucleus of the Amygdala, Basolateral Amygdala, Structural MRI

Disclosure: Nothing to disclose.

M20. Brain Activation During Interference Inhibition and Error Processing Predicts Symptom Improvement Following Cognitive Behavioral Therapy in Obsessive Compulsive Disorder

Kate Fitzgerald, Luke Norman, Mike Angstadt, Kristin Manella, James Abelson, Joseph Himle, Stephan Taylor*

University of Michigan, Ann Arbor, Michigan, United States

Background: Cognitive behavioral therapy with exposure and response prevention (CBT-ERP) is the gold standard psychotherapeutic treatment method for obsessive compulsive disorder (OCD). However, the extent to which patients experience symptom reduction from CBT-ERP varies, and up to half of those treated do not fully respond. Moreover, the mechanisms that underlie differences in symptom reduction following treatment are poorly understood. Given that effective engagement with CBT-ERP is assumed to rely on executive functions, it might be hypothesized that individual differences in brain activation during executive function tasks would be associated with treatment response to CBT-ERP. In OCD, recent meta-analytic evidence points to abnormal engagement of cingulo-opercular network in patients relative to unaffected controls, with underactivation during interference inhibition and hyperactivation during error processing, but whether these neural abnormalities predict response to CBT-ERP is unknown.

Methods: 65 patients with OCD (age range 12-45, 40 males, 31 medicated) were randomly allocated to receive either 12 weeks of CBT-ERP or an active control treatment (stress management training; SMT). Prior to treatment, patients completed a functional magnetic resonance imaging (fMRI) version of the incentive flanker task (IFT), which probes neural activation to interference inhibition and error processing. Symptoms were assessed at baseline and post-treatment using the (Children's) Yale-Brown Obsessive-Compulsive Scale ((C)Y-BOCS). Whole-brain regression analyses examined whether brain activation during interference inhibition and error processing was associated with symptom change following treatment in CBT-ERP and SMT groups (height threshold $p < .001$ uncorrected, cluster threshold $p < .05$ FWE corrected).

Results: As predicted, the CBT-ERP group (mean (C)Y-BOCS change = -12.31, SD = 6.61, range -24.5 to 1.5) showed greater symptom reduction following treatment compared with the SMT group (mean (C)Y-BOCS change = -4.49, SD = 7.98, range -26 to 11.5; $F(1,163) = 18.18$, $p < .001$). Nonetheless, there was a wide range of response in both CBT-ERP and SMT groups, and even some patients receiving SMT exhibited reduction in OCD symptoms. In the CBT-ERP group, symptom reduction was predicted by greater baseline activation of left inferior frontal gyrus (IFG), right IFG/anterior insula and dorsomedial prefrontal cortex during interference inhibition, but lesser left anterior insula activation during error-processing (all $p < .05$, corrected). In the SMT group, there were no areas of activation that significantly predicted treatment response.

Conclusions: Patients with OCD typically show reduced activation of cingulo-opercular network regions during interference inhibition relative to unaffected controls, as well as increased brain activation in the same network following erroneous responses. We have previously argued that this pattern of neural abnormalities explains why patients become stuck in 'compulsive loops', as detected erroneous OCD behaviors remain uncorrected by an underactivated inhibitory control network. The current findings suggest that intact cingulo-opercular functioning may allow patients to engage more effectively with CBT-ERP treatment, perhaps due to a greater capacity for inhibiting maladaptive responses to symptom triggers and for learning and implementing newer, more adaptive behaviors and coping strategies. The presence of significant predictors of symptom reduction for CBT, but not SMT, suggests that cingulo-opercular circuit function may have mechanistic significance specific to CBT-ERP. Additional work examining subjects before and after treatment will be needed to determine whether modulation of cingulo-opercular network functioning also mediates OCD symptom change with CBT, and whether it could serve as a target for novel interventions designed to augment CBT effects.

Keywords: Obsessive-Compulsive Dlerisorder (OCD), Cingulo-Opercular Network, Cognitive Behavioral Therapy, Predictors of Response

Disclosure: Nothing to disclose.

M21. Regionally Specific Alterations and Clinical Correlates of Cerebral GABA in Posttraumatic Stress Spectrum Adults

Isabelle Rosso, Elizabeth Olson, J. Eric Jensen, Scott Rauch*

McLean Hospital, Belmont, Massachusetts, United States

Background: Posttraumatic stress disorder (PTSD) has been associated with hyper-responsivity of the insular cortex and hypo-responsivity of the medial prefrontal cortex (mPFC) during symptom provocation and exposure to fear-inducing stimuli, consistent with altered excitability of brain regions mediating fear conditioning and extinction. As the brain's principal inhibitory neurotransmitter, γ-aminobutyric acid (GABA) exerts a prominent role in modulating neuronal excitability. Although brain GABA can be reliably assessed with advances in magnetic resonance spectroscopy (MRS), there have been few MRS GABA studies in PTSD. In a pilot study from our laboratory, we previously reported lower right anterior insula (AI) GABA in adults with PTSD compared with healthy comparison (HC) participants (Rosso et al 2013). In the current study, we compared GABA levels in two brain areas implicated in PTSD and fear (mPFC, right AI) and in one control brain area (right posterior temporal cortex) between adults with DSM-IV PTSD, trauma-exposed non-PTSD comparison (TENC) subjects, and HC subjects without any reported Criterion A trauma. We hypothesized that there would be group differences in mPFC and AI GABA but not in temporal cortex GABA. We also predicted that GABA alterations would be associated with dimensional measures of PTSD symptom severity and trauma exposure.

Methods: All participants (ages 20-50) underwent a psychiatric interview with the Structured Clinical Interview for DSM-IV (SCID-IV I/P), and PTSD and TENC participants also completed the Clinician Administered PTSD Scale (CAPS). The CAPS was used to establish PTSD diagnosis and dimensional symptom cluster scores (re-experiencing, hyperarousal, and avoidance symptoms). The Dissociative Experiences Scale (DES), completed by all participants, provided a dimensional measure of dissociation. Trauma exposure also was assessed quantitatively in all participants using the Life Events Checklist (LEC) which indexes lifetime exposure (number of traumas directly experienced and witnessed). Participants underwent MRS scanning on a 3 T Siemens Trio with a 32-channel head coil. MEGAPRESS data were collected from voxels in the mPFC ($2.5 \times 2.5 \times 3$ mL; 39 PTSD, 32 TENC, 37 HC with good quality spectra), right AI ($2 \times 2 \times 3$ mL; 38 PTSD, 31 TENC, 38 HC), and temporal cortex ($2 \times 2 \times 3$ mL; 39 PTSD, 31 TENC, 36 HC). GABA was normalized to total creatine (Cr).

Results: The three groups were comparable on age and sex distributions, and PTSD and TENC participants did not differ significantly on number of lifetime traumas (LEC score). Compared with HC, PTSD and TENC participants had significantly lower GABA/Cr in the mPFC voxel ($F(2,104) = 5.56$, $p = .005$) and in the AI voxel ($F(2,104) = 4.01$, $p = .02$), but not in the temporal cortex voxel ($F(2,103) = 0.25$, $p = 0.78$). Neither mPFC GABA/Cr nor AI

GABA/Cr was associated with CAPS re-experiencing, hyperarousal, or avoidance scores. However, there was a significant association of DES scores with mPFC GABA/Cr, both in the combined PTSD + TENC group (r (70) = -0.24, p = .04) and in the overall sample (r (107) = -0.24, p = .02). LEC scores were significantly negatively correlated with mPFC GABA/Cr (r (107) = -0.21, p = .03) and AI GABA/Cr (r (107) = -0.29, p = .003). Finally, in a multiple regression entering both DES and LEC scores as predictors of mPFC GABA/Cr, DES score remained a statistically significant effect (t = -1.99, p = .05) but not LEC score (t = -1.36, p = 0.18).

Conclusions: We found regionally specific lower GABA in the mPFC and right AI but not right posterior temporal cortex, in patients with PTSD and trauma-exposed adults without PTSD, compared with non-traumatized healthy adults. These findings suggest that GABA is lower in brain areas implicated in fear and arousal regulation, and that this is related to aspects of trauma-related psychopathology but not a biomarker of diagnosis per se. We replicate our initial report that right AI GABA is lower in PTSD and extend that finding by showing that lower GABA also is seen in adults with histories of significant trauma who never developed PTSD. This relationship with trauma exposure is further corroborated by the negative correlation between right AI GABA and number of traumatic life events. Although mPFC GABA reductions also scaled with lifetime trauma, they were more strongly associated with a dimensional measure of dissociation. This finding may be consistent with growing evidence that dissociative states have distinct neural correlates within PTSD symptomatology, including differentially high excitability of the medial prefrontal cortex.

Keywords: Post Traumatic Stress Disorder, MR spectroscopy, Dissociation, insular cortex, Medial Prefrontal Cortex

Disclosure: Aptinyx Inc, Consultant

M22. Thyroid Hormone Modulation of Anxiety and Trauma-Related Plasticity in the Amygdala

Stephanie A. Maddox, Michelle X. Chen, Brianpaul J. Robert, Kerry J. Ressler*

McLean Hospital, Harvard Medical School, Belmont, Massachusetts, United States

Background: The thyroid hormone (TH) system has been associated with anxiety, depression and well implicated in early nervous system development. Despite this early progress, almost nothing is known about the potential role that the TH system may play in mediating synaptic plasticity that is relevant for anxiety and trauma-related behaviors.

Methods: Non-biased RNA-sequencing and targeted qPCR was used to examine the regulation of genes in the amygdala in fear conditioned mice. Local amygdala infusions of the TH triiodothyronine (T3) or the dual TH receptor (TR) TR-alpha (TRa) and TR-beta (TRb) antagonist 1-850 were used to examine the role of TRs in fear memory consolidation and associated gene transcription. Additional experiments examined the effect of these pharmacological agents on anxiety-like behaviors using the open field test. Additional studies employing a diet-induced model of hypothyroidism were conducted to examine the behavioral and molecular consequences that occur as a result of diminished TH function. Hypothyroid animals were administered local amygdala infusions of T3 hormone to examine the role of amygdala TRs on traumatic memory formation.

Results: Using nonbiased RNA-sequencing from amygdala punches taken 2 h after fear conditioning, we revealed dynamic regulation of seven TH related genes in the amygdala in response to trauma, Ttr (lg2fc = -2.52, q < 0.05), Trhr (lg2fc = -0.44, q,0.05), Trh (lg2fc = -1.21, q < 0.05), Trip11 (lg2fc = 1.05, q < 0.05), Rxrg (lg2fc = 0.31, q < 0.05), Dio2 (lg2fc = 0.41, q < 0.05), and Med12 (lg2fc = -0.28, q < 0.05. Additionally, using targeted qPCR, we demonstrated a significant fear conditioning-related increase in TRa (T(17) = -2.48, p < 0.05) and TRb (T(17) = -1.47, p = 0.05) mRNA in the amygdala compared to control animals and TRa and TRb protein expression levels in the amygdala using immunohistochemistry. Next, using directed intra-amygdala infusions of either T3 or 1-850, we examined the effect of TR activation and inhibition at the time of fear conditioning on fear memory consolidation 24 h later. We found that mice receiving infusions of T3 30 min prior to conditioning had enhanced levels of freezing during the conditioning session (T(21) = 4.101, p < 0.05) and enhanced levels of freezing 24 h later during the long-term memory test (T(21) = 1.65, p = 0.05) compared to vehicle controls. Conversely, we found that infusions of 1-850 resulted in no difference in freezing level during fear conditioning (T(22) = -0.28, p > 0.05) but dramatically reduced long-term memory 24 h later (T (22) = 2.96, p < 0.05) suggesting impaired memory consolidation. We also examined the effect of intra-amygdala T3 on anxiety behavior using the open field test and T3 on fear memory with infusions occurring immediately after conditioning. Infusions of T3 resulted in increased time spent in the periphery of the open field arena (T(13) = -2.11, p = 0.027). Infusions immediately after fear conditioning failed to alter fear memory expression 24 h later (T (13) = 0.41, p > 0.05). Interestingly, hypothyroid animals also displayed heightened anxiety, as measured using the open field test (T(22) = -4.34, p < 0.01), and impaired traumatic memory consolidation (T(22) = 2.82 p < 0.01). Western blots examining protein level molecular differences with hypothyroidism revealed reduced expression of EGR1, Arc, and GAD67 (all p < 0.05). Examination of transcriptional alterations in the amygdala that accompany hypothyroidism revealed increased Reln, Trh, and Nr3c1 mRNA (all p < 0.05) and decrease Dio3 mRNA (p < 0.05). Infusions of T3 into the amygdala of hypothyroid animals was found to reverse the traumatic memory consolidation impairment (T(10) = 2.04, p = 0.03).

Conclusions: These data suggest that T3 is anxiogenic and that activation of TRs at the time of trauma exposure or fear conditioning is rapid and must occur at the initiation of trauma to impact subsequent fear expression. Additional experiments have revealed that infusions of 1-850 at the time of fear conditioning alter the expression of many fear and memory related genes suggesting that TRs may mediate trauma-related gene expression in the amygdala. Examination of molecular and behavioral alterations that accompany hypothyroidism revealed alterations in classic plasticity related genes and proteins in the amygdala, as well as increased anxiety-like behaviors. While the mechanisms for heightened anxiety and yet impaired trauma-relevant memory consolidation in hypothyroid animals remain under active investigation, our rescue experiment which replaced T3 directly into the amygdala suggests that THs play a critical role in mediating trauma-relevant memory formation. In sum, these data strongly implicate for the first time a dynamic role for the thyroid hormone axis in the amygdala in modulating anxiety and trauma-relevant neuroplasticity.

Keywords: Thyroid Hormone, Traumatic Memories, Anxiety

Disclosure: Nothing to disclose.

M23. Exploring Floatation-REST as a Novel Intervention for Anxiety Sensitivity

Justin Feinstein, Sahib Khalsa, Hung-Wen Yeh, Obada Al Zoubi, Murray Stein, Martin Paulus*

Laureate Institute for Brain Research, Tulsa, Oklahoma, United States

Background: Floatation-REST (Reduced Environmental Stimulation Therapy), an intervention which attenuates exteroceptive sensory input to the nervous system, has recently been found to reduce state anxiety across a diverse clinical sample with high levels of anxiety sensitivity (Feinstein et al., 2018). To further examine this anxiolytic effect, the present study investigated the physiological changes induced by Floatation-REST and assessed whether individuals with high anxiety sensitivity experienced any alterations in their awareness for interoceptive sensation while immersed in an environment lacking exteroceptive sensation.

Methods: Thirty-seven participants (23 females; 14 males) with high anxiety sensitivity (Anxiety Sensitivity Index-3 total score ≥ 30) were recruited across a spectrum of anxiety and stress-related disorders (posttraumatic stress, generalized anxiety, panic, agoraphobia, and social anxiety), most (n = 35) with comorbid unipolar depression. Each participant was randomly assigned to undergo a 90-minute session of Floatation-REST or an exteroceptive comparison condition, and then crossed over to the other condition following a 1-week washout period. Measures of self-reported affect and interoceptive awareness were collected before and after each session, and electrocardiogram and blood pressure were collected during each session using wireless and waterproof sensors. All measures were analyzed by linear mixed-effects models using fixed-effects of Time and Session, and a subject-specific random intercept.

Results: Relative to the comparison condition, Floatation-REST significantly enhanced awareness and attention for cardiorespiratory sensations ($p < .0001$). Physiological measures collected during the float session showed indications of a rapid relaxation response, including a significant reduction in diastolic blood pressure (on the order of 10 mm Hg) and a significant increase in normalized high-frequency heart rate variability ($p < .0001$ for both measures). The degree to which floating increased heart rate variability was associated with the magnitude of the anxiolytic effect.

Conclusions: Floatation-REST induced a strong relaxation response consistent with increased parasympathetic outflow. At the same time, the float environment enhanced awareness for cardiorespiratory sensations in a clinical sample with high anxiety sensitivity. The unique juxtaposition between heightened interoceptive awareness in the context of a relaxed physiological background state may confer unique opportunities for the treatment of anxiety sensitivity.

Keywords: Anxiety, Interoception, Novel Therapeutics, Mindfulness

Disclosure: Nothing to disclose.

M24. Computational Modeling of Biases Influencing Threat Detection

Tamara Sussman, Jingwen Jin, Akos Szekely, Christian Luhmann, Aprajita Mohanty*

Columbia University Medical Center, New York, New York, United States

Background: We frequently use prior knowledge in a "top-down" manner to anticipate and detect threats in our environment in day-to-day life. However, most research has attributed fast and accurate detection of threatening stimuli to automatic or "bottom-up" processing. This relationship between anticipation and threat detection is particularly important in anxiety disorders, which are characterized by inaccurate, negative predictions about the future. In two experiments, we examined whether prior knowledge regarding threat and the likelihood of its occurrence facilitates perceptual decision-making. We examined the role of bias in facilitating threat-related perceptual decision-making by modeling this process using the drift–diffusion model (DDM), in which bias is computed as a shift in starting point or rate of evidence accumulation.

Methods: In experiment 1, participants (n = 31; 21 women; mean age 20.26 ± 1.90 years) viewed fear cues (the letter F), or neutral cues (the letter N) followed perceptually degraded fearful face (FF) or neutral face (NF) images, presented for 100 ms at each participant's individually determined perceptual threshold for FF and NF. The fear cue indicated that participants would make a "fearful or not" decision whereas the neutral cue indicated a "neutral or not" decision regarding the subsequently presented faces. We will refer to this cue-related information as "prior salience." Based on their response, we determined whether participants perceived the face as fearful (FR) or neutral (NR).

In experiment 2, a separate sample of participants (n = 29; 22 women; mean age 20.41 ± 2.11 years) performed a modified version of the same task such that cues additionally provided information regarding the probability of the targets to be presented (referred to as "prior probability"; 25%, 50%, or 75%) in addition to information regarding the salience of the subsequent face.

To examine the impact of prior salience (experiment 1) or prior salience and prior probability (experiment 2) on decision parameters, the DDM was fitted to the RT and response data. In the DDM, stochastically sampled evidence is accumulated in a single decision-variable from a starting point between the two decision boundaries. This starting point forms the baseline from which evidence accumulation starts. Evidence accumulation begins upon stimulus presentation and the rate at which evidence is accumulated towards a decision is called the drift rate. The drift rate reflects the effectiveness of the signal extraction from the surrounding noise.

Results: Results from the both experiments demonstrate that threat cues improve perceptual sensitivity (experiment 1: $t(30) = 4.36$, $p < .001$; experiment 2: $F(1, 28) = 18.24$, $p < .001$) and speed of decision-making (experiment 1: $F(1, 30) = 11.92$, $p = .002$; experiment 2: $F(1, 28) = 38.15$, $p < .001$). Additionally, in experiment 2, prior probability also increased the sensitivity ($F(2, 56) = 5.26$, $p = .008$) and speed ($F(2, 56) = 3.46$, $p = .038$) of decisions, with higher probability cues leading to faster, more accurate choices.

Results from DDM model comparison indicated that the best-fitting model for experiment 1 allowed starting point to vary by prior salience, and drift rate to vary by both prior salience and the type of stimulus. The best fitting model for experiment 2 was the same, except that it additionally allowed starting point to vary by prior probability.

DDM analyses of experiment 1 data revealed that the starting point was shifted towards the fear decision boundary (posterior probability that $zFC > .5 = .993$), for trails starting with FC. NC did not shift the starting point towards an NR decision boundary, the posterior probability that $zNC < .5 = .305$. In both experiments, compared to NC, FC also resulted in faster evidence accumulation for both FF, with posterior probability of $vFC/FF > vNC/FF = .967$ (experiment 1), $vFC/FF > vNC/FF = .986$ (experiment 2) and for NF, with a posterior probability of $vFC/NF > vNC/NF = .999$ (experiments 1 & 2).

In experiment 2, for FC trials, change in prior probability shifted the starting point closer to FR decision boundary, with the posterior probability that $zFC75\% > zFC50\% = .802$ and that $zFC50\% > zFC25\% = .958$, with the absolute estimates of all three shifted closer to FR decision boundary (the probability of $z > .5$ was .996 for FC25%, .999 for FC50%, and .999 for FC75%). In contrast, increases in prior probability of NC did not shift the starting point.

Conclusions: These findings establish the importance of top-down factors in understanding how the perceptual system

prioritizes threatening stimuli. Results indicate that threat cues enhanced the sensitivity and speed of perceptual decision-making. DDM modeling results indicate this threat-related enhancement occurs via 1) threat- and probability-related shifting of the starting point of the evidence accumulation process closer to the threat decision boundary and 2) faster evidence accumulation or drift rate after encounter with the stimulus following fear cues.

This study quantifies bias and clarifies overlapping and dissociable biasing mechanisms by which prior knowledge impacts perceptual decision-making. Elucidation of these mechanisms particularly import in anxiety, which is distinguished from fear due to its anticipatory nature. Extending the present research could clarify how anticipatory factors and biased threat-perception contribute to the development and maintenance of anxiety disorders.

Keywords: Computational Modeling, Threat Faces, Top-Down Control, Visual Perception

Disclosure: Nothing to disclose.

M25. Early Life Adverse Experiences and Obsessive-Compulsive Disorder: A Study With Patients, Siblings and Controls

*Fabiana Costa, Carolina Cappi, Marcelo Batistuzzo, Roseli Shavitt, Guaraci Requena, Euripedes Miguel, Marcelo Hoexter**

University of Sao Paulo, Sao Paulo, Brazil

Background: Early life adverse experiences are risk factors for obsessive-compulsive disorder (OCD), but studies investigating the relationship between early life adverse experiences, obsessive-compulsive disorder and psychiatric comorbidities are scarce. Moreover, the whole of experiential avoidance, resilience, and dissociation experiences in mediating these relationships is less clear. The present study examines the relationship between early life adverse experiences, experiential avoidance, resilience, dissociation and general psychopathology in a sample of patients with OCD, siblings and controls.

Methods: The Maltreatment and Abuse Chronology of Exposure (MACE) scale was used to assess early-life adversity in 24 participants with OCD, 24 siblings and 24 matched healthy controls. Experiential avoidance was measured with the Multidimensional Experiential Avoidance Questionnaire (MEAQ) and with the Acceptance and Action Questionnaire (AAQ II); resilience was measured with the Resilience Scale for Adults (RSA); and the Dissociative Experiences Scale (DES) assessed dissociation. The Kruskal–Wallis nonparametric analysis of variance was used to test between-group differences. Then, post hoc pair wise comparisons (Wilcoxon test) were performed considering a $p < 0.017$.

Results: MACE emotional abuse scores were different between groups. Post hoc pair wise comparisons showed that patients with OCD presented higher emotional abuse scores compared to healthy controls ($p < 0.017$). There were no differences between patients and siblings and between siblings and controls in terms of MACE scores. Patients presented higher scores in experiential avoidance compared to controls as measures by the MEAQ ($p < 0.0001$), but there were no difference between patients and siblings and between siblings and controls. In terms of AAQ II, avoidance was higher in OCD patients compared both to siblings ($p = 0.002$) as well as to controls ($p < 0.0001$). Siblings and controls did not differ. Resilience was lower in patients with OCD compared both to siblings ($p < 0.003$) and to controls ($p < 0.014$), though there were no differences between siblings and controls. Dissociation scores were not different between-groups.

Conclusions: Results of this study suggests that emotional abuse during childhood and adolescence may play a role as a risk factor for OCD. On the other hand, experimental avoidance and resilience should be considered as potential factors mediating the relationship between early life adverse experiences and OCD.

Keywords: Adverse Childhood Experiences (ACE), Obsessive-Compulsive Disorder (OCD), Resilience, Avoidance, Dissociation

Disclosure: Nothing to disclose.

M26. The Lipidome in PTSD

Sabra Inslicht, Ritu Roy, Adam Olshen, Callan Lujan, Aditi Bhargava, Thomas Neylan*

University of California, San Francisco, San Francisco, California, United States

Background: Post-traumatic stress disorder (PTSD) affects approximately 8% of the US population and 22% of US veterans returning from Iraq and Afghanistan. Not only does PTSD impact psychological well-being, it also has been associated with physical health concerns, including greater inflammation, metabolic syndrome, gastrointestinal (GI) illness, and even early mortality. Impaired glucocorticoid regulation associated with PTSD may increase risk for chronic health conditions, since glucocorticoids regulate metabolism of proteins, carbohydrates, and lipids including processes such as gluconeogenesis (protein to carbohydrate conversion) and redistribution of fat. In addition, specific fatty acid/amino acid metabolites can render PTSD patients more susceptible to neuronal excitability, signal transduction, and inflammation. Elevated concentrations of serum lipids were associated with combat-related PTSD. Veterans with combat-related PTSD are at a higher risk for arteriosclerosis, thus elevated or dysregulated serum lipids may contribute to increased immune and cardiovascular responses in PTSD. The aims of this study were two-fold. First, to ascertain if plasma lipid metabolites were associated with PTSD relative to healthy controls. Second, to examine if the plasma lipid profile was associated with sex. We predicted that both PTSD and male sex would be associated with higher levels of peripheral lipid metabolites that are known to traverse the blood-brain barrier and negatively affect health.

Methods: A metabolomics analysis has the potential to explain the regulation of metabolic pathways and networks of physiologically relevant interactions that lead to increased health risks in PTSD. As a global and unbiased approach, metabolomics identifies changes in circulating small molecules that affect cell and physiological function and can provide a more comprehensive examination of the broad range of physiological pathways that may be missed with more traditional, targeted approaches. Metabolomic analyses were performed on plasma samples obtained from fasting male and pre-menopausal follicular phase female subjects with chronic PTSD ($N = 44$) and trauma-exposed, age-matched controls ($N = 44$). Participants were between the ages of 20 and 50, primarily civilians (89%), healthy, free of medications, alcohol and drugs, and limited to one cup of caffeine daily. Plasma samples were assayed for lipids, fatty acids, sphingolipids, and short-chain fatty acid metabolites using Time-of-Flight Mass Spectrometer (Agilent Technologies 6220 TOF) coupled with an Ultra HPLC. Statistical analyses were performed using the R/Bioconductor statistical framework. Metabolomic data were transformed to log base 2 scale. Undetected metabolomic values were replaced by 1/10 of minimum value where necessary. Wilcoxon's rank-sum tests were performed for univariate and moderated t-tests from Bioconductor limma package for multivariate analyses. P-values were adjusted for multiple testing.

Results: Metabolic analyses indicated that 100/2,390 lipid metabolites were significantly associated with PTSD (97 lipid metabolites were upregulated and 3 were downregulated; adjusted p-value < .05). Lipid metabolites that were altered in PTSD included sphingomyelins, ceramides, and phosphatidylcholines. Two lipids were upregulated (one of which was acylcarnitine) and 1 (sphingomyelin) downregulated in males compared to females. Multivariate analyses revealed no significant interactions between PTSD and sex for any of the lipid metabolites.

Conclusions: Complementing previous findings of an association between hyperlipidemia in PTSD, the metabolomics approach allowed for the identification of lipid metabolites that were associated significantly with PTSD. Our findings are consistent with a previous report of alterations in sphingomyelin metabolism as measured peripherally in combat Veterans with PTSD and in several studies of individuals with major depressive disorders. Sphingolipids constitute a physical barrier in the brain and provide key functions including cell signaling. Sphingomyelin hydrolyses into ceramide and phosphorylcholine. Acid sphingomyelinase, a lipid metabolizing enzyme responsible for this effect is increased in major depression and is reduced with tricyclic antidepressant intake. Acid sphingomyelinase has a role in interleukin-1 release from brain astrocytes, hypothalamic-pituitary-adrenal axis function and has been associated with cardiovascular disease. As such, sphingolipid metabolism may have a role in neuroendocrine and immune alterations in PTSD and associated cardiometabolic health conditions. While there is some evidence that ceramides in the plasma and brain are correlated and cross blood–brain barrier in rats, whether peripheral lipids are an indirect marker of central lipid metabolism has yet to be determined. Identification of key lipid metabolites in conjunction with steroid hormone biomarkers of PTSD may lead to a more precise and reliable phenotype and a clearer understanding of associations between the brain and glucocorticoid and inflammatory pathways to disease in individuals with PTSD.

Keywords: PTSD, Lipids, Metabolomics

Disclosure: Nothing to disclose.

M27. A Computational Approach to Predict Clinical Features of PTSD: An fMRI and Machine Learning Study

Amin Zand Vakili, Jennifer Barredo, Emily Aiken, Benjamin Greenberg, Linda Carpenter, Noah Philip*

Alpert Medical School, Brown University, Providence, Rhode Island, United States

Background: Post Traumatic Stress Disorder (PTSD) is a prevalent and debilitating condition with complex and variable presentation. Core PTSD symptoms (re-experiencing, avoidance, mood/cognition, and arousal) are highly correlated, yet patients often manifest different symptom subsets despite sharing the same categorical diagnosis. Prior research suggests that different PTSD symptom domains might arise from at least partially distinct brain networks. Here, we employed data-driven machine learning to evaluate whether cortical and subcortical functional connectivity might predict a given patient's PTSD symptom profile. This could provide dimensional approaches to PTSD diagnosis, a greater understanding of the underlying neurobiology, and lead to individualized and rationally targeted treatments.

Methods: Resting state fMRI was acquired in 47 patients with PTSD (some with comorbid depression) in a mixed veteran and general population sample. We extracted time course data from 100 brain regions of interest (ROIs) based on multi-modal parcellation of cortical regions (Glasser et al. 2016). These regions were within neural networks implicated in PTSD, named in the default mode, salience, and executive networks. The resulting ROI time series data were cross-correlated and then converted to z-scores to improve normality using Fisher's transformation.

The resulting high-dimensional matrix of 4,950 potential independent variables was reduced to 46 components with principal component analysis. Sparse (LASSO) regression with a wrapper feature selection algorithm was then applied to this dimensionality-reduced dataset to predict each of the four PCL-5 subscales (i.e., re-experiencing, avoidance, mood/cognition, and arousal). We then utilized full iterative leave-one-out cross-validation to evaluate regression performance.

Results: LASSO regression applied to fMRI connectivity data significantly predicted PTSD symptom profiles in this sample. The goodness of fit of the model, defined by the coefficient of determination (R2) for re-experiencing, avoidance, mood symptoms, and arousal, was 0.45, 0.35, 0.33, and 0.37, respectively. All were statistically significant ($t(45) = 6.01$, $t(45) = 4.953$, $t(45) = 4.706$, and $t(45) = 5.12$ respectively, $p < 0.0001$ in all cases). The results did not depend on the number of items left out in cross-validation, reducing the likelihood of overfitting. Subscales were well-predicted by 4 to 7 of the 46 available principal components.

The principal components contributing to the prediction of cognitive/mood symptoms, arousal, and re-experiencing were distinct. Functional connectivity amongst anterior lateral orbitofrontal cortex (associated with affective processing) was stronger in individuals with greater mood/cognitive symptoms. In contrast, strong connectivity amongst dorsolateral prefrontal subregions implicated in executive control was seen in those with fewer of these symptoms. Functional connectivity between pars triangularis, a region implicated in both executive and default mode networks, was associated with greater arousal symptoms, whereas connectivity between dorsolateral prefrontal executive regions was observed in those with fewer arousal symptoms. Moreover, connectivity of pars opercularis, a control region contributing to action planning, was more strongly anticorrelated with anterior cingulate subregions involved in salience processing in individuals with more severe mood/cognitive symptoms.

Conclusions: This, to our knowledge, is the first attempt to identify biological correlates of PTSD symptom subclasses using a purely computational approach. A machine learning algorithm trained on functional connectivity data was able to successfully predict the detailed symptom profile and subscale scores in patients with PTSD. The resulting predictions were made using shared yet distinct connectivity components. Expansion of this work could lead to a better understanding of PTSD psychopathology and help us target treatments to specific symptom domains. More directly targeting the biological nexus of a particular class of symptoms could potentially lead to more rapid and complete clinical improvements in patients with PTSD.

Keywords: Post Traumatic Stress Disorder, Resting State Functional Connectivity, Machine Learning, fMRI Biomarkers

Disclosure: Nothing to disclose.

M28. Extracellular Regulated Kinase 2 Within the Lateral Habenula Promotes Resilience to Emotional and Physical Stress During Adolescence

Lyonna Parise, Omar Sial, Astrid Cardona, Eric Parise, Eric Nestler, Scott Russo, Carlos Bolanos-Guzman*

Icahn School of Medicine at Mount Sinai, New York, New York, United States

Background: Most stress research to date has focused on the effects of physical stress, yet evidence demonstrates that emotional stress is just as deleterious as physical offenses, thus

highlighting the necessity for models of stress that focus on non-physically invasive insults. To this end, the chronic social defeat stress (CSDS) paradigm has been adapted to include both a physical (PS) and emotional stress (ES) component. Known as the vicarious social defeat stress model (VSDS), mice exposed to ES exhibit similar behavioral and biological outcomes as those exposed to PS such as increased anxiety-like responses and social avoidance, as well as deficits in the forced swim test, and increased serum corticosterone. One advantage of the CSDS paradigm is the ability to separate between susceptible and resilient phenotypes. Interestingly, the parameters which identify these phenotypes have not yet been applied to behavioral outcomes of VSDS experienced during adolescence. This is surprising given the high incidence of mood-related disorders diagnosed during adolescence and the lack of effective treatment options for this particular population. Indeed, there is much interest in targeting novel brain substrates that may be involved in stress-related dysfunction and develop more efficient therapeutics. In particular, the lateral habenula (LHb) has recently been implicated in mediating depression-related phenotype, however, the underlying mechanisms are poorly understood. Extracellular regulated kinase ½ (ERK2) activity within the mesolimbic reward pathway has been shown to regulate stress and antidepressant-like behavioral reactivity and given the prominent regulatory function LHb serves in this circuit, it is likely that ERK2 plays a role within the LHb in mediating stress-related behaviors.

Methods: Adolescent male mice were exposed to 10 days of VSDS and their behavioral reactivity to anxiety- and stress-eliciting situations was assessed 24 h and 1 month after the last stress exposure. A separate group of mice were used for tissue collection 48 h after the last defeat bout in order to measure mRNA expression of ERK2 within the LHb. To determine the functional role of ERK2 signaling within the LHb, we delivered herpes simplex virus (HSV) vectors overexpressing GFP (HSV-GFP) or ERK2 (HSV-wtERK2) and then assessed reactivity to stress. To help elucidate ERK2's role in antidepressant treatment, a separate group of mice were exposed to CSDS and then treated with a single intraperitoneal injection of 20 mg/kg ketamine. Twenty-four hours later, KET-exposed mice were given an intra-LHb infusion of the ERK inhibitor U0126, or its vehicle and their behavior assessed.

Results: Adolescent mice exposed to VSDS demonstrate a similar split in susceptibility versus resilience as observed in adult mice exposed to CSDS. Surprisingly, the phenotype identified (i.e., susceptible or resilient) during adolescence is maintained into adulthood. When tested 24 h after VSDS exposure, the susceptible mice spent significantly less time in the center of the open field arena, suggesting increased anxiety. In addition, when tested one month later in the elevated-plus maze (EPM), susceptible mice spent significantly less time in the open arms of the EPM as compared to the resilient mice, also indicative of an anxiogenic response. Additionally, when given the choice between water and a sucrose solution, susceptible mice do not show the expected preference for sucrose, suggesting heightened levels of anhedonia. Interestingly, after 10 days of stress exposure, ERK2 mRNA was decreased in the LHb of both ES- and PS-exposed susceptible mice. Resilient mice did not show this reduction in ERK2 mRNA expression within the LHb. When subjected to the accelerated CSDS paradigm, HSV-GFP-infused ES- and PS-exposed mice exhibit avoidance to the novel social target, however, the mice microinfused with HSV-wtERK2 showed interaction scores similar to non-stressed controls. Given that overexpression of ERK2 in the LHb promotes resilience, we assessed how ERK2 inhibition could influence the antidepressant efficacy of KET. After 10d of CSDS, mice given KET exhibited an attenuation of social avoidance and, surprisingly, inhibition of ERK2 by U0126 blocked the antidepressant effects of KET.

Conclusions: These findings suggest that ERK2 in the LHb is capable of modulating responsiveness to stress and supports the hypothesis that the antidepressant action of KET are, at least in part, mediated by ERK2 activity within the LHb.

Keywords: ERK, Lateral Habenula, Adolescence, Social Defeat Stress, Emotional Stress

Disclosure: Nothing to disclose.

M29. Maternal Care Affects the Development of Fear Learning in Adolescent Nonhuman Primates: Relationship With Prefrontal 5HT1A Receptor Binding & Attention Bias to Threat in Nonhuman Primates

Elyse Morin, Alison Wakeford, Brittany Howell, Dora Guzman, Jerrold Meyer, Erin Siebert, Andrew Kazama, Jonathon Nye, Mar Sanchez*

Emory University Yerkes National Primate Research Center, Atlanta, Georgia, United States

Background: Childhood maltreatment is associated with increased risk for psychopathology, and social and cognitive deficits. Consistent with human evidence linking early life stress (ELS) with poor emotional/stress regulation, as seen in anxiety and mood disorders, our lab has reported that maternal maltreatment (MALT) leads to increased emotional reactivity, anxiety, and impulsive aggression in nonhuman primates. It is unclear if this is due to enhanced fear learning or impaired modulation of fear responses. These questions can be probed using fear-potentiated startle (FPS) paradigms where the inability to modulate fear-conditioned responses by safety cues have been found to be translational biomarkers for disorders such as PTSD. This study used a well-established rhesus model of MALT, which consists of spontaneous and comorbid physical abuse and rejection, leading to infant distress.

Methods: The long-term outcome of ELS on fear learning was assessed in 25 adolescent macaques (4.5-5.5 yrs), half experienced MALT during infancy ($n = 14$; 8 M, 6 F), and the other half competent maternal care (Control: $n = 11$; 5 M, 6 F). It was hypothesized that MALT animals would have higher baseline and FPS, take longer to discriminate fear/safety to attenuate startle, and show impaired extinction. An AX + /BX- fear/safety signal paradigm measured baseline acoustic startle response as an indicator of anxiety, FPS, attenuation of startle by safety signals, and extinction. Attention bias to emotionally valent stimuli was also determined during adolescence using the dot probe task. Due to its role in emotional/stress regulation, prefrontal serotonin (5HT) 1 A receptor binding potential (BP) was also examined using PET imaging during adolescence.

Results: Baseline startle was higher in MALT than Control, particularly in females, and remained high throughout several rounds of testing, suggesting impaired desensitization to the startle cue. During discrimination training, % FPS was significantly lower in females than males; however, MALT females showed a higher transfer of fear to the safety cue during early training than Control females, suggesting fear generalization. A significant negative correlation was found between PFC 5HT1A receptor BP and startle measures ($r = -0.481$, $p = 0.0173$), such that reduced BP was predictive of increased baseline startle amplitude, consistent with human studies on anxiety and depression. In the dot-probe task, MALT animals showed higher reaction times to social threatening images than Controls, suggesting interference of stimuli with negative valence on attentional control and cognitive processes ($F(1,22) = 4.5$, $p = 0.0463$). Higher emotional reactivity during infancy in MALT animals predicted attention bias towards threat ($\beta = -0.14$, $t = -6.1$, $p = 0.002$), whereas higher levels of prenatal cortisol exposure was associated with attention bias away (avoidance of) threat ($\beta = 0.27$, $t = 2.8$, $p = 0.037$) in both MALT and Control groups.

Conclusions: This suggests developmental alterations in fear learning related to MALT, especially in females, leading to difficulties in discrimination learning and generalized fear. This interpretation is supported by higher measures of trait anxiety in baseline startle, as well as reduced PFC 5HT1A receptor BP in maltreated animals. Altogether, these findings suggest that different postnatal experiences and early biobehavioral mechanisms regulate the development of fear/stress regulation and emotional attention biases during adolescence.

Keywords: Early Life Stress, Adolescence, Nonhuman Primate Models

Disclosure: Nothing to disclose.

M30. Maternal Immune Activation Impairs Behavioral Flexibility and Alters Transcription in Frontal Cortex

Susan Powell, Dionisio Amodeo, ChiYu Lai, Omron Hassan, Eran Mukamel, Margarita Behrens*

University of California, San Diego, La Jolla, California, United States

Background: Epidemiological studies suggest that the risk of neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia is increased by prenatal exposure to viral or bacterial infection during pregnancy. It is still unclear how activation of the maternal immune response interacts with underlying genetic factors to influence observed ASD phenotypes.

Methods: The current study investigated how maternal immune activation (MIA) in mice impacts gene expression in the frontal cortex in adulthood, and how these molecular changes relate to deficits in cognitive flexibility and increases in repetitive behavior that are prevalent in ASD. Poly(I:C) (20 mg/kg) was administered to dams on E12.5 and offspring were tested for social approach behavior in a 3-chambered social approach task, repetitive grooming, and probabilistic spatial reversal learning in adulthood (n = 8 vehicle; n = 9 Poly(I:C)). The frontal cortex of MIA offspring were harvested at 27 weeks (Poly(I:C) offspring = 9 and vehicle offspring = 8). We employed next-generation high-throughput mRNA sequencing (RNA-seq) to comprehensively investigate the transcriptome profile in frontal cortex of adult offspring of Poly(I:C)-exposed dams.

Results: Both Poly(I:C)-MIA and control mice demonstrated comparable learning of the initial spatial discrimination, with no significant main effect of treatment on the number of trials to criterion ($t(15) = -1.47$, NS). On the following day mice were first required to demonstrate retention of the previous spatial acquisition. We found no main effect of treatment on the number of trials to retention criterion ($t(15) = -0.34$, NS), showing that both groups had comparable retention and did not differ on recall of the previous day's learning. Once performance reached retention criterion, mice immediately began reversal trials. We found that MIA mice required more trials to reach a performance criterion for reversal learning (significant main effect of treatment, $t(15) = -5.18$, $p < 0.001$). To determine the nature of the reversal learning deficits in Poly(I:C)-MIA mice, we therefore analyzed perseverative errors. There was no significant difference in perseverative errors between Vehicle and Poly(I:C)-MIA mice ($t(15) = 1.56$, NS). Poly(I:C)-MIA mice committed significantly more regressive errors during reversal learning ($t(15) = 7.92$, $p < 0.05$). Impaired social behavior is a core ASD phenotype and can be altered by MIA. We found that Poly(I:C)-MIA mice spent less time sniffing an unfamiliar mouse compared to vehicle-treated mice ($t(15) = 3.90$, $p < 0.01$), indicating reduced social approach behavior. We found a trend toward increased grooming in MIA mice (145 ± 26 s for Poly(I:C)-MIA vs. 95 ± 11 s for controls, $onnt(15) = -1.65$, $p = 0.12$). Out of 12,626 genes expressed in frontal cortex, we identified 24 differentially expressed (DE) genes in Poly(I:C)-MIA mice relative to controls (FDR < 0.1, fold-change > 1.1). The disruption of genes involved in glutamatergic neurotransmission (Grm7), K + ion channel activity (Kcnk1) as well as mTOR signaling (Rictor) can be long-lasting after an environmental insult during embryonic development. We hypothesized that Poly(I:C) treatment affect developmentally regulated genes. Consistent with this, 87.5% of DE genes in MIA offspring are genes that are differentially expressed during fetal to adult brain development. Furthermore, Grm7, Rictor, Rpl29rt and Hist1h2bc were associated with altered behavioral phenotypes. The causal mediation and interaction analyses indicated that expression of Kcnk1 was altered by MIA and was associated with reversal learning. Finally, the GSEA analysis indicated that prenatal Poly(I:C) may disrupt ion channel activity, particularly K + ion channels, through a subtle increase in expression of a set of genes involved in voltage-gated and inward rectifying K + channels.

Conclusions: Our study characterized frontal cortex transcriptome profile of a viral-mimic of MIA effects and its correlation with behavioral phenotypes relevant to ASD. Poly(I:C)-MIA led to an impairment in reversal of spatial discrimination and in social approach behavior, similar to two core features of ASD. Long-term effects of MIA involved dysregulated expression of genes involved in glutamatergic pathway, mTOR signaling and potassium ion channel activity. These gene expression-phenotype correlations provide insight into genes that may underlie the ASD-like behavioral phenotype in the MIA mouse model.

Keywords: Neurodevelopmental Disorders, RNA-Sequencing, Maternal Immune Activation, Reversal Learning, Social Behavior

Disclosure: Nothing to disclose.

M31. Social Isolation During Adolescence Modulates Cognition and Motivation in Adulthood

Gregory Carr, Gongliang Zhang, Michael Noback, Noelle White, James Barrow*

Lieber Institute for Brain Development, Baltimore, Maryland, United States

Background: Social isolation (SI) during adolescence affects neurodevelopment and is a significant risk factor for psychiatric disorders in later life. In mammals, adolescence is a critical period in which social interaction with peers is essential for normal brain development. SI during adolescence is associated with increased neuroinflammation and altered brain structure and neurochemistry. These SI-mediated effects may underlie SI-associated risk, but the pathologically relevant effects of SI are not clear. Previous research has shown that SI from postnatal day 21 to 35 in mice impairs myelination, alters neuronal excitability in the medial prefrontal cortex (mPFC), and modulates behavior in adulthood. SI in humans has also been shown to alter sleep quality, but sleep has not been studied in the mouse model. Here we describe a new set of studies investigating the effects of SI during adolescence on sleep quality and cognitive function during adulthood.

Methods: Male and female C57BL/6 J mice were weaned at postnatal day 21 and randomly assigned to group housing with littermates or isolated housing until postnatal day 35. After postnatal day 35, isolated mice were paired and lived in these pairs for the remainder of the experiments. All behavioral experiments were started after postnatal day 63, at least four weeks after the end of the isolation period. Separate cohorts of mice were tested in behavioral assays including locomotor activity, 48-hour home cage monitoring, social interaction, touchscreen-based progressive ratio breakpoint tasks and

continuous performance tasks (CPT). The behavioral results presented include data from independent cohorts of mice from different litters and breeding pairs (n = 8-10/group).

Results: Male SI mice are hyperactive ($p < 0.05$) and have impaired sleep quality compared to group-housed male mice. Male SI mice have more and shorter bouts of sleep during the dark phase of the light cycle compared to group-housed mice ($p < 0.01$). There was no difference in the total amount of sleep. Female SI mice were no different from group-housed female mice on locomotor activity or sleep behavior. In the progressive ratio breakpoint task, male SI mice have a significantly higher breakpoint compared to group-housed mice, indicating greater motivation to work for a food reward. SI increased the breakpoint without modulating the total number of rewards taken on an FR1 reinforcement schedule. Additionally, preliminary results suggest that male SI mice also show better performance on the CPT sustained attention task utilizing the same food reward as the progressive ratio task (strawberry milk).

Conclusions: These results provide further evidence that SI during adolescence modulates behavior in adulthood. To our knowledge, this is the first evidence that SI in mice impacts sleep behavior, a well-established relationship in the clinical literature. Additionally, we show that SI in males increases motivation to work for a food reward without significantly altering the hedonic value of the specific reward. This suggests that SI may increase the salience of specific environmental stimuli. Our preliminary data showing improved performance in the CPT supports this conclusion. Future experiments will aim to determine whether these findings extend to other types of appetitive and aversive stimuli.

Keywords: Attention, Sleep Disturbance, Reward Processing

Disclosure: Nothing to disclose.

M32. A Randomized Controlled Trial of Ketamine for Adolescent Treatment-Resistant Depression

Jennifer Dwyer, Sarah Yip, Gerard Sanacora, Michael Bloch*

Yale Child Study Center, New Haven, Connecticut, United States

Background: Nearly one in four adolescents will experience major depressive disorder (MDD), and suicide is the 2nd leading cause of death in this age group. 40% of adolescents with MDD fail to respond to initial treatment with selective serotonin reuptake inhibitors (SSRIs). Better treatments for adolescent depression are urgently needed. Ketamine has rapid antidepressant and anti-suicidal effects in adults with treatment resistant-depression (TRD), but there have been no prospective controlled trials in adolescents. The adolescent brain is a unique pharmacologic substrate and the proposed sites of ketamine's action (e.g. prefrontal cortex and hippocampus) are actively maturing during this time. Thus, it is important to carefully and directly test ketamine's antidepressant effects in adolescents with TRD.

Methods: We have conducted a midazolam-controlled cross-over trial to evaluate the effects of ketamine in treatment-refractory adolescent MDD over four weeks. Adolescents (13-17 years old) must have failed at least one adequate trial of a standard antidepressant to enroll. On day 1 and day 14 adolescents receive either ketamine (0.5 mg/kg over 40 minutes) or midazolam (0.045 mg/kg over 40 minutes). Subjects stayed on their psychiatric mediations, with stable dosing for the four weeks prior to the trial and the duration of the trial. For the primary outcome, paired t-tests compare MADRS score at 1 day following infusion between midazolam and ketamine. Scores of the other rating scales and timecourse are assessed as secondary measures. A subset of subjects (n = 5) also underwent MRI neuroimaging at baseline, one day following ketamine, and one day following midazolam.

Results: Recruitment for this trial will complete as of October 1, 2018 at which point the we will have enrolled at least 18 pediatric subjects with significant, refractory depressive symptoms. Five of these underwent neuroimaging. Preliminary analysis will be presented in this poster.

Conclusions: Adolescent TRD is a significant public health problem that is associated with significant morbidity and mortality. The brain undergoes substantial maturation during childhood and adolescence, and novel therapeutics must be carefully tested with attention to developmental context. Here we report the results of the first randomized controlled clinical trial of ketamine in adolescents with treatment-resistant depression.

Keywords: Adolescent Depression, Ketamine, Clinical trial

Disclosure: Nothing to disclose.

M33. Decision-Making Predicts Escalating Cannabis Use Among Adolescent Girls and Boys

Raul Gonzalez, Samuel Hawes, Ileana Pacheco-Colón*

Florida International University, Miami, Florida, United States

Background: Individuals with substance use disorders often exhibit impairments in decision-making (DM): the ability to make optimal choices among competing options with uncertain outcomes (reviewed in Bechara, 2005). Deficits in DM have been linked to dysfunction in several cortico-limbic structures including the OFC, PFC, ACC, and insula, which are implicated in addiction neuropathophysiology. However, the evidence for DM impairments among cannabis users is mixed (reviewed in Crean, Crane, & Mason, 2011). Importantly, questions remain regarding whether DM deficits are evident in adolescent cannabis users and whether DM performance may precede and influence cannabis use trajectories. In this study, we examine whether DM performance predicts prospective growth in cannabis use among an adolescent sample and whether sex-differences are evident.

Methods: Participants were 401 predominantly Hispanic (90%) adolescents recruited from middle- and high-schools in the Miami-Dade area. Most were at risk for cannabis use escalation based on their self-reported drug use history and ranged in age from 14 to 17 ($M = 15.40$, $SD = .72$). Data were collected at five bi-annual assessments across 2.5 years. The sample exclusion criteria comprised history of neurological, learning, or severe psychiatric disorders, head injury with loss of consciousness greater than 10 minutes, and history of significant drug and alcohol use. The 4-hour assessment spanned demographic, mental health, patterns and prevalence of substance use and substance use disorders, as well as neurocognitive functioning. DM was assessed with the Iowa Gambling Task (IGT; Bechara et al. 1994), the Game of Dice Task (GDT; Brand et al., 2005), and the Cups Task (CT; Levin & Hart, 2003), which assess DM under conditions of either ambiguity or specified risk, and under conditions of possible loss or gain. All study participants (n = 401) provided baseline data and retention rates across follow-up assessments remained high (94%-98%).

Results: Full information maximum likelihood (FIML) estimates were used to handle missing data. No differences were found for any study variable when comparing between participants having complete data and those missing data for any assessment. Four indices of performance across three DM tasks were used to construct a latent DM variable. These included the reverse-scored IGT Net Total, the number of risky choices in the GDT, and the total number of risky choices in the gain and loss domains from the CT. Confirmatory factor analysis (CFA) revealed that all four indices loaded significantly on the latent DM variable and the data

provided a good fit to the model (CFI = .98; RMSEA = .03). Latent growth curve modeling (LGCM) was used to delineate the longitudinal course of CU. First, analyses examined the shape and model fit of the CU trajectories. Subsequently, analyses were conducted to determine whether baseline DM scores predicted the developmental course of CU when controlling for participant age, estimated IQ, and race/ethnicity. Finally, we examined whether there was an interaction effect between participant sex and scores on the latent DM variable in the prediction of the LGCM of CU. This interaction effect was estimated using the latent moderated structural equation (LMS) method (Klein & Moosbrugger, 2000). All models used maximum likelihood estimation with standard errors and a chi-square statistic that are robust to nonnormality (MLR) in Mplus 7.0. Initial examination of the unconditional CU growth model revealed acceptable model fit ($\chi 2$ (32) = 53.76, p = .009; CFI = .93, RMSEA = .08). The mean estimated intercept (M = .82, SE = .18) and linear slope (M = .41, SE = .04) were both significant and positive (p-values < .001), indicating a systematic increase in the average rate of CU across the adolescent study period. Statistically significant variance estimates were also found for the intercept ($\delta 2 = 7.12$, p < .001) and linear slope ($\delta 2 = .46$, p < .001) of the CU trajectory, indicating significant within-individual variability in initial levels and change over time in CU. In addition, results from subsequent analyses showed that DM predicted increased rates of CU across the adolescent follow-up period (B = .15, SE = .05; p = .01), even after controlling for participant age, estimated IQ, and race/ethnicity. However, there was no evidence of a significant interaction between participant sex and the latent DM variable (B = .11, SE = .19; p = .55) on CU growth.

Conclusions: Our results indicate that poorer DM predicts increasing use of cannabis during adolescence in both girls and boys. This lends further support to the contention that prevention strategies aimed at improving DM (e.g., Alfonso et al., 2011) may be of some benefit in reducing adolescent cannabis use. These results need to be replicated in more racially/ethnically diverse samples. Future analyses will explore whether specific aspects of DM are more relevant than others and whether mental health variables moderate or mediate this effect. Funded by R01DA031176 to RG.

Keywords: Cannabis Use, Risky Decision-Making, Adolescent

Disclosure: Nothing to disclose.

M34. Mistimed Network Connectivity Associated With Cognitive Control Deficits in Adolescents and Young Adults With ASD

Marjorie Solomon, Marie Krug, Cory Coleman, Matthew Elliott, Jeremy Hogeveen, Tara Niendam, Ragland Dan, Cameron Carter*

University of California, Davis, Sacramento, California, United States

Background: Most individuals with Autism Spectrum Disorder (ASD) exhibit cognitive control (CC) deficits that persist into adolescence and young adulthood. CC deficits may be associated with the difficulties in social functioning, adaptive functioning and restricted and repetitive behaviors that are characteristic of many affected individuals, making it important to understand the precise nature of these deficits. Previous fMRI studies have found that typically developing (TYP) individuals develop a mature LPFC/Parietal network in adolescence, which aids them in successfully inhibiting responses on incongruent trials. Individuals with ASD, however, may continue to rely more heavily on a less mature dACC/LPFC network when required to implement CC. We use data from the completed first wave of a five-year cohort-sequential study of adolescents and young adults with ASD to investigate potential group differences in behavioral performance and neural recruitment during a rapid event-related version of the Preparing to Overcome Prepotency (POP) task in participants ages 12-22 years old.

Methods: Participants included 60 individuals with ASD (mean age = 17.6 years; mean IQ = 103) diagnosed using gold standard measures and 69 individuals with TYP (mean age = 17.3 years; mean IQ = 109). They completed 4 28 trial runs of the rapid Preparing to Overcome Prepotency (rPOP) task in the scanner. In the rPOP, they were first presented with a fixation cross. This was followed by a cue signaling whether they should push a button on the same side (cued by a green square) as indicated by the probe, which was an arrow, or to the opposite side relative to where the arrow pointed (cued by a red square). After an inter-stimulus interval, the probe arrow was presented. Both inter-stimulus and inter-trial intervals were jittered (mean time = 4,500 milliseconds (ms)). Data was acquired using a 3 Tesla Siemens Tim Trio with a 32-channel head coil. Data were preprocessed and analyzed using SPM12. Cue and probe phases of red and green trials were modeled separately in the GLM. Error and post-error trials were modeled separately from correct trials and excluded from contrasts. The GLM included translational and rotational movement and ART outlier regressors. Seed to voxel whole brain functional connectivity (fc) analyses were implemented using PPI in the CONN functional connectivity toolbox (http://www.nitrc.org/projects/conn). Dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate (dACC) seeds were derived from the Schaefer et al. (2017) Atlas.

Results: Behavioral performance on the task as indexed by the inverse efficiency score (IES; RT/accuracy) showed that there was a main effect of diagnosis (F = 3.95, p < .05) a trend level main effect of cue type and a significant cue type X diagnosis interaction (F = 3.99, p < .05), indicating that the ASD group was less efficient at the task. Whole brain analyses showed no group differences in recruitment for the red-green contrasts in either the cue or the probe. FC analyses showed that during the cue phase, the TYP versus the ASD group exhibited greater fc between the DLPFC seed and parietal cortex, left hippocampus, and pre and postcentral gyri; and greater fc between the dACC seed and bilateral parahippocampal gyrus, and the medial precuneus. During the cue phase of the task, the ASD versus the TYP group demonstrated greater fc between the DLPFC seed and the parietal cortex, right insula, and right middle and inferior frontal gyri; and greater fc between the dACC seed and the insula and the right inferior frontal gyrus. During the probe phase of the task, the TYP versus the ASD group showed greater fc between the DLPFC seed and the ACC, anterior PFC, and the insula; and greater fc between the dACC seed and middle and inferior frontal gyri, while the ASD versus the TYP group showed greater fc between the dACC and other PFC regions. At cue, for the ASD group, greater dACC-right inferior frontal gyrus and DLPFC-middle frontal gyrus fc was associated with poorer task performance, while greater dACC to fc connectivity (characteristic of the TYP group) was correlated with better task performance. At the probe, greater DLPFC-insula fc (characteristic of the TYP group) was associated with better task performance in the ASD group.

Conclusions: Seed to voxel fc analyses using PPI illustrated that during the presentation of red cues compared to green cues, both the ASD and TYP groups showed significant fc between frontal seeds and parietal regions. However, at cue the TYP group showed greater fc between seed regions and the hippocampal regions perhaps suggesting the retrieval of learned rules, while the ASD group showed greater fc between dACC and DLPFC seeds and insula and middle and inferior frontal gyri. At the probe, greater connectivity in these regions was seen for TYP compared to ASD, providing evidence that cognitive control processes are mistimed in ASD and involve greater insula and less hippocampal recruitment in the preparatory phases of the task. Associations with task performance provide evidence that the mistiming found

in ASD is detrimental to task performance and that the networks recruited by the TYP group are more effective.

Keywords: Cognitive Control Network, Adolescent Brain and Cognitive Development Study, Functional Magnetic Resonance Imaging

Disclosure: Nothing to disclose.

M35. Maturational Changes in Event-Related Potential Components, Cortical Thickness, and Substance Use Disorder Outcome in Young Adulthood

Shirley Hill, Stuart Steinhauer, Brian Holmes, Jeannette Locke-Wellman*

Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania, United States

Background: Familial risk differences in amplitude of specific ERP components have been demonstrated in multiple replications across labs. Some of these differences appear to change with development most likely in association with maturation of brain structures. Cortical thickness is one measure of brain morphology that changes with development. With the capability of assessing multiple brain regions using FreeSurfer, we tested whether regional differences in cortical thickness map to specific ERP measures.

Methods: Adolescent and young adult male and female participants (N = 217) with a mean age of 25.2 + 4.9 years; from high (N = 118) and low risk (N = 99) for alcohol dependence families were scanned using magnetic resonance imaging (MRI) at 3 T. Cortical thickness was analyzed using FreeSurfer. The participants were part of longitudinal study in which multiple event-related potential recordings were obtained during childhood, adolescence, and young adulthood. Using the visual ERP recording nearest in time to the MRI scan, preliminary analyses were completed to determine the patterns of associations between brain regions and ERP components. Those regions showing significant association were tested for familial risk group differences with those showing significance entered into a survival model to determine their relationship to substance use disorder outcome.

Results: Among the significant associations with familial risk were cortical thickness of the right hemisphere (rh) parsopercularis and the temporal pole in the left hemisphere (lh). These regions were significantly related to risk group status: lh temporal pole ($F = 4.97$, df 1, 215, $p = 0.027$) and the rh parsopercularis ($F = 6.98$, df = 215, $p = 0.009$). These variables, along with ERP characteristics at baseline (median age = 11 years) and follow up (median age = 24 years), Iowa Gambling Test scores, and impulsivity scores when entered into a survival model showed several significant predictors of SUD outcome, some spanning a 13 year follow up period.

Conclusions: Neural activity reflected in P300 amplitude is positively related to cortical thickness in regions found to differ by familial risk status and involved in impulsivity and decision-making.

Keywords: Cortical Thickness, Event-Related Potentials, Alcohol and Substance Use Disorders

Disclosure: Nothing to disclose.

M36. ADHD Symptom Severity in Children is Associated With Reduced Sleep Slow Wave Activity and Default-Mode Network Connectivity After Acute Sleep Restriction

Jared Saletin, Jessica Haddad, Gabriela De Queiroz Campos, Mary Carskadon, Daniel Dickstein*

Alpert Medical School, Brown University, Providence, Rhode Island, United States

Background: Attention-deficit-hyperactivity disorder (ADHD) is commonly associated with disrupted sleep. Unclear, however, is whether ADHD symptoms convey vulnerability to neural consequences of sleep loss. Thus, we conducted a within-subject extended wakefulness protocol combining quantitative analysis of the sleep EEG with next-day functional neuroimaging of resting-state networks in a sample of children across symptom-severity.

Methods: Eight medication-naïve children (2 F; age: 11.3 ± 1.3 years) without mood or anxiety comorbidity were assessed for ADHD symptoms (inattention, hyperactivity) using average parent and teacher Conners-3 T-scores. Participants slept on a 1-week 9.5-hour schedule (2100h-0630h) before entering the lab for an adaptation session followed by two consecutive nights of sleep: a night of 9.5-hours time-in-bed, and a subsequent night of sleep, restricted to 4-hours time-in-bed (0230h-0630h). Sleep was monitored by a 25-channel topographical EEG array. Each morning (~0900 h) participants completed a resting-state functional magnetic resonance imaging scan, allowing within-subject comparisons of rested wakefulness (RW) with sleep restriction (SR). We examined (1) whether cortical dynamics of sleep homeostasis (indexed by NREM slow wave activity [SWA]; EEG power in the 0.6 – 4.8 Hz band) following sleep restriction are modulated by ADHD symptoms, and (2) how connectivity within the default-mode-network shifts as a function sleep loss and symptom severity.

Results: When examining polysomnographic sleep, our sleep restriction protocol was successful in increasing the proportion of time spent in slow wave sleep ($p < .001$) as well as increasing EEG SWA across the entire scalp ($p < .05$). Turning next to inter-individual differences, we identified a local difference in recovery SWA as a function of symptoms. Heightened ADHD symptoms were associated with an attenuated recovery increase in SWA over frontocentral cortex (EEG derivation FCz; $p < .05$). Turning next to brain connectivity the morning after SR, we identified a group-wise reduction in DMN connectivity in SR, compared to RW ($t(7) = -3.03$, $p = .019$). However, more severe ADHD symptoms were associated with greater reductions in DMN connectivity; both for hyperactivity ($b = -.0031$; $t = -4.01$; $p = .007$; $r2 = .45$) and inattention ($b = -.0029$; $t = -2.56$; $p = .042$; $r2 = .35$).

Conclusions: These initial results suggest young children struggling with attention deficits may be more severely impacted by sleep loss. First, their ability to illicit a robust recovery response in EEG slow wave activity is diminished, perhaps implying insufficient restoration of brain function the next morning. Second, symptoms were equally associated with greater sleep-restriction-induced reductions in neural connectivity following extended wakefulness. We are currently expanding the sample while exploring interactions between sleep physiology and next-day network integrity in both accounting for symptoms, and ultimately, cognitive and behavioral impairments. More generally, however, these data underscore the critical importance of considering sleep as a contributory factor to the neurobiology of ADHD and indicates sleep as a potential modifiable factor in these youth with profound impact for daytime function.

Keywords: Sleep, Sleep Deprivation, ADHD, Resting State Functional Connectivity, Quantitative EEG

Disclosure: Nothing to disclose.

M37. Computational Approaches for Early Emerging Heterogeneity and Disorder Risk

Suma Jacob, Jason Wolff, Colleen Doyle, Michael Steinbach, Vipin Kumar, Jed Elison*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Variability across the typical-to-atypical continuum and heterogeneity within and across early emerging psychiatric disorders remains a challenge for identifying biological mechanisms and targeted treatments. In this project, we are using two unsupervised data-driven computational approaches to identify profiles of risk for early atypicality in neurodevelopment. Using 1) Factor Mixture Modeling (FMM) and 2) Anomaly Detection to identify single cases or outlier clusters of children, we combine these complementary procedures in order to stratify clusters of cases based on a behavioral risk profile. Our goal is to identify high-risk children at rates consistent with epidemiological estimates of ASD and associated developmental disabilities (e.g., language or global developmental delay).

Methods: We collected parent-report data from 1570 children between 17- 25 months of age in a community sample. Caregivers filled out Video-Referenced Rating of Reciprocal Social Behavior, the Repetitive Behavior Scale for Early Childhood (RBS-EC), and the MacArthur-Bates Communicative Development Inventories (MCDI), and demographic information online. A subset of participants was invited for follow-up assessments before thirty-six months of age.

Results: With the FMM analyses, we identified five subgroups. Follow-up with a subsample of 107 children confirmed the predictive validity of the risk profiles, showing significant differences between high-, moderate-, and low-risk groups on internalizing, externalizing, and dysfunctional behavior. Comparison of high- and low-risk groups revealed large effect sizes for internalizing ($d = 1.39$), externalizing ($d = 0.83$), and dysregulation ($d = 1.87$). With the Anomaly Detection analyses, we determined that 80 children had local outlier factor (LOF) anomaly scores > 1.32 out of the overall sample of 1570 toddlers. This represents about 5% of the sample and is consistent with prevalence data for developmental delay and ASD. The longitudinal follow up subsample ($N = 107$) allowed us to determine that the subset of children with higher LOF scores maintained higher risk symptoms when they were reassessed six months later (e.g. continued to show social impairment).

Conclusions: Combining computational approaches that identify subgroups and outliers may be required to capture the heterogenous profiles of children at risk for neurodevelopmental disabilities. We anticipate that clusters and profiles identified through computational analyses (FMM, Anomaly Detection) will be differentiated by dimensional cognitive and behavioral features, including cases of ASD or related childhood disorders that are clustered into distinct groupings. Next steps include larger samples and longitudinal clinical assessments to determine co-existing risk for emerging anxiety, affective, and/or behavioral disorders. These computational approaches will allow us to model heterogeneity in early emerging child psychiatry disorders.

Keywords: Computational Psychiatry, Neurodevelopmental Disorders, Early Identification of Risk

Disclosure: Roche/Genentech, Advisory Board

M38. Microbiome-Bile Acid Cross-Talk as a Mechanism Underlying Antipsychotic-Induced Weight Gain

Erika Nurmi, Jude McElroy, Reimond Costa, Laughlin Christopher, James McCracken, Gerhard Hellemann, Kym Faull, Chadi Calarge, Lauren Seaman*

University of California, Los Angeles, Los Angeles, California, United States

Background: Weight gain and metabolic syndrome are common and serious treatment-limiting adverse effects of medications commonly used to treat mental illness, especially antipsychotic drugs. Children and adolescents are at increased risk for these side effects, resulting in substantial morbidity and dysfunction. While the mechanism of antipsychotic-induced weight gain (AIWG) is poorly understood, emerging preclinical and clinical data suggest a role for the gut microbiome. AIWG is absent in germ-free mice but can be induced by microbiome transplant. Likewise, AIWG in rodents can be ameliorated by an oral antibiotic cocktail. In humans, treatment with the antipsychotic risperidone (RSP) produces "obesogenic" microbiome shifts in children, an effect that was magnified in those with significant weight gain.

Given a growing appreciation for the role of bile acids (BA) in energy balance and microbiome-BA interaction in the gut, we tested whether BAs might represent a downstream effector of microbiome changes. BAs can serve as signaling molecules regulating energy balance through their activity at the hepatic nuclear receptor farnesoid X (FXR). Primary BAs (cholic acid [CA] and chenodeoxycholic acid [CDCA]) synthesized by the host are FXR agonists. Endogenous primary BAs are converted to secondary BAs by epimerase + gut bacteria and reabsorbed into the portal circulation. In contrast to the primary BAs, the secondary BA ursodeoxycholic acid (UDCA) acts as an FXR antagonist. Therefore, shifts in the balance of host-derived primary BAs and microbiota-derived secondary BAs could result in weight gain and metabolic dysfunction through downstream competitive effects on FXR signaling.

Methods: In 30 youth from the NIMH-funded RUPP-RSP clinical trial of children with autism spectrum disorder, we measured plasma levels of the five most prevalent human BAs at baseline and after 8 weeks of RSP treatment. Using mass spectrometry, we analyzed and compared changes in primary versus secondary BAs longitudinally.

Results: We observed marked changes in the total BA pool and diversity, with predominant increases in primary BAs. Primary BAs were significantly ($p = 0.01$) more pronounced in those with high (increased 6-fold) versus low (doubled) AIWG. This pattern was replicated in an independent sample of 4 subjects started on RSP with moderate weight gain. Both CDCA and UDCA measures at baseline and 8 weeks were available for 28/30 RUPP participants. 12 of these 28 displayed a significant change (from baseline to 8 weeks) in either CDCA or UDCA (> .5 SD). In this subset showing BA change with RSP, the ratio of the change in CDCA to the change in UDCA differentiated those with AIWG ($\Delta CDCA/\Delta UDCA > 1$) from those without ($\Delta CDCA/\Delta UDCA < 1$). This algorithm correctly predicts AIWG status in 11/12 (92%) participants whose ratios change ($p = 0.001$), with a sensitivity of 100% and specificity of 86%. Sex, age, race/ethnicity, and RSP dose/plasma level were tested but did not contribute to BA differences. Test-Retest reliability of CDCA, UDCA, and primary BA repeated measurements in the same individual ($N = 2$) were precise within 4 nmol/L.

We hypothesized that a $\Delta CDCA/\Delta UDCA < 1$ could occur when epimerase + bacteria are unavailable to convert CDCA to UDCA, resulting in excess CDCA and AIWG. Therefore, we examined whether relative abundance of the most common species of epimerase + bacteria (B. fragilis) was affected by RSP exposure. As predicted, in a previously published longitudinal sample of 5 subjects, the relative abundance of B. fragilis decreased over 200-fold after 1-3 months of RSP exposure.

In order to explore whether these effects are specific to AIWG, we tested a small pilot sample of children taking SSRIs. 10 youth were selected, 5 with moderate (> 1 Z-score) SSRI-induced weight gain (SIWG) and 5 without. While no effects were statistically significant in this very small sample and the effect sizes of differences were smaller than those observed in AIWG, the trends were in the same direction, with individuals with greater weight gain showing greater elevation in primary BA and $\Delta CDCA/\Delta UDCA$

> 1. Using this ratio, SIWG status can be correctly predicted in 6/8 (75%) of individuals with BA change on an SSRI.

Conclusions: Our preliminary data suggests that antipsychotics impact BA pathways and that alterations to the BA balance may contribute to AIWG, a link that to our knowledge has not been previously investigated. We have shown that RSP-exposed children exhibit substantial changes in their BA pool, with opposite patterns of primary vs. secondary BAs seen in youth at risk versus protected from AIWG. If proven, clear targeted interventions are currently available that may mitigate adverse effects. UDCA is available orally as a gallstone treatment and epimerase + bacteria are a chief component of probiotics. Drugs directly impacting FXR signaling are under development and prebiotic strategies could also prove useful. A better understanding of this complex mechanism will provide the foundation for targeted treatment strategies for drug-induced and, potentially, other-cause weight gain and metabolic dysfunction.

Keywords: Antipsychotic-Associated Obesity, Gut Microbiome, Bile Acids

Disclosure: Nothing to disclose.

M39. Association of Childhood Adversity With Differential Susceptibility of Transdiagnostic Psychopathology in Adulthood

Cristina Albott, Miriam Forbes, Justin Anker*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Multivariable comorbidity research indicates that childhood adversity increases the risk for the development of common mental disorders. This risk is explained by two underlying transdiagnostic constructs, internalizing and externalizing, which are amplified by environmental stressors. The differential susceptibility model suggests that this interaction of risk and environment is bidirectional: at risk individuals respond to stressful environments "for worse" but also respond "for better" in low-stress environments. The present study tested the differential susceptibility model by examining how a history of childhood adversity influences the impact of environmental stress on transdiagnostic psychopathology factors.

Methods: Data were drawn from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), an observational longitudinal survey. Data from adults (aged 18 years and older) that completed the survey at two time points: Wave 1 (2001 to 2002) and Wave 2 (2004 to 2005) (N = 34,458) were used for the analyses. We created latent variables of internalizing, externalizing, and general psychopathology factors based on the number of psychiatric diagnoses. By comparing data collected at Wave 1 to Wave 2, intra-individual change scores were calculated for adult stressful life events and transdiagnostic psychopathology factors (i.e., internalizing-fear, internalizing-distress, externalizing, and general psychopathology). Analyses examined how childhood adversity exposure moderated the relationship between change in adult stressful life events and change in adult transdiagnostic psychopathology factors. Data were analyzed using repeated measures linear mixed-effects models.

Results: Childhood adversity significantly moderated the relationship between changes in adult stressful life events and changes in all transdiagnostic psychopathology factors. Specifically, higher levels of childhood adversity were related to a stronger relationship between adult stress and adult transdiagnostic psychopathology factors. Further, there were significant differences between childhood adversity groups in the mean scores of all transdiagnostic psychopathology factors for both increases in stressful life events and decreases in stressful life events, providing preliminary evidence for differential susceptibility.

Conclusions: The findings of this study contribute to our understanding of the enduring effects of childhood adversity. The results provide empirical support for the hypothesis that childhood adversity may represent a plasticity factor—rather than only increasing individuals' vulnerability to stressful life events. Further research is needed to replicate this finding, and subsequently to understand whether the goal of psychiatric interventions should be to focus on reducing environmental stressors, or on attempting to identify and modify the endogenous processes that underlie heightened reactivity to the environment.

Keywords: Childhood Adversity, Internalizing Disorders, Externalizing Disorders, Early Life Adversity, Stress Reactivity

Disclosure: Nothing to disclose.

M40. Genetic Risk for Alzheimer's Disease and Functional Brain Connectivity in Children and Adolescents

*Luiza Axelrud, João Sato, Marcos Santoro, Fernanda Talarico, Daniel Pine, Luis Rohde, Andre Zugman, Edson Amaro, Rodrigo Bressan, Rodrigo Grassi-Oliveira, Pedro Pan, Andre Simioni, Hakon Hakonarson, Elisa Brietzke, Ary Gadelha, Renata Pelegrino, Marcelo Hoexter, Euripedes Miguel, Sintia Belangero, Giovanni Salum**

Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Background: Previous research suggested regions prone to accumulate tau aggregates in late-life form ten tau pathology networks. Nevertheless, studies investigating the impact of genetic risk for Alzheimer's disease on early brain connections are lacking. Here we aim to investigate whether the polygenic risk score for Alzheimer's disease influences the connectivity of brain regions susceptible to tau pathology during neurodevelopment.

Methods: Participants were youth aged 6 to 14 years, recruited in Porto Alegre (discovery sample, n = 349) and São Paulo (replication sample, n = 315), Brazil. The polygenic risk score for Alzheimer's disease was calculated using summary statistics from the International Genomics of Alzheimer's Project. 6-min resting state fMRI was obtained from all participants. The connections between the local maxima of tau pathology networks were used as dependent variables.

Results: The polygenic risk score for Alzheimer's disease was associated with the connectivity between right precuneus and right superior temporal gyrus ($\beta = 0.2$, padjusted = 0.032 for discovery sample; $\beta = 0.2$, $p = 0.018$ for replication sample), regions associated with the ventral Default Mode Network and language network, respectively.

Conclusions: Therefore, brain connectivity between areas susceptible to tau pathology might be affected in youth with genetic susceptibility to Alzheimer's disease. This suggests a neurodevelopmental contribution to Alzheimer's disease pathogenesis.

Keywords: Alzheimer's Disease, Brain Connectivity, Children and Adolescents

Disclosure: Nothing to disclose.

M41. Differences in Brain Myelination Patterns Associated With 7q11.23 Copy Number Variations

Enock Teefe, Michael Gregory, J. Shane Kippenhan, Tiffany Nash, Shannon Grogans, Samuel Elliott, Franchesca Kuhney, Daniel Eisenberg, Carolyn Mervis, Karen Berman*

National Institutes of Health, Bethesda, Maryland, United States

Background: Genetic variation is translated to cognitive and behavioral features through molecular, cellular, and systems-level neurocircuitry. Copy number variations (CNVs), in particular, have been strongly associated with neuropsychiatric disorders, but the underlying neurogenetic mechanisms are still largely unknown and likely complex. Disorders with well-circumscribed CNVs and highly consistent behavioral and cognitive features provide a privileged setting to understand how these neurogenetic mechanisms translate into brain phenotypes and ultimately into complex behaviors. In this study, we investigated two such disorders, Williams syndrome (WS) and 7q11.23 duplication syndrome (Dup7). WS and Dup7 are related, rare neurodevelopmental disorders for which affected individuals possess either hemideletions (one copy, as in WS) or duplications (three copies, as in Dup7) of the same ~1.5 megabases of the 7q11.23 chromosomal locus. These two CNV-related disorders also contrast in their cognitive and behavioral presentations. While WS is typified by a hypersocial personality, deficits in visuospatial construction, and relative strength in concrete language abilities, individuals with Dup7 typically exhibit social anxiety and have visuospatial skills at the level expected for their language abilities. Though prior neuroimaging studies have identified gray- and white-matter alterations in WS, structural brain changes in Dup7 have yet to be examined. No studies have directly measured brain myelination in either disorder. Here, we tested for 7q11.23 CNV-related changes in brain myelination using an MRI technique called Multicomponent Driven Equilibrium Single Pulse Observation of T1 and T2 (mcDESPOT), which provides regional quantitative measures of Myelin Water Fraction (MWF).

Methods: Fifteen children with WS (mean age = 13.3 ± 3.9 years; 11 girls), 11 children with Dup7 (age = 13.1 ± 3.4 years; five girls), and 32 unrelated typically developing children ([TD]; age = 13.3 ± 3.7 years; 15 girls) underwent neuroimaging using a GE 3T-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-recover SPGR sequence. Voxel-wise MWF maps for each participant were calculated using a three-pool model, which determined MWF, intra/extracellular water fraction, and the free water fraction. Multivariate modeling was carried out to determine voxels where MWF was associated with 7q11.23 CNV ($p < 0.05$, FWE-corrected for multiple comparisons), covarying for age and sex.

Results: Nine clusters showed a positive association between MWF and 7q11.23 copy number (Dup7 > TD > WS). These clusters included white-matter underlying bilateral occipito-temporal junction, inferior parietal lobules, orbitofrontal cortex, left superior temporal gyrus and frontal operculum. No associations in the opposite direction (WS > TD > Dup7) were observed.

Conclusions: These results indicate that 7q11.23 CNVs alter myelination of brain regions implicated in visuospatial and social processing and suggest a central role for white matter alterations in the neuropathology of these behavioral domains. Ongoing studies will combine multimodal neuroimaging methods and longitudinal modeling in these participants to identify neural pathways where there is a convergence of evidence for effects of 7q11.23 CNV on developmental trajectories.

Keywords: Williams Syndrome, Myelin Imaging, Copy Number Variants, 7q11.23

Disclosure: Nothing to disclose.

M42. Measuring Regional Cerebral Perfusion in Adults and Children With Williams Syndrome Using Oxygen-15 Water PET and Arterial Spin Labelling MRI

Michael Gregory, J. Shane Kippenhan, Carolyn Mervis, Daniel Eisenberg, Mbemba Jabbi, Philip Kohn, Tiffany Nash, Lalith Talagala, Karen Berman*

National Institute of Mental Health, Bethesda, Maryland, United States

Background: Williams syndrome (WS) is caused by hemizygous deletion of approximately 1.6 megabases at chromosomal locus 7q11.23. Individuals with WS are characterized by marked visuospatial construction deficits, hypersociability, and mild to moderate intellectual disability with relative sparing of concrete language. Because the genes within the hemideleted region of chromosome 7 are known, WS has been used as a model for understanding how genetic changes translate into alterations in complex behaviors through brain function. Previous work has shown that adults with WS have altered regional cerebral blood flow (rCBF), as measured by oxygen-15 water positron emission tomography (PET) scanning, particularly of the hippocampus and insula (Meyer-Lindenberg, et al., 2005; Jabbi, et al., 2012). However, it is unclear when during development these differences arise. Because PET scanning requires administration of radiotracers, use of this method with children is precluded. Instead, arterial spin labelling (ASL) with MRI scanning has allowed for non-invasive quantification of rCBF without exposure to radiation or the need for an IV contrast agent. Here, we measured rCBF in adults with WS using the oxygen-15 water PET method, and in children with WS using ASL MRI.

Methods: Fourteen adults with WS (mean age = 27.8 ± 9.3 years, seven males) and 14 healthy adults (32.6 ± 7.9 years, eight males) completed resting-state oxygen-15 water PET scanning on a GE PET scanner (four 60-second scans/participant using 12 mCi/scan). Ten children with WS (15.2 ± 4.6 years, one male) and 19 TD children (15.2 ± 4.7 years, three males) underwent 3D pseudo-continuous ASL scanning using a 3 T GE MRI scanner. PET images were background subtracted, aligned across scans, registered to each participant's structural MRI image, normalized to a group-specific template in MNI space, and smoothed using a 10 mm FWHM kernel. Data were compared across groups using SPM5. ASL rCBF images were aligned to each individual's structural MRI scan, normalized to a group specific template in MNI space, and smoothed using a 6 mm FWHM kernel. Data were compared across groups using AFNI tools. Resulting statistical maps were thresholded at $p < 0.005$, uncorrected and compared across modalities for convergence of results.

Results: PET and ASL methods both revealed differential rCBF in the cerebellum such that individuals with WS had greater rCBF than unaffected individuals, particularly in the vermis. Individuals with WS also showed decreased rCBF with both methods in the bilateral insulae, bilateral intraparietal sulci (IPS), left fusiform gyrus, left amygdala, and bilateral motor cortex. PET imaging, but not ASL, showed significantly lower rCBF in the hippocampi of participants with WS, while ASL showed significantly lower rCBF of the left orbitofrontal cortex and dorsal anterior cingulate in participants with WS.

Conclusions: We used two independent methods to show that regional cerebral blood flow is significantly altered in individuals with WS, in two independent cohorts at different stages of development. The results were largely convergent both between the two modalities and with previously published work showing structural and functional brain alterations in WS. Previous work has shown that the cerebellum is physically larger in both children and adults with WS, and this size has been related to variations in

cognitive abilities (Menghini, et al., 2013). Prior work also has identified altered rCBF, gray matter volume, and function of the insula in WS (Jabbi, et al., 2012), consistent with the current findings. Further, significant evidence implicates the IPS as a hub of dysfunction in WS, particularly as related to visuospatial deficits (Sarpal, et al., 2008). Other work has implicated the amygdala in the hypersocial personality (Schwartz, et al., 2017) and has found altered organization of the corticospinal tracts leading to the motor cortex (Marenco, et al., 2007). At the same time, the methods were not convergent with regard to the hippocampi, anterior cingulate, and orbitofrontal cortex. However, these regions all have been previously identified as having significance for the WS neurobehavioral phenotype. Further work will be required to determine whether this lack of convergence is due to the relatively small sample size, to the participants being at different stages of development, or to methodological differences between the PET and ASL rCBF methods.

Keywords: Perfusion, Cerebral Blood Flow, 7q11.23, Copy Number Variation, Neurodevelopmental Disorders

Disclosure: Nothing to disclose.

M43. Sex Differences in Brain Network Connectivity Prior to Puberty

Katherine Reding, Shau-Ming Wei, Michael Gregory, Pedro Martinez, Elizabeth Robinson, Jasmin Czarapata, Jordan Barone, Austin Boroshok, J. Shane Kippenhan, Philip Kohn, Lynnette Nieman, Jack Yanovski, Peter Schmidt, Karen Berman*

National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, United States

Background: Sex differences in the prevalence of several behavioral disorders emerge during adolescence and are thought to be related, at least in part, to the (re)activation of the hypothalamic pituitary gonadal axis (i.e., puberty). One hypothesis is that the rise of gonadal steroids during this time affects neurodevelopment such that boys and girls differentially become more (or less) vulnerable to specific disorders. Neuroimaging data point to both sex and developmental differences in the functional connectivity (FC) of several resting state networks, including the Default Mode Network (DMN) and Executive Control Network (ECN), and alterations in FC have been associated with psychopathology during adolescence. First, to establish a normative baseline, we tested for sex differences in resting-state FC in healthy, typically developing children prior to puberty. Then, to probe the stability of these sex differences, we examined FC across pubertal development and into adulthood.

Methods: One hundred and eighteen children, adolescents, and adults were enrolled. Pubertal stage (PS) for child and adolescent participants was defined by clinical exam based on a five- stage scale assessing breast development in girls and testicular volume in boys. Prepuberty was defined by the absence of secondary sex characteristics (PS1), while the pubertal group ranged from PS2-5. All participants completed two six-minute resting state fMRI scans on a 3 T GE MRI scanner, and data were concatenated (for a total of 12 minutes), motion-corrected (framewise displacement < 0.5 mm), spatially smoothed (6 mm FWHM), and bandpass filtered ($0.008 < f < 0.1$) using AFNI and normalized to MNI space using ANTs. Signals associated with nuisance variables, as determined by anatomical CompCor, and motion parameters were removed. Resting-state data were first analyzed in the prepubertal cohort using a connectome-wide association study (CWAS) to identify clusters of voxels showing sex differences in connectivity across the brain. These CWAS-derived clusters, delineating overall, across-the-brain prepubertal sex differences, were then used as seed regions in a whole-brain voxel-wise analysis to delineate the direction, magnitude, and anatomical locale of the underlying differential FC. To examine the development of prepubertal sex differences, the significant regions identified in the CWAS analysis of the prepubertal children were also used to probe FC in both the pubertal and adult groups. Specifically, Pearson's r values were extracted from each region of interest to identify the main and interaction effects of developmental group (prepubertal, pubertal, adult) by sex (male, female) on FC.

Results: There were 41 prepubertal children (8.7 ± 0.3 yrs, 43.9% girls), 31 pubertal adolescents (13 ± 0.6 yrs, 45.2% girls), and 46 adults (30.5 ± 3.8ys, 58.7% women). CWAS within the prepubertal group identified a cluster in the medial prefrontal cortex (mPFC) that showed the most robust sex difference ($p < 0.001$, uncorrected). The mPFC was then used as a seed-region to identify the directionality and magnitude of this sex difference in whole-brain FC. There were seven resulting clusters with more robust mPFC FC in girls than boys, including areas within the Default Mode and Executive Control Networks ([DMN, ECN], $p's < 0.05$, FDR-corrected). There were no regions where FC was more robust in boys than girls. To extend these prepubertal DMN and ECN findings to the pubertal and adult groups, we examined functional connectivity between the mPFC seed and one canonical cluster from each network (as defined by the prepubertal group findings). For the DMN, the mPFC seed showed a significant sex-by-developmental group interaction with the canonical posterior cingulate cortex ($p < 0.001$, corrected): the prepubertal sex difference (girls > boys) in FC was not observed in puberty but re-emerged in adulthood ($p's < 0.005$, corrected). For the ECN, the mPFC seed showed a significant sex-by-developmental group interaction with the canonical dorsolateral prefrontal cortex (dlPFC) seed ($p < .001$, corrected): the observed prepubertal sex difference (girls > boys) in FC was not found in the pubertal or adult groups ($p's < 0.005$, corrected).

Conclusions: Prior to the onset of puberty, girls show higher mPFC FC to regions within the DMN and ECN compared to boys. These sex differences prior to puberty may reflect earlier sex-specific exposures to adrenal sex steroids (or their metabolites) secondary to an earlier onset of adrenarche in girls and/or greater ovarian-derived estrogen exposure, or they may occur independently of direct hormonal action. Across developmental groups, prepubertal sex differences in FC between mPFC and DMN were not observed in puberty but reemerged in adulthood, whereas prepubertal sex differences in FC between mPFC and ECN were not observed in either puberty or adulthood. These data are consistent with previous neuroimaging studies across development suggesting that the DMN and ECN are still maturing through early adolescence and, thus, may undergo significant restructuring during puberty. Moreover, these results emphasize the importance of establishing sex differences prior to the onset of puberty – a time of relative absence of sex steroid hormone in comparison to mid to late puberty – for elucidating the roles of sex steroid hormones on brain function throughout pubertal development.

Keywords: Puberty, Default mode network (DMN), Resting State Functional Connectivity, Connectome-wide association study, Sex Differences

Disclosure: Nothing to disclose.

M44. Functional MRI Markers of Transdiagnostic Risk for Psychopathology: A Meta-Analysis

Jacqueline Clauss, Daphne Holt*

Harvard Medical School, McLean Hospital, Massachusetts General Hospital, Belmont, Massachusetts, United States

Background: In recent decades, increasing emphasis has been placed on identifying high-risk individuals and understanding the neurobiology of risk for psychiatric disease. Reproducible, brain-based biomarkers for psychiatric disease may provide the basis for using quantitative targets in early intervention. While individual illnesses, such as depression or psychosis, have been associated with specific risk profiles, increasing evidence suggests that many of the genetic and environmental risk factors initially linked to distinct psychiatric illnesses are shared across conditions. This is consistent with the well-established clinical overlap observed across psychiatric disorders, i.e., comorbidity is the rule rather than the exception, as well as data showing that early, subsyndromal symptoms, such as mild depression and psychosis-like symptoms, increase risk for a range of illnesses. However, despite this convergent evidence for some shared neurobiological mechanisms across illness and risk categories, there have been few studies that have tested for common patterns of brain structure or function across at-risk individuals. Given this gap in the literature, we conducted a voxel-wise meta-analysis of functional magnetic resonance imaging (fMRI) studies of individuals who were considered at-risk for the following disorders: affective, anxiety, psychotic, and substance use.

Methods: A systematic review of published task-based fMRI studies of subjects at risk for psychopathology was performed, using search terms such as "risk for psychopathology", "longitudinal neuroimaging", "at risk mental state", "depression risk", "behavioral inhibition", and "inhibited temperament". References in identified publications were also examined for additional studies to include. Included studies used a task during fMRI data collection, conducted whole brain analyses, and examined a "high-risk" group, as defined by clinical high risk (i.e., the presence of subsyndromal symptoms), temperamental high risk (i.e., behavioral inhibition), or familial high risk. Studies which did not list peak voxel coordinates in either Montreal Neurological Institute (MNI) or Talairach space were excluded. For each study, if a longitudinal analysis was performed, the coordinates for the comparison of the high-risk group who later developed symptoms versus high risk group without symptoms were included. Otherwise, the coordinates for the comparison of the high-risk group versus the control group were included. Thirty-one studies were identified as examining risk for psychopathology using functional MRI, totaling 1,236 participants. Of these studies, 13 examined risk for anxiety (513 subjects), six examined risk for depression (194 subjects), 10 examined risk for psychosis (331 subjects), and two examined risk for substance use (200 subjects). Study samples included adolescents and young adults (age range (years): 12-34; mean: 20). A wide range of tasks, i.e., cognitive and emotion paradigms, were employed. The meta-analysis was conducted using GingerALE software (version 2.3.6; http://brainmap.org/ale). This software uses an activation likelihood estimation (ALE) to test for overlap among foci across studies. A random-effects model was used. All data were transformed to MNI space using the tal2icbm function within the GingerALE software and peak coordinates were modeled with a 3D Gaussian kernel with a FWHM of 8.5–9.5 (i.e., a larger FWHM was used for studies with fewer subjects). Studies were combined by calculating the union of each individual study, with a voxel p-value of .01 and a cluster size of 25 voxels (200 mm3).

Results: Compared to the controls, the transdiagnostic high-risk subjects showed lower activation across paradigms of the left caudate and left thalamus (both $p < .01$, $k > 25$), and showed increased activation of the right globus pallidus.

Conclusions: The findings of this meta-analysis of 31 fMRI studies suggest that dysregulation of key nodes of the basal ganglia, the caudate nucleus, thalamus, and globus pallidus, is associated with signs of increased risk (i.e., subsyndromal symptoms or familial risk) for a number of serious mental illnesses. These results are consistent with prior evidence for abnormalities of the basal ganglia in affective, anxiety, psychotic and substance use disorders. Abnormalities in basal ganglia function may be related to alterations in hedonic processing, as hedonic function has been shown to be affected in each of these disorders. We can interpret these results as suggesting that one perturbation in basal ganglia function increases risk for many or all of these illnesses; alternatively, distinct (but overlapping) forms of basal ganglia dysfunction may increase risk for separate conditions or illness categories. These findings must be interpreted with caution, however, given the heterogeneity of the sample and analysis methods used, and the wide range of tasks employed in these studies. Replication of these results in an independent, prospectively collected sample is needed. Overall, this study indicates that such transdiagnostic approaches may produce new clues regarding the potential links between broadly shared genetic and environmental risk factors and the biological mechanisms of neuropsychiatric disease.

Keywords: Early identification of risk, Functional MRI (fMRI), meta-analysis

Disclosure: Nothing to disclose.

M45. Adolescent Changes in Task fMRI Bold Signal Accounting for Longitudinal Reductions in Global Grey Matter Perfusion

Marisa Silveri, Huanjie LI, Julia Cohen-Gilbert, Jennifer Sneider, Derek Hamilton, Emily Oot, Anna Seraikas, Maya Rieselbach, Carolyn Caine, Sion Harris, Lisa Nickerson*

McLean Hospital, Harvard Medical School, Belmont, Massachusetts, United States

Background: Adolescence is a period of development characterized by rapid changes in brain structure, function, and neurochemistry, including changes in prefrontal cortex (PFC) and related neurocircuitry that are paralleled by improvements in frontally-mediated cognitive skills such as inhibitory control. Developmental changes in adolescence also have been observed in spatial memory skills, subserved by integration of prefrontal and hippocampal circuitry. Incongruous maturation rates across these brain systems can manifest in maladaptive behaviors, helping to explain why rates of risk-taking are elevated during adolescence. Longitudinal studies identifying developmental changes in functional activation during blood oxygen level dependent (BOLD) task fMRI typically do not account for developmental changes in cerebral blood flow (CBF), which through neurovascular coupling can lead to non-specific changes in BOLD signals. Thus, the objective of the current study was to examine the impact CBF has on developmental changes in BOLD signal acquired during inhibitory control on an emotional Go-NoGo task (eGNG) and during memory retrieval on a virtual Morris Water task (MWT), while controlling for developmental changes in CBF.

Methods: Multimodal neuroimaging data were acquired using a Siemens 3 T TIM Trio, using multiband BOLD fMRI during the eGNG and virtual MWT, and using pseudo-continuous arterial spin labeling (PCASL) to quantify CBF at rest. Alcohol- and substance-naïve and psychiatrically healthy adolescents ($n = 74$) were recruited into a three-year longitudinal study, with task-related BOLD activation and CBF currently being examined in a subset of participants who completed baseline and one-year follow-up scans. Longitudinal changes in CBF averaged over gray matter were assessed via paired-t test ($p < 0.05$). Longitudinal changes in brain activation during tasks were first assessed via higher-level general linear modeling (GLM) for selected contrasts of interest from statistical modeling at the subject level via paired-t test with FLAME mixed effects analysis (cluster-based thresholding, $z = 3.1$, $p < .05$). To assess the impact of longitudinal changes in global

gray matter CBF on BOLD signal changes between year one and year two, two higher-level models were run that assessed differences in activation first without and then with average grey matter CBF included as a regressor (non-parametric permutation testing, $p < 0.05$ corrected).

Results: Across imaging visits, there was a significant decrease in global gray matter perfusion, with 13.7% lower CBF at one-year follow-up, $p < .001$. Significant BOLD activation differences were observed between baseline and one-year follow-up on the MWT in left PFC, left lateral occipital cortex and precuneus cortex ($N = 17$, retrieval > motor contrast), all nodes in a left-lateralized frontoparietal network implicated in explicit memory retrieval. BOLD activation changes were observed in the absence of performance differences, and results remained unchanged when controlling for CBF. For the emotional Go-NoGo task ($N = 16$, negative > neutral contrast), no activation differences were observed between baseline and one-year follow-up (with no effect of controlling for CBF), although faster reaction times at follow-up were evident without a change in error rates over time. Results also remained unchanged when controlling for CBF.

Conclusions: Neurobiological interpretations of developmental changes in BOLD fMRI, or lack thereof, remain difficult to elucidate due to potential confounds associated with longitudinal changes in other factors that contribute to BOLD signals such as CBF. Indeed, longitudinal quantification of CBF is necessary to reconcile functional brain activation patterns, observed during rest or task performance, that change during development. To this end, in this preliminary investigation and using the current data processing procedures, the significant 13.7% decrease in CBF did not appear to influence longitudinal profiles of fMRI task BOLD signal on memory retrieval or emotional response inhibition. Additional analyses of these two distinct cognitive tasks, including assessing the contribution of regional CBF values, are underway to more deeply probe relationships between brain function, task performance and CBF. Taken together, dynamic functional changes suggestive of increased brain efficiency are clearly underway during this short one-year time span. Characterization of such developmental patterns are crucial for informing the search for biomarkers of risk for hazardous behaviors during adolescence, including initiation of alcohol and substance use and mood and anxiety symptoms that increasingly emerge during the second decade of life.

Keywords: Adolescence, Functional MRI (fMRI), Perfusion, Emotional Response Inhibition, Spatial Memory

Disclosure: Nothing to disclose.

M46. Maternal Diet, Placenta Leptin Methylation, and Infant Growth

*Teresa Daniels, Alexander Sadovnikoff, Corina Lesseur, Carmen Marsit, Audrey Tyrka**

Medical School of Brown University / Butler Hospital, Providence, Rhode Island, United States

Background: High and low birthweight, as well as early gestational age, increase risk for a variety of medical and psychiatric conditions. Several factors influence birthweight and gestational age; preclinical and clinical studies show that maternal diet is an important factor. Leptin is a hormone that regulates satiety, body weight, and reproductive and developmental functions, and may be involved in the association between maternal nutrition, maternal obesity and infant outcomes. DNA methylation of placenta genes, such as leptin, may occur in response to exposures and may program subsequent infant development. This study examined maternal diet, placenta leptin gene methylation, and neonatal growth in a sample of healthy neonates and their mothers.

Methods: Healthy neonates and their mothers ($N = 135$) were recruited within 1-2 days following delivery at Women and Infants Hospital in Providence, RI.

A structured interview was conducted to assess the weekly servings of various types of food consumed by the mothers. Maternal weight, pregnancy weight gain, infant weight, and maternal health, medications, and vitamin use were obtained from the medical record. The leptin single nucleotide polymorphism (SNP) rs2167270 was genotyped, and bisulfate pyrosequencing was used to measure methylation of CpG sites in the promoter region of the leptin gene in placenta samples.

Results: Genotype was a significant predictor of leptin methylation ($p < .05$), and after controlling for this and demographic and weight-related covariates, lower levels of leptin methylation were significantly associated with higher intake of sugared drinks ($p < .05$), white carbohydrates ($p < .05$), and whole grain carbohydrates ($p < .05$). Lower levels of leptin methylation were associated with smaller infant head circumference ($p < .05$), but not significantly associated with birthweight ($p = .11$) or gestational age at birth.

Conclusions: These findings show the importance of intake of sugar and carbohydrate consumption for methylation of the placental leptin gene. Because methylation reduces gene transcription, lower methylation may indicate a placental response to high carbohydrate food that would result in higher levels of this satiety/metabolic hormone during fetal development. Lower levels of methylation (which are expected to lead to higher levels of the hormone) were also linked to smaller head circumference, suggesting the possibility that higher placenta leptin concentration may have important effects on growth and brain development.

Keywords: Leptin, Developmental Psychopathology, Diet Induced Obesity

Disclosure: Nothing to disclose.

M47. Probing Supplementary Motor Area in Tic Disorders Using Repetitive Transcranial Magnetic Stimulation: A Preliminary Study

Christine Conelea, Brianna Wellen, Sarah Coleman, Lizzy Egbert, Kathryn Cullen, Benjamin Greenberg, Kelvin Lim*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Chronic tic disorders, including Tourette Syndrome, are neurodevelopmental conditions that impact 1-3% of children and are associated with multiple child-onset psychiatric disorders. Tics are rapid, repetitive movements and vocalizations frequently cued by aversive somatosensory experiences called "premonitory urges." Tic suppression is the primary target of treatment, but between 30-70% of those with tics do not benefit from available interventions, which include medication and behavioral therapy. The mechanisms underlying tic suppression remain poorly understood but likely involve complex interactions between the brain and one's immediate environmental context (e.g., tic-specific consequences, concurrent behavior, emotional state). Supplementary motor area (SMA) is a cortical region that plays a key role in facilitating context-dependent motor output, is hyperactive in those with tics, and has begun to be explored as a neural target for treatment using repetitive transcranial magnetic stimulation (rTMS). The current study aimed to probe the role of SMA in voluntary tic suppression using a novel methodology integrating rTMS with the Tic Suppression Task (TST), an established direct-

observation behavioral paradigm capable of assessing context-specific tic fluctuations.

Methods: Participants in this preliminary study are youth ages 12-18 years with chronic tics (N = 9 to date; n = 6 males) who completed a 1) clinical assessment, 2) brain MRI to functionally localize SMA, and 3) single session of 1 Hz or sham rTMS over SMA paired with pre-post administration of the TST. Contexts assessed in the TST included 3 min conditions of free to tic, instructions to suppress tics, and instructions to suppress tics paired with contingent reinforcement for tic-free periods. Conditions were randomly repeated twice each using a multi-element withdrawal design, and dependent variables included tic frequency (tics per min) and participant self-rated premonitory urge intensity (on a scale of 0-8). Tic frequency was determined by a video coder blind to stimulation and TST conditions, and all videos were double coded for inter-rater reliability purposes. Preliminary analyses utilizing single subject analysis visual inspection procedures and Cohen's d effect size calculations (Olive & Smith, 2005) were used to identify data trends.

Results: Results indicate that sham rTMS was generally associated with little change in tic suppression, while active 1 Hz rTMS participants showed a general enhancement in tic suppression. For example, tic frequency during suppression showed greater pre-post reduction for those receiving active (mean change = 3.56 tics per min, d = .81) vs. sham rTMS (mean change = 0.38 tics per min; d = .37). Further, premonitory urge intensity during suppression showed greater pre-post reduction in active rTMS (mean change = 2.88, d = 1.77) compared to sham (mean change = 0.38, d = 0.19). Emerging patterns of heterogeneous response were also identified within the active rTMS group. Youth who were already able to suppress (i.e., near-zero tic frequency in TST suppression contexts pre-rTMS) had no noticeable change. Most notably, those who had difficulty suppressing before rTMS showed greater tic suppressibility following rTMS. Post-rTMS, several youth showed equal tic frequencies across suppression contexts, suggesting enhanced suppression without the need for a supporting reward contingency.

Conclusions: Overall, these preliminary data support methodology feasibility, sensitivity to detect clinically meaningful change across different contexts following acute rTMS administration, and ability to detect patterns of individual response. The results support the potential promise of this method for youth with the least ability to suppress tics, the group in greatest need of new clinical interventions.

Keywords: Tourette Syndrome, Tic Disorders, Repetitive Transcranial Magnetic Stimulation (rTMS), Neuromodulation, Adolescent

Disclosure: Nothing to disclose.

M48. Biotypes Defined by Topological Data Analysis Distinguish Adolescent Suicidality More Precisely Than Depression Diagnosis

Jessica Nielson, Kathryn Cullen*

University of Minnesota Medical School, Minneapolis, Minnesota, United States

Background: Depression is a complex disorder that commonly emerges during adolescence. Traditional approaches investigating the biology of depression using diagnostic criteria have been hampered by inconclusive results, potentially due to significant biological heterogeneity associated with this syndrome. Novel strategies are needed to parse the heterogeneity and identify biologically meaningful subgroups in order to tailor treatment around that biology. Machine learning approaches are taking center stage in the age of computational psychiatry as promising tools to aid in our understanding of complex neuropsychiatric disorders. The present study leverages existing data from a completed, multi-modal study of adolescents with and without major depressive disorder (MDD) and applies a novel computational strategy with the goal of generating new hypotheses about precision treatment targets for adolescents to aid in future clinical trials and treatment decision support for adolescent MDD. We hypothesized that this approach would reveal a biologically-based stratification of adolescents that would be capable of guiding the design of personalized interventions.

Methods: Data from 122 adolescent males and females aged 12-20 years (82 patients with MDD and 40 age-matched healthy controls) were examined. Data included basic demographics and diagnostic information, depression severity, multiple measures of other psychopathology, cognitive performance for decision making and attention, heart rate variability, assessment of stress through cortisol values, and neuroimaging data. The neuroimaging data included structural information (cortical thickness and brain volume derived from FreeSurfer processing of high-resolution T1 images), functional MRI results (amygdala responses to negative stimuli) and resting-state functional connectivity metrics within key networks of interest. Data were analyzed using an emerging big-data tool known as topological data analysis (TDA) that combines methods of algebraic topology and geometry to derive a multidimensional network of data that can be used in combination with standard machine learning approaches to cluster patients based on health metrics. Although the original study was designed to examine biological differences between adolescents with MDD versus controls, based on the emerging understanding that MDD diagnosis may not be the most accurate strategy for parsing biological data, we did not include MDD diagnosis or symptoms to define the network in the TDA analysis. Rather, the network was defined by brain structure and function, autonomic function, cortisol responses, cognitive performance, and other (non-MDD) psychopathology measures. Patients were clustered using a Norm Correlation metric combined with Multidimensional Scaling (MDS) set at a resolution of 30 and a gain of 3.0 to render a network topology with approximately 2-3 patients per node to maximize the distribution of heterogeneity across the resulting network. To better understand the clusters of patients that were identified and to generate new hypotheses for treatment targets, we examined how biological and behavioral variables differed between clusters of patients using the Kolmogorov-Smirnoff (KS) test.

Results: Several clusters emerged from the TDA, with a large cross-shaped network topology that clustered the majority of the adolescents into 108 connected nodes (N = 97). Smaller separate clusters emerged, one with 9 nodes (N = 11), one with 3 nodes (N = 3), and multiple individuals that were not connected to any other groups (N = 11). Subsequent analyses focused on the large network that contained 97 adolescents. Within this larger network, 4 subgroups were identified that showed distinct differences between domains. Between the top and the bottom clusters of the larger network, adolescents differed significantly in cortical gray (KS = .97, p < .0001) and white matter volume (KS = .88, p < .0001) and suicidality (KS = .81, p < .0001), with less of a significant difference in total MDD symptoms (KS = .58, p = .009). Between the left and right clusters of the network, adolescents were significantly different on measures of cognitive function related to decision making (KS = .94, p < .0001) and attention (KS = .94, p < .0001), and heart rate variability (KS = .79, p = .001). In contrast, the diagnoses of the adolescents were distributed throughout the network, suggesting that while these clusters were driven by important clinical and biological information, they were not driven by diagnosis.

Conclusions: Here we provide proof of concept for a novel machine learning tool to cluster adolescents based on cognitive

function, psychopathology, neuroimaging, and heart rate variability, as opposed to standard DSM diagnoses for MDD. Our findings suggest relationships between suicidality and brain structure may be independent of relationships between cognitive function and heart rate variability in adolescents. Further, biologically-driven clusters separated adolescents with suicidality from those without, even though suicidal symptoms weren't included in the algorithm. With this approach, we are beginning to hone in on precise hypotheses about subgroups of adolescents characterized by features such as suicidality, impaired heart rate variability, abnormal brain structure, and cognitive impairment that may guide development of future biologically-motivated treatments that are personalized to the adolescents' clinical and biological profile.

Keywords: Machine Learning Clustering, Adolescent Depression, Suicidality, Computational Psychiatry

Disclosure: Nothing to disclose.

M49. Prenatal Fatty Acid Levels Longitudinally Predict Childhood Processing Speed in a Large Population Sample

Katherine Karlsgodt, Tanja Vrijkotte, Arne Popma, Bart Peters*

University of California, Los Angeles, Los Angeles, California, United States

Background: The pre and perinatal environment, including availability of critical nutrients, can have a profound impact on offspring across development. In particular, fatty acids have been associated with a range of developmental outcomes including cognitive variability and neuropsychiatric symptoms. An early deficiency in long-chain polyunsaturated fatty acids (LC-PUFAs), which play an essential role in early neurodevelopment, may have long term impacts on cognitive function. Here, we investigated the association of prenatal LC-PUFA biostatus, specifically, the ratio of omega-6 to omega-3 fatty acids, to childhood cognitive function at age 5-6 years. We specifically examined processing speed, as it may be a core cognitive process that can have substantial effects on other downstream higher-level cognitive functions and it is impaired in schizophrenia.

Methods: Our participants were children from the Amsterdam Born Children and their Development Study (Amsterdam-ABCD) birth cohort. We selected participants who had both prenatal fatty acid data along with childhood cognitive function data ($n = 1793$) as measured with the Amsterdam Neuropsychological Tasks (ANT) battery, specifically the Baseline Speed (BS) task. Regression analyses were employed, predicting processing speed and response stability with omega-6 and omega-3 fatty acid levels, adjusted for potential confounders.

Results: We found that both the prenatal omega-6/omega-3 ratio as well as omega-6 and omega-3 fatty acid levels separately significantly predicted performance on the cognitive measures. Specifically, we found significant relationships between response speed and omega-6/omega-3 ratio ($p = .002$), such that a higher omega-6/omega-3 ratio predicted higher (slower) processing speed. When we looked at the individual components of this ratio, we found that total omega-3 levels showed a significant prediction of processing speed, such that a higher percentage of omega-3 predicted lower (faster) processing speed ($p = .005$). Further, total omega-6 percentage significantly predicted processing speed such that higher levels of omega-6 were associated with slower processing speed ($p < .0001$). We also looked at individual PUFAs, finding significant relationships between the omega-3 fatty acids EPA ($p = .008$), ALA ($p = .004$), and DHA (.018), as well as the omega-6 fatty acid AA ($p = .027$) but not LA.

Conclusions: These findings indicate that prenatal fatty acid levels may be one potential factor that can contribute to later variability in cognitive function. Furthermore, fatty acids are of interest, as they have been linked to a number of neuropsychiatric disorders, including schizophrenia. Taken together with findings of early childhood cognitive deficits in schizophrenia, this indicates that early exposure to fatty acids may be an important developmental factor to consider.

Keywords: Cognition, Fatty Acids, Prenatal, Brain Development, Nutrition

Disclosure: Nothing to disclose.

M50. Sub-Clinical Brain Failure: Identification of High Risk Mortality Patients and Prediction of Patient Outcomes Associated With Delirium With a Novel Bispectral EEG Device

Gen Shinozaki, Nicholas Bormann, Aubrey Chan, Kasra Zarei, Nicholas Sparr, Mason Kilsares, Lindsey Gaul, Gabrielle Duncan, Sydney Jellison, Kumi Yuki, Sayeh Sabbagh, Matthew Karam, Nicolas Noiseux, Eri Shinozaki, Sangil Lee, John Cromwell*

University of Iowa, Iowa City, Iowa, United States

Background: Delirium is common and dangerous yet is underdiagnosed and undertreated due to lack of effective screening methods. Undetected delirium in hospitalized elderly patients substantially increases mortality, length of stay (LOS), and post-discharge institutionalization rates. In addition to delirium being a very dangerous condition for patients, the cost associated with delirium are immense. Annual financial losses due to delirium are estimated to be over $150 billion in the U.S. alone. To address this issue, we aimed to develop an innovative, noninvasive, user-friendly, objective EEG device with bispectral electroencephalography (BSEEG) for mass screening of delirium. Also, we aimed to test if such objective EEG device can predict patient outcomes related to delirium, such as hospital LOS, discharge disposition, and mortality.

Methods: Study subjects were recruited from the University of Iowa Hospitals and Clinics upon admission and assessed for the presence of delirium with the Confusion Assessment Method for ICU (CAM-ICU), and Delirium Rating Scale (DRS). For enrolled subjects, we obtained 10 minutes of EEG recording with two channels from a handheld EEG device twice a day during their hospital stay. We analyzed those raw EEG data by converting it to digital signals with spectral density analysis and an additional algorithm to differentiate the two groups with and without delirium; we also compared their outcomes including hospital LOS, discharge to nursing home, and mortality.

Results: From January 30, 2016, to October 30, 2017, 820 patients were approached and a total of 428 patients were enrolled in the study. Three hundred thirty-seven out of 428 patients were 55 yo or older, and 274 out of 337 had BSEEG scores available for analysis. In some cases, BSEEG scores could not be calculated due to poor signal quality. In the group 55 yo or older, 37.2% of patients were categorized as delirious. The study population was also independently divided into two groups—BSEEG-positive, indicative of more low-frequency components in their brain waves; and BSEEG-negative, indicative of less low-frequency components in their brain waves—based on a threshold to differentiate patient outcomes as described in the following section.

Data from 274 subjects was analyzed to establish an association between BSEEG score and delirium status. Logistic regression showed significant association between delirium category and BSEEG score ($P = 6.39 \times 10–6$, unadjusted; $P = 1.22 \times 10–5$, adjusted for age, gender, and CCI).

BSEEG Score and Patient Outcomes: To test the usefulness of the BSEEG score to predict patient outcomes, we used outcome data available from 274 subjects who were 55 yo or older to investigate the association of BSEEG scores obtained at the time of enrollment with patient outcomes commonly affected by delirium. Specifically, we assessed hospital LOS, discharge disposition, and mortality. First, LOS and BSEEG scores were significantly correlated ($P = 0.00099$, unadjusted; $P = 0.0014$, adjusted for age, gender and CCI). This indicates that a higher BSEEG score coincides with an increase in a patient's LOS.

Second, we compared the discharge outcome and BSEEG score. When BSEEG was compared between those who were discharged to their home and those discharged not to home including death during hospitalization, a higher BSEEG score was significantly associated with discharge not to home ($P = 0.0038$, unadjusted; $P = 0.0090$, adjusted for age, gender, and CCI). Third, when we analyzed the hazard ration (HR) for mortality controlling for age, gender, and CCI, the HR based on 1 SD change of BSEEG score was 1.44 (1.12 to 1.84, $P = 0.004$). Even after controlling for clinical delirium status in addition to age, gender, and CCI, the HR based on BSEEG score remained significant at 1.35 (95% confidence interval = 1.04 to 1.76, $P = 0.025$). Further, we assessed if there was also a correlation between groups based on BSEEG scores and all-cause mortality at the end of our study period in patients in our dataset, because association between delirium and mortality has been shown previously in the literature. We first assessed overall survival rates among our study participants, which showed differences between those with and without delirium ($P = 0.0038$). Second, we tested a group difference based on a BSEEG cut-off score and confirmed that the BSEEG-positive group showed worse survival compared to the BSEEG-negative group ($P = 0.0032$).

We further analyzed the survival data to detect differences among delirious cases and non-delirious controls as a function of group differences in BSEEG scores. Delirious cases with a positive BSEEG score showed the highest mortality. In contrast, those patients categorized as delirious but with a negative BSEEG score had lower mortality, similar to that of non-delirious controls with a negative BSEEG score. Moreover, those thought to be non-delirious controls based on results of clinical assessment but with a positive BSEEG score had a higher mortality, even compared to those patients with clinical delirium but with a negative BSEEG score.

Conclusions: The BSEEG algorithm was used to differentiate a patient population with prolonged hospital LOS, discharge not to home, and also poor survival. This result indicates that among those who we cannot clinically identify as delirious, there are certain populations showing EEG changes who are at high risk of poor survival. If we can identify this population appropriately with our BSEEG method and intervene properly, those lives can be saved.

Keywords: Mortality, Delirium, Electroencephalography
Disclosure: Predelix Medical LLC, Stock / Equity

M51. Signaling Pathway Screening to Identify Neuroinflammatory Mediators of Ion Channel Dysfunction

Paul Wadsworth, Oluwarotimi Folorunso, Nghi Nguyen, Aditya Singh, David Brunell, Clifford Stephan, John Allen, Fernanda Laezza*

University of Texas Medical Branch of Galveston, Galveston, Texas, United States

Background: Neuronal firing is a highly regulated process that depends on the stability of ion channel macromolecular complexes, which in turn rely on the integrity of cellular signaling networks. In neuropsychiatric disease states, the cellular milieu of neurons is skewed toward pro-inflammatory mediators that may have drastic physiological consequences on neuronal firing, especially in subpopulations of neurons vulnerable to disease such striatal medium spiny neurons (MSNs). In these cells, intrinsic firing depends upon the voltage-gated Na + (Nav) channel macromolecular complex. This complex is made up of multiple Nav channel regulators including fibroblast growth factor 14 (FGF14), which we have previously demonstrated affects the biophysical properties and cellular targeting of the Nav channel. However, the specific upstream signaling events that control this complex have not been well characterized. Here, we posited that the cytokine tumor necrosis factor-α (TNF-α), which has been previously shown to modulate Nav1.6 firing, could play a role in regulating the FGF14 interaction with the regulatory C-tail of Nav1.6 through Ser/Thr and/or Tyr kinase phosphorylation events downstream of the TNF receptor. This pathway might provide a mechanistic basis of selective neuronal vulnerability in MSNs and open the door for rapid screening and discovery of signaling pathways that may be implicated in reward-related disorders.

Methods: LCA constructs were subcloned into vectors under the control of G418 and puromycin and linearized prior to insertion in HEK293 cells for the development of a double stable cell line. We employed LCA for the HTS of six compound libraries available in 384-well formats: the Custom Clinical Collection, National Cancer Institute, Prestwick Chemical Library, Selleck Bioactive Collection, Sigma-Aldrich LOPAC Collection, and the UT Austin Combined Kinase Collection.

Results: To characterize the specific cellular signaling mechanisms that regulate the Nav channel complex, we conducted an in-cell HTS against the FGF14:Nav1.6 complex with LCA. We developed a double-stable HEK293 cell line expressing both CLuc-FGF14 and CD4-Nav1.6-NLuc and validated this line using control treatments and comparison with transient transfection. We subsequently fine-tuned the assay for 384-well plates by optimizing multiple parameters including cell density, media volume, incubation times, and enhancer/inhibitor controls to achieve a Z-score of ≥ 0.5, signifying a viable in-cell assay. Using homogeneously suspended cells in 40 μL of serum-free media and TNF-α and MNS as the enhancing and inhibitory controls, respectively, a Z-score of 0.6-0.7 was obtained for each plate. Following assay development, we screened > 4,500 small molecules targeting known mediators of cellular signaling. Compound libraries were screened in duplicate, and an overall Z-score was calculated for each plate to ensure that assay rigor was maintained across the screening. Compound toxicity was assessed in parallel using the CellTiter-Blue Cell Viability Assay, and effects on luciferase alone were assessed via counter-screening against full-length luciferase reconstituted in HEK293 cells. Following removal of these potential false-positives, compounds were ranked by a combination of %maximal luminescence and individual Z-scores, which were calculated based on the mean and SD of its respective plate controls (0.3% DMSO). Preliminary hits were identified using cut-offs of $Z \leq -3.5$ and ≥ 50% reduction in complex formation for inhibitors and $Z \geq 2$ and ≥ 130% increase in complex formation for enhancers. Hits were then selected based on potency as assessed by an 8-point dose response. Rationally guided hit assessment revealed an over-representation of structurally diverse compounds against two known mediators of TNF-α signaling, JAK2 and Src tyrosine kinases, including TG101348 ($IC50 = 12.3$ μM), WP1066 ($IC50 = 4.1$ μM), Bosutinib ($IC50 = 9$ μM), and Quercetin ($IC50 = 5.7$ μM). Bioinformatic analysis revealed a probable JAK2 phosphorylation motif in FGF14 at Y158, which is a previously identified hot-spot at the FGF14:Nav1.6 channel interface. We are currently validating these findings using a variety of biochemical, biophysical and electrophysiological assays to evaluate the impact of TNF-α signaling on intrinsic firing of MSN.

Conclusions: We have developed a rigorous assay capable of rapidly screening compounds against PPI in the cellular milieu, and this tool could be adapted to study other protein pairs implicated in neuropsychiatric disorders. Furthermore, our screening of kinase inhibitors has identified JAK2 as a key regulator of the Nav complex, which may contribute to vulnerability to depression and mood disorders in MSNs in states of neuroinflammation. Altogether, our results for the FGF14:Nav complex demonstrate that this assay is a powerful new tool capable of identifying potentially dysfunctional signaling pathways that could be targeted for therapeutic development in neuropsychiatric disorders.

Keywords: Neuroinflammation, High-Throughput, Signaling networks, Ion Channels, Protein:Protein Interactions

Disclosure: Nothing to disclose.

M52. Blood-Brain Barrier Dysfunction and Autoantibodies Promote Amyloid Internalization in Early Alzheimer's Disease Pathogenesis With Diagnostic and Therapeutic Implications

Eric Goldwaser, Nimish Acharya, Robert Nagele*

University of Maryland Medical Center / Sheppard-Pratt, Baltimore, Maryland, United States

Background: Aging related neurocognitive disorders such as Alzheimer's disease (AD) are poorly understood from a pathophysiologic standpoint. Moreover, treatment efforts have remained limited to symptomatic management, and proven minimally effective at delaying the progression of the disease when it is clinically diagnosed. Recently, antibody subsets, namely natural autoantibodies (aAb), have been shown to be effective blood-borne biomarkers able to accurately detect mild-moderate AD. Their mechanistic role in early AD, including blood-brain barrier (BBB) dysfunction and amyloid plaque development, as well as utility at diagnosing pre-symptomatic stages are of extreme importance in helping to define new therapeutic targets.

Methods: To explore features of early AD pathophysiology, immunohistochemistry (IHC) slides were prepared from various human cortical sections, including entorhinal and hippocampal tissue, in AD, disease- and age-matched controls. For BBB breakdown and antibody leakage experiments, a traditional secondary antibody was foregone, and biotinylated anti-human IgG was used as a primary antibody, detecting endogenous immunoglobulin already present in the native tissue. To study the dynamic sequences observed on IHC, a cell culture model was adapted using SH-SY5Y cells following established protocol for their maintenance, growth, and differentiation. Immunofluorescence microscopy assessed the internalization and subcellular trafficking of Aβ42 and various surface proteins co-administered with human IgG aAb species. Cultures were treated with 100 nM Aβ42, reproducing physiologic concentrations, for up to 72 h. Other dishes were treated with Aβ42 and human serum obtained from young-aged non-demented control (YC), old-aged non-demented control (OC), and AD patient at 1:50 dilutions. Lastly, human protein microarrays were employed to assay these aAbs as diagnostic biomarkers for early-stage AD detection and disease staging, as well as identifying individual proteins that may be targets of amyloid burdening sequences. Sera from 50 early AD subjects (with confirmed low CSF Aβ42), along with 186 other samples from mild-moderate AD, Parkinson's disease, multiple sclerosis, breast cancer, and healthy controls were compared, and candidate biomarkers and test utility were evaluated with Random Forest and receiver operating characteristic (ROC) curve analysis.

Results: IHC experiments showed that blood-borne, brain-reactive aAbs bind selectively to pyramidal neurons and trigger pathological changes, including intraneuronal accumulation of A□42 and expansion of the lysosomal compartment. Concurrent findings included BBB breakdown and leakage of serum emanating radially in a cloud-like morphology. Neuronal surface protein α7nAChR, known Aβ42 high-affinity target, co-localized in consecutive IHC slides with CathepsinD, a lysosomal marker, as well as with IgG-positive intracytoplasmic granules throughout the main axonal process and dendritic tree.

We then investigated aAb-mediated receptor endocytosis following BBB breakdown in a cell culture model better able to capture the neuronal dynamics at play. Co-localization of IgG, α7nAChR, and Aβ42 were temporally related to the early endosomal marker, Rab11, and at later time points to the lysosomal marker, LAMP-1. Lastly, results using monovalent F(ab) antibody fragments generated from purified IgG in AD patient serum suggest that endocytosis of Aβ42 is triggered by the cross-linking capacity of neuron-binding aAbs. When tracked over time, these coupled events showed aAb-mediated endocytosis and accumulation of exogenous surface protein, IgG, and Aβ42 within the lysosomal compartment, consistent with the AD brain IHC correlates.

The cell culture experiments showed that this co-localization represented the retrograde transport of an endocytic process attempting to digest Aβ42. The extent of Aβ42 internalization needed to cause cellular damage occurred when coalesced Aβ42 granules were rendered indigestible, under conditions of co-administered purified IgG fractions from AD sera. By cleaving the purified aAbs into monovalent F(ab) fragments, basal internalization rates of Aβ42 were not able to induce the same degree of neuronal damage. However, when the fragments were treated with a secondary F(ab) antibody and cross-linking capabilities restored, internalization rates were rescued, and cellular death again ensued.

Lastly, the microarray data generated a panel of the top 50 autoantibody biomarkers necessary to detect early AD and diagnosed with 100 percent overall accuracy (AUC = 1; sensitivity = 100%; specificity = 100%; PPV = 100%; NPV = 100%) from later stages of AD, Parkinson's disease, multiple sclerosis, breast cancer, and age-, disease-, and gender-matched controls.

Conclusions: These results suggest that BBB breakdown and subsequent leakage of Aβ42 and brain-reactive aAbs act together to drive amyloid plaque development in early AD. Furthermore, these aAbs can be identified in the sera and stratified against phenotypic states of disease, thus allowing for a novel diagnostic capable of differentiating and staging AD, even at the preclinical phases with perfect accuracy. Overall, the data submit aAbs and BBB compromise may be an important risk factor for the initiation and progression of AD as well as other neurodegenerative diseases.

Keywords: Translational Biomarker Development, Preclinical Alzheimer's Disease, Blood-Brain-Barrier, Antibody

Disclosure: Nothing to disclose.

M53. Depressive Symptoms, Cortical Amyloid, and Cognitive Decline in Older Adults

Jennifer Gatchel, Jennifer Rabin, Rachel Buckley, Joseph Locascio, Yakeel Quiroz, Patrizia Vannini, Rebecca Amariglio, Dorene Rentz, Nancy Donovan, Deborah Blacker, Keith Johnson, Reisa Sperling, Gad Marshall*

Harvard Medical School, Massachusetts General Hospital, McLean Hospital, Boston, Massachusetts, United States

Background: Previous work has shown a cross-sectional association between depressive symptoms and in vivo cerebral tau (FTP

positron emission tomography (PET) imaging) in cognitively normal older adults. While this and other evidence support a relationship between depressive symptoms and in vivo measures of Alzheimer's Disease (AD) pathology, it remains unclear how depressive symptoms together with cortical amyloid (Pittsburgh Compound B (PiB) PET) relate to cognitive decline in older adults.

Methods: To address this question, 279 cognitively normal older individuals (males and females) from the Harvard Aging Brain Study underwent annual assessment with the Geriatric Depression Scale (GDS) and the preclinical Alzheimer's Disease Cognitive Composite (PACC), as well as baseline amyloid (Pittsburgh Compound B (PiB)) PET imaging; average follow up time was 4.4 years. A mixed model was run with dependent variable PACC, a random intercept and slope for each subject, and fixed predictors: baseline PACC, baseline GDS and amyloid, baseline GDS X amyloid interaction, time, the interaction of predictors with time, and covariates sex, baseline age, and education. To investigate longitudinal depressive symptoms, time-varying GDS was entered into the model in place of baseline GDS.

Results: In the model with baseline GDS, greater age ($p = 0.0001$), greater amyloid (0.002), and lower baseline PACC ($p < 0.0001$) were associated with PACC decline, but baseline GDS did not predict PACC decline. In the time-varying GDS model, higher GDS was associated with worse PACC ($p = 0.0003$), but only at amyloid levels above 1.1.

Conclusions: Greater depressive symptoms over time in the setting of elevated amyloid (PiB PET) are associated with worse cognition in older adults who may be at risk for AD. Together, findings support the potential prognostic utility of depressive symptoms together with AD pathology in identifying individuals at risk for cognitive decline.

Keywords: Depression, Alzheimer's Disease, Cognitive Decline, Amyloid, PET Imaging

Disclosure: Nothing to disclose.

M54. Multiplexed, Quantitative Proteomic Analysis of Cynomolgus Monkey Tissue as Well as Tau + and TDP43 + Behavioral Variant Frontotemporal Dementia Human Tissue to Enable Biomarker Discovery and Development

Abstract not included.

M55. Efficacy and Safety of Dasotraline in Adults With Binge-Eating Disorder: A Randomized, Double-Blind, Fixed-Dose Trial

*Robert Goldman, James Hudson, Susan McElroy, Carlos Grilo, Joyce Tsai, Ling Deng, Justine Kent, Antony Loebel**

Sunovion Pharmaceuticals, Inc., Fort Lee, New Jersey, United States

Background: Dasotraline is a potent inhibitor of human dopamine and norepinephrine transporters (uptake IC50 of 3 nM and 4 nM, respectively) with a PK profile characterized by slow absorption (tmax, 10-12 h), and a long elimination half-life (t½, 47-77 h) resulting in stable plasma concentrations over 24 h with once-daily dosing. In a previous placebo-controlled, flexible-dose trial, dasotraline (4-8 mg/d) demonstrated significant efficacy in the treatment of binge eating disorder (BED). The aim of this replication study was to evaluate efficacy and safety of fixed doses of dasotraline (4 mg/d and 6 mg/d) in the treatment of patients with moderate to severe BED.

Methods: Patients meeting DSM-5 criteria for BED were randomized to 12 weeks of double-blind treatment with fixed doses of dasotraline (4 mg/d and 6 mg/d), or placebo. All patients randomized to dasotraline received 4 mg/d during the first 2 weeks, after which those assigned to the higher dose group received 6 mg/d. The primary efficacy endpoint was change in the number of binge-eating days per week at week 12. Secondary efficacy endpoints included change on the Binge Eating Clinical Global Impression of Severity (BE-CGI-S), the Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) and the proportion of patients who achieved 4-week cessation of binge eating episodes. Efficacy was assessed using a mixed model for repeated measures analysis estimating the least squares (LS) mean difference in change from baseline between groups on the intent-to-treat (ITT) population. To control the overall type I error rate, a pre-specified sequential testing procedure was used.

Results: A total of 491 patients were randomized, of whom a total of 485 were in the ITT population (dasotraline 6 mg/d ($N = 162$), 4 mg/d ($N = 161$), or placebo ($N = 162$). Baseline characteristics for the combined patient sample: female, 84%; mean age, 37.6 years, mean number of binge eating days per week, 4.22; mean CGI-S score, 4.4; mean BMI, 34.5 kg/m2. At week 12, treatment with dasotraline was associated with significant reduction in number of binge eating days per week in the 6 mg/d group vs. placebo (LS mean -3.47 vs. -2.92; difference [SE], -0.55 [0.19], $P < 0.01$), and non-significant improvement in the 4 mg/d group vs. placebo (LS mean: -3.21; difference, -0.29 [0.19], $P = 0.12$). Outcomes on secondary measures and p-values (not adjusted for multiplicity) generally also favored dasotraline. Changes on the BE-CGI-S for the 6 mg/d and 4 mg/d groups vs. placebo were -2.27 vs. 1.77 ($P < 0.01$), and -2.13 vs. 1.77 ($P < 0.05$), respectively. On the YBOCS-BE scores for the 6 mg/d and 4 mg/d groups the changes were -15.2 vs. -11.8 ($P < 0.01$) and -14.1 vs. -11.8 ($P < 0.05$), respectively. The proportion of patients who achieved 4-week cessation of binge eating episodes was 34.0%, 33.5% and 30.2% for the dasotraline 6 mg/d ($p = 0.64$), dasotraline 4 mg/d ($p = 0.80$), and placebo groups, respectively. The most common adverse events (incidence ≥ 5% and ≥ 2-times placebo) on dasotraline 4 mg/d and 6 mg/d vs. placebo were insomnia (40.1% and 29.8% vs. 13.5%), dry mouth (26.5% and 21.1% vs. 6.7%), decreased appetite (16.0% and 9.3% vs. 6.7%), nausea (13.0% and 11.8% vs. 5.5%), anxiety (13.6% and 8.7% vs. 2.5%), decreased weight (7.4% and 8.7% vs. 1.2%), constipation (6.8% and 3.7% vs. 1.8%), and dizziness (5.6% and 5.0% vs. 1.8%). Discontinuation due to an adverse event occurred in 14.2% of patients on dasotraline 6 mg/d, 8.7% on dasotraline 4 mg/d, and 1.2% on placebo. Changes in systolic and diastolic blood pressure were minimal. Mean baseline to endpoint change in supine heart rate on dasotraline 6 mg/d and 4 mg/d vs. placebo was + 6.2 bpm and + 4.8 vs. + 0.2 bpm.

Conclusions: In this double-blind, 12-week, placebo-controlled, fixed-dose study, treatment with dasotraline 6 mg/d (but not 4 mg/d) was associated with a significant reduction in the frequency of binge eating days per week. Both dasotraline 6 mg/d and 4 mg/d treatment groups were associated with reduced obsessional thoughts and compulsive behaviors and greater overall improvement in symptom severity. Dasotraline was safe and generally well-tolerated at both doses; most common adverse events were insomnia, dry mouth and headache.

Keywords: Binge Eating Disorder, Dasotraline, Efficacy, Safety, Randomized Double-Blind

Disclosure: Sunovion, Employee

M56. Increased Functional Connectivity Between Ventral Attention and Default Mode Networks in Adolescents With Bulimia Nervosa

Mirjana Domakonda, He Xiaofu, Lee Seonjoo, Marilyn Cyr, Rachel Marsh*

Hartford Hospital / Institute of Living, Hartford, Connecticut, United States

Background: Bulimia nervosa (BN) is characterized, in part, by excessive concern with and selective attention to body shape and weight (shape/weight). Such negative self-referential thoughts contribute to the maladaptive pattern of food restriction, binge eating, and purging that defines BN. Behavioral data suggest that BN pathology is associated with excessive attention to self- and shape/weight-related stimuli, but the ventral attention (VAN) and default mode (DMN) networks that support attentional and self-referential processes are understudied in BN. We assessed whether altered functional connectivity within and between the VAN and DMN contributes to such excessive concerns in adolescents with BN, early the course of the disorder.

Methods: Resting-state functional magnetic resonance imaging scans (GE Signa 3 T) were acquired from 33 BN and 37 healthy comparison (HC) adolescents (aged 12 to 21 years), group-matched by age, race, and body mass index. Seed-based region-of-interest (ROI) analyses were performed via the CONN toolbox to examine group differences in functional connectivity within and between the VAN and DMN. ROIs for the VAN, including the ventrolateral prefrontal cortex (VLPFC), right posterior superior temporal gyrus (pSTG) and ventral supramarginal gyrus (rvSMG) were selected based on a prior study of this network. ROIs for the DMN were defined a priori in the CONN toolbox. Results were age-adjusted and thresholded at a false discovery rate (FDR) of p-FDR $< .05$. Spearman's correlations were performed to explore associations of VAN-DMN connectivity with BN symptoms, body shape/weight concerns, and sustained attention on the Continuous Performance Test (CPT).

Results: Compared to HC adolescents, those with BN showed significantly increased positive connectivity between rvSMG and all DMN regions (p-FDRs $< .021$), as well as between VLPFC and left lateral parietal cortex (p-FDR $< .036$). Positive mean VAN-DMN connectivity was also detected in BN compared to healthy adolescents ($p \leq .003$). Within-network connectivity did not differ between groups. VAN-DMN connectivity was associated with the frequency of BN symptoms (ps $< .028$, uncorrected), and body shape/weight concerns in the BN group (ps $< .047$, uncorrected). No significant group-by-CPT interactions on VAN-DMN connectivity were detected.

Conclusions: Increased positive VAN-DMN connectivity in adolescents with BN may reflect abnormal engagement of VAN-mediated attentional processes at rest, perhaps related to their excessive attention to self-referential thoughts about body shape/weight. Future studies should investigate whether altered VAN-DMN connectivity precedes the onset of BN or arises as a result of the disorder, in hopes that these neuroimaging findings could guide the development of circuit-based targeted interventions aimed at reducing excessive body shape/weight concerns that tend to perpetuate maladaptive BN behaviors.

Keywords: Eating Disorders, Functional MRI (fMRI), Adolescence

Disclosure: Nothing to disclose.

M57. Investigating Neural Taste Discrimination in the Insula Across Adolescence and Adulthood

Marisa DeGuzman, Megan Shott, Guido Frank*

University of Colorado Anschutz Medical Campus, Aurora, Colorado, United States

Background: Investigating how taste stimuli are perceived and encoded in the brain could improve our understanding of eating disorder neurobiology. For example, previous evidence from our lab suggests that adults with either anorexia nervosa or obesity exhibit reduced taste discrimination compared to adults who are healthy or recovered from anorexia nervosa. However, there remains a gap in our understanding of what role age plays in taste discrimination. Adolescence is an important period in both normal neurodevelopment and eating disorder onset, therefore, we compared neural taste discrimination between healthy adolescents and adults within the insula, the primary taste cortex.

Methods: Study participants included a total of seventy-one healthy females with no medication use and no history of major medical or psychiatric illness. Thirty of these were in the adolescent group (mean age $= 15.2 +$ /- 1.9 y, age range $=$ 12-17 y) and forty-one in the adult group (mean age $= 26.5 +$ /- 5.4 y, age range $=$ 19-43 y). Participants rated 2 ml samples of a 1 M sucrose solution and a neutral artificial saliva solution for both pleasantness and sweetness on a 1-9 scale. During functional magnetic resonance imaging, participants received 1 M sucrose solution, neutral artificial saliva solution, or no solution (nothing). First-level contrast images were analyzed using general linear models and three contrasts of interest were computed for each subject: Sucrose-Neutral, Sucrose-Nothing, and Neutral-Nothing. Whole brain activation was compared between groups at FWE-corrected and 10 voxel threshold and parameter estimates were extracted from insula regions of interest for post-hoc group comparisons of each contrast. Multivariate Bayesian pattern analysis and cross-validation tested taste classification accuracy (i.e. neural taste discrimination) in bilateral insula. Rank transformation was applied to data that were determined non-normally distributed using the Shapiro-Wilk test.

Results: No differences in subjective taste pleasantness ratings were found between the age groups. While the groups rated the sweetness of the sucrose solutions similarly, adults rated the neutral solution significantly sweeter ($M = 1.2 +$ /- 0.6) than the adolescents ($M = 1.0 +$ /- 0.0); $t(69) =$ -2.08, $p < 0.05$. However, no group differences were found in insula classification accuracy. Further, no significant correlations were found between age and classification accuracy. The whole brain analysis (FWE-corrected, 0 voxel threshold) revealed greater overall bilateral insula and striatum activation in adolescents compared to adults across all three taste contrasts. Post-hoc analyses showed statistically significantly greater adolescent activation in bilateral insula activation for two of the taste contrasts: Sucrose-Nothing $F(6, 62) = 2.99$, $p < 0.05$; Wilk's $\Lambda = 0.775$, partial eta squared $= .225$); Neutral-Nothing $F(6, 62) = 5.02$, $p < 0.0005$; Wilk's $\Lambda = 0.673$, partial eta squared $= .327$). There was also a trend toward significantly greater activation in adolescents for the Sucrose-Neutral contrast $F(6, 62) = 2.22$, $p < 0.053$; Wilk's $\Lambda = 0.823$, partial eta squared $= .177$).

Conclusions: Results of our neural taste discrimination analysis suggest that healthy adolescents and adults discriminate the sucrose and neutral taste stimuli similarly. However, the group difference in subjective sweet taste ratings of the neutral solution, point toward potential age effects on higher order flavor perception, but this requires further investigation. The greater insula BOLD response found in the adolescents is a novel finding that suggests adolescence is associated with hyper-responsiveness to both sweet and neutral taste stimuli. Perhaps the insula desensitizes from adolescence to adulthood or it "learns" with age to discriminate the tastes, resulting in less activation later in life. While the insula contains the primary taste cortex, it is also central for interoceptive awareness and is a part of the brain's reward circuitry. Interestingly, the adolescents here also showed greater activation in the striatum in response to the taste stimuli, supporting evidence of higher reward circuit activation in adolescence. This apparent discrepancy, where taste discrimination is similar, yet overall insula BOLD response differs, raises further questions about how sensory integration may interact with the greater sensitivity that has previously been shown in adolescent reward circuitry. Future studies should aim to understand how these neural responses relate to risk for eating disorder development in healthy individuals and to current eating

behaviors in individuals with eating disorders. In addition, neural taste discrimination should later be explored in adolescents with anorexia nervosa and other eating disorders.

Keywords: Insula, fMRI, Taste

Disclosure: Nothing to disclose.

M58. Subcortical Shape Deformations in Bulimia Nervosa

Laura Berner, Zhishun Wang, Mihaela Stefan, Seonjoo Lee, Zhiyong Huo, Marilyn Cyr, Rachel Marsh*

University of California, San Diego, San Diego, California, United States

Background: Bulimia nervosa (BN) is associated with significant medical complications and psychosocial impairment, and more than half of individuals with BN do not respond to first-line treatments. Improved understanding of the neurobiological mechanisms that may promote and maintain symptoms is critical to the development of novel, targeted interventions. FMRI data suggest BN is associated with functional abnormalities in frontostriatal and frontolimbic circuits, but subcortical alterations remain relatively uninvestigated. Moreover, findings from existing studies have been mixed, likely because of small sample sizes and the inherent inability of voxel-based morphometry to differentiate effects of shape, location, and size. The current study used vertex-wise shape analyses to overcome these limitations and estimate precisely localized deformations on the surface of subcortical structures in a large sample of adolescent and adult females with BN compared with group-matched healthy controls.

Methods: High-resolution anatomical MRI scans were acquired from 62 females with full and subthreshold BN (18.73 ± 3.98 years) and 65 matched healthy controls (19.31 ± 5.71 years). A Bayesian model-based segmentation toolbox in FSL (FIRST) was used to segment each anatomical image and create vertex meshes for 15 subcortical structures (brain stem and bilateral nucleus accumbens, putamen, caudate, palladium, thalamus, hippocampus, and amygdala). Vertex indices were calculated based on the signed perpendicular distance from the surface mesh of the corresponding structure in the MNI template. Positive indices represented outward deformations on the surface of a given structure and negative indices represented inward deformations or inversions. Additionally, we computed the volume of each subcortical structure by generating a mask file in 3D volume space for each structure and multiplying the number of voxels in the mask by voxel size (mm). General linear models compared groups and assessed the significance of group-by-age interactions on the shape and volume of subcortical structures. Exploratory analyses in the BN group examined associations of the shape of each subcortical structure with illness severity in the past 28 days and illness duration.

Results: Subcortical volumes did not differ across groups, but vertex-wise analyses revealed inward shape deformations in the BN compared to HC group on the surface of anterior aspects of the lateral and medial right pallidum ($pFWE = 0.038$). Inward deformations on the right pallidum were associated with more frequent binge eating episodes ($pFWE = 0.013$) and longer illness duration ($pFWE = 0.005$), whereas inversions on the surface of right caudate and left putamen were specifically associated with self-induced vomiting. Inward deformations on the thalamus ($pFWE = 0.028$) and amygdala ($pFWE = 0.0002$) were more pronounced with advancing age in the BN group.

Conclusions: This is the first study to examine subcortical shape abnormalities in a large sample of adolescents and adults with BN. As has been observed in studies of other disease states, vertex-wise shape analyses were more sensitive than volumetric analyses, permitting detection of localized deformations on the surface of subcortical structures that comprise both reward and cognitive control circuits. Inversions detected on the ventromedial pallidal surface may contribute to altered reward sensitivity, excessive eating, and difficulties learning new goal-directed behaviors, whereas dorsal anterior lateral inversions may contribute to generalized and eating-specific disinhibition. Inward deformations on the surface of left thalamus were more pronounced in older individuals with BN but unassociated with illness duration, perhaps suggesting abnormal development of this structure. Inward deformations on the surface of right amygdala were associated with both age and illness duration, suggesting that these surface abnormalities may reflect an altered developmental trajectory, a consequence of prolonged bulimic symptoms, or both.

Keywords: Bulimia Nervosa, Subcortical Shape Analysis, Binge Eating, Basal Ganglia, Mesolimbic Circuitry

Disclosure: Nothing to disclose.

M59. Examining Interoceptive Awareness as a Differential Predictor of Eating Disorder Treatment Outcomes Across Diagnoses in a Partial Hospital Setting

Tiffany Brown, Angeline Krueger, Erin Reilly, Christina Wierenga, Walter Kaye*

UCSD, San Diego, California, United States

Background: Interoceptive awareness (IA) has received attention in the literature as a factor that may be relevant to the onset and maintenance of eating disorders (EDs). Both self-report and behavioral data suggest that individuals with EDs demonstrate alterations in IA, and that IA may relate to worse outcomes. However, IA is a multi-faceted construct, and different facets of IA may be more relevant to certain subgroups. Research testing links between IA and ED symptoms are challenging to interpret, due to the fact that popular measures of IA assess awareness of both interoceptive states and emotions. The Multidimensional Assessment of Interoceptive Awareness (MAIA) provides a nuanced assessment of various factors contributing to IA. To date, no studies have examined which MAIA subscales predict ED outcomes longitudinally, and no studies have evaluated whether these associations vary across diagnostic categories. Thus, the present study examined whether MAIA subscales accounted for treatment response, and whether effects varied across diagnoses.

Methods: Adult and adolescent patients with anorexia nervosa – restricting subtype (AN-R, $n = 171$), anorexia nervosa binge-purge subtype (AN-BP, $n = 78$), and bulimia nervosa (BN, $n = 141$), enrolled in a partial hospitalization program (PHP), completed the MAIA and the Eating Disorder Examination-Questionnaire (EDE-Q) at treatment admission and discharge. The average length of stay in treatment was $M(SD) = 83.72(60.85)$ days. The MAIA is a validated self-report instrument that assesses eight facets of interoceptive body awareness: Noticing (the awareness of one's body sensations); Not-Distracting (the tendency to not ignore sensations of pain/discomfort), Not-Worrying (the tendency to not react with distress/worry to sensations of pain/discomfort), Attention Regulation (the ability to sustain attention to body sensations), Emotional Awareness (the awareness of connection between body sensations and emotional states), Self-Regulation (the ability to regulate distress by attending to body sensations), Body Listening (listening to the body for insight), and Trusting (experiencing one's body as safe and trustworthy). The EDE-Q is a well-validated self-report measure that assesses Global eating pathology over the last 28 days, along with four subscales: Restraint, Eating Concern, Shape Concern, and Weight Concern.

Regression analyses examined whether changes in the subscales of the MAIA at admission predicted EDE-Q scores at discharge, controlling for EDE-Q scores at admission. All analyses were run separately in AN-R, AN-BP, and BN patients.

Results: Regression analyses predicting EDE-Q Global and EDE-Q Restraint scores demonstrated that for AN-BP patients, higher Noticing (p-values < .05), lower Not Worrying (p-values < .04), and lower Emotional Awareness scores at admission (p-values < .02) predicted worse outcome at discharge, while no subscales of the MAIA predicted outcomes for AN-R or BN patients. Similarly, for EDE-Q Eating Concern, in AN-BP patients, higher Noticing ($p = .04$), lower Not Worrying ($p < .001$), lower Emotional Awareness scores ($p = .02$), and lower Self-Regulation ($p = .03$) predicted worse eating concerns at discharge. For BN patients, higher Body Listening ($p = .046$) at admission predicted higher eating concerns at discharge. No subscales predicted outcome in AN-R patients. Regarding EDE-Q Shape Concern, lower Not Worrying scores ($p = .02$) predicted higher shape concerns for AN-BP patients, while lower Trusting ($p = .03$) predicted higher shape concerns for BN patients. No subscales predicted outcome in AN-R patients. Similarly, for EDE-Q Weight Concern, lower Not Worrying ($p = .001$) and lower Emotional Awareness scores ($p = .03$) predicted higher shape concerns for AN-BP patients, while subscales predicted outcome in AN-R or BN patients.

Conclusions: Findings provide support for the importance of IA in accounting for ED treatment response but suggest that the relevance of the construct to outcome may vary across diagnoses. In particular, IA as measured by the MAIA appears to have greater prognostic value for AN-BP patients as compared to AN-R or BN patients. Specifically, greater distress/worry in response to uncomfortable body sensations and lower awareness of the connection between body sensations and emotional states were the most potent predictors of poor eating disorder outcomes in AN-BP patients. These results align with previous research supporting the negative prognostic value of anxious and alexithymic symptoms in AN-BP samples and suggest that targeting these constructs may be particularly useful for improving outcome in this group. For BN patients, greater listening to the body for insight predicted higher eating concerns at discharge, which may reflect faulty interoceptive signaling in BN patients around sensations of hunger/fullness. The lack of prognostic validity for the MAIA in the AN-R sample is surprising and may reflect poor insight into interoceptive difficulties using self-report measures. Overall, findings support recent research demonstrating altered interoceptive processing in eating disorders and call for continued research examining how this construct plays a role in the etiology and maintenance of eating disorders.

Keywords: Eating Disorders, Interoceptive Awareness, Clinical Predictors, Anorexia Nervosa, Interoception

Disclosure: Nothing to disclose.

M60. Sex-Dependent Neurobiological Features of Prenatal Immune Activation via TLR7

Galen Missig, James Robbins, Emery Mokler, Christopher McDougle, William Carlezon*

Harvard Medical School, Belmont, Massachusetts, United States

Background: Epidemiological evidence indicates that immune activation during pregnancy via infection or autoimmune disease is a risk factor for neuropsychiatric illness. Work from our lab and others has demonstrated that prenatal immune can cause long-lasting behavioral and neurophysiological alterations in offspring. Previous prenatal immune activation protocols have primarily involved administration of agents to mimic infection that target subtypes of the toll-like receptor (TLR) family, a class of receptor proteins that regulate innate immune responses. As examples, TLR3 recognizes Poly I:C and TLR4 recognizees lipopolysaccharide (LPS). In this study we examined the role of TLR7 in prenatal immune activation, considering evidence that this receptor subtype is implicated in the etiology of autoimmune diseases.

Methods: We administered subcutaneous injections of the selective TLR7 agonist imiquimod (IMQ, 5.0 mg/kg) or vehicle to timed-pregnant dams (C57BL/6 J mice) on embryonic days (E) 12, 14, and 16. Over the first 13 weeks of postnatal development, we assessed the offspring on a battery of behavioral tests that include ultrasonic vocalizations (USVs), open field, social approach, reciprocal social interaction, as well as on measures of circadian activity and temperature. In a parallel set of experiments, we collected whole brain sections for microglia histology and tissue punches of the dorsal striatum for RNA-sequencing. All data were analyzed using ANOVAs and post hoc tests.

Results: Mice exposed to prenatal IMQ exhibit a behavioral phenotype characterized by decreases in anxiety-like behavior, a fragmentation of social behavior, and an alteration in USV production ($p's < 0.05$). This phenotype is readily distinguishable from those seen following prenatal activation of TLR3 and/or TLR4. On many of these measures there are significant sex differences. Additionally, mice exposed to prenatal IMQ have normal baseline locomotor activity but are hyperactive in response to various types of stimuli including the presence of a social partner, circadian cues, or gonadal hormone fluctuations ($p's < 0.05$). Prenatal IMQ exposure causes a decrease in microglia density and an increase in the number of microglia ramifications in numerous brain areas, with particularly strong effects in striatum ($p's < 0.05$). RNA-sequencing of the dorsal striatum revealed that prenatal IMQ exposure induces differential expression of hundreds of genes (adjusted $p's < 0.05$), especially those encoding synaptic components, cell adhesion molecules, and glial markers. However, there are dramatic sex differences, with virtually no overlap in differentially expressed genes between males and females.

Conclusions: Prenatal immune activation with a TLR7 agonist produces a behavioral phenotype and changes in microglia that are distinct from previous models using other TLR ligands. Underlying this phenotype is a propensity for "conditional hyperactivity", reflected by an exaggerated response to some types of internal and external stimuli. Further, genome-wide analysis of mRNA identified numerous molecular pathways affected by prenatal IMQ exposure but demonstrated profound sex differences in the directions and patterns of expression. Considered with the existing literature, our findings suggest that early immune system activation can promote various—and sometimes even opposite—developmental trajectories, depending on the type and/or pattern of TLRs activated.

Keywords: Maternal Immune Activation, Neuroimmunology, Toll-Like Receptors (TLRs), Prenatal Exposure, Prenatal Infection

Disclosure: Nothing to disclose.

M61. Genome-Wide Expression Profiling of Suicide

Giovanna Punzi, Gianluca Ursini, Leonardo Collado-Torres, Joo Heon Shin, Roberto Catanesi, Andrew Jaffe, Thomas Hyde, Joel Kleinman, Daniel Weinberger*

Lieber Institute for Brain Development, Baltimore, Maryland, United States

Background: Suicide is the 10th leading cause of death for all age group combined and is on the rise across the U.S., according to recent reports by the Centers for Disease Control and Prevention (CDC).

As suicidal ideation is a limited predictor of outcome, recent research has turned to the detection of biological markers for the development of prevention approaches. This may be especially relevant for suicides by violent means, since features of impulsive aggression represent a better predictor of self-destructive acting-out, a strong behavioral endophenotype, as well as a valuable research target, being associated with higher prevalence and lethality. In this regard, in completed suicides, the biology underling the choice of a violent method should represents a more precise feature to target in order to detect genetic signatures for the behavior at large.

Previous discovery findings and further replication suggest that differences in dorso-later prefrontal cortex (DLPFC) expression of a human-specific non-coding RNA (lincRNA) may influence emotional regulation, aggressive behavior and suicide by violent means.

Methods: In the present study, RNA sequencing (RNA-seq) data from post mortem human brain (228 Caucasian patients; adults) were examined to validate, at genome-wide level of significance, association of the lincRNA specifically with suicide by violent means, and to detect further candidates potentially related to the same signal. The sample size had the appropriate power (> 80%) to detect genes differentially expressed with a log2 fold change of 0.3. Attribution of suicidal method was determined blind to the post mortem RNA-seq data. Cause and manner of death and contributory causes or medical conditions related to death were obtained from medical examiner documents. Cases where manner of death was pending or not determined at the time of the curation, and suicidal samples with ambiguous, or indefinable means of suicide, in regard to the level of violence employed, were excluded. Among the remaining suicides, most deaths distinctly fell within the violent or non-violent category. When this was not obvious, an in-depth behavioral assessment was obtained using detailed narrative summaries based on all available sources of historical information, including interviews with next of kin. The differential expression analysis was conducted on all features, including genes, exons, junctions and expressed regions data, correcting for diagnosis, sex, age, and qSVs, a measure of RNA integrity. A gene-set enrichment analysis was also performed on the top-list differentially expressed features.

Results: At PFDR-corr. ≤ 0.05, minimal signal (i.e. ~10 expressed regions) arose when comparing non-suicide with suicide (all kinds of method); differentially expressed features further decreased when looking only at suicide by non-violent means. However, comparison between non-suicides and suicides specifically by violent means produced a remarkably greater list of features (i.e. over 1400 expressed regions). These results confirm our previous findings and suggest the engagement of specific signaling. Finally, gene-set analysis testing a catalog of immune genes on the genes differentially expressed in suicide by violent means points to the microglia, and complement, as the most enriched features ($p = 6.72e-05$ and $p = 2.67e-05$, respectively).

Conclusions: These results confirm that classifying suicide by method is key in revealing the underlying different biology.

Keywords: Brain, Suicide, RNA-seq

Disclosure: Nothing to disclose.

M62. Resting State Connectivity of the VTA Predicts Trait-Based Impulsivity in Healthy Adults

Pamela DeRosse, Toshikazu Ikuta, Ashley Moyett, Anil Malhotra*

The Donald & Barbar Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, New York, United States

Background: The Ventral Tegmental Area (VTA), a group of neurons located close to the midline on the floor of the midbrain, is the origin of the dopaminergic cell bodies of the mesocortico-limbic dopamine system. Not surprisingly, the VTA has been widely implicated in disorders characterized by impulsive behavior including addiction. To date, studies examining the relationship between VTA activity and variations in impulsive behavior have primarily focused on state-dependent activation to reward using task-based fMRI. Few studies have examined whether task-free resting state activity of the VTA is associated with variation in trait-based measures of impulsivity. Thus, the present study examined whether connectivity of the VTA during rest was associated with variation in a trait-based measure of impulsivity.

Methods: Healthy volunteers ($N = 89$; 55% female; Mage = 36.60 ± 14.53) were administered the Temperament and Character Inventory (TCI), which provides scores for four domains of temperament that are thought to be largely heritable including: novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P). Resting-state fMRI (rs-fMRI) data were collected on a GE Signa HDx 3 T scanner. The primary analyses examined the association between NS and whole brain connectivity of the VTA, defined by the Harvard Ascending Arousal Network Atlas (Edlow et al. 2012). To examine the specificity of our results to Novelty Seeking, the remaining 3 subscales from the TCI (HA, RD and P) were also examined.

Results: Novelty Seeking (NS) showed significant inverse correlations with connectivity between the VTA and the 1) right inferior frontal gyrus (IFG) (MNI: + 14 + 22 + 80; 819 voxels), 2) right superior frontal gyrus (SFG) (MNI: + 48 + 22 + 12; 448 voxels), and 3) left superior parietal lobule (SPL) (MNI:-34 -42 + 64; 404 voxels). No significant correlations were found for any other TCI domains and VTA connectivity. Post hoc regression analyses examining the contributions of the 4 traits comprising the Novelty Seeking score, including Exploratory Excitability (NS1), Impulsiveness (NS2), Extravagance (NS3) and Disorderliness (NS4), revealed that the association between VTA connectivity and Novelty Seeking was driven entirely by Impulsiveness (NS2).

Conclusions: The present results suggest that spontaneous fluctuations in BOLD signal that are synchronized between the VTA and frontal/parietal regions may be related to trait-based measures of impulsivity. These findings add to prior studies implicating task-dependent activation in the VTA to impulsivity and may provide further insight into the role of the VTA in disorders characterized by impulsive behavior.

Keywords: Impulsivity, Ventral Tegmental Area (VTA), Healthy Individuals

Disclosure: Nothing to disclose.

M63. Dexmedetomidine (dex) and Agitation – Part 2: Randomized, Placebo-Controlled, Adaptive Design Study to Determine Optimal the Dose in Healthy Elderly Volunteers and Volunteers With Mild Probable Dementia of the Alzheimer's Type

Sheldon Preskorn, Neil O'Neill, Martin Kankam, Bradley Vince, Frank Yocca*

University of Kansas School of Medicine, Wichita, Kansas, United States

Background: Dexmedetomidine (DM) is a selective alpha-2 adrenergic agonist currently marketed for intravenous (IV) administration to sedate non-intubated patients prior to and/or during surgical and other procedures and to sedate intubated and mechanically ventilated patients during treatment in an intensive care setting. IV DM has also been used for the treatment of

agitation in individuals with a range of disorders, most notably delirium. For these reasons, DM may be useful for the treatment of agitation in patients with various neuropsychiatric disorders including senile dementia of the Alzheimer's Type (SDAT) and acute psychotic disorders including schizophrenia. For these uses, an oral formulation would offer advantages over the currently approved product which is limited to IV administration. The goal of this adaptive design study was to establish the optimal dose of DM capable of producing sedation as a surrogate for an anti-agitation effect without producing any clinically meaningful effects on blood pressure (BP)/heart rate (HR).

Methods: This Phase 1 b study employed a randomized, placebo-controlled, double-blind, adaptive design. Sequential cohorts (n = 8, 6 on DM & 2 on placebo) were infused intravenously with DM. Subjects in the initial cohorts were initially healthy, elderly (55 – 75 years of age) volunteers. Subjects in later cohorts were elderly volunteers healthy except for having mild probable SDA. Both sexes were included in all cohorts. In the first cohort, the drug was administered IV over a dose range from 0.1 to 0.6 mcg/kg/hour. Each infusion rate was administered for 30 minutes. After 30 minutes, the dose was increased by an additional 0.1 mcg/kg/hour until the subject achieved a predetermined level of sedation, mild drowsiness as assessed by the Richmond Agitation-Sedation Scale (RASS) or a pre-specified reduction in BP and/or HR. The dosing rate was adjusted for subsequent cohorts based on the results of preceding cohorts. Continuous assessment was made of level of arousal, BP and HR. Plasma samples were collected before dosing and then every 15 minutes for the determination of DM concentration. Statistics were descriptive and correlational in terms of pharmacodynamic and pharmacokinetic relationships.

Results: The results of cohorts 1 and 2 established 0.3 mcg/kg/hour as the optimal starting dose. DM produced a RASS score of -1 (drowsiness) in subjects at concentration which did not produce clinically meaningful effects on BP and/or HR. The effect was evident in 11/12 subjects (92%) on DM. A RASS – 1 was seen in 1 out of 4 Individuals (25%) on placebo. The effect occurred within 30 minutes of starting the dose which produced the desired effect. For subjects on DM, the decrease in arousal persisted for 1.5-2 h, a clinically relevant duration. Plasma drug concentration correlated with dosing rate and with drug effect both within and between subjects. Gender affected drug responsiveness with males requiring twice the dose of DM compared to females. Inter-individual variability in drug concentration and effect was established and will be addressed by the development of dose titration strategies. The cohort with SDAT is being conducted at the time this poster is being submitted but should be completed in time for inclusion in the poster presented at the meeting.

Conclusions: This study also demonstrated the efficiency of an adaptive design approach to early phase CNS drug development. Specific to DM, this study found:

(1) Arousal sedation can be achieved without producing clinically meaningful effects on BP/HR.
(2) Plasma concentrations of the drug were correlated with both onset and offset of effect within a subject.
(3) There was interindividual variability is response with approximately 1/3 being sensitive, 1/3 being intermediate, and 1/3 being insensitive.
(4) There was a gender difference in drug effect (i.e., females more sensitive)
(5) With completion of the SDAT cohort, the study will determine whether there is in meaningful shift in the dose-response curve because of having this condition.

Using this information, an oral formulation is being developed for further trials in individuals with clinically meaningful agitation.

Keywords: Dexmedetomidine, Agitation, Locus Coerulues

Disclosure: Bioxcel Therapeutics Inc, Consultant

M64. Dynamic Coding of Reward and Impulsivity in Dopaminergic VTA Neurons

Tzvia Pinkhasov, Sarah Starosta, Adam Kepecs*

Stony Brook University School of Medicine, Stony Brook, New York, United States

Background: Impulsivity is a debilitating trait that characterizes numerous psychiatric conditions including attention deficit/hyperactivity disorder, bipolar disorder, and substance abuse disorders. Imaging and pharmacological studies have implicated the dopamine (DA) system in impulsivity across species, a neuromodulator also central to reward processing, motivation and learning. Because impulsive actions often occur during the process of obtaining a reward, we sought to parse out the dopaminergic contribution to impulsive actions, distinct from reward expectancy. To address this question, we recorded dopaminergic activity in ventral tegmental area (VTA) of mice, a major dopaminergic center that projects strongly to the frontal cortex and striatum.

Methods: We developed a new behavioral task to probe the relationship between reward expectation and impulsive action on a trial-to-trial basis and tease apart dopamine's roles in reward expectancy, impulsivity and attentional lapses from the ability to withhold pre-potent actions. We designed a cued-reward lick withholding task for head-fixed mice in which subjects were trained to withhold from licking during a reward-predicting auditory cue (2 s) in order to earn water reward. We used three different auditory cues that predicted three different reward sizes (big, small, none). The cue was restarted as many times as the animal licked prematurely (before the 2 second cue period was over). Thus, the duration of the tone and licking patterns provided a quantitative, trial-by-trial measure of an animal's impulsivity level. We employed fiber photometry to study the temporal profile of DA activity and record the activity of DA cells in the VTA during the cued-reward lick withholding task. We used a transgenic Cre-driver line to specifically target dopaminergic cells and have them express GCaMP6f, an activity dependent fluorophore. Fluorescence collected through an implanted optic fiber in the VTA was then used as a proxy for the average activity of the DA population. Data from 3 male and 2 female mice were collected in this study.

Results: Our behavioral results show that mice acted more impulsively in anticipation of the larger reward and were least impulsive when the cue predicted no reward ($F(4) = 25.9327$, $P < 0.01$, $\eta 2 = 0.5583$). Our photometry results demonstrate that VTA DA neurons were activated by both the reward and reward-predicting cues and their activity was proportional to reward size and value, consistent with previous observations. We found that DA activity during the reward cue was predictive of the impulsivity level (no, low, or high impulsivity) during each trial, independent of predicted reward size. Moreover, DA activity prior to the reward cue also predicted impulsivity, even before a mouse could predict the value of upcoming reward. Interestingly, we found that DA activity in the VTA during reward consumption was greater when the mouse was impulsive compared to when it was not impulsive, for the exact same reward amounts.

Conclusions: Using a novel cued-reward lick withholding task we confirmed that DA encodes reward value, in line with the previous literature. We were also able to identify for the first time that VTA DA activity predicts impulsive vs. non-impulsive states independent of reward, suggesting a direct relationship between the activity of these neurons and the ability to suppress impulsive actions. Based on these results we will be able to determine DA's

causal role in impulsivity, using optogenetic manipulation of VTA DA neurons during distinct phases of the trial based on our photometry recordings. By building on the results from classical neuropharmacology studies, we were able to tease apart how DA predicts reward and impulsivity in distinct moments during lick withholding performance.

Keywords: Dopamine, Impulsivity, Photometry, Reward-Based Decision-Making, Ventral Tegmental Area (VTA)

Disclosure: Nothing to disclose.

M65. Serotonin 1B Receptors Modulate Impulsive Action but Not Impulsive Choice via GABAergic Signaling

*Valerie Magalong, Maliha Sultana, Peter Balsam, Rene Hen, Kate Nautiyal**

Dartmouth College, Hanover, New Hampshire, United States

Background: Dysregulated impulsive behavior is found in many psychiatric disorders including substance use disorder, pathological gambling, and attention deficit hyperactivity disorder. Many studies have addressed the role of dopamine in the neural mechanisms underlying impulsivity, however, serotonin also modulates impulsive behavior. Adding to the complexity, impulsivity can be fractionated into multiple dimensions (e.g., action and choice), and is also associated with a number of related behavioral phenotypes such as reward sensitivity, sensation seeking, risky decision making, and habit formation. Our studies aim to investigate the neural circuits which modulate impulsive behavior, as well as the behavioral constructs that contribute to impulsivity.

Methods: Our previous work shows that an absence of serotonin 1B (5-HT1B) receptors in mice results in increased impulsive behavior that is due to a lack of heteroreceptor (but not autoreceptor) expression during adulthood (rather than development). Recently, our work explored the mechanisms through which 5-HT1B receptor signaling influences the neural and behavioral mechanisms of impulsivity. Impulsive action, impulsive choice, reward sensitivity, habit formation and motivation were all measured with operant paradigms following whole brain and tissue specific knockout of 5-HT1B in male and female mice. Using miniature microscopes to image calcium activity of single cells in vivo during operant behavior, we also assessed the impact of the absence of 5-HT1B receptors on circuits that are known to influence impulsivity.

Results: Tissue-specific knockouts revealed that an absence of 5-HT1B receptors on GABAergic neurons resulted in increased impulsive behavior. Behavioral screens revealed that an absence of 5-HT1B receptor expression results in increased impulsive action, and no change in impulsive choice. Additionally, the knockouts showed increased motivation for reward and increased reward sensitivity, but no effects on habit formation, compulsive behavior, or extinction. Furthermore, changes in impulsive action correlated with increases in motivation but not reward sensitivity or other behavioral measures. Current in vivo calcium imaging studies are aimed at investigating the mechanisms underlying 5-HT1B receptor-dependent inhibitory control. Our preliminary experiments have focused on imaging dopamine cell activity in a 5-HT1B-sensitive GABA-GABA-DA circuit, as well as 5-HT1B receptor positive dopamine-responsive cells.

Conclusions: Overall, our results point to a role for serotonin modulation of impulsivity via influence on GABAergic signaling. Current work is aimed at identifying the neural circuit mechanisms through which 5-HT1B receptors mediate this behavioral regulation and identifying the extent to which 5-HT1B receptors influence related behavioral phenotypes. Importantly, these effects are dependent on adult expression suggesting a potential avenue for pharmacological treatment for psychiatric disorders which include dysregulated impulsive behavior.

Keywords: Impulsivity, 5-ht1b, Neural Circuits, Reward Sensitivity, GABA

Disclosure: Nothing to disclose.

M66. Susceptibility to Stress-Induced Anhedonia is Associated With Neurotransmitter Plasticity in the Dorsal Raphe Nucleus

*Nandkishore Prakash, Davide Dulcis, Andre Der-Avakian**

University of California, San Diego, La Jolla, California, United States

Background: Anhedonia, or diminished interest or pleasure, is a core symptom of major depressive disorder and is common in other mood disorders. Stress is known to produce anhedonia in some individuals (susceptible), but not others (resilient). We hypothesized that neurotransmitter plasticity, an alteration of neurotransmitter expression in response to activity leading to changes in behavior, may play a role in susceptibility to stress.

Methods: We used the intracranial self-stimulation (ICSS) procedure to measure anhedonia in rats. Rats were trained to respond to stimulation of the posterior lateral hypothalamus, part of the brain's reward circuitry. The minimum current needed to elicit a response was defined as the reward threshold. Rats underwent 21 days of social defeat and their reward thresholds were measured daily. An increased threshold from baseline was interpreted as a sign of anhedonia. Their brains were subsequently processed for immunohistochemical detection of neurotransmitter markers. To examine effects of activity manipulation on neurotransmitter plasticity, Cre-dependent viral expression of excitatory DREADDs in a CRH-Cre transgenic rat strain was used to drive changes in neuronal activity.

Results: Susceptible rats developed anhedonia in response to chronic social defeat while resilient rats did not. Susceptible rats showed a significant 2-fold increase in number of serotonergic (TPH2 +) neurons in the ventral sub-nucleus of the dorsal raphe nucleus (DRv), compared to resilient rats or non-stressed controls. Other sub-nuclei of the dorsal raphe nucleus did not show significant differences in TPH2 + neuron number across groups. The total number of neurons in the DRv did not change across groups, indicating that a reserve pool of mature neurons in the DRv acquired serotonergic identity only in susceptible rats following chronic stress. Preliminary immunohistochemistry data suggest that the reserve pool may be a glutamatergic population in the DRv, known to co-express serotonin and project to reward regions of the brain. Preliminary results suggest that activating a GABA/CRH input to the dorsal raphe nucleus from the central amygdala reduces the number of serotonergic neurons in controls and ameliorates the effect of stress on the number of serotonergic neurons in the dorsal raphe nucleus.

Conclusions: Our results suggest that neurotransmitter plasticity occurs in the dorsal raphe nucleus in response to chronic social stress, is bidirectional, and is subject to modulation by the central amygdala. Current experiments aim to manipulate inputs to the dorsal raphe nucleus to understand how circuit activity drives transmitter plasticity and behavior. Collectively, these data reveal a potentially novel mechanism underlying susceptibility and resilience to stress-induced anhedonia.

Keywords: Social Defeat Stress, Anhedonia, Reward, Intracranial Self-Stimulation, Dorsal Raphe Serotonin Neurons

Disclosure: Nothing to disclose.

M67. Social Adversity During Adolescence Weakens Goal-Directed Decision Making in Adulthood

*Elizabeth Hinton, Shannon Gourley**

Emory University School of Medicine, Atlanta, Georgia, United States

Background: Depression is often precipitated by social adversity, particularly during adolescence, and is more prevalent in women. Identifying the durable consequences of social adversity experienced during adolescence is of great importance.

Methods: Female mice were isolated or group-housed from postnatal day (P) 31-60. At P60, all mice were re-housed into social groups to identify and correct the durable consequences of social poverty – specifically, those that present despite normalization of the social environment.

Results: A history of isolation reduced 2′,3′-Cyclic-nucleotide 3′-phosphodiesterase (CNPase) expression, consistent with prior investigations, and validating our method. Isolation during adolescence also induced hypocortisolemia early in the dark cycle, when corticosterone (CORT) should otherwise be elevated. Given that CORT tone is a key regulator of dendritic spine turnover, we investigated dendritic spine densities on deep-layer ventromedial prefrontal cortical (vmPFC) excitatory neurons, revealing spine excess. Mice with a history of social isolation were simultaneously less adept at selecting actions based on their consequences, a vmPFC-dependent function, and they developed anhedonic-like behavior. Chemogenetic silencing of the vmPFC impaired the ability of typical mice to select actions based on their outcomes but corrected decision-making abnormalities and anhedonic-like behavior in mice with a history of social isolation.

Conclusions: The social milieu sculpts prefrontal cortical development. Our findings reveal previously unappreciated neuroanatomical and functional consequences of social poverty experienced during adolescence. This information may inform strategies for improving mental health in humans.

Keywords: Juvenile, Decision Making, Habit, Depression, Cortisol

Disclosure: Nothing to disclose.

M68. Acetylcholinergic Mechanisms of Depressive-Like Behaviors Induced by Seasonally Relevant Reductions in Active Photoperiod

Zackary Cope, Maria Lavadia, Aniek Joosen, Davide Dulcis, Marina Picciotto, Yann Mineur, Jared Young*

University of California, San Diego, La Jolla, California, United States

Background: Environmental factors, such as seasonal variations in day length, can influence switching between mood states in bipolar disorder (BD) in a direction-specific manner. Consistent with sufferers of Seasonal Affective Disorder, BD patients exhibit depressive episodes as light availability decreases in Fall and Winter. Treatments seeking to maintain stability of photoperiod (timed light exposure, social rhythm therapy) can support a euthymic state (reviewed in Young and Dulcis, 2015). Pharmacological-induced increase of acetylcholine using physostigmine induces depressive-relevant behavior in mice, such as increased immobility of mice in the Forced Swim Test (FST, Mineur et al., 2013) and can induce depression in sufferers of BD (Janowsky et al. 1972). The present studies were designed to test the hypothesis that acetylcholine (ACh) signaling is necessary for the expression of depressive-like behaviors following exposure to short-active photoperiod (SAP).

Methods: Expt. 1: C57BL/6 mice were pretreated 0.03 mg/kg with the AChesterase (AChE) inhibitor physostigmine (0.03 mg/kg) or saline 30 minutes before FST followed by the muscarinic ACh receptor (mAChR) antagonist scopolamine (SCOP, 0.03, 0.05 mg/kg) or the nicotinic ACh receptor (nAChR) antagonist mecamylamine (MEC, 0.56, 0.75 mg/kg). Expt. 2: Mice were housed in SAP (19 H light: 5 H dark) for 2 weeks before FST testing, on which they received 0.03 mg/kg SCOP or 0.56 mg/kg MEC. Expt. 3: Mice were administered low doses of SCOP and MEC to assess possible additive contributions of each ACh target. Expt. 4: AAV was used to deliver human (h)AChE to increase ACh metabolism specifically in the hippocampus to determine its sufficiency to block SAP effects.

Results: Expt. 1: SCOP ($F(2,49) = 5.3$, $p < 0.01$) and MEC ($F(2,52) = 4.6$, $p < 0.05$) selectively decreased FST immobility in mice pretreated with the physostigmine. Immobility was not significantly decreased in mice pretreated with saline ($F < 1$, ns). Expt. 2: SAP significantly increased immobility in two separate cohorts ($F(1,70) = 6.5$, $p < 0.05$, $F(1,143) = 4.3$, $p < 0.05$). In cohort 1, treatment with 0.03 mg/kg SCOP reduced immobility irrespective of photoperiod condition ($F(1,70) = 6.9$, $p < 0.05$). As per our a priori planned hypotheses, it was discovered that this main effect was driven by significantly reduced immobility in the SAP only, not in the NAP mice. In cohort 2, 0.56 mg/kg MEC slightly reduced immobility irrespective of photoperiod condition, but not significantly ($F(1,143) = 2.0$, $p = 0.15$). Expt. 3: Two ineffective doses of antagonist (0.3 mg/kg MEC, 0.01 mg/kg SCOP), additively decreased FST immobility ($F(3,142) = 3.0$, $p < 0.05$), [although SAP did not significantly increase immobility in this cohort ($F(1,142) < 1$, $p > 0.05$)]. Expt. 4: Preliminary results indicate a significant virus*photoperiod interaction ($F(1,43) = 16.98$, $p < 0.01$) with hAChe decreasing immobility selectively in SAP mice. Full data and confirmatory immunohistochemistry for experiment 4 will be shown.

Conclusions: These results indicate a necessity for increased hippocampal ACh neurotransmission in the expression of SAP-exposure-induced depressive-like behaviors. Further, although nAChR and mAChRs both influence depression-relevant behaviors, antagonism of mAChRs may be more effective in reducing SAP exposure-induced depression-relevant behaviors. In sum, these results provide evidence for AChergic mechanisms in driving seasonally depressed affective states in response to shortened day lengths.

Keywords: Depression, Seasonal Affective Disorder, Bipolar Disorder, Hippocampus, Acetylcholine

Disclosure: Nothing to disclose.

M69. Microglia and Complement Activation in Chronic Stress-Induced Depressive-Like Behavior

*Talisha Davis, Babak Baban, Anilkumar Pillai**

Medical College of Georgia, Augusta, Georgia, United States

Background: Accumulating evidence suggests that the immune system plays an important role in the pathophysiology of depression. As a fundamental factor in the provocation of depression, chronic stress is associated with dysregulated immunity and subsequent inflammation. However, there is a critical need for studies that are designed to determine the role of specific components of the immune system in MDD in order to identify novel therapeutic targets. We recently reported a critical role of complement system in depression. In the present study, we examined the mechanisms involved in chronic stress-induced complement activation.

Methods: We used real time PCR to analyse gene expression whereas immunoblotting and immunofluorescence analyses for protein levels of complement components. The C1q and C3 expression were determined in mice following chronic unpredictable stress (CUS).

Results: C3 and C1qa (a key component of classical pathway) are highly expressed in the brain samples from mice exposed to CUS. CUS increased the expression of tumor necrosis factor α (TNFα, a key inflammatory molecule implicated in depression and known to induce complement activation) in microglia. Moreover, CUS-induced complement activation and depressive-like behavior were attenuated by TNF inhibition using TNFα KO mice or inhibition of microglia activation using minocycline.

Conclusions: Our findings identify the role of microglia in chronic stress-induced complement activation and depressive-like behavior in mice.

Keywords: Complement, Stress, Microglia

Disclosure: Nothing to disclose.

M70. The Involvement of SKA2, a Novel GR Interaction Partner, in Stress-Related Psychiatric Disorders

Jakob Hartmann, Nils Gassen, Harry Pantazopoulos, Claudia Klengel, Nina Dedic, Katelyn Li, Kathrin Hafner, Kenneth McCullough, Rhomberg Thomas, Torsten Klengel, Sabina Berretta, Kerry Ressler*

Harvard Medical School, Belmont, Massachusetts, United States

Background: Mood and anxiety disorders represent a major disease and social burden worldwide, but the underlying molecular mechanisms are still poorly understood. In recent years, evidence has emerged for the crucial role of genes involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, especially in the context of stress-related psychopathologies such as anxiety and depression. The glucocorticoid receptor (GR) is the main mediator of the negative feedback loop of the HPA axis in response to stress. The Ska2 gene, encoding the spindle and kinetochore associated complex subunit 2, has previously been identified as GR interaction partner. Interestingly, single nucleotide polymorphisms and epigenetic status within the Ska2 gene, as well as gene expression alterations, have been associated with posttraumatic stress disorder and suicide risk in several studies in the past. Yet, little is known about the underlying molecular mechanisms and the role of Ska2 in the brain. Therefore, we set out to further investigate the role of Ska2 in the CNS and validate it as a potential candidate gene in the context of stress-associated psychiatric disorders.

Methods: We conducted Immunohistochemistry (IHC) to study the expression pattern of Ska2 in human postmortem hippocampus and amygdala samples and in the mouse brain. Additional co-immunoprecipitation (co-IP) assays addressed whether SKA2 physically interacts with the GR in the mouse brain and in human postmortem brain samples. Moreover, we performed GR reporter gene activity (MMTV-Luc) assays and qPCR following Ska2 perturbation to investigate the receptors activity and downstream effects in neuronal cell culture. Western blot analyses were performed to examine SKA2 protein expression in basolateral amygdala (BLA) samples of individuals with bipolar depression and matched controls. Stress-induced changes in Ska2 mRNA expression in mice were investigated via qPCR following fear conditioning.

Results: IHC analyses in human postmortem hippocampus and amygdala samples revealed a prominent expression of SKA2 in Vglut1-positive, glutamatergic neurons. Moreover, co-IPs revealed a physical interaction between SKA2 and GR in the mouse brain and human postmortem samples. In addition, Ska2 knockdown in mouse neuroblastoma (N2a) cells led to significantly reduced GR reporter gene assay activity, while Ska2 overexpression resulted in the opposite effect (2-Way ANOVA, interaction: $F(14,42) = 16.38$, $p < 0.0001$). Along these lines, Ska2 knockdown led to significantly altered mRNA expression of GR target genes Fkbp5 (t-test, $T(21) = 2.683$, $p < 0.05$) and Id3 (t-test,, $T(22) = 5.762$, $p < 0.001$). Interestingly, we detected significantly increased SKA2 protein levels in the BLA of individuals with bipolar depression compared to matched controls (ANCOVA, $F = 5.83$, $p < 0.025$, $n = 14$ per group). Detailed mapping and co-labeling studies in mice also revealed a distinct pattern of Ska2 expression in neurons of the BLA, as well as in the hippocampus (HC), medio-dorsal thalamus, the paraventricular nucleus of the hypothalamus and throughout the cortex. Most of the Ska2-positive neurons also expressed the GR. Consequently, we assessed whether acute stress is able to modulate Ska2 gene expression. Using qPCR, we found dynamic changes of Ska2 mRNA expression four hours after stress (fear conditioning, 5 tone/foot shock pairings). Stressed mice showed significantly decreased Ska2 mRNA levels in the HC ($T(18) = 2.446$, $p < 0.05$, $n = 8$ (ctrl), $n = 12$ (stress)) and increased levels in whole amygdala punches ($T(15) = 2.693$, $p < 0.05$, $n = 5$ (ctrl), $n = 12$ (stress)) compared to baseline controls (home cage group).

Conclusions: Our findings reveal Ska2 as a novel GR interaction partner in brain regions associated with emotion processing and cognition. Further experiments showed that Ska2 gene expression is dynamically regulated by stress exposure and that SKA2 is able to positively modulate GR signaling and its downstream targets, providing a mechanistic link to its association with stress-related psychopathologies. Collectively, our data point to an important, and thus far unappreciated, role of Ska2 in stress-related psychiatric disorders, which is relevant to our understanding of the molecular mechanisms underlying such diseases.

Keywords: Bipolar Disorder, PTSD, Suicide, HPA axis, Glucocorticoid Receptor

Disclosure: Nothing to disclose.

M71. Omega-3 Polyunsaturated Fatty Acid Biostatus Modulates Behavioral and Neurochemical Responses to Ketamine in Rats

*Ruth Asch, Diana Lindquist, Jennifer Schurdak, Robert McNamara**

University of Cincinnati College of Medicine, Cincinnati, Ohio, United States

Background: Although the pathophysiology of mood and psychotic disorders is associated with a dysregulation in prefrontal cortex (PFC) glutamate homeostasis, little is known about pathogenic mechanisms and associated risk factors. Mood and psychotic disorders are also associated with deficits in long-chain omega-3 fatty acids including docosahexaenoic acid (DHA), and we recently reported that glutamate and DHA levels are inversely correlated in the rat PFC using in vivo proton magnetic resonance spectroscopy (1 H MRS). Ketamine has acute antidepressant effects as well as psychotogenic effects, and has been shown to stimulate glutamate release and promote synaptic connectivity in the PFC. The present study investigated the effects of altered PFC DHA levels on dynamic glutamate synaptic responses elicited by ketamine using behavioral, gene expression, and 1 H MRS assays.

Methods: From P21 to P90, male rats were maintained on a diet with no n-3 fatty acids (Deficient, DEF), a diet fortified with preformed DHA (fish oil, FO), or a control diet fortified with alpha-linolenic acid (CON). In the first cohort, locomotor activity in response to acute ketamine (30 mg/kg, $n = 8$/diet group) or vehicle (saline, 1 ml/kg, $n = 8$/diet group) was assessed in automated activity chambers. At 90 minutes post-injection, rats

were sacrificed, and the PFC isolated for qRT-PCR analysis. Genes associated with glutamatergic synaptic activity (cFos, ARC), neurotransmission (NMDA, AMPA, mGluR), and plasticity (GAP-43, PKCgamma, PKCzeta) were investigated. In the second cohort, metabolite concentrations were acquired from the mPFC of isoflurane-anesthetized CON (n = 11), DEF (n = 10), and FO (n = 10) rats prior to and following a ketamine challenge (30 mg/kg) using 1 H MRS. Postmortem PFC DHA composition was determined by gas chromatography.

Results: Compared with CON rats, PFC DHA levels were significantly lower in DEF rats (-30%, $p < 0.0001$) and significantly higher in FO rats (+ 13%, $p = 0.003$). There were no diet group differences in novelty- or saline-induced locomotor activity. Ketamine significantly increased locomotor activity and this response was significantly attenuated in FO rats compared with CON and DEF rats. Ketamine robustly increased cFos expression in the PFC, and this response did not differ significantly between diet groups. Ketamine did not significantly alter the expression of other genes of interest. In the 1 H MRS experiment, the ketamine challenge significantly decreased glutamate concentrations, and increased the glutamine/glutamate ratio, and these responses did not differ between diet groups. Ketamine significantly increased the GABA/glutamate ratio in DEF rats but not CON or FO rats.

Conclusions: Ketamine-induced increases in PFC neuronal activation and reductions in glutamate concentrations are not significantly altered by PFC DHA levels. However, higher PFC DHA levels are associated with a diminished locomotor response to acute ketamine and are protective against ketamine-induced alterations in the inhibitory/excitatory balance in the PFC. Together these preclinical findings suggest that DHA biostatus modulates behavioral and neurochemical responses to acute ketamine and may therefore impact the psychotropic effects of ketamine in human subjects.

Keywords: Ketamine, Omega-3 Fatty Acids, Glutamate

Disclosure: Nothing to disclose.

M72. Hippocampal Proteome Biosignatures of Major Depressive Disorder

Maura Boldrini, Huber Gonzalez, Shujuan Tao, Yan Liu, Gorazd B. Rosoklija, Victoria Arango, Andrew J. Dwork, Lewis Brown, J. John Mann*

Columbia University, New York, New York, United States

Background: Major depressive disorder (MDD) will be the leading cause of global disease burden by 2030 (WHO, 2012), is associated with cognitive dysfunctions involving the hippocampus (HC): negative feedback and set shifting, attention control, memory and executive function (Keilp et al, 2012). The prefrontal cortex (PFC)-amygdala-HC circuit (Thierry et al, 2000) is involved in the pathogenesis of MDD and neuronal, glial and dendrite spine changes were detected in these regions (Licznerski and Duman, 2013). We found more smaller DG volume in unmedicated MDD (uMDD) compared with non-psychiatric controls (NC) and MDD treated with selective serotonin reuptake inhibitors (MDD*SSRI) (Boldrini et al, 2013). Smaller HC volume in MDD (McKinnon et al, 2009) may be due to decreased number and length of dendrites, and cell size and/or density (Boldrini et al, 2013; Rajkowska et al, 2005; Rajkowska et al, 1999; Stockmeier et al, 2004), apoptosis (Lucassen et al, 2001), and/or blunted neurogenesis (Boldrini et al, 2014; Boldrini et al, 2012), although there is an ongoing debate on levels of adult neurogenesis in human (Boldrini et al, 2018; Kempermann et al, 2018; Sorrells et al, 2018). Data-driven and hypothesis-driven approaches to neuroscience are complementary (Bouchard et al, 2016). The complexity of the human brain and the polygenic nature of neuropsychiatric diseases require data-driven approaches to assess numerous pathways at the same time (Shin et al, 2014). Gene expression and proteomics studies are used to identify biosignatures of psychiatric diseases and treatment response (McKenzie et al, 2017; Rangaraju et al, 2017; Rha et al, 2017; Wingo et al, 2017).

Methods: We studied the proteome of the postmortem anterior DG/CA4 from fully characterized (Kelly and Mann, 1996) uMDD, MDD*SSRI and NC (n = 12/group). Subjects were 14-84 yrs of age, 10 MDD subjects died by suicide; females were four per group. The DG/CA4 region was cut with a bistoury from fresh frozen post-fixed HC, digested and used for proteomics assays. Shotgun proteomics liquid chromatography-tandem mass spectrometry (LC-MS/MS) was run for 120 minutes; two chromatograms were recorded for each biological replicate, in traveling-wave ion mobility spectrometry (TWIMS) MSE resolution mode (Brown, 2014). Results were analyzed with MSE/IdentityE algorithm (PLGS software v2.5 RC9), and annotations with identifications from MS data were processed using ProteinLynx Global Server (PLGS 2.2.5, Waters Corp.), and analyzed with Elucidator Protein Expression Analysis System (v4.0.0.2.31, Ceiba Solutions). We used Rosetta Elucidator post-processing (http://www.rosettabio.com/) (Levin et al, 2011), created Association Networks for Differentially Expressed Proteins, and used Database for Annotation, Visualization and Integrated Discovery (https://david.ncifcrf.gov). Our quality control indices, for considering a protein a good candidate, were: $p < 0.001$, fold change of at least 20-25%, peptide count above two, good maximum protein score and peptide score. To validate differentially expressed proteins in the DG/CA4, we performed immunohistochemistry (IHC) following our protocols (Boldrini et al, 2018), and Western Blots (WB) and quantified proteins using Image Studio Lite (LI-COR, Lincoln, NE), correcting optical density by that of the housekeeping gene GAPDH.

Results: Functions of the proteins differentially expressed between uMDD, MDD*SSRI and NC included one or more of the following: acetylation, adhesion, axon, differentiation, Golgi apparatus, maturation, methylation, microtubule, migration, neurogenesis, neuron, plasticity, proliferation, secretory granule, synaptic. This list included Secretogranin-2 (Scg2), VGF (non-acronymic), ES1 protein homolog, mitochondrial (ES1), and Heat Shock Protein 70 (HSP70). Using IHC cells immunoreactive for each protein were found in the human DG and proteins were detectable with WB in DG/CA4 from the same subjects included in the study.

Conclusions: Scg2 is a marker for cell differentiation (Courel et al, 2014) that has been proposed as tractable target for neurological and psychiatric disorders (Bartolomucci et al, 2010). Scg2 is lower in cerebrospinal fluid in Bipolar Disorder (Jakobsson et al, 2013), clusters with the neuropeptide VGF, which is induced after fear conditioning, increasing BDNF/TrkB signaling and CREB phosphorylation (Lin et al, 2015). ES1 currently has no known functions but was found increased in fetal down syndrome brains (Shin et al, 2004). Hsp70 is involved in cellular repair (Mashaghi et al, 2016) and its expression is an indicator of neuronal stress (Sasara et al, 2004). There have been mixed findings regarding the association of mutated Hsp70 and MDD (Takimoto et al, 2003), and Hsp70 is higher in women with MDD (Pasquali et al, 2017). Different variants of the Hsp70 gene may affect antidepressant response (Pae et al, 2007).

Proteins identified as differentially expressed in MDD and with SSRI treatment are involved in neuroplasticity, cell repair, stress responses. Proteins are the ultimate functional product of genetic and epigenetic changes, and proteomics analyses can reveal protein networks of biological significance. We can identify proteins that co-regulate biological processes in MDD and with SSRI treatment, which could hardly be discovered studying one molecule at the time. Proteins identified can be tested as potential biomarkers for in vivo imaging, screening tests, and drug targets.

Keywords: Proteomics, Hippocampus, Mitochondria, Neuroplasticity, Antidepressants

Disclosure: Nothing to disclose.

M73. Essential Role for NPAS4 in Chronic Social Defeat Stress-Induced Anhedonia- and Anxiety-Like Behavior

Makoto Taniguchi, Jordan Carter, Jaswinder Kumar, Christopher Cowan*

Medical University of South Carolina, Charleston, South Carolina, United States

Background: In susceptible individuals, the experience of stressful life events can suppress the future ability to experience pleasure, reduce motivation for reward pursuit and increase general anxiety. Deficits in the reward-related behavior, or anhedonia, is a key feature of the diagnosis of Major Depressive Disorder (MDD) and is strongly associated with the predicted severity and persistence of the disorder. In patients suffering from stress-related mental illnesses and MDD, and in several preclinical animal models, there are enduring changes observed in the prefrontal cortex (PFC) activity and E/I synapse balance, and restoration of PFC E/I balance has antidepressant effects. Several preclinical depression models have linked chronic pathological stress experiences with changes in PFC gene expression, epigenetic modifications to DNA and histones, dysfunction of neuronal circuits, and persistent deficits in reward-related behaviors. Physical or emotional stress alters the expression of several transcription factors, including activity-dependent immediate early genes (IEGs). We recently found that the activity-regulated transcription factor, Neuronal PAS domain protein 4 (NPAS4), is transiently induced in the PFC by stress. NPAS4 is reported to modulate excitatory and inhibitory synapses and synaptic transmission, and as such, is well-positioned to mediate stress-induced changes in neural circuitry and stress-regulated behavior. In this study, we investigated the role and regulation of PFC NPAS4 in the chronic stress-induced changes in social, natural reward preference and motivation, and anxiety-like behaviors.

Methods: The chronic social defeat stress (CSDS) assay was performed using standard conditions, including 5-10-min daily defeat bouts with a novel CD-1 strain aggressor followed by 24-hrs of co-housing in a divided cage. After 10 days of CSDS, experimental mice were subjected to a battery of test including social interaction, sucrose preference, Y-maze, open field exploration, elevated plus maze, and sucrose self-administration. Npas4 mRNA (qRT-PCR) and protein (IHC) expression were examined in reward-related brain regions following acute or chronic SDS. NPAS4 IHC was performed to examine co-localization with cell type-specific markers, including CaMKIIalpha and Parvalbumin. mPFC-specific knockdown of NPAS4 levels was accomplished in adult C57Bl/6 J mice using adeno-associated viruses (AAVs) expressing Npas4 shRNA or a scrambled control.

Results: We found that acute and chronic SDS induces transient Npas4 mRNA expression in the mPFC and NAc, and the induction of Npas4 mRNA in the mPFC was significantly lower in CSDS compared to the first defeat experience. We find that NPAS4 protein in the mPFC is expressed predominantly in CaMKII-alpha-(+), layer 2/3 excitatory pyramidal neurons with no NPAS4 detected in PV(+) GABAergic interneurons. We found that reduction of NPAS4 levels using bilateral infusions of AAV-shNpas4 or AAV-shControl into the PFC of adult C57Bl6J mice altered behavioral changes induced by CSDS. Unlike control mice, the AAV-shNpas4PFC mice after CSDS failed to develop a reduction in sucrose preference (anhedonia-like behavior). AAV-shNpas4PFC mice also failed to develop an increase in anxiety-like behavior in the OFT. In contrast, AAV-shNpas4PFC mice do develop normal social interaction deficits in the 24-hr novel animal interaction test. Interestingly, AAV- shNpas4PFC mice alter motivation to work for a naturalistic reward in the progressive ratio test following a stable acquisition of sucrose self-administration – an effect observed in the susceptible animals as defined during by post-CSDS social interaction test.

Conclusions: Our findings indicate that acute and chronic SDS induces strong and transient NPAS4 expression predominantly in the pyramidal neurons of layer 2/3 in the mPFC, and this induction is attenuated following chronic SDS. Viral-mediated reduction of Npas4 in PFC blocks the development of CSDS-induced anhedonia-like and anxiogenic phenotypes, without altering social avoidance. These findings reveal a novel role for PFC NPAS4 in the development of these CSDS-induced depression-related behaviors and indicate that social avoidance and anhedonia/anxiety phenotypes are dissociable and are possibly produced by distinct molecular and circuit mechanisms. Finally, since NPAS4 is reported to regulate GABAergic synapses formed onto excitatory cortical neurons, ongoing studies are investigating how NPAS4 might regulate circuit and synaptic changes underlying chronic stress-induced hypofrontality states.

Keywords: Social Defeat Stress, Transcription Factor, Immediately Early Gene, Anhedonia, Anxiety

Disclosure: Nothing to disclose.

M74. Impact of CYP2C19 and CYP2D6 Genotypes on Clinical Outcomes and Side Effects in Patients Receiving Escitalopram and Aripiprazole for Major Depression: Results From the CAN-BIND Cohort

Kazunari Yoshida, Farhana Islam, Victoria Marshe, Malgorzata Maciukiewicz, Raymond Lam, Glenda MacQueen, Benicio Frey, Roumen Milev, Sagar Parikh, Claudio Soares, Rudolf Uher, Gustavo Turecki, Susan Rotzinger, Jane Foster, Sidney Kennedy, Daniel Mueller*

Pharmacogenetic Research Clinic, Centre for Addiction and Mental Health, Toronto, Canada

Background: Existing pharmacotherapy for major depressive disorder (MDD) is modestly effective, with vastly variable outcomes. The activity of cytochrome P450 (CYP) drug-metabolizing enzymes has been shown to have major contributions to the variability in antidepressant plasma levels and thereby affecting treatment outcome. Specifically, increased, decreased, or absent CYP enzyme function due to genetic variability influences plasma drug and metabolite concentrations. The objective of the investigation was to examine the contribution of genetic variations in CYP2C19 and CYP2D6 genes in individual's treatment with escitalopram (ESC) and aripiprazole (ARI) augmentation.

Methods: Our sample included 178 individuals between 18-60 years of age and diagnosed with MDD (MADRS ≥ 24) from the Canadian Biomarker Integration Network in Depression (CAN-BIND) cohort. Participants receive protocolized treatment with open-label ESC (10-20 mg/d) for 8 weeks, where responders (i.e. ≥ 50% reduction in baseline MADRS score) continued ESC treatment while non-responders were augmented with an add-on medication, ARI (2-10 mg/d); each group for up to 16 weeks. Plasma levels of drug and metabolite concentrations were collected at Weeks 2, 10, and 16. Side effects were assessed using the Toronto Side Effects Scale (TSES) and Sexual Side Effects Questionnaire (SexFX).

Given that CYP2C19 and CYP2D6 are the major metabolizing enzymes of ESC and ARI, respectively, metabolizer types (i.e., extensive, intermediate, poor and rapid metabolizers) were determined by assessing functionally relevant polymorphism by use of an established open-array platform. We investigated associations between metabolizer status and plasma drug/metabolite concentrations, as well as response status and side effects.

Results: ESC plasma levels and metabolite/ESC ratios were significantly different across CYP2C19 metabolizer status groups (Kruskal-Wallis, FDR corrected $p < 0.001$). In comparing the largest groups, extensive (EM, $n = 123$) and intermediate (IM, $n = 42$) metabolizers, IMs showed consistently higher ESC levels across week 2 (10 mg, MIM = 26 ± 9 ng/mL, MEM = 18 ± 8 ng/mL), week 10 (20 mg, MIM = 43 ± 18 ng/mL, MEM = 32 ± 15 ng/mL), and week 16 (20 mg, MIM = 46 ± 20 ng/mL, MEM = 30 ± 14 ng/mL). CYP2D6 EMs showed the highest metabolite/ESC ratio at Weeks 2 and 16 after adjusting for time-since last dose ($F(2, 176) = 3.6$, $p < 0.01$). CYP2D6 metabolizer types showed significant differences in ARI/metabolite ratio at Weeks 10 and 16 in individuals in the ESC + ARI treatment arm ($p < 0.001$), as well as, nominal difference in ARI blood concentrations at Week 16 ($p < 0.05$). However, there were no association between CYP2C19 and CYP2D6 metabolizer status and clinical response at Week 8 or 16.

For side effects, the frequency and severity of drowsiness were associated with ESC levels nominally at Week 2 (per 100 ng/mL, OR = 0.8 [0.7, 1.0], uncorrected $p = 0.08$) and significantly at Week 10 for both the ESC monotherapy (OR = 1.5 [1.1, 2.0], $p = 0.01$; $p = 0.02$) and ESC + ARI treatment groups (OR = 0.7 [0.6, 1.0], $p = 0.08$; $p = 0.03$). ESC metabolite levels showed a strong association with frequency (OR = 1.6 [1.1, 2.1]; $p = 0.005$) and severity (OR = 1.6 [1.1, 2.2]; $p = 0.008$) of dizziness at Week 10 and a trend for frequency (OR = 1.3 [1.0, 1.8]; $p = 0.06$) at Week 16 for only the ESC + ARI treatment group. Likewise, frequency and severity of blurred vision (OR = 0.7 [0.5, 1.0]; OR = 0.6 [0.4, 1.0]; $p = 0.03$, $p = 0.02$) and headache (OR = 1.5 [1.0, 2.2]; $p = 0.05$) was influenced by ESC levels in this group at Week 16. Finally, ESC levels were associated nominally with frequency of weight gain (OR = 1.4 [1.0, 2.0], $p = 0.08$) and significantly with severity of weight gain (OR = 1.7 [1.1, 2.7], $p = 0.03$) at Week 10 for only the ESC + ARI treatment group. In terms of sexual side effects, after adjusting for baseline sexual function, age and sex, metabolite/ESC ratio at Week 16 was significantly associated with total sexual functioning and global impression scores in the ESC + ARI treatment group ($\beta = 2.6$, $\beta = 1.5$, $p < 0.05$) and nominally in ESC monotherapy ($\beta = -1.4$, $\beta = -0.8$, $p < 0.1$).

Conclusions: CYP2C19 and CYP2D6 genotypes are associated with steady state ESC and ARI levels, respectively, metabolite levels and metabolite/drug ratio, but does not show an association with response status. For side effects, frequency and severity of drowsiness show an association with ESC levels in both ESC monotherapy and ESC + ARI adjunctive therapy groups. However, only the ESC + ARI adjunctive therapy showed an association between frequency and severity of dizziness, blurred vision, headache and weight gain with ESC or its metabolite levels. Cases where opposite effects were observed between ESC monotherapy and ESC + ARI treatment groups suggest that ARI augmentation moderates the side effects associated with ESC. Further analyses will be presented how metabolizer status and plasma levels is associated with cognitive performance scores.

Keywords: Pharmacogenetics, Escitalopram, Aripiprazole, Depression, CYP2D6

Disclosure: Nothing to disclose.

M75. Synapses and Cognition in Aging – Does Depression Accelerate the Decline?

*Sophie Holmes, Robert Pietrzak, Sjoerd Finnema, Maggie Davis, Nicole DellaGioia, Mika Naganawa, Nabulsi Nabeel, Matuskey David, Ronald Duman, Gerard Sanacora, Carson Richard, Krystal John, Irina Esterlis**

Yale Translational Brain Imaging Program, New Haven, Connecticut, United States

Background: Aging has widespread effects on the brain, affecting molecules, cells, vasculature, gross morphology, and cognitive function. Major depressive disorder (MDD), a highly prevalent and disabling psychiatric disorder, may accelerate brain aging, with some data suggesting it adds up to 10 years to the chronological age of chronically depressed individuals. To date, however, no known in vivo study has evaluated how MDD may accelerate brain aging at the molecular level. We conducted a novel positron emission tomography (PET) imaging study to evaluate synaptic density, emotional processing and cognitive functioning in MDD individuals across a wide age range. The radioligand [11 C]UCB-J was used to quantify synaptic vesicle glycoprotein 2 A (SV2A) in the brain, which we previously showed to be a robust marker of synaptic density.

Methods: Ten unmedicated individuals with MDD (mean age = 40.1 ± 14.6) and ten age-, sex-, and smoking-matched healthy controls (HC; mean age = 36.4 ± 13.8) participated in a [11 C]UCB-J PET scan. Binding potential (BPND) was computed in the dorsolateral prefrontal cortex (dlPFC) and hippocampus (HIP) with the white matter centrum semiovale as reference region. Magnetic resonance imaging (MRI) was performed prior to PET to guide the placement of regions of interest. Control and MDD individuals participated in a comprehensive psychiatric assessment battery to assess mood (HAM-D, MADRS), anxiety (STAI, HAM-A), and other depression related symptoms. Cognitive function was assessed using the Cogstate cognitive battery.

Results: Results revealed a significant interaction of MDD x age in predicting synaptic density, with individuals with MDD having significantly more pronounced age-related decline in synaptic density in the HIP ($F = 13.55$, $p = 0.002$) and dlPFC ($F = 7.47$, $p = 0.015$). The magnitudes of differences in slopes between the MDD and HC groups were very large in both the HIP and dlPFC (Cohen $d = 1.8$ in HIP and 1.4 in dlPFC). Results also revealed that lower synaptic density in the dlPFC was associated with greater severity of anhedonia symptoms ($\beta = -0.55$). Furthermore, we observed that lower synaptic density in the dlPFC in the MDD group was associated with worse performance on measures of attention ($r = -0.54$) and executive function ($r = -0.43$); and that lower synaptic density in the HIP was associated with worse performance on measures of visual learning ($r = -0.30$) and verbal memory ($r = -0.43$). Individuals with MDD also showed greater age-related reductions in verbal memory, attention, and working memory (all $F's > 3.41$, all $p's < 0.09$), with lower synaptic density in HIP linked to greater reductions in verbal learning ($r = -0.54$), and lower synaptic density in dlPFC linked to greater reductions in attention and working memory ($r's = -0.51$ and -0.54).

Conclusions: To our knowledge, these data provide the first in vivo evidence for a role of MDD in accelerating age-related changes in synaptic density in the HIP and dlPFC. They further suggest that greater changes in synaptic density are associated with more pronounced age-related changes in cognition, thus supporting the hypothesis that MDD may be a prodrome to dementia.

Keywords: Synaptic Density, Depression, Aging, Human Imaging

Disclosure: Nothing to disclose.

M76. Relationship Between the Antidepressant Effects of Esketamine Nasal Spray and Perceptual Disturbances

*Li Chen, Xiang Li, Rosannne Lane, Maura Furey, Jaskaran Singh, Wayne Drevets, Guang Chen**

Janssen Research & Development LLC of Johnson & Johnson, San Diego, California, United States

Background: Clinical studies report that ketamine and esketamine produce antidepressant effects at subanesthetic doses. Both

compounds also produce transient perceptual side effects within the same dose ranges. Previous reports showed that the increases in perceptual measures are associated with greater improvement on depression severity ratings after single iv ketamine infusion (Luckenbaugh et al., 2014; Niciu et al., 2018). Niciu et al also reported that depersonalization component scores also correlated with better improvements on depression ratings after single iv ketamine infusion. Other studies have been unable to replicate these findings (Valentine et al., 2011; Murrough et al., 2013). Notably, Nugent et al (2018) reported a statistical trend toward a correlation between the increases in perceptual effects and the increases in depression measures in healthy subjects receiving single ketamine iv infusion. In the current study, we conducted post-hoc analyses of data from a Janssen R&D phase 3 study to assess the relationship between the effects of esketamine nasal spray on ratings of depression severity and ratings of perceptual disturbance in participants with TRD.

Methods: The clinical sample was drawn from a randomized, double-blind, active-controlled, multicenter study in male and female adult participants with TRD (NCT02418585). Subjects received flexible dosing intranasal esketamine (56 mg or 84 mg) plus an oral antidepressant or an oral antidepressant plus intranasal placebo twice per week plus a newly initiated oral antidepressant (AD) for 28 days. The Montgomery–Åsberg Depression Rating Scale (MADRS) and the Clinician Administered Dissociative States Scale (CADSS) were used as measures of depression severity and perceptual effects, respectively. The primary outcome measure was assessed by the difference in the change in MADRS between study arms at Day 28.

Spearman coefficients were computed to assess the relationships between MADRS changes (i.e. change from baseline) at Day-2 (the day after the first IN treatment) and Day 28 (the day of last assessment of the induction phase of the study), and CADSS increases following the first administration of esketamine (i.e. post-treatment peak values) at Day-1.

In the post-hoc analyses on the temporal profile study of the CADSS and MADRS changes, a mixed model for repeated measures (MMRM) was used. The model included treatment (IN esketamine + oral antidepressant, oral antidepressant + IN placebo), visit, country, class of oral antidepressant (SNRI or SSRI) and treatment-by- visit as fixed effects, and baseline CADSS (before treatment at Day 1) as covariates.

Results: Of the randomized participants, 197 completed the double-blind period. Change in MADRS total score with esketamine nasal spray and oral antidepressant was superior to oral antidepressant and placebo nasal spray at Day 28 (LS mean [SE] difference vs. antidepressant plus placebo -4.0 [1.69], 95% CI: -7.31, -0.64; 1-sided $p = 0.010$); likewise, clinically meaningful improvement was observed with esketamine nasal spray plus oral antidepressant at earlier time points, including Day 2 (1-day post-treatment) (Popova V., et al. reported at the American Psychiatric Association Annual Meeting, 2018).

The CADSS total, depersonalization, derealization and amnesia scores after first treatment did not correlate significantly with changes on the MADRS either at Day 2 in the esketamine + AD ($n = 109$) or the placebo + AD groups ($n = 99$) (lowest p-value > 0.48) or at Day 28 in the esketamine + AD ($n = 101$) or placebo + AD ($n = 96$) groups (lowest p-value > 0.14).

The temporal profile of MADRS response over repeated esketamine dosing indicates that MADRS continues to improve over time (day 2-28). The least square mean of the reductions from baseline scores are -8.2 on day 2 and -19.8 on Day 28. The effects of Day and of Treatment are significant (Day: $p < 0.001$, Treatment: $p = 0.0049$), while the interaction of Day and treatment is not significant ($p = 0.5341$).

The temporal profile of CADSS response over repeated esketamine dosing indicates that the peak CADSS scores decrease over time. The least square mean of CADSS increases from baseline scores are 8.1 and 3.3 after first and last treatments in esketamine arm. Meanwhile, the mean CADSS scores in the group receiving placebo + AD maintains between 0.3 to 0.7 over time. The interaction of Day and treatment is significant ($p < 0.001$).

Conclusions: During the administration of esketamine nasal spray plus oral AD, the increases in the CADSS total and component scores did not correlate significantly with the improvement in MADRS scores at either of the two timepoints examined. Furthermore, the MADRS total scores continued to decrease, indicating improvement of depression with repeated dosing of either esketamine + AD or placebo + AD, while the CADSS scores showed attenuation with repeated dosing in the esketamine arm. The observation that with repeated dosing of esketamine, the perceptual effects diminish while the antidepressant effects increase, is consistent with the lack of correlation between the change in MADRS scores and the change in CADSS scores. A variety of evidence suggests that NMDAR antagonism is the primary direct pharmacological action of ketamine and esketamine at antidepressant doses. The current data nevertheless suggest that distinct mechanisms may underlie the antidepressant and perceptual actions of esketamine, although both actions might be triggered by the same initial target(s) or through different subtypes of NMDARs.

Keywords: Ketamine, Esketamine, Depression, Antidepressant, Dissociation

Disclosure: Johnson and Johnson, Employee

M77. Testing a Synergistic, Neuroplasticity-Based Intervention for Depression: Study Design and Preliminary Findings From an RCT of Intravenous Ketamine Plus Neurocognitive Training

Rebecca Price, Benjamin Panny, Michelle Degutis, Crystal Spotts, M. Beth Minnigh, Sam Poloyac, Cassandra Gibson, Sanjay Mathew, Robert Howland*

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Depression has been described as a problem of impaired neuroplasticity (e.g., prefrontal synaptic depression) at the molecular level, and decreased cognitive flexibility and prefrontal cortex (PFC) control at the neurocognitive level. Intravenous ketamine, which displays rapid antidepressant properties, is posited to reverse depression by rapidly enhancing molecular neuroplasticity; but surprisingly little is known regarding its effects on depressed patients' neurocognitive processing. We posit that ketamine will rapidly increase cognitive flexibility and the PFC's influence on affective regions, allowing for rigid, negative biases in cognition to be rapidly reversed. We hypothesize these neurocognitive changes may be linked to individual differences in blood levels of a specific ketamine metabolite, (2 R,6 R)- hydroxynorketamine (HNK), which has been linked to antidepressant-like effects in animal models. We further hypothesize these neurocognitive changes will provide a clinical window of opportunity in which to introduce automated neurocognitive training techniques, which will consolidate adaptive forms of cognitive processing (specifically, positive implicit representations of self) while neuroplasticity remains high. Training adaptive forms of processing after first 'priming' the brain with ketamine represents a potentially synergistic treatment approach that could extend the acute effects of a single ketamine infusion beyond its typical 3-7-day window, efficiently fostering antidepressant effects that are both rapid and enduring.

Methods: In this randomized controlled trial (NCT03237286), 150 unipolar depressed adults who have failed at least one FDA-approved antidepressant medication are randomized to one of three intervention arms: (1) a single infusion of ketamine (0.5 mg/kg over 40 min) followed by 4 days of active cognitive training (n

= 50); (2) ketamine infusion followed by four days of sham cognitive training (n = 50); or (3) saline infusion followed by four days of cognitive training (n = 50). Concurrent antidepressant treatments (e.g., medications, therapy) are allowed as long as treatments are stable for 4 weeks prior to enrollment. Outcome measures span multiple levels of analysis. Patients complete repeated in-person assessments over a 30-day period (including clinical, neuroimaging, cognitive, implicit information processing, and serum ketamine metabolite measures) and are followed with remote assessments (e.g., self-report symptoms, implicit information processing) over the following year.

Results: This poster will present the study design and preliminary analyses from this ongoing NIMH-funded R01. Key findings from the first cohort of 21 patients include the following:

1. (2 R,6 R) HNK blood levels are sustained at detectable levels in some patients for several days following a single ketamine infusion. The timeframe observed roughly corresponds to the 3-7-day clinical response window observed in prior ketamine trials.
2. The overall clinical response rate post-infusion (collapsing across ketamine/saline arms for blinded analysis) is 52.4% (11/21 responders). Assuming a null response to saline and based on the 2:1 allocation to ketamine:saline, this 52.4% response would be consistent with a 70-80% response rate in the ketamine arm, consistent with previous trials.
3. In blinded analyses comparing infusion acute responders (n = 11) to non-responders (n=10), decreased self-reported depression (QIDS-SR) scores are observed in responders and are sustained well into the follow-up period, which now extends to 4-months in some patients. Decreased self-reported depression (relative to baseline) is observed at every assessment out to 4-months post-infusion among responders (p<.05), while non-responders' self-reported depression does not differ from baseline.

Conclusions: In this ongoing study, we hypothesize that after priming brain plasticity with ketamine, training positive self-representations could provide an exceedingly efficient, low-cost, portable, non-invasive, safe, and highly dissemination-ready strategy for exploiting and extending ketamine's rapid antidepressant effects. In preliminary blinded analyses, acute infusion responders show improvement in depression symptoms over a more sustained interval (i.e., 4 months following a single infusion) than has been observed in previous ketamine trials which (a) recruited more treatment-resistant patients and (b) did not include a synergistic neurocognitive/behavioral intervention. This study also aims to provide novel, integrative information on neurocognitive intermediaries bridging ketamine's molecular and mood effects. Preliminary analyses show that (2 R,6 R)-HNK levels are detectable in patients' serum for several days following a single infusion. Individual differences in these blood levels will be examined in relation to other outcomes across clinical and neurocognitive levels of analyses.

Keywords: Ketamine, Cognitive Neuroscience, Depression

Disclosure: Nothing to disclose.

M78. Is Sleep Disturbance Linked to Short- And Long-Term Outcomes Following Acute- and Continuation- Phase Treatments for Recurrent Depression?

Elaine Boland, Jeffrey R. Vittengl, Lee Anna Clark, Michael E. Thase, Robin B. Jarrett*

Veterans Administration Medical Center, Philadelphia, Pennsylvania, United States

Background: The field continues to search for treatments that eliminate depression. Sleep disturbance has been shown to predict increased rates of non-remission, with mixed evidence that persistent sleep disturbance is associated with greater likelihood of relapse and recurrence after antidepressant therapies. To date, studies have been limited by single, baseline assessments of sleep disturbance that do not reflect how changes in sleep disturbance over the course of acute-phase treatment may affect outcomes. Similarly, the literature is lacking studies that evaluate repeated measures of sleep disturbance across continuation-phase treatment, assess how changes in sleep disturbance during acute-phase treatment response may be related to subsequent depression relapse and recurrence, and examine how continuation-phase treatment may additionally improve sleep disturbance. The current study addresses these limitations, assessing how changes in sleep disturbance measured repeatedly across both acute- and continuation-phase treatment affected post-treatment outcomes. We hypothesized that greater overall levels of sleep disturbance and less improvement in sleep disturbance during acute-phase cognitive therapy (A-CT) would predict lower remission and recovery rates, and shorter time to relapse or recurrence of major depressive disorder (MDD). We also examined the potential impact of continuation-phase treatment on sleep among higher risk A-CT responders.

Methods: Analyses were conducted on 523 adults with MDD who consented to 12 weeks of A CT followed by a randomized controlled trial of continuation-phase cognitive therapy (C-CT) or fluoxetine (FLX) versus pill placebo with clinical management to prevent depressive relapse for A-CT responders considered at higher risk of relapse/recurrence (defined by any Hamilton Rating Scale for Depression (HRSD-17) score ≥ 7 at any of the final seven consecutive acute-phase treatment visits). Continuation-phase treatment across all modalities was delivered over 10 sessions; 4 biweekly and 6 monthly visits for a total of 8 months. Patients were monitored for an additional 24-month, treatment-free follow-up period totaling 32 months of follow-up. Sleep disturbance was assessed using the global severity scale of the Pittsburgh Sleep Quality Index (PSQI) and a sleep problems scale derived from 8 sleep items from depression rating scales (i.e., Hamilton Rating Scale for Depression (HRSD-17), Beck Depression Inventory, and the Inventory of Depressive Symptomatology Self-Report). Sleep was assessed at weeks 1, 4, 5 and 12 of A CT, and approximately every 4 months throughout the continuation and follow-up phases. We used multilevel models to evaluate trajectories of sleep disturbance and depression improvement across A-CT. Individual intercepts and slopes were retained and entered into Cox regression models to predict remission (defined as the last 7 consecutive HRSD-17 scores < 7 or "return to usual self" according to the Longitudinal Interview Follow-up Evaluation), recovery (remission lasting 8 or more months), relapse (exacerbation of the presenting episode after a response but before recovery), and recurrence (meeting DSM-IV criteria for MDD following recovery) of MDD. We used multilevel models to test the effects of continuation treatments on sleep disturbance.

Results: Although patients with greater average sleep disturbance during A-CT were less likely to achieve response, defined as an absence of DSM-IV major depressive disorder and an HRSD-17 score ≤12, and remission, overall there were significant improvements in depression symptoms (d = 2.6) and sleep quality (PSQI d = 1.0, sleep problems d = 1.2) over the course of A-CT. Response and remission were more likely for patients who exhibited greater reduction in sleep disturbance during A-CT. Patients with greater reduction in sleep disturbance during A-CT also achieved post-acute remission and recovery sooner. Continuation-phase treatment did not further improve sleep disturbance, but improvements made during the A-CT were maintained for 32 months among the higher risk responders.

Neither average levels of A-CT sleep disturbance nor change in sleep disturbance predicted relapse or recurrence.

Conclusions: Sleep disturbance among patients with recurrent MDD improves substantially during A-CT. Because greater reductions in sleep disturbance during A-CT were associated with more rapid recovery from depression, our findings support careful targeting of sleep disturbance during A-CT. Further research is needed to determine the extent to which full normalization of sleep is related to complete recovery from a depressive episode. Continuation-phase treatment does not appear to improve sleep quality further in this sample, but the extent to which maintenance of sleep quality during continuation-phase treatments may confer protection against depressive relapse/recurrence should be explored in future studies.

Keywords: Sleep, Depression, Treatment

Disclosure: Nothing to disclose.

M79. The Use of a Mobile Cognitive Intervention to Target Cognitive Control Dysfunction in Middle Aged and Older Adults With Depression: Evidence for Target Engagement

Faith Gunning, Joaquin Anguera, Pat Arean*

Weill Cornell Medical College, White Plains, New York, United States

Background: Poor cognitive control is common in older adults with major depressive disorder (MDD) and is linked to poor antidepressant response. Thus, alternative treatments for depression are needed, particularly for those individuals who exhibit cognitive control dysfunction. Further, interventions for depression that can be easily disseminated could greatly enhance the clinical impact of a neuroscience-informed interventions. Project EVO (or "EVO") is a mobile therapeutic video game that has been shown to reduce older adults' susceptibility to interference by augmenting cognitive control abilities (i.e., sustained attention and working memory abilities) through individualized adaptive algorithms (Anguera et al., Nature, 2013).

Methods: In a sample of 36 middle-aged and older adults (both sexes), we examined the mechanism of action of EVO at the circuitry level (resting state and task-based functional MRI), performance level (computerized measures of working memory and sustained attention), and at the self-report level of analysis. These measures of cognitive control network functions were completed at baseline during a major depressive episode and following 4-weeks of at home use of EVO. Participants ranged in age from 45 to 75 years of age and had evidence of cognitive control dysfunction at the time of enrollment into the study. Change was defined a priori as a z score of > .5 from pre to post use of EVO. Z scores were calculated for each individual from each measure (task-based fMRI, resting state fMRI, task performance, self-report).

Results: Results indicate that greater than 66% of patients showed a significant improvement, as measured by z score > .5, in cognitive control network functions following EVO. These changes were observed as increased bilateral activation of the middle frontal gryri and the dorsal anterior cingulate cortex in response to incongruent stimuli on a Stroop Flanker Task. In addition, greater patients showed a significant increase in functional connectivity in the left middle frontal gyrus and bilateral dorsal anterior cortex from pre to post use of EVO. Significant improvements in cognitive control functions were also apparent at the performance (TOVA) and self-report (FrsBe) levels of analyses. Mood symptoms, while not a primary outcome for this phase of the work, showed significant improvement from pre to post-EVO ($p < .05$). In addition, we explored changes in other brain networks as measured by resting state functional connectivity.

Conclusions: These results indicate that a therapeutic video game approach may target cognitive control dysfunction and offer an alternative treatment for middle-aged and older adults who suffer from MDD with concurrent cognitive control dysfunction.

Keywords: Experimental Therapeutics, Cognitive Control Network, Major Depressive Disorder, Resting-State Functional MRI, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

M80. Transcranial Magnetic Stimulation Causally Influences the Subcallosal Cingulate Cortex Indexed by Interleaved TMS/fMRI

Desmond Oathes, Romain Duprat, Morgan Scully, Hannah Long, Kristin Linn, Joseph Kable, Joshua Gold, Michael Platt, Yvette Sheline*

Perelman School of Medicine University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: There is burgeoning evidence that targeting regions of the lateral prefrontal cortex with transcranial magnetic stimulation (TMS) according to high resting correlation with the subcallosal cingulate cortex results in effective treatment of refractory major depressive disorder (MDD). However, an outcome as complex as clinical improvement is likely mediated by changing many brain areas/networks. Therefore, the question of whether targeted TMS actually has causal influence over the region of subcallosal cingulate related to MDD remained open prior to this study.

Methods: We used individualized brain stimulation targets from an initial resting fMRI scan generated by seeding an MDD abnormality meta-analysis defined region of the subcallosal cingulate and choosing a surface accessible region with the strongest time series correlation for targeting TMS. In a mixed gender cohort (approximately equal) of 32 healthy participants, we subsequently interleaved 70 single TMS pulses with functional MRI acquisitions (2.4 s TR including 400 ms gap for TMS) at 120% of motor threshold defined for each participant. As a control site and as typically done in TMS experiments, we stimulated the primary motor cortex with the same sequence for comparison with the subcallosal cingulate target. Following standard event-related fMRI processing, we extracted average percent signal BOLD responses for the subcallosal cingulate region of interest then used a within-subjects paired-t test to establish the differential effect of TMS site on target response.

Results: TMS to the primary target induced a negative deflection in the BOLD signal (>3% signal change) that was significantly larger than the deflection in response to the control site (motor cortex) stimulation (~1% change), $t(31)=2.273$, $p=0.30$, partial $eta2=0.143$. There was no interaction between the TMS evoked response and gender, age or years of education.

Conclusions: We for the first time provide causal evidence that a region of the lateral prefrontal cortex with highly correlated BOLD signal to the subcallosal cingulate cortex has the ability to causally drive this target region in healthy individuals. We show that individualized fMRI guided brain stimulation can be an effective tool in guiding non-invasive circuit engagement that is assumed to underlie clinical response across a variety of conditions to this treatment modality. Our ongoing work will continue this investigation in a patient population.

Keywords: Interleaved TMS/fMRI, Anterior Cingulate Cortex (ACC), Subcallosal Cingulate, Major Depressive Disorder (MDD), Resting-state fMRI

Disclosure: Nothing to disclose.

M81. Is There an Association Between Subjective and Objective Measures of Cognition and Brain Structure in Bipolar Disorder?

Isabelle Bauer, Thomas Meyer, MonJu Wu, Benson Mwangi, Giovana Zunta-Soares, Jair Soares*

University of Texas Medical School, Health Science Center at Houston, Houston, Texas, United States

Background: Cognitive deficits are strong predictors of social functioning and treatment response. Further, experimental studies have demonstrated a strong link between subjective rating of cognitive deficits, poor intrinsic motivation, and reduced cognitive performance. To date, the neurocognitive literature of bipolar disorder (BD) has primarily investigated objectively measured cognitive function deficits in relation to structural abnormalities in fronto-limbic, cingulate, and striatal regions. There is sparse but clinically relevant evidence showing that BD patients are more likely than healthy controls to report cognitive deficits prior to performing cognitive tasks. No published study has, however, explored the link between subjective and objective measures of cognitive performance and brain structures in BD.

Methods: The study included 24 healthy controls (36.18±11.18 years, 15 F) and 45 remitted patients with BD (35.92±12.33 years, 31 F). Computerized measures of complex processing speed, sustained attention, and reward-related decision making were used for the objective assessment of cognitive functioning. Participants completed mood questionnaires and measures of cognitive self-concept and intrinsic motivation. Brain measures of interest included Freesurfer-generated cortical thickness and volumes of the frontal pole, hippocampus, precuneus, inferior temporal, thalamus, caudate, and striatum.

Results: BD patients self-reported poorer attentional abilities and intrinsic motivation compared to healthy controls. They displayed increased risk-taking and had fronto-temporal structural abnormalities. Self-reported cognitive difficulties correlated weakly with risk-taking but were strongly associated with current residual depressive symptoms. There was no significant correlation between fronto-temporal measures, risk taking and subjective cognitive measures.

Conclusions: BD patients' perceptions of their abilities may not be an indicator of their cognitive performance. Patients' current mood state influences their perceptions of cognitive competence. Functional brain imaging measures may be better suited for answering questions on the link between brain performance, and subjective/ objective cognitive abilities.

Keywords: self-Efficacy, Risk-Taking, Neuroanatomy, Bipolar Disorder

Disclosure: Nothing to disclose.

M82. Assessment of Cognitive Function in Bipolar Disorder With Passive Smartphone Keystroke Metadata: A BiAffect Digital Phenotyping Study

Olusola Ajilore, John Bark, Alexander Demos, John Zulueta, Jonathan Stange, Jennifer Duffecy, Faraz Hussain, Scott Langenecker, Peter Nelson, Kelly Ryan, Melvin McInnis, Alex Leow*

University of Illinois at Chicago, Chicago, Illinois, United States

Background: Cognitive dysfunction in bipolar disorder has been shown to be present even in the euthymic state. Cognitive dysfunction in bipolar disorder has been associated with poor treatment response and increased risk of relapse. There has been recent attention on digital phenotyping and passive sensing through smart, connected devices to probe cognition in real-world settings. Our passive sensing, BiAffect, is a custom-built smartphone keyboard that captures keystroke metadata ('how you type, not what you type'). In previous studies, our group has demonstrated that BiAffect-derived keystroke metadata is associated with mood symptom severity and can be used prospectively to predict changes in mood in patients with bipolar disorder. For the present study, we hypothesized that typing metadata would be significantly associated with cognitive domains measured with traditional neuropsychological testing.

Methods: 18 participants with bipolar disorder and 12 healthy comparison subjects from the Prechter Longitudinal Study of Bipolar Disorder at the University of Michigan were provided a mobile phone with a customized keyboard that passively collected keystroke metadata. Participants also completed a neuropsychological battery including the Tower of London task and the Trail Making Test. Select BiAffect-derived time-based metrics (interkey delay, typing speed) were associated with processing speed and set-shifting on the Trail Making Test. A measure of disorder in typing and time to make a move on the Tower of London were compared using Shannon entropy.

Results: Processing speed, as measured by Trail Making Test (part A), was significantly correlated with average interkey delay (i.e., time since last key, $r = .5$, $p < .001$) and keys/second ($r = -.54$, $p < .001$). Set shifting, as measured by Trail Making Test-Part B, was highly associated with average time since last key ($r = .68$, $p < .00001$) and keys/second ($r = -.62$, $p < .00001$). Participants with bipolar disorder had significant increases in entropy in interkey delay times ($p = .048$, $d = -.83$) and entropy of Tower of London move times ($p = .029$, $d = -.84$). Furthermore, Entropy in interkey delay was significantly associated with entropy in Tower of London moves in participants with bipolar disorder only ($r=.78$, $p=.001$), with a trend level group x association interaction ($p = .05$).

Conclusions: This pilot study demonstrates that passive, unobstrusive smartphone keystroke metadata can be used to probe cognitive function and dysfunction in bipolar disorder, revealing multi-scalar behavioral features accessible through digital assays.

Keywords: Bipolar Disorder, Cognitive Functioning, Digital Assessment, Smartphone-Based App

Disclosure: Nothing to disclose.

M83. High Sensitivity C-Reactive Protein is Associated With Poorer Cognitive Performance in Bipolar Disorder

Caitlin Millett, M. Mercedes Perez-Rodriguez, Emmett Larsen, Megan Shanahan, Katherine Burdick*

Brigham & Women's Hospital, Boston, Massachusetts, United States

Background: Data support the notion that 40-60% of patients with bipolar disorder (BD) have neurocognitive deficits. It is increasingly accepted that functioning in BD is negatively impacted by these deficits, yet they have so far not been a target for treatment. This is, in part, due to a lack of understanding of the biological mechanisms underlying cognitive impairment in BD. The biomarkers that predict cognitive deficits in BD are largely unknown, however, recent evidence suggests that inflammation may be associated with poorer cognitive outcomes in BD. To address gaps in knowledge regarding inflammatory biomarkers in cognition in BD, we measured peripheral high sensitivity C-reactive protein (hsCRP) in a large sample of euthymic men and women with BD ($n=223$). We hypothesized that higher hsCRP

concentrations would predict poorer performance on neurocognitive assessments.

Methods: We have completed an analysis of hsCRP in a large euthymic BD sample (n=223, 48% female, 18-65 y) and a healthy control (HC) sample (n=52, 58% female, 20-70 y). Blood was drawn within one week of neurocognitive testing by a research nurse and tested for hsCRP concentration on an electrochemiluminescence (ECL) multiplex-based assay platform. A one-way multivariate analysis of covariance (MANOVA) was used to assess the performance of the highest hsCRP quartile (n=54) against the remaining lower quartiles (n=158) on cognitive tests. Results were covaried with clinical correlates where appropriate.

Results: We found a statistically significant effect of hsCRP quartile on cognitive performance in the BD group, with significant effects on several individual cognitive tests: those will high hsCRP had worse performance on Controlled Oral Word Association Task (p=0.003), Wisconsin Card Sorting Task (p=0.003), WAIS block design (p=0.005), vocabulary (p=0.004) and similarities (p=0.002), also reading mind in the eyes (p=0.001) and MCCB reasoning and problem solving (p=0.037). We also found evidence of cognitive decline in the highest hsCRP quartile compared to the lowest hsCRP quartile (p=0.047). Lastly, we performed a regression analysis of a composite cognitive Z score. A significant model (n=180, F=34.8, p<0.001, Adjusted R2=0.57) revealed significant predictors of overall cognition in the BD group, including CRPlog (β=-0.123, p=0.016) and other predictors.

Conclusions: We have examined hsCRP, a peripheral inflammatory marker, in a large euthymic BD group. Our results indicate that higher hsCRP concentrations are associated with broad cognitive dysfunction in BD. Elucidating the underlying pathophysiology of cognitive decline in BD will help to develop new treatments in an area that has thus far been understudied.

Keywords: Inflammation, Cognition, Mood Disorder

Disclosure: Nothing to disclose.

M84. Combinatorial Pharmacogenetic Testing-Informed Medication Switching From Genetically Incongruent to Congruent Medications Leads to Decreased Side Effect-Burden for Patients With Depression

John Greden, Sagar Parikh, Anthony Rothschild, Michael Thase, Boadie Dunlop, Charles DeBattista, Charles Conway, Brent Forester, Francis Mondimore, Richard Shelton, Matt Macaluso, James Li, Krystal Brown, Alexa Gilbert, Lindsay Burns, Michael Jablonski, Bryan Dechairo*

University of Michigan Comprehensive Depression Center, Ann Arbor, Michigan, United States

Background: Major depressive disorder (MDD) is a leading cause in world burden of disease (World Health Organization). Standard antidepressant treatments result in partial, delayed or absent treatment responses and increasing side effect (SE) burden with each antidepressant trial. Medication safety and SEs play a large role in the path to treatment resistance in MDD (TRD). Precision medicine, such as genetic biomarkers, would hypothetically improve rates of clinical response, remission, and maintenance of overall patient wellness.

A field of precision medicine, pharmacogenetics (PGx), has been studied for several decades with the ultimate goal to optimize medication treatment decisions. Previous results were disappointing and have become controversial, partially because of the small number of genes and variants studied, small sample sizes, and short-term studies. Recently, clinical advances have led to combinatorial PGx algorithms that integrate multiple pharmacokinetic (PK) and pharmacodynamic (PD) genes specific to each medication rather than the historical approach of large panels including single gene-single medication pairs alone. Here, we present SE data from the largest, longest, randomized, and patient/rater-blinded psychiatric combinatorial PGx study in patients with MDD and inadequate response and/or SEs to medication.

Methods: This study included 60 academic and community sites and was funded by Assurex Health. Patients had a diagnosis of MDD, QIDS-C16 score ≥11, and had failed ≥1 antidepressant trial in the current episode. Patients were randomized 1:1 to a combinatorial PGx-guided or unguided treatment group. PGx test results were withheld from clinicians in the unguided arm until unblinding after the 8 wk visit whereas the guided group clinicians had access to the testing to inform medication decisions throughout the study. Raters were blinded to treatment group and timeline. Patients were blinded to treatment group at baseline, 4 wk, and 8 wk; un-blinding could occur after week 8. The study continued with time points at 12 and 24 wk. The PGx test stratified medications based on severity of gene-drug interactions (GDI) based on a combinatorial algorithm incorporating PK and PD GDIs. Congruency is defined as medications with fewer GDIs residing in the "use as directed" and "use with caution" bins whereas incongruence is defined as medications with severe GDIs residing in the "use with increased caution and more frequent monitoring" bin. Patient-reported side effects were assessed as the mean number of SEs and proportion of patients reporting SEs according to study arm and congruence of baseline medication. SEs were only included with a probable causal link to medication (e.g. categorized as likely, probably, possibly, or definitely relating to medication).

Results: 1,671 patients with MDD were evaluated for 24 wks. At 8 wks, there were no significant differences in patients experiencing SEs and SE burden between the PGx-guided and unguided groups [15.6% (88/560) versus 15.3% (93/607), p=0.881 and 0.243 versus 0.237, p=0.855, respectively]. In the subgroup of patients taking "incongruent" medications at baseline (n=213), significantly fewer patients who switched to congruent medications by 8 wk experienced SEs compared to those who remained on incongruent medications [6.5% (5/77) versus 16.5% (22/136), p=0.045]. Patients in this baseline incongruent subgroup who became congruent by 8 wk also had significantly fewer SEs compared to those who remained incongruent (0.065 versus 0.242, p=0.002).

Conclusions: Medication treatment decisions guided by combinatorial PGx testing for patients with MDD who have failed at least one antidepressant medication trial result in reduced side effect frequency and burden. Patients switched from genetically incongruent to genetically congruent medications have the greatest benefit from combinatorial PGx testing.

Keywords: Pharmacogenomic-Guided Treatment Recommendations, Treatment Resistant Depression, Major Depressive Disorder (MDD), Drug Side Effects, Pharmacogenetic Response

Disclosure: Janssen Pharmaceutical, Advisory Board, Naurex (Allergan), Advisory Board, Cerecor Pharmaceutical, Advisory Board, Assurex Health, Consultant, NeuralStem, Advisory Board, Sage Therapeutics, Advisory Board, National Network of Depression Centers, Board Member, American Foundation for Suicide Prevention, Board Member, Canadian Depression Research Intervention Network, Advisory Board, Le Royal, Advisory Board, Depression and Bipolar Support Alliance, Board Member, Psychiatric Research Society Board of Directors, Board Member, Genomind, Inc., Advisory Board

M85. Pharmacological Considerations in Pregnant and Postpartum Women With Bipolar Disorder

Wendy Marsh, Kailai Duan, John Straus, Nancy Byatt*

University of Massachusetts, Worcester, Massachusetts, United States

Background: With a rate of up to 1 in 8 women becoming depressed in the pregnancy and postpartum (perinatal) period, mood episodes during the perinatal period are receiving increased and due attention. While evidence-based treatments for depression (and anxiety) include non-pharmacological approaches such as therapy, the best data for mood stabilization in bipolar disorder is medication based. While the pharmacological treatment of unipolar depression is gaining traction in obstetrics, the status of pharmacological considerations of bipolar disorder in perinatal women is less well documented. We hypothesize that in perinatal care providers of pts with mental illness both bipolar disorder and medications used to treat bipolar are increasingly being discussed in phone call consultations with perinatal psychiatrists.

Methods: Data was collected from, the Massachusetts Child Psychiatry Access Program for Moms (MCPAP for Moms), a population-based program to help health care providers address mental health and substance use disorders among pregnant and postpartum women. Clinical encounter data from community health care providers with MCPAP for Moms perinatal psychiatrists were collected during telephone consultations. Descriptive statistical methods were used.

Results: From Jul 2014 to June 2018, MCPAP for Moms served 4,544 women, of whom 579 or 12.7% in which bipolar spectrum was considered in the differential. Bipolar disorder came in third of mental health issues requested to be addressed. First anxiety/stress disorders spectrum 39.8% (n=1810) followed closely by depressive disorder spectrum at 36.2% (n=1650). Medication treatments (antipsychotics, anti-epileptics, lithium) associated with bipolar disorder treatment were discussed in 16.0% (n=729) of encounters. More than one medication type or diagnosis can be associated with one encounter. Frequency of bipolar diagnosis and bipolar medication discussion will be presented over time.

Conclusions: Bipolar disorder is being considered in perinatal women in whom their health care provider is concerned about their mental health. Despite relatively high risk of teratogenicity with many traditional mood stabilizers (example valproate) and relative paucity on information on safety in pregnancy on many newer mood stabilizers (example atypical antipsychotics) compared to fist line treatments in depression and anxiety such as selective serotonin reuptake inhibitors, discussion of mood stabilizing medication in pregnant and postpartum women is taking place.

Keywords: Bipolar Disorder, Pregnancy, Pharmacology

Disclosure: Nothing to disclose.

M86. Cellular Aging Associated With Severe Stress in Suicidal Patients

Ricardo Caceda, Sue Griffin, Pedro Delgado, Jorge Gamboa*

Stony Brook University, Stony Brook, New York, United States

Background: Telomere length, a marker of cellular aging, is associated with psychological stress and several psychiatric disorders including major depression. Suicide is usually associated with mental illness. Suicidal crises are usually triggered by overwhelming psychological pain and overtly psychosocial stressful situations. We previously described shorter telomere length in individuals with current suicidal ideation than in recent suicide attempters. Here we aim to test the temporal dynamics of psychological pain and stress on cellular aging in suicidal individuals.

Methods: We measured buccal cellular and mitochondrial telomere length, salivary cortisol, psychological pain, depression, hopelessness and demographic variables in depressed adult patients hospitalized for acute suicide risk in an academic center: current suicidal ideation (n = 131) and recent suicide attempt (n= 84) within the previous 5 days.

Results: The suicidal ideation group had more severe depression, psychological pain, longer mitochondrial telomere length, and higher salivary cortisol than the suicide attempt group. Telomere length was negatively associated with depression, suicidal ideation, salivary cortisol and psychological pain severity. In the suicide attempter group telomere length was associated with time since the attempt.

Conclusions: Our findings suggest that the decrease telomere length in suicidal patients may be more influenced by the overtly stressful nature of a suicidal crisis, rather than suicidal behavior itself.

Keywords: Suicide, Acute Stress, Telomere

Disclosure: Nothing to disclose.

M87. Real-Time fMRI as a CBT Adjunct: Predicting the Behavioral Impact of Neurofeedback

Kathryn Dickerson, Katherine MacDuffie, Jeff MacInnes, Kari Eddington, Timothy Strauman, R. Alison Adcock*

Duke University, Durham, North Carolina, United States

Background: Cognitive behavioral therapy (CBT) focuses on changing inaccurate, negative thoughts and behaviors. Though a handful of studies have begun to examine the neural correlates of CBT, no study to date has combined rtfMRI neurofeedback with CBT with the goal of evaluating therapeutic efficacy. An experiment from our group aimed to do so by showing individuals how brain activation within the anterior cingulate cortex (ACC) changes in response to 1) personalized, negative autobiographical memories or worries (e.g., death of parent) and 2) use of a therapeutic strategy (e.g., regulate). Prior analyses of our data showed that ACC neurofeedback "strength" (cingulate activation for STRATEGY – MEMORY trials) correlated with self-reported immediate post-scan strategy efficacy ratings and predicted strategy efficacy and frequency ratings one-month post-scan. The aim of the present report is to identify whole brain predictors of behavioral change following neurofeedback, both to understand the neural mechanisms of CBT and for continued intervention development.

Methods: We recruited individuals (male and female) who had completed a standardized course of CBT as part of a clinical trial (N=24). Participants in our study (N=13) provided a list of personal episodic negative memories or worries as well as strategies used to cope with their mood. During neurofeedback runs, participants viewed a feedback summary after each MEMORY and STRATEGY trial as an index of how brain activity from their cingulate cortex changed in response to negative memories/worries and therapeutic strategies. During post-scan analyses, we constructed a whole brain general linear model with the following predictors: baseline BDI score, medication status, time since CBT completion, feedback values for the MEMORY trials, feedback values for the STRATEGY trials, emotionality of the MEMORY trials, follow-up strategy frequency ratings, and follow-up strategy efficacy ratings. We were specifically interested in examining brain regions engaged during MEMORY trials, STRATEGY trials, comparison between the two trial types, and given our prior findings – what correlated with self-reported strategy efficacy and frequency of use.

Results: We first examined whether brain activation correlated with clinical symptoms. We observed that during Memory trials (relative to Strategy trials), baseline BDI scores positively correlated with activation within the inferior frontal gyrus and supramarginal gyrus. Given our prior findings that ACC neurofeedback "strength"

correlated with self-reported strategy efficacy and frequency, we next examined if any additional brain regions tracked perceived strategy efficacy or frequency. Indeed, during Strategy trials (relative to Memory trials), activation within the periaqueductal gray nucleus (PAG), insula, and temporal pole predicted self-reported frequency of strategy use one-month post-scan (i.e., more PAG activation was associated with greater frequency of strategy use). All results are whole brain, cluster corrected with FSL Flame 1 to $p<0.05$ (thus correcting for multiple comparisons).

Conclusions: Activation in regions associated with physical and emotional pain (e.g., PAG and insula) were engaged when using strategies to regulate sad memories/worries. This suggests that though using strategies to regulate negative memories/worries may be an emotionally painful process, it may still be fruitful as PAG and insula activation also predicted strategy use one month later. These results contribute novel findings regarding the neural mechanisms underlying CBT and suggest novel brain regions as potential future targets.

Keywords: Major Depressive Disorder (MDD), Real-time fMRI Neurofeedback, Anterior Cingulate Cortex (ACC), Cognitive Behavioral Therapy

Disclosure: NeuroLeadership Institute, Consultant

M88. Reward-Circuit Biomarkers of Risk and Resilience in Adolescent Depression

Adina Fischer, Monica Ellwood-Lowe, Natalie Colich, Anna Cichocki, Tiffany Ho, Ian Gotlib*

Stanford University, San Carlos, California, United States

Background: There is an estimated 36% cumulative incidence of Major Depressive Disorder (MDD) in adolescent females in the United States. Dysfunctional reward processing underlies core features of major depressive disorder, including anhedonia, depressed mood, and decreased motivation. While there is growing knowledge of reward processing dysfunction in adolescent depression, researchers have ignored underlying neural mechanisms of resilience. Here, we examine neural correlates of reward processing that characterize resilience and risk in adolescents at risk for depression, an essential step toward advancing our understanding of how to strengthen resilience to psychopathology in at-risk youth.

Methods: 50 adolescent females were followed longitudinally through age 18: 32 at-risk adolescents who either did not experience depression (resilient; n=17) or had previously experienced a depressive episode (remitted-depressed; n=15), and 18 low-risk healthy controls. Participants completed clinical assessments at 18-month intervals and completed an fMRI reward-processing task in late adolescence. We conducted predictive modeling using logistic regression with a priori reward regions of interest (ROIs).

Results: At-risk resilient and remitted-depressed adolescents exhibited less striatal and supramarginal gyrus activation than did controls during anticipation of reward versus loss ($Z>2.3$ cluster-level $p<0.05$). Resilient adolescents also exhibited greater activation than did remitted-depressed adolescents in the middle frontal gyrus during anticipation of reward versus loss, and less activation in the superior frontal gyrus and cuneus during outcome of reward versus loss ($Z>2.3$ cluster-level $p<0.05$). Using predictive modeling, we found that ventral anterior cingulate cortex and bilateral putamen activation during reward processing distinguished resilient from remitted-depressed at-risk adolescents with 83% accuracy.

Conclusions: Distinct patterns of neural activation in the processing of reward appear to be markers of risk and resilience that may be targets for prevention and treatment approaches aimed at strengthening adaptive reward processing in at-risk adolescents.

Keywords: Risk and Resilience, Major Depressive Disorder (MDD), Adolescence, Reward Circuitry, fMRI Biomarkers

Disclosure: Nothing to disclose.

M89. Interleukin-8 (but Not Interleukin-6) Shares Genetic Overlap With Risk for Suicide Attempt: The Confounding Roles of Sex and BMI

Emma Knowles, Joanne Curran, Ana Leandro, Harald Göring, Rene Olvera, Ravi Duggirala, Laura Almasy, John Blangero, David Glahn*

Yale University, Hartford, Connecticut, United States

Background: Suicide is major public health concern. In the United States alone the rate of suicide attempts has risen by 30% since 1999 and research shows that those attempts are not always preceded by a known mental health condition. Suicide is preventable if risk can be identified and appropriate interventions provided promptly. To this end it is imperative to identify robust and reliable indicators, or biomarkers, of suicide risk that transcend traditional diagnostic boundaries. Previous work has revealed a relationship between increased inflammation and risk for suicidal behavior, but it is not clear the extent to which these alterations are genetically linked or if they are driven by environmental confounds (e.g. sex or BMI). We present the first study to directly address whether the shared etiology is due to genetic factors while considering the role of potential confounds.

Methods: Genetic analyses were conducted in SOLAR in a sample of 1884 Mexican-American individuals from extended pedigrees (83 families, mean size = 21.67 individuals, range 2-178 individuals). The sample was 60.43% female and had a mean age of 42.04 years (sd = 15.74 years, range = 18-97 years). Using bivariate polygenic models, genetic correlations were calculated between IL-6 and IL-8 and lifetime risk for suicide attempt. The effects of sex, BMI, depression, medication, and smoking status were considered on the genetic overlap between phenotypes.

Results: 159 individuals endorsed having attempted suicide in their lifetime ($h2 = 0.47$, $p = 2.68\times10\text{-}05$). IL-6 ($h2 = 0.17$, $p = 5.46\times10\text{-}05$) and IL-8 ($h2 = 0.30$, $p = 4.54\times10\text{-}14$) were significantly heritable. Genetic correlation analysis (including significant covariates) revealed a significant correlation between risk for suicide attempt and IL-8 ($\rho g = 0.49$, $se = 0.17$, $p = 3.16\times10\text{-}03$). BMI was a significant covariate of IL-6 ($p=9.85\times10\text{-}29$) and interestingly the genetic correlation between suicide attempt and IL-6 was significant only if BMI was removed as a covariate ($\rho g = 0.53$, $se = 0.19$, $p = 6.93\times10\text{-}03$). Suicide attempts were significantly more common in females ($p=0.01$) and the genetic relationship between IL-8 and suicide attempt appeared to be driven by females ($\rho g = 0.57$, $se = 0.17$, $p = 6.49\times10\text{-}03$), it was not significant in males alone ($\rho g = 0.26$, $se = 0.49$, $p = 0.61$). The inclusion of major depression, and medication or smoking status in the model did not alter the results.

Conclusions: Previous literature on inflammation and suicide has placed greater focus on IL-6 than IL-8 as a marker of risk; but the present results demonstrate that IL-8 (but not IL-6) have shared genetic influences with risk for suicide attempt and that this is a sex-specific effect driven by females, which may explain why it has previously been overlooked. It appears that the effects of BMI on inflammation levels might have confounded results from previous studies that have placed greater emphasis on IL-6 for suicide risk.

Keywords: Suicide, Inflammation, Peripheral Biomarker, Mood Disorder, Sex

Disclosure: Nothing to disclose.

M90. A Magnetic Resonance Spectroscopy Study of Glutamate and Other Metabolites in Fronto-Limbic Regions in Adolescents and Young Adults at Increased Genetic Risk for Bipolar Disorder

Rhoshel Lenroot, Bronwyn Overs, Brenda Ta, Gloria Roberts, Caroline Rae, Janice Fullerton, Philip Mitchell*

University of New South Wales, Albuquerque, New Mexico, United States

Background: Individuals at high genetic risk for bipolar disorder (BD) have shown differences in structure and function of fronto-limbic brain regions that are associated with emotional regulation. Genetic risk for BD is also associated with risk of depressive and anxiety disorders, which may indicate progression towards BP. Glutamate has been implicated in the pathophysiology of BD. There have been few previous magnetic resonance spectroscopy (MRS) studies in at-risk individuals and results have been mixed. We therefore used proton magnetic resonance spectroscopy (MRS) to measure glutamate (Glu) N-acetylaspartate (NAA), creatine (Cre), choline (Cho), and myo-inositol (MI) in a large cross-sectional sample of at-risk adolescents and young adults and to test for effects of age and lifetime history of a depressive or anxiety disorder. We hypothesized that glutamate levels would be increased in high-risk youth and NAA would be decreased.

Methods: Population: 188 individuals aged 14-33, including 98 (43 male) at-risk (AR) first degree relatives of individuals with BP and 90 (41 male) community controls (CON) recruited as part of the Bipolar Kids & Sibs study (for details see (1)). CON excluded history of BP or psychosis but could have other anxiety or depressive disorders. AR or CON with history of either a DSM-IV anxiety or depressive disorder were designated Dx+, those without as DX-. The DX+ group included 47 AR and 20 CON. MRS acquisition: MRS data was acquired on a 3 T Philips Achieva scanner using PRESS (TR/TE 2000/40 ms, 90° flip angle, spectral bandwidth 2000hz, 2 acquisitions per ROI) anterior cingulate (ACC, 20 ×20 ×20 mm), left and right hippocampi (30 ×20 ×15 mm). Structural MRI was acquired to quantify voxel tissue composition. MRS analysis: Spectra were quantified using jMRUI(2). Residual water signals were removed prior to fitting and water peaks measured from unsuppressed spectra. Final sample size after removal of data due to poor-quality spectra, missing covariate data, diagnostic discrepancies, and outliers was 159 ACC (78 control), 120 L hippocampus (49 control), and 98 R hippocampus (43 control). The Dx+ subset included 39 Dx+ AR and 13 Dx+ CON. Gln was analyzed within subset of data with adequate GLN estimates (Cramer Rao lower bound < 50% for ACC, Gln estimate < 3SDs for Hippocampus): this included 78 for the ACC (33 control), 104 and 89 for left and right hippocampi respectively. Metabolites are reported as ratio to water. Statistical analysis: Linear mixed effects models were used including fixed effects of group (AR or CON), gender, age, gray matter percentage (gm%) and presence of lifetime diagnosis of depression or anxiety disorder. Bilateral hippocampal metabolite ratios were included in a single model, with hemisphere as a repeated and fixed factor. In instances where hemisphere interactions were observed, additional unilateral models were run to explore the effects within each hemisphere separately. A backwards selection method was used to define the final model for each metabolite ratio.

Results: Cr levels were higher in hippocampus in AR than CON ($t=2.20$, $p=.03$). There were no other significant group differences between AR and CON. For the ACC model containing NAA, an interaction of age with group was seen (all reported results significant at $p<.05$): NAA levels decreased with age in CON but increased in AR. History of a depressive or anxiety disorder affected metabolite levels: in R and L hippocampus Gln and Cho levels were higher in Dx+ than Dx-. Several metabolites showed interactions between risk status and history of anxiety or depression. In the ACC, Cr was higher in AR Dx+ but not different in CON. NAA was lower in CON Dx- than CON Dx+, but the pattern as reversed in the AR subjects. In R and L hippocampus, Cho was lower in AR Dx+ than AR Dx-, but higher in CON Dx+ than CON Dx-. Age also interacted with Dx: in the ACC, Gln increased with age in Dx+, but did not show age effects in Dx-.

Conclusions: In the largest study reported to date of metabolite levels in fronto-limbic areas in adolescents and young adults at increased genetic risk for BD, we found increased hippocampal Cr in the at-risk group and evidence of complex interactions of genetic risk, history of anxiety or depressive disorder, and age. Previous reports in smaller studies have had mixed results, but overall not found a strong effect of genetic risk on metabolite levels (3). Our findings are consistent with this, but the presence of interaction effects suggests that history of mood and anxiety symptoms and developmental effects may be contributing to variability in MRS results. Limitations of the study include cross-sectional design, smaller number of CON subjects with history of anxiety and mood disorders, and challenges measuring Gln at 3 T. Future directions include analysis of metabolite levels against symptom scores rather than categorical diagnoses, and comparison of metabolite levels in the subset of AR individuals who develop bipolar disorder.

Keywords: Proton Magnetic Resonance Spectroscopy, Bipolar Disorder, High Risk, Glutamate

Disclosure: Nothing to disclose.

References:

1) Perich et al., J Psych Res 2015 62:71.

2) Stefan et al., Measurement Sci and Tech 2009 20:104036

3) Hajek et al., J Psych Neurosci, 2008 33:531

M91. Escitalopram Response is Associated With Pre-Treatment Neuraland Clinical Correlates of Anhedonia

Katharine Dunlop, Sakina Rizvi, Xiamen Leng, Stefanie Hassel, Stephen Strother, Raymond Lam, Roumen Milev, Susan Rotzinger, Jane Foster, Benicio Frey, Sagar Parikh, Claudio Soares, Rudolf Uher, Gustavo Turecki, Glenda MacQueen, Jonathan Downar, Sidney Kennedy*

Weill Cornell Medical College, New York, New York, United States

Background: Anhedonia is a core feature of major depression, and is associated with dysfunction

in mesocorticolimbic regions for reward. High anhedonia a negative predictor of antidepressant

response. However, it is unknown whether anhedonia and brain dysfunction also negatively

predicts escitalopram response. Therefore, the aim of this study is to identify pre-treatment

predictors of escitalopram response using clinical and fMRI correlates of anhedonia.

Methods: 134 men and women were recruited as part of the Canadian Biomarker Integration

Network in Depression. Patients underwent 8 weeks of open-label escitalopram treatment. K-means clustering using MADRS scores was used to identify MDD groups with similar trajectories of antidepressant response. Using two valid instruments, we assessed anhedonia severity at baseline and at 8-weeks. All participants completed a monetary incentive delay task (MIDT) in the fMRI at baseline, 2-weeks and 8-weeks. All analyses were

executed in FSL using default preprocessing and first-level statistics.

Results: Patients clustered into 'fast' responders, 'slow' responders and non-responders. Slow

responders and non-responders reported significantly higher pre-treatment anhedonia ($p < 0.05$)

relative to fast responders and controls. Ventral striatal functional connectivity throughout the task correlated with anhedonia severity in healthy controls; this relationship was absent in the MDD

group. Task-evoked mesocorticolimbic and medial parietal activity differentiated escitalopram

non-responders from escitalopram responder groups.

Conclusions: The results indicate that escitalopram non-responders display significantly higher

clinical and neural correlates of anhedonia. Future work will incorporate genetic and molecular

factors of reward processing that may likely impact escitalopram response, as well as machine

learning processes to assess the individual-level prediction accuracy of these features.

Keywords: Brain Based Markers for Depression, Anhedonia, Depression, Functional MRI (fMRI), Escitalopram

Disclosure: Nothing to disclose.

M92. Association Between Depression Severity and Hippocampal Volumes in Vietnam War Veterans With PTSD, TBI, Both, or Neither

*An Li, Sonja Stojanovski, Arielle Levy, Gabriel Devenyi, Mallar Chakravarty, Anne Wheeler**

SickKids Research Institute, Toronto, Canada

Background: High comorbidity is found between post traumatic stress disorder (PTSD), traumatic brain injury (TBI) and depression and reduced hippocampal volume has been associated with all three conditions suggesting that the etiology and neural basis of these disorders may overlap. The objective of this study was to examine whether the association between depression severity and hippocampal volume is moderated by the presence of TBI or PTSD.

Methods: The Alzheimer's Disease Neuroimaging Initiative – Department of Defence (ADNI-DOD) dataset of aging veterans was utilized for the study. Hippocampal volumes including subfields and extrahippocampal white matter projections were automatically extracted from T1-weighted MRIs in veterans with PTSD (n=48), TBI (n=13), PTSD&TBI (n=19), and healthy aging controls (n=44) using the MAGeT brain segmentation pipeline. Depression severity was assessed with the geriatric depression scale. Linear models were used to examine relationships between hippocampal volumes and depression severity, as well as interactions with group membership.

Results: A negative association between hippocampal volumes and depression severity in veterans was moderated by the presence of PTSD such that in the two PTSD groups there was no association between hippocampal volume and depression severity. This effect was observed in both the hippocampus and extrahippocampal white matter projections and was most pronounced in the left hemisphere.

Conclusions: These results suggest that the relationship between hippocampal volume and depression severity is moderated by the presence of PTSD. Distinct neural bases of depression severity in veterans with TBI and PTSD potentially indicate distinct etiology of depression symptoms that may benefit from different types of treatments.

Keywords: Depression, Traumatic Brain Injury, Post Traumatic Stress Disorder, Hippocampal Volume, Veterans

Disclosure: Nothing to disclose.

M93. Aberrant White Matter Microstructure Relates to Elevated Irritability in Pediatric Bipolar Disorder and Disruptive Mood Dysregulation Disorder

Julia Linke, Nancy Adleman, Joelle Sarlls, Andrew Ross, Samantha Perlstein, Heather Frank, Kenneth Towbin, Daniel Pine, Ellen Leibenluft, Melissa Brotman*

National Institutes of Health, NIMH, Bethesda, Maryland, United States

Background: Longitudinal data showed that chronic pediatric irritability, which affects approx. 10 million youth in the U.S., does not confer the risk to develop bipolar disorder (BD). This led to the creation of the DSM-5 diagnosis of disruptive mood dysregulation disorder (DMDD). Albeit on a different timescale, both DMDD and BD share an elevated proneness to anger, but whereas numerous diffusion tensor imaging (DTI) studies in BD suggested altered myelin plasticity as a key mechanism in this disorder, DTI has not yet been applied in DMDD. Research on how BD and DMDD differ with regard to structural connectivity might guide the development of targeted interventions for these different, but equally impairing phenotypes.

Methods: We acquired DTI data from 118 participants (BD=36, DMDD=44, HV=38). After preprocessing with TORTOISE applying robust tensor fitting, images of fractional anisotropy (FA), longitudinal diffusivity (LD) and radial diffusivity (RD) were processed with tract based spatial statistics. Next, the three measures were used in an ANCOVA each with age, sex and medication load as nuisance variables and to train Gaussian process classifiers to predict, which group participants belong to. Finally, we determined how results relate to the symptom dimension of irritability.

Results: In BD vs. HV, we observed widespread reductions in FA and increased RD centered at the corticospinal tract (5206 voxels, pmin=0.0002). In DMDD vs. HV, reductions in FA were confined to the anterior corpus callosum (1494 voxels, pmin=0.007) and negatively associated with the symptom dimension of irritability ($rS = -.34$, $p < .001$) and with reduced LD (1453 voxels, pmin=.0002). In BD vs. DMDD, FA in the corticospinal tract and the posterior corpus callosum was reduced. While we observed a negative association between FA in the corticospinal tract and irritability ($rS = -.39$, $p < .001$), there was a positive association in the posterior corpus callosum in DMDD only ($rS=.55$, $p=.0001$). The Gaussian process classifier could discriminate between BD and HV with an accuracy of 75%, and between DMDD and HV with an accuracy of 68%.

Conclusions: We replicated findings of widespread reduced FA and increased RD in BD, supporting the hypothesis of altered myelination in BD. Alterations in DMDD were more regionally discrete and related to altered longitudinal diffusivity. Reduced FA in the anterior corpus callosum observed in both patient groups and previously associated with working memory performance and the corticospinal tract relevant in BD only and previously associated with processing speed were associated with elevated levels of irritability. In DMDD only, irritability was positively associated with FA in the posterior corpus callosum. From a clinical perspective, these findings will contribute to the pathophysiological understanding of DMDD and its differentiation from BD.

Keywords: Irritability, Disruptive Mood Dysregulation Disorder, Bipolar Disorder, Diffusion Tensor Imaging (DTI), Machine Learning Classification

Disclosure: Nothing to disclose.

M94. Cortical Thickness Increases With Levomilnacipran in a Randomized Placebo-Controlled Trial in Late-Life Depression

*Beatrix Krause, Lisa Kilpatrick, Prabha Siddarth, Kelsey Laird, Linda Ercoli, Yesenia Aguilar-Faustino, Katherine Narr, Helen Lavretsky**

Semel Institute for Neuroscience & Human Behavior, Los Angeles, California, United States

Background: Late-life depression (LLD) is frequently comorbid with medical and cognitive disorders and can results in an inadequate treatment response. More efficacious treatment to improve mood, cognition and quality of life in LLD are urgently needed. Levomilnacipran (LMIL) is a novel anti-depressant whose effects on neuroplasticity have not yet been investigated. We investigated the effect of LMIL on brain cortical thickness in a randomized control trial (RCT).

Methods: Twenty-nine adults>60 years with major depression (48.3% female; mean age=71.5[SD=5.8] years; mean education=16.0[SD=1.7] years) were randomized to either LMIL or placebo for 12 weeks. Inclusion criteria were a Hamilton Depression Scale (HAMD) >16. T1-weighted images were acquired at baseline and 12-weeks using a Siemens 3 T Prisma system. Freesurfer version 6.0 was used for cortical reconstruction and a whole-brain longitudinal voxel-wise two-stage model was used to compare the between-group symmetrized percent change in cortical thickness across treatment. Age and total intracranial volume were included as covariates. Voxel threshold was set 1.3-5 and Monte-Carlo cluster threshold to 1.3. The smoothing factor was set to 15 full-width half-maximum.

Results: Of the 29 randomized subjects, 15 subjects (6 LMIL and 9 placebo) completed the study. Dropout rates did not significantly differ between groups. Both groups improved in HAMD (LMIL median change=-14, p=.06; Placebo=-8, p=.004; between-group, p=.5) but LMIL showed greater rates of remission (LMIL=57%; Placebo=33%, p=0.3). In addition, the LMIL group showed larger increases in cortical thickness in the right postcentral gyrus (primary somatosensory) X=44, Y=-26.9, Y=53.8; cluster size=966mm2), the precentral gyrus (primary motor) (X=17.3, Y=-22.1, Z=15.7; 948.9mm2), and the lateral occipital cortex (visual cortex) (X=19.6, Y=-94.9, Z=15.7; 930mm2) while the placebo group decreased over time.

Conclusions: Both, LMIL and placebo groups showed improvement in depression severity with higher remission rates in the LMIL group. However, the LMIL group demonstrated a gain or preservation of cortical thickness in primary sensorimotor and visual regions in contrast to decreases in thickness in the placebo group. Larger studies are necessary to detect drug/placebo differences in clinical outcomes in relationship to brain neuroplasticity.

Keywords: Late-life Depression, CNS Clinical Trials, Neuroimaging Biomarkers, Cortical Thickness, Levomilnacipran

Disclosure: Allergan, Grant

M95. Obesity is a Predictor of White Matter Microstructure Damage in Cingulate Gyrus of Euthymic Bipolar Patients

*Ramiro Reckziegel, Monise Costanzi, Isadora B. Remus, Leticia S. Czepielewski, Pedro D. Goi, Mireia F. Vianna-Sulzbach, Raffael Massuda, Clarissa Gama**

Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, Porto Alegre, Brazil

Background: Obesity is associated with both structural and functional changes of the central nervous system, and has a high prevalence in BD. It is defined by a body mass index (BMI) higher than 30, which is associated with illness severity, worse functioning status and cognitive impairment. Such deficits are possibly related to microstructural damage in the connective tracts of white matter. Diffusion tensor imaging (DTI) has been employed as a highly sensitive tool to investigate microstructural changes in white matter structure. Fractional anisotropy (FA) is the most commonly used parameter as it is the best estimate of fiber integrity as well as axonal and myelin degeneration. It has been reported an association with BMI in depressed BD patients, but not in euthymia nor in comparison with a control group (CTR). Therefore, our aim was to test the association between body mass index (BMI) and white matter integrity in euthymic patients with bipolar disorder (BD) and healthy controls (CTR) by diffusion tensor imaging study.

Methods: One hundred and one individuals were assessed for magnetic resonance imaging, consisting in 35 patients with BD and 66 CTR. We acquired high-resolution volumetric T1 and T2 weighted, and DTI data on a 1.5 T Philips scanner. A linear regression models were performed to test the hypothesis controlling for age, sex and skull size.

Results: BMI predicted fractional anisotropy (FA) of the cingulate gyrus terminal endings in individuals with BD (Left: $r^2 = 0.235$, $t = -2.792$, $\beta = -0.455$, $p = 0.010$, Right: $r^2 = 0.265$, $t = -2.060$, $\beta = -0.329$, $p = 0.050$), but not in CTR. When we analyzed all participants together including a BMI x group interaction, it explained the variation of the average cingulate gyrus FA better than BMI or group alone ($r^2 = 0.217$, $t = -1.976$, $\beta = -1.090$, $p = 0.052$).

Conclusions: Obesity predicted white matter microstructural damage to the cingulate fibers in patients with BD during euthymia. The structural neurological damage we found in our sample associated with BMI is likely to be a systemic consequence of a pervasive pattern of inflammatory toxicity. The association between obesity and white matter microstructural damage was present regardless acute symptomatology, but only in patients, suggesting a cumulative effect of combined pro-inflammatory states.

Keywords: Bipolar Disorder, Obesity, White Matter, DTI

Disclosure: Daiichi-Sankyo, Advisory Board, Janssen-Cilag, Advisory Board

M96. A Network Model of Resting-State Brain Connectivity Predicts Heterogeneous Symptoms of Major Depression

*Yu Meichen, Kristin A. Linn, Russell Shinohara, Mary Phillips, Desmond Oathes, Maria Oquendo, Melvin McInnis, Maurizio Fava, Madhukar Trivedi, Myrna Weissman, Yvette Sheline**

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Major depressive disorder (MDD) is characterized by heterogeneous symptoms, the neurobiological basis of which is still largely unknown. Brain network studies have consistently reported disruptions of several resting-state networks (RSNs) in MDD patients, including hypoconnectivity in the frontoparietal network (FPN), and hyperconnectivity in the default mode network (DMN) and between the DMN and FPN. In this study we aimed to identify the correlations between network abnormalities and symptoms using canonical correlation analysis (CCA), a powerful multivariate correlation approach aiming to seek maximal correlations between two groups of variables.

Methods: We used a multi-site sample of patients from the EMBARC dataset (n = 189 MDD: n = 39 demographically matched

healthy controls). Unmedicated participants were recruited from four clinical sites: Columbia University (CU), Massachusetts General Hospital (MGH), the University of Texas Southwestern Medical Center (TX), and the University of Michigan (UM). All participants provided written informed consent and the institutional review boards from the four clinical sites approved all study procedures. Both patients and healthy individuals were administered the Structured Clinical Interview for DSM-IV-TR, the Hamilton Depression Rating Scale (HAMD), Quick Inventory for Depression Symptomatology (QIDS), Mood and Anxiety Symptom Questionnaire (MASQ), Concise Associated Symptoms Tracking (CAST), Concise Health Risk Tracking (CHRTP-propensity), Concise Health Risk (CHRTP-risk), Childhood Trauma Questionnaire (CTQ), Snaith-Hamilton Pleasure Scale (SHAPS), NEO-Five Factor Inventory (NEO) and Speilberger State Anxiety Inventory (STAI). T1-weighted (T1) images were processed using the ANTS Cortical Thickness pipeline and two resting-state fMRI runs were collected for each participant. Time series data from each participant were processed using the XCP Engine, which uses an optimized confound regression procedure to reduce the influence of subject motion. After standard processing we ran a pipeline for statistical harmonization of data collected from multiple sites to correct for site effects. We then computed within and between network metrics for all of the standard Power networks, resulting in 55 variables. We clustered item level clinical symptoms across the 216 items, producing 4 different clusters. Using CCA, we correlated the 55 network variables with the 4 clinical symptom clusters.

Results: Within-network connectivity was decreased in several task-positive networks, including the FPN, the dorsal attention network (DAN) and cingulo-opercular network (CON), but increased in the DMN and salience network (SAN). The between-network connectivity was increased in DAN, FPN, DMN and SAN, particularly in the DAN and FPN. The 216 item-level clinical data were clustered into 4 types of depression symptoms: a depression composite (general mood symptoms, anhedonia, anxiety, neuroticism, and suicidal tendency), positive traits (extraversion, openness, agreeableness, conscientiousness and positive childhood experiences), emotional neglect/abuse, and physical abuse. We detected a CCA mode, which linked these depression symptoms to specific brain network connectivity: 1) the depression composite was mainly correlated with between network connectivity of DAN-VAN; 2) emotional neglect/abuse was mainly correlated with between-network connectivity involving the FPN and DAN; 3) positive traits were specifically associated with the network connectivity in subcortical areas and the CON.

Conclusions: Overall, our study detected associations between functional connectivity and behavioral measures. It proposes a predictive network model to bridge the heterogeneous symptoms and abnormal network architecture in MDD. RSN connectivity patterns may assist in the interpretation of the underlying neurobiological basis for MDD symptoms and serve as a useful biomarker in understanding the disease.

Keywords: fMRI, Resting State Networks, Canonical Correlation Analysis (CCA)

Disclosure: Nothing to disclose.

M97. Sex Hormones, Resting Regional Cerebral Blood Flow With PET, and Resting Functional Connectivity With fMRI in Healthy Women and Women With PMDD

Shau-Ming Wei, Erica Baller, Pedro Martinez, Katherine Reding, Philip Kohn, J. Shane Kippenhan, Michael Gregory, Angela Ianni, David Rubinow, Peter Schmidt, Karen Berman*

National Institute of Mental Health, Bethesda, Maryland, United States

Background: Basic and clinical studies demonstrate that the sex hormones estradiol and progesterone modulate neurocircuitry related to cognition and affective regulation in healthy women and those with premenstrual dysphoric disorder (PMDD). PMDD, a prevalent and debilitating condition that affects 3-15% of women of reproductive age, refers to the appearance of mood and behavioral symptoms in the luteal (post-ovulatory/premenstrual) phase of the menstrual cycle. Abnormal behavioral responsivity to the natural fluctuation of ovarian hormones is implicated in the pathophysiology of PMDD, but the neural substrates of this differential behavioral sensitivity remain poorly characterized. In this study, we used a six-month pharmacological hormone manipulation protocol in healthy women and women with PMDD to investigate the effects of estradiol and progesterone on two measures of resting brain function: regional cerebral blood flow (rCBF) with the oxygen-15 water positron emission tomography (PET) method and resting state functional connectivity (rs-FC) with fMRI.

Methods: Forty-three healthy, asymptomatic women and 20 women with PMDD underwent two eyes-open resting PET scans (10 mCi of oxygen-15 water/scan, GE Advance [Milwaukee] three-dimensional PET scanner [septa retracted, 4.25 mm slice separation, 35 slices, axial field of view 15.3 cm]) during each of three hormone conditions: ovarian suppression induced by the gonadotropin-releasing hormone agonist leuprolide acetate (Lupron), Lupron plus estradiol replacement, and Lupron plus progesterone replacement. After preprocessing, the two resting rCBF scans of each subject were averaged and entered into a voxel-wise random effects analysis to determine brain regions showing an interaction between diagnosis and hormone condition as well as main effects of hormones at a threshold of $p<0.001$, uncorrected.

Additionally, to test for main effects of hormones in rs-FC, seven healthy, asymptomatic women underwent two rs-fMRI scans (GE 3 T scanner, TR/TE=2000/25 ms, 2.5×2.5×2 mm voxels) during the same hormone manipulation protocol. fMRI preprocessing included motion correction, normalization to MNI space, censoring of corrupted volumes, anatomic CompCor, and bandpass filtering. A subgenual cingulate region, which showed a diagnosis-by-hormone interaction in the PET resting rCBF analysis, was used as a seed ROI and a seed-based correlation analysis was performed at an exploratory threshold of $p<0.005$, uncorrected.

Results: The resting PET rCBF analysis showed a significant interaction between diagnosis and hormone condition in the subgenual cingulate. Post-hoc analyses revealed that in the healthy cohort who did not have PMDD, there were no hormone condition-related differences in rCBF in this region. In contrast, in women with PMDD, we saw differential modulation by ovarian steroids in this subgenual cingulate region. Specifically, in the Lupron alone (hypogonadal) condition (when PMDD symptoms are typically in remission), resting rCBF was higher compared with estradiol or progesterone replacement (when recurrence of PMDD symptoms has been observed).

The fMRI study of rs-FC in healthy women revealed several regions in the default mode network that showed differential connectivity with the subgenual cingulate across hormone conditions. These regions included the medial orbitofrontal cortex (mOFC), parahippocampus, and posterior cingulate. Specifically, FC of the subgenual cingulate with the parahippocampus and posterior cingulate was increased during both estradiol and progesterone replacements compared with Lupron alone. FC between the subgenual cingulate and the mOFC was increased during estradiol replacement and decreased during progesterone replacement compared with Lupron alone.

Conclusions: Our results demonstrate that in PMDD, exposure to experimentally controlled, physiologically relevant levels of ovarian hormones differentially impact resting rCBF in the subgenual cingulate, a region implicated in the pathophysiology

of affective disorders. In healthy women, subgenual cingulate rCBF as measured with a gold standard PET technique, was not altered by hormonal condition, but resting state fMRI revealed that functional connectivity of this region with areas in the default mode network was modulated by estradiol and progesterone. These data provide a framework for understanding the impact of ovarian hormones on the neural control of affective state and the propensity for mood destabilization in PMDD.

Keywords: PET Imaging, Resting-State fMRI, Estradiol, Progesterone, Affective Disorders

Disclosure: Nothing to disclose.

M98. Dentate Gyrus Volume is Associated With Childhood Maltreatment and Depression Severity in Adolescents

*Theo van Erp, Robert Jirsaraie, Megan Faulkner, Kiana Scambray, Julia Fong, Derek Taylor, Uma Rao**

University of California, Irvine, Irvine, California, United States

Background: Early adverse experiences, including childhood maltreatment (MALTX), are a common risk factor for depression, accounting for up to 50% of the attributable risk for the disorder. Important clinical differences exist with respect to age of onset, symptoms, treatment response and clinical course between depressed individuals with or without MALTX, suggesting that there are two distinct subtypes. Neurobiological differences also exist, with documented differences in hippocampal volume between these two subtypes. We present initial findings from an ongoing study, examining the relationship between hippocampal subregion volumes and dimensional measures of MALTX and depression severity scores in adolescents. Based on prior studies in adults, we hypothesized significant negative relationships between dentate gyrus (DG), Cornu Ammonis 3 (CA3), or subiculum volumes and MALTX and depression severity.

Methods: Twenty participants [mean age (SD) = 15.5 (1.5); 13 females] were recruited into a multi-modal imaging study examining the main and interactive effects of MALTX and depression on neural circuitry in adolescents. Hippocampal subregion volumes for DG, CA3 and subiculum were extracted from high-resolution T1-weighted and Turbo Spin Echo scans using Automated Hippocampal Subfield Segmentation (ASHS version 2.2.0-118). MALTX and depressive symptom assessments included the Childhood Trauma Questionnaire (CTQ), the Childhood Adversity Interview (CAI), and the Beck Depression Inventory (BDI) for which total scores were computed. Relationships between the regional volumes and symptom severity scores were assessed using linear regression (R's gam), statistically controlling for age and sex. Initial exploratory analyses examining possible interactive effects of MALTX and depression were performed on all hippocampal subregion volumes [CA1, CA2, ectorhinal, entorhinal, perirhinal, and parahippocampal (PHC) cortexes].

Results: There were significant negative associations between dentate gyrus volume and CAI and BDI scores. Associations between dentate gyrus volume and the CTQ score showed similar patterns but were not significant. Moreover, initial exploratory analyses showed a significant interaction between CAI and BDI scores on PHC volumes indicating the combination of MALTX and depression severity was associated with greater reduction in PHC volume compared to either condition alone.

Conclusions: We found, to our knowledge for the first time, significant relationships among dentate gyrus volume, MALTX and depression severity in adolescents. The stronger relationships between dentate gyrus volume for the CAI compared to the CTQ may suggest that interview-based MALTX data (CAI) are more reliable than questionnaire-based data (CTQ). These findings are consistent with observations in adult humans and rodents. We also found initial evidence for interactive effects of MALTX and depression on PHC volumes. While the findings from these initial analyses will need to be confirmed as more study data are collected, they provide, to our knowledge, the first evidence that MALTX and depression are associated with aberrant dentate gyrus development and that they may have interactive effects on PHC development.

Keywords: Depression, Maltreatment, Adolescent, Imaging, Hippocampus

Disclosure: Nothing to disclose.

M99. Cell -Specific Ablation of Microglial Pattern Recognition Receptors Rage and TLR4 Alters Susceptibility to Depressive-Like Behaviors After Chronic Unpredictable Stress

Tina Franklin, Ronald Duman*

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Chronic stress promotes dysregulation of the innate immune system leading to enhanced inflammatory signaling often associated with depressive symptomology. Growing evidence suggests that innate immune cells such as microglia, promote neuroinflammation in response to stress by releasing danger associated molecular pattern (DAMP) molecules leading to increased inflammatory signaling through their ligation to pattern recognition receptors (PRR) such as toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE). Our previous studies show that microglial RAGE is upregulated in response to chronic unpredictable stress (CUS) and enhanced microglial RAGE expression coincides with the onset and recurrence of stress-induced depressive-like behaviors. Most importantly, constitutive RAGE KO mice show partial attenuation of stress-induced behavioral effects. These novel findings suggest that stress-induced depressive-like behaviors are partially mediated by enhanced microglial DAMP signaling due to increased receptor availability. In this study, we hypothesize that microglial RAGE or TLR4 deletion will attenuate depressive-like behaviors following stress due to suppressed DAMP signaling. Moreover, we hypothesize that the combined deletion of both microglial RAGE and TLR4 in RAGE/TLR4 double knockout mice (RGTR-DKO) will enhance resilience against stress-induced depressive-like behaviors.

Methods: To test this hypothesis, we generated RAGEfl/fl: CX3CR1CreERT, TLR4fl/fl:CX3CR1CreERT and RAGEfl/fl: TLR4fl/fl: CX3CR1CreERT mice and utilized tamoxifen-induced Cre recombinase system for cell-specific knockout of microglial RAGE, TLR4 or both, respectively. Cre negative animals are used as controls. Tamoxifen-induced conditional knockout (KO) mice were tested for cognitive, anxiety and depressive-like behaviors at baseline and after CUS exposure using novel object recognition (NOR), forced swim test (FST), open field test (OFT) and three chambers social interaction (SIT). Microglial morphology was assessed immediately following CUS exposure to determine if microglial PRR deficient mice display reduced microglial reactivity following chronic stress exposure compared to littermate controls.

Results: Microglial TLR4 and RAGE/TLR4 (RGTR) deletion attenuated stress-induced depressive-like behaviors in adult male mice. Stress-induced microglial reactivity was reduced in TLR4 and RGTR knockout animals compared to WT controls. Interestingly, microglia-specific RAGE deletion induced a pro-depressive phenotype in stress-naïve animals. Moreover, microglial RAGE deletion neither enhanced nor prevented depressive-like behaviors following chronic stress exposure.

Conclusions: These results suggest that microglial RAGE and TLR4 signaling have opposing roles in stress-induced depression risk. Microglial RAGE signaling appears to be important for the attenuation of stress-induced behavioral effects while microglial TLR4 signaling enhances vulnerability to depressive-like behaviors. Together, these data provide novel insights into the role of microglial RAGE and TLR4 signaling in stress-induced microglial reactivity and the development of depressive-like behaviors.

Keywords: Depression Inflammation Cytokine, Depression-like Behavior, Innate Immunity, DAMPs, Pattern Recognition Receptors

Disclosure: Nothing to disclose.

M100. Association of Cerebral Intrinsic Activity With Symptomatology in Drug-free Patients With Major Depressive Disorder

*Xinyu Hu, Lianqing Zhang, Hailong Li, Xuan Bu, Weihong Kuang, John A. Sweeney, Qiyong Gong, Xiaoqi Huang**

West China Hospital of Sichuan University, Chengdu, China

Background: Recent neuroimaging studies of major depression (MDD) have highlighted the disrupted topological organization of large-scale functional and structural brain networks in depression (Gong and He, 2015). The relation of different regional brain alterations to different symptom dimensions of MDD remains to be fully characterized. We therefore explore the relations of altered functional cerebral intrinsic activity and symptom dimensions of depression in a relatively large sample of medication-free patients with MDD using regional measures of ALFF and functional connectivity (FC) analysis.

Methods: The study was approved by the local ethical committee and written informed consent was obtained from all subjects. A total of 144 medication-free MDD patients and 86 age and sex matched healthy control subjects (HCS) were studied. Clinical symptoms were evaluated using the 17-item Hamilton Depression Rating Scale (HAMD).

The MRI examinations were performed via a 3-Telsa MRI system (Trio; Siemens, Erlangen, Germany) with an 8 channel phase array head coil. The rs-fMR images were obtained via a gradient-echo echo-planar imaging sequence (TR/TE=2000/30msec, flip angle=90°, slice thickness=5 mm with no gap, 30 axial slices, 175 volumes in each run). Subjects were instructed to relax with their eyes closed without falling asleep during MR examination.

Image preprocessing was performed using DPABI software (Version 2.3, http://rfmri.org/DPABI). Calculation of amplitude of low-frequency fluctuation (ALFF) maps was implemented in REST (http://www.restfmri.net) running under Matlab. Regions with abnormal ALFF values in MDD patients relative to HCS were treated as seed regions for functional connectivity studies. The statistical analyses of ALFF and seed-based FC maps between MDD patients and HCS were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). In all image analyses, statistical inferences were made at $P < 0.05$ using AlphaSim correction to correct for multiple comparisons.

HAMD-17 items were assigned to the following subscales: 'Core affective symptoms' (items 1, 2, 7, 8, 10, 13), 'Sleep' (items 4, 5, 6), 'Activity' (items 7, 8), 'Psychic Anxiety' (items 9, 10), 'Somatic Anxiety' (items 11, 12, 13) and "Delusion"(items 2, 5) according to a previous study (Serretti et al, 1999). Correlation analysis was conducted to assess the relationship between these MDD symptomatology dimensions and averaged eigenvalues of brain regions with altered ALFF and associated FC group differences using the eigenvariate option in SPM8.

Results: Relative to HCS, MDD patients showed lower ALFF in the posterior cingulate gyrus (PCC) and higher ALFF in bilateral orbital frontal cortex (OFC) ($P < 0.05$, with AlphaSim correction). Seed-based FC analysis revealed elevated functional connectivity between PCC and bilateral dorsal cerebellum and between bilateral OFC and bilateral anterior putamen (AP) in the MDD group, while FC between PCC and medial prefrontal cortex was decreased in MDD patients.

ALFF in the PCC was negatively correlated with the HAMD total score ($r = -0.194$; $P = 0.02$), the "sleep" subscale score ($r = -0.208$; $P = 0.013$) and item 16 score for weight loss ($r = -0.208$; $P = 0.013$). The increased FC between PCC and the right dorsal cerebellum was positively correlated with "delusion" subscale score ($r=0.210$, $P=0.012$).

Conclusions: This study added new information about regional changes of intrinsic neural activity in MDD, and it associated changes in FC. In addition, we found association of specific symptoms of depression with brain intrinsic activity in PCC, OFC, cerebellum and AP. One important specific finding was the demonstration of a dissociation of brain activity between OFC and PCC in the MDD patients. The alteration of cerebellar function which correlated with "delusion" subscale suggest its involvement in the cognitive aspects of MDD.

Keywords: Major Depressive Disorder (MDD), Resting-State fMRI, Symptomatology, Functional Connectivity, ALFF

Disclosure: Nothing to disclose.

M101. Classifying Suicidal Behavior Using Resting State Functional Connectivity and Structural Neuroimaging: A Machine Learning Approach

*Savannah Gosnell, Christopher Fowler, Ramiro Salas**

Baylor College of Medicine, Houston, Texas, United States

Background: About 80% of patients who commit suicide do not report suicidal ideation the last time they speak to their mental health provider, highlighting the need to identify biomarkers of suicide behavior. Our objective was to identify neural suicide behavior biomarkers for building a model to classify psychiatric inpatients.

Methods: Suicidal and non-suicidal psychiatric inpatients were recruited over 4.5 years as a part of this case-control study. Eighty percent of the sample was used to determine significant differences in structural and resting state functional connectivity measures throughout the brain. These measures were used in a random forest classification model, which was tested on the remaining 20%.

Inpatients were recruited from the Menninger Clinic, a psychiatric hospital, and neuroimaging was performed close to admittance at the Core for Advanced MRI at Baylor College of Medicine in Houston, Texas.

Inpatients (n=423 of ~600 approached, not excluded for any psychiatric disorder, with no contraindication for neuroimaging and deemed mentally stable enough for MRI) were included if they met suicide criteria determined using the Columbia Suicide Severity Rating Scale (based on previous attempt and current ideation) or control criteria (no previous suicide attempt and no lifetime ideation). Participants had at least one psychiatric disorder (mainly major depression, anxiety, personality, and substance use disorders), and were predominantly Caucasian.

Results: The study classified suicidal (n=63, age=30.56 (11.81) years, males=40.5%) and non-suicidal psychiatric inpatients (n=65, age=34.33 (13.3) years, males=64.2%). The model built on 80% of these inpatients resulted in sensitivity=79.4% and specificity=72.3% using a random forest model. This was replicated in an independent sample (n=32) with sensitivity=81.3% and specificity=75.0%.

From the 57 features that showed significant differences between the two groups and were used for machine learning (in the 80% training sample), 6 were replicated in the 20% testing sample (including resting state functional connectivity between frontal and insular/putamen, habenula and parahippocampal, and amygdala and temporal regions).

Conclusions: Neuroimaging (an unbiased biomarker) can be used to classify suicidal behavior in psychiatric inpatients without observing any clinical features. In the future, clinicians may use neuroimaging to inform the determination of suicide risk.

Keywords: Suicide Prediction, Machine Learning Classification, Resting State Functional Connectivity, Habenula

Disclosure: Nothing to disclose.

M102. Gender-Based Differences in the Association of C-Reactive Protein (CRP) With Resting State Brain Connectivity in Major Depressive Disorder: Findings From the EMBARC Study

Cherise Chin Fatt, Manish Jha, Abu Minhajuddin, Brittany Mason, Tracy Greer, Madhukar Trivedi*

University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, United States

Background: Elevated levels of c-reactive protein (CRP), an inflammatory biomarker, have been associated with reduced connectivity of striatum with other brain regions in previous neuroimaging studies. While gender significantly moderates the association of peripheral inflammation with depressive symptoms severity, it's effect on the association of CRP with functional connectivity remains unknown.

Methods: Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study participants with plasma samples and completed rsfMRI scans available at baseline (total n=204, male n=67, female n=137) were included. Using magnetic resonance imaging, resting-state functional connectivity were computed after parcellating cortical (pacel n=100) and subcortical (parcel n=21) regions based on previously published atlas. Plasma CRP levels (log-transformed due to skewed distribution) were measured with commercially-available ELISA kits. Separate linear regression analysis was conducted for each connectivity pair (connectivity pairs n=7260) as dependent variable, gender-by-logCRP interaction as primary independent variable, and ethnicity, race, site, body mass index, and age as covariates. Gender-stratified analyses were used to interpret the significant interaction.

Results: Gender significantly (all $p<0.05$ after false discovery rate correction) moderated association of logCRP with connectivity of bilateral striatum with left posterior hippocampus and of superior medial frontal region (default mode network) with orbital middle frontal region (executive control network). In all these connectivity pairs, higher levels of CRP were associated with reduced connectivity in females (r= -0.08 to -0.13) but increased connectivity in males (r= 0.37 to 0.48).

Conclusions: Gender is an important biological factor that differentially affects the association of peripheral inflammation with alterations in resting state brain connectivity.

Keywords: Resting State Functional Connectivity, CRP, Major Depression Disorder

Disclosure: Nothing to disclose.

M103. Quantification of Norepinephrine Transporter Occupancy of Venlafaxine Extended-Release in Patients With Major Depressive Disorder Using Positron Emission Tomography and Radioligand [18 F]FMeNER-D2

*Ryosuke Arakawa, Per Stenkrona, Akihiro Takano, Jonas Svensson, Max Andersson, Sangram Nag, Yuko Asamin, Yoko Hirano, Christer Halldin, Johan Lundberg**

Karolinska Institutet, Stockholm, Sweden

Background: Venlafaxine ER is an extended-release (ER) formulation of venlafaxine, with documented clinical effect for treatment for depression. It is categorized as combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) based on the in vitro affinity data of 5-HT transporter (5-HTT) and NE transporter (NET) (Ki 82 nM and 2480 nM, respectively) [1]. Due to the large discrepancy of the affinity between 5-HTT and NET, the in vivo effect of clinical doses of venlafaxine on NE reuptake has been questioned, especially in the lower dose range. While 5-HTT occupancy of clinically relevant doses of venlafaxine in the human brain has been reported previously [2,3], there has been no report of in vivo NET occupancy in the human brain.

[18 F]FMeNER-D2 is a positron emission tomography (PET) radioligand which binds reversibly and selectively to NET. A method for reliable quantification of [18 F]FMeNER-D2 binding in human brain has been described [4]. The applicability of [18 F]FMeNER-D2 PET in clinical occupancy studies has been reported previously.

The aim of this study was a) to verify that clinically relevant doses of venlafaxine occupies NET in the living human brain, and b) to identify the relationship between oral dose and NET occupancy in patients with major depressive disorder (MDD) using PET and [18 F]FMeNER-D2.

Methods: This was an open-label, single center, exploratory PET study. Eleven MDD patients (age range, 22 - 65 y; mean ± SD, 37.8 ± 12.1; six females, five males) who had responded to venlafaxine ER treatment were recruited. The dose of venlafaxine ER had been fixed for at least 2 weeks before the PET measurement. The subjects did not take any other antidepressants and psychotropic agents or any other medication that might influence 5-HT and NE transmission for at least 4 weeks before the PET measurement. Nine control subjects (20 - 62 (39.9 ± 14.4) y; three males, six females) were recruited. No medications were allowed for at least 2 weeks before the PET measurement. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden, and the Radiation Safety Committee at the Karolinska University Hospital Solna in Stockholm, Sweden. After thorough oral and written information of the study, and before any study related activity took place, written informed consent was obtained from all participants.

Each subject participated in one PET measurement with [18 F]FMeNER-D2. For MDD patients, the last administration of venlafaxine ER was approx. 5 h before the radioligand injection. The emission data was collected from 120 minutes to 180 minutes after the radioligand injection using a HRRT system. T1-weighted magnetic resonance imaging (MRI) was also performed for the anatomical reference for PET images.

For all MDD patients, venous blood samplings were performed to measure the plasma concentration of venlafaxine and O-desmethylvenlafaxine. Total active moiety as sum of both compounds was chosen as the parameter of interest, because O-desmethylvenlafaxine also has affinity for both 5-HTT and NET (Ki: 40.2 nM and 3385 nM, respectively) [5].

Anatomical regions of interest (ROIs) were delineated on the reoriented MRI image using the Automated Anatomical Labelling (AAL) template. [18 F]FMeNER-D2 binding potential (BPND) was quantified by the area under the curve (AUC) ratio method with thalamus as target and caudate as reference regions:

AUCthalamus / AUCcaudate – 1. NET occupancy (%) was calculated as (BPND:baseline – BPND:treatment) / BPND:baseline × 100. The mean BPND of control subjects was used as BPND: baseline for all the MDD patients.

Results: Injected radioactivity was 278 ± 47 MBq (mean ± SD) and 268 ± 53 MBq for MDD patients and control subjects, respectively. Molar radioactivities was 66 ± 28 GBq/μmol and 68 ± 32 GBq/μmol at time of injection. Injected mass was 1.6 ± 0.6 μg and 1.5 ± 0.6 μg. There was no statistical difference between MDD patients and control subjects (Student's t-test: p = 0.68 – 0.88).

Daily doses of venlafaxine ER varied between 37.5 and 225 mg/day, plasma concentrations of total active moiety at time of PET between 108 and 947 ng/mL, and NET occupancy for all MDD patients in thalamus between 17 and 53 %. The NET occupancy increased in a dose and concentration dependent manner.

Conclusions: This study demonstrates for the first time that clinically relevant doses of venlafaxine ER block the NET in the living human brain. The present data is thus in line with the notion that venlafaxine ER exert its clinical effect via blockade of not only 5-HTT but also NET.

Furthermore, NET occupancy was identified already at 37.5 mg oral dose (significantly lower BPND compared to control group; p<0.01). This indicates that NET occupancy may be a clinically relevant mechanism of action of venlafaxine already in low clinical doses.

Results from clinical trials suggest that the clinical effect of a combination of 5-HTT and NET blockade is superior to 5-HTT blockade only [6,7]. Our data confirm that this mechanism may indeed be present in MDD patients treated with venlafaxine.

Keywords: PET, serotonin and norepinephrine reuptake inhibitor, Major Depressive Disorder (MDD), [18 F]FMeNER-D2

Disclosure: Nothing to disclose.

M104. Treatment Effects of Lithium Monotherapy on Serotonin Transporter and Serotonin-1A Binding & Prediction of Clinical Response in Bipolar Depression

Ramin Parsey, Mala Ananth, Elizabeth Bartlett, Xuejing Lin, Laura Kunkel, Nehel Vadhan, Gregory Perlman, Michala Godstrey, Daniel Holzmacher, Chuan Huang, R. Todd Ogden, Christine DeLorenzo*

Stony Brook University Medical School, Stony Brook, New York, United States

Background: Abnormalities of the serotonergic system are thought to play a critical role in mood disorders including bipolar depression (BPD). Lithium is the first line of therapy and one of the few effective treatments in BPD. It has been hypothesized that lithium works by enhancing serotonergic transmission (Carli et al. 1997, Carli and Reader 1997, Bauer et al. 2003). Whether these mechanisms are via increases in serotonin (5-HT) release (through the 5-HT1A receptor) or changes to the 5-HT transporter (5-HTT) uptake remain to be seen. Preclinical studies have shown increases in 5-HTT density (Bmax) in cortical regions following chronic lithium treatment (Carli and Reader 1997), but not in subcortical regions known to be affected in BPD and major depression, including midbrain and amygdala (Oquendo et al. 2007, Miller et al. 2013, Miller et al. 2016). Rodent studies also show that lithium monotherapy decreases 5-HT1A receptor densities in the frontal cortex and hippocampus (Hotta et al. 1986, Mizuta and Segawa 1988, Odagaki et al. 1990, Bauer et al. 2003), but not in the dorsal raphe nucleus (McQuade et al. 2004), suggesting that lithium treatment has a specific effect on post-synaptic 5-HT1A receptors, but not somatodendritic (raphe) 5-HT1A receptors. Here we examined the effects of lithium monotherapy on 5-HTT and 5-HT1A in vivo binding potential in BPD. Additionally, we investigated whether there was a relationship between change in 5-HTT or 5-HT1A binding following lithium treatment and clinical response. Finally, we investigated the potential of 5-HTT or 5-HT1A to predict post-treatment response. We hypothesized that: a) lithium monotherapy would increase 5-HTT cortical binding towards control levels and would decrease 5-HT1A binding post-synaptically; b) lithium-induced increases in 5-HTT or decreases in 5-HT1A binding would associate with better clinical response; c) lower pretreatment 5-HTT binding or higher 5-HT1A binding would predict better clinical response.

Methods: 19 medication-free patients with BPD currently in a depressive episode were imaged using the 5-HTT tracer [11 C]DASB and the 5-HT1A tracer [11 C]CUMI-101. BPD subjects then received eight weeks of standardized monotherapy with lithium and were scanned a second time following treatment with both tracers. Scans were acquired on a Siemens ECAT HR+ scanner for 90 minutes ([11 C]DASB) or 120 minutes ([11 C]CUMI-101) after tracer injection. Arterial blood samples were collected to calculate the metabolite-corrected arterial input function, or a validated simultaneous estimation algorithm was used to compute the arterial input function using a single venous or arterial blood sample (Ogden et al. 2010). Time activity curves were fit with likelihood estimation in graphical analysis (LEGA) (Ogden et al. 2007) to calculate [11 C]DASB total distribution volume (VT), from which the outcome measure VT/fP was calculated using the tracer plasma free fraction fP, as it has been shown that no brain region is completely devoid of [11 C]DASB binding (Parsey et al. 2006). LEGA was also used to obtain estimates of [11 C]CUMI-101 BPF (Bmax/KD)(Milak et al. 2010). Lithium treatment response was determined using the 24-item Hamilton Depression Rating Scale (HDRS-24) (Hamilton 1960). In [11 C]DASB linear models, midbrain, amygdala and anterior cingulate cortex were examined as a priori regions of interest. In [11 C]CUMI-101 linear models, the raphe nucleus was examined a priori and then 12 post-synaptic regions were considered (Sullivan et al. 2009). The parcellation of these regions are based on separately acquired MRI images.

Results: The data revealed no significant differences between pre- and post-lithium treatment scans using VT/fP [11 C]DASB binding, or BPF [11 C]CUMI-101 binding (both p>0.05). Additionally, we found no significant relationship between change in 5-HTT binding or change in 5-HT1A binding pre-to-post lithium treatment and treatment response (both p>0.05). We found a significant relationship between both pretreatment 5-HTT [11 C]DASB (all regions p=0.003-0.015) and 5-HT1A [11 C]CUMI-101 (amygdala p=0.016; hippocampus p=0.015; parahippocampal gyrus p=0.013; temporal cortex p=0.039) binding and post-lithium treatment clinical response, where lower pretreatment binding predicted improved clinical response.

Conclusions: To our knowledge, this is the first report of the effects of lithium on the serotonergic system, in vivo. Our findings indicate that lithium did not significantly alter 5-HTT or 5-HT1A binding post-treatment, and that there was no relationship between change in binding and clinical response for either tracer. These findings suggest that lithium does not act directly on 5-HTT or 5-HT1A to mediate treatment response. Interestingly, we find that pretreatment changes in the serotonergic system are predictive of clinical response following lithium treatment compounding the serotonergic hypothesis of mood disorders and suggesting lithium may act via other serotonergic proteins (e.g. 5-HT1B (Riad et al. 2000, Li et al. 2004, Polter and Li 2011)) to mediate treatment response. Future studies with tracers that target other serotonergic proteins and increased sample sizes are needed to further corroborate these findings and better understand the effect of lithium on the serotonergic system.

Keywords: PET Imaging, Bipolar Disorder, lithium treatment

Disclosure: Nothing to disclose.

M105. Ultra-High Field MRI of Mood-Related Circuit Disturbances in Depression: A Systematic Comparison Between 3-Tesla and 7-Tesla

Laurel Morris, Prantik Kundu, Sara Costi, Abigail Collins, Molly Schneider, James Murrough, Gaurav Verma, Priti Balchandani*

Icahn School of Medicine at Mount Sinai, New York, New York, United States

Background: Ultra-high field 7-Tesla (7 T) MRI has the potential to advance our understanding of neuropsychiatric disorders, including major depressive disorder (MDD). To date, few studies have quantified the advantage of resting state functional MRI (fMRI) at 7 T compared to 3-Tesla (3 T).

Methods: We conducted a series of experiments that systematically quantified the improvement in temporal signal-to-noise ratio (tSNR) of a multi-echo multi-band fMRI protocol with ultra-high field 7-Tesla, compared to 3-Tesla MRI in healthy controls (HC). We also directly tested the enhancement in ultra-high field 7-Tesla fMRI signal power by examining the ventral tegmental area (VTA), a small midbrain structure that is critical to the expected neuropathology of MDD but difficult to discern with standard 3-Tesla MRI.

Results: We demonstrate 200-300% improvement in tSNR and resting state functional connectivity metrics provided by ultra-high field 7-Tesla fMRI compared to the same imaging protocol with 3-Tesla, indicating enhanced power for detection of functional architecture. A multi-echo based acquisition protocol and signal denoising pipeline afforded greater gain in signal power at ultra-high field compared to classic acquisition and denoising pipelines. Furthermore, ultra-high field fMRI revealed mood-related neurocircuit disturbances in patients with MDD compared to HC, which weren't detectable with 3-Tesla fMRI.

Conclusions: Ultra-high field 7 T fMRI may provide an effective tool for studying functional neural architecture relevant to MDD and other neuropsychiatric disorders.

Keywords: Human Neuroimaging, 7-Tesla, Depression, Ventral Tegmental Area (VTA)

Disclosure: Nothing to disclose.

M106. Impaired Brain Insulin Signaling Moderates Antidepressant Response to Ketamine

Susannah Tye, Joshua Price, Mark Frye, Kathryn Cullen, William Bobo*

Queensland Brain Institute, St Lucia, Australia

Background: Low-dose ketamine is effective in a subset of patients with treatment-resistant depression. Using an animal model of antidepressant-resistance we have identified an association between brain insulin signalling and antidepressant-like behavioural responses to ketamine in the forced swim test. The mechanistic role of insulin signalling in ketamine's mechanism of action and its potential for use as a clinical biomarker remains to be determined.

Methods: Rodent Studies: Wistar rats (6-8 wks) were pre-treated with saline (0.9%/d;14d) or adrenocorticotropic hormone-(1-24) (ACTH 100 µg/d;14d; n=64). Animals received ketamine hydrochloride (10 mg/kg) or vehicle saline (0.9%) 1 h prior to behavioral tests (open field test (OFT) and forced swim test (FST). All animals were euthanized 90 mins following treatment. Brain, plasma and peripheral blood mononuclear cells (PBMCs) were collected and snap frozen on dry ice. Brain and PBMC tissue from these animals was harvested and cultured for subsequent ketamine, insulin and glucose assays. Brain and PBMC cell cultures were exposed to ketamine and/or insulin (10 µg, 5 mins) ex vivo and change in mammalian target of rapamycin (mTOR) expression and glucose uptake was determined. Total and phosphorylated levels of insulin signalling pathway proteins in prefrontal (PFC) brain and PBMC tissues was quantified using standard ELISA and western blot procedures. Human studies: Adolescent (n=13) and adult patients (n=12) with treatment resistant depression received serial infusions of ketamine (0.5 mg/kg infused over 100 mins in adults and over 40 mins in adolescent subjects). PBMCs were collected immediately prior to and following the first ketamine infusion. As for animal studies, cells were stimulated ex vivo with insulin (10 µg, 5 mins) and change in mTOR expression was determined using ELISA. Insulin-mediated changes in mTOR were compared between individuals that achieved remission following serial ketamine infusions and those that did not.

Results: Results demonstrated that ketamine reduced FST immobility in a subset of tricyclic antidepressant-resistant animals ($p<0.05$). Ketamine's antidepressant actions in the FST correlated with levels of phosphorylated insulin signaling proteins (Akt: $p<0.05$; mTOR: $p<0.01$; and GSK3: $p<0.01$) in PFC and PBMC tissue of ACTH-treated animals, but not saline treated controls. Correlations between brain insulin signalling pathway protein activation and blood glucose levels was also observed (mTOR: $p<0.05$; and GSK3: $p<0.05$). Further, we demonstrated that changes in blood glucose and phosphorylated levels of mTOR and GSK3 in WBCs differentiated ACTH pre-treated ketamine responders from non-responders ($p<0.05$). Cell culture assays confirmed a ketamine acted directly on brain and PBMC tissue to increase glucose uptake and stimulate release of insulin, concurrent with activation of insulin signalling pathway proteins ($p<0.05$). In human subjects, the ex vivo insulin stimulation assay further demonstrated that change in PBMC mTOR levels following 5 mins insulin exposure after the first ketamine infusion was significantly greater in both adolescent ($p<0.05$) and adult ($p<0.05$) individuals that remitted following serial ketamine infusions. No difference was observed in mTOR levels following exposure to insulin in PBMCs of either adolescent or adult subjects for samples collected immediately prior to initiation of ketamine treatment.

Conclusions: These findings suggest the antidepressant-like effects of ketamine in treatment-resistant individuals is associated with direct modulation of insulin signalling and glucose uptake. The direct effects of ketamine on insulin signaling and glucose uptake may serve as critical co-regulators of antidepressant response in individuals with dysregulation of metabolic responses. Importantly, cell signaling responses to insulin following first exposure to ketamine may serve as a valuable predictor of long-term clinical response.

Keywords: Ketamine, Treatment Resistant Depression, Insulin, mTOR

Disclosure: Nothing to disclose.

M107. Effects of Early Life Adversities on Acetylcarnitine Deficiency and Insulin Resistance in Patients With Major Depression

Carla Nasca, Benedetta Bigio, Katie Watson Lin, Josh Dobbin, Marin Kautz, Ashly Cochran, Thalia Robakis, Alison Myoraku, James Beasley, Tonita Wroolie, Sarah Young, Aleksander Mathe, James Kocsis, James Murrough, Francis Lee, Bruce McEwen, Natalie Rasgon*

Rockefeller University, New York, New York, United States

Background: The lack of biomarkers to identify target populations greatly limits the promise of precision medicine for major depressive disorder (MDD), a primary cause of disability and risk factor for

suicide. Early life adversities (ELA), such as childhood trauma, are risk factors for poor mental health outcomes in adulthood. The biological pathways leading from risk to outcomes are yet-to-be fully elucidated. The endogenously produced molecule acetyl-L-carnitine (LAC) is an epigenetic modulator of central glutamatergic function and a candidate biomarker of insulin resistance (IR). In rodents with depressive-like traits and peripheral IR, LAC levels are markedly decreased and signal decreased acetylation of histones underlying transcriptional regulation of the metabotropic glutamate receptors mGluR2 in the ventral hippocampus and corresponding dendritic plasticity. We evaluated here a role of LAC and IR in in patients with MDD and history of ELA.

Methods: Study participants were recruited at three independent sites, the Weill Cornell Medicine, the Mount Sinai Icahn School of Medicine and Stanford University. Plasma distribution of LAC and the internal control free-carnitine were determined in 45 healthy controls (HC) and 116 patients with MDD using UPLC-MS/MS and ESI-MS/MS; insulin resistance and sensitive was assessed by fasting plasma glucose (FPG) and insulin (FPI) levels, body mass index (BMI), weight and HOMA, Matsuda index and glucose and insulin responses to oral glucose challenges. Depression severity was assessed with the HDRS-21. Physical, sexual and emotional abuses as well as physical and emotional neglect were assessed with the Childhood Trauma Questionnaire. Two-tailed t-tests, chi-square, Pearson correlations and multiple regression were used as appropriate to specific analyses.

Results: LAC (and not free-carnitine) is significantly lower in patients with MDD compared to HC ($p<0.0001$, power 0.99, effect size=0.8), independently of psychotropic drug treatment, as we recently reported. Within the group of patients with MDD, the LAC deficiency was greater with stronger severity, earlier disease onset and history of treatment resistant depression, which was associated with childhood trauma. Our new data in subjects screened for insulin resistance and sensitivity, show that IR was worst with higher reported rates of childhood trauma in that patients who reported higher rates of specific types of childhood trauma had higher levels of FPI and HOMA (FPI: $r=0.6$, $p=0.004$; HOMA: $r=0.52$, $p=0.004$).

Conclusions: Our new translational findings suggest that a LAC deficiency and IR may define metabolic endophenotypes of MDD with a vulnerability memory that may be tracked back to ELA. Identifying the role of ELA on metabolic risk factors contributing to behavioral states in patients with MDD can lead to a mechanistic framework for development of a precision medicine approach for preemptive tailored interventions based upon endogenous drug-targets. Studies leveraging the use of brain-derived exosomes are ongoing to evaluate the contribution of central metabolic functions on the peripheral deficiency in LAC and IR in these metabolic endophenotypes of MDD.

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Keywords: Metabotropic Glutamate Receptor 2 (mGluR2), Epigenetic, Childhood Trauma, Insulin Resistance, Biomarker

Disclosure: Nothing to disclose.

M108. Differential Gene Expression in Response to Estradiol Withdrawal in Perimenopausal Depression

Sarah Rudzinskas, Jessica Hoffman, David Rubinow, David Goldman, Peter Schmidt*

National Institute of Mental Health, Rockville, Maryland, United States

Background: Perimenopause, the transition women undergo prior to menopause, has been linked to an increased incidence of depression. Women in the perimenopausal period are 1.5-3x more likely to be diagnosed with major depressive disorder or develop depressive symptoms compared with women who have not entered perimenopause, or women several years past menopause (Cohen et al, 2006). Further, there is evidence that suggests estradiol withdrawal is linked to Perimenopausal Depression (PMD), as 5-10% of women develop depressive symptoms after discontinuing hormone therapy (Ockene et al, 2005). Additionally, peri/postmenopausal women with even minor depression are at an increased risk of cardiovascular mortality (Wassertheil-Smoller et al, 2004). Clinical studies show both the therapeutic benefits of estradiol (E2) in perimenopausal depression (PMD) (Schmidt et al, 2000, Soares et al, 2001) and the symptom-provoking effects of E2-withdrawal in women with past PMD, which are not experienced by those without past PMD (Schmidt et al, 2015). It has been suggested that a heightened sensitivity to changes in ovarian steroids such as E2 may contribute to the onset of PMD.

Methods: We created lymphoblastoid cell lines (LCLs) derived from blood samples from women with a past PMD ($n=8$), or asymptomatic controls (AC) ($n=9$). These LCLs were examined in 3 different experimental conditions: 1) vehicle-treated media, 2) E2-treated media, or 3) E2-treated media which was changed to vehicle-treated media and collected 24 h later, to mimic E2-withdrawal on a cellular level. Levels of E2 in cell culture media were confirmed using High Performance Liquid Chromatography/Tandem Mass Spectrometry. Cells were collected and examined for changes in gene expression levels using whole-transcriptome RNA sequencing on polyAAA selected mRNA. EDGE-R analysis of differential gene expression was used to detect significant transcript expression changes between women with PMD and AC in all three treatment conditions. DAVID, GSEA, and other pathway analyses were applied to the results. Quality control measures and unsupervised clustering analyses were performed for quality control in CLC Bio 11.

Results: We hypothesized that the differential affective/behavioral responsivity to E2-withdrawal in PMD could be observed on a cellular level. In support of this hypothesis, there were 534 Differentially Expressed Genes (DEGs) in LCLs between AC women and women with PMD after E2-withdrawal with an uncorrected $p<0.05$. Of these DEGs, the gene CXCL10 which has been previously linked to cardiovascular disease, is significantly upregulated ($p<1.55\times10\text{-}5$) in the cells of women with past PMD and had the most extreme increase in transcription in the E2-withdrawal treatment condition. In contrast, a gene coding an enzyme CYP7B1, which is responsible for the metabolism of the steroids DHEA and pregnenolone, is also significantly upregulated ($p<5.6\times10\text{-}4$) in PMD, but E2-treatment or withdrawal had no further effect on transcript expression. Furthermore, network analysis with GSEA and DAVID has revealed that there are several molecular pathways that appear to be differentially altered in women with PMD.

Conclusions: Results support the hypothesis that the differential responsivity to E2-withdrawal in PMD could be linked to dynamic gene expression changes on a cellular level. These findings also suggest a possible contributor to the increased cardiac risk associated with depression and menopause. Current data may suggest that both intrinsic genetic differences as well as differential sensitivity to E2-withdrawal could underlie the behavioral symptomology of PMD. Further studies are underway to replicate these changes in DEG findings in an independent cohort of AC and PMD cases.

Keywords: Menopause, Neuroendocrinology, Late-life Depression, Estradiol, Perimenopausal Depression

Disclosure: Nothing to disclose.

M109. Electrical Field Based Prediction of ECT Induced Clinical Effect: A Multisite Longitudinal Neuroimaging Study

Miklos Argyelan, Leif Oltedal, Benjamin Wade, Zhi-De Deng, Georgios Petrides, Anil Malhotra, GEMRIC Consortium, Christopher Abbott*

Hofstra Northwell School of Medicine, Glen Oaks, New York, United States

Background: Treatment-resistant depression (TRD) is one of the leading causes of disability worldwide (Kessler et al. 2005; Rush et al. 2006). To date, electroconvulsive therapy (ECT) remains the most effective approach for the treatment of TRD, as well as the most established neuromodulatory technique (UK ECT Review Group 2003; Fink & Taylor 2007). Despite intensive research, however, the mechanism of action for ECT remains unknown. No prediction of ECT-induced efficacy or side effects is possible at the individual level. Thus, identifying target mechanisms would not only improve current deployment of bioelectric approaches (ECT, TMS, tDCS, DBS) as part of a precision medicine approach but could also lead to the development of novel therapies (Insel 2014).

One interesting and not well-understood aspect of ECT is its direct electrical effect on the brain. It is thought that ECT induced seizure is the necessary component of the treatment effect, however recently this dogma has been challenged (Sackeim 2015; Regenold et al. 2015). Besides, electromagnetic, but non-seizure causing neuromodulatory treatments, such as TMS, proved to be efficient in the treatment of depression. Therefore, in this study, we set out to investigate the direct effect of the ECT induced electrical field (EF) in a multisite longitudinal neuroimaging study.

Methods: We analyzed N=153 (94 F, age: 57.3 +- 17.1) patients who underwent right unilateral (RUL) ECT for depression and had two brain MRIs, first at baseline, second at the end of the ECT course. Patients were followed clinically and MADRS was administered at baseline and the end of the ECT course. The range of the number of ECT was 7 to 15. We estimated ECT induced EF with ROAST v1.1 (Huang et al. 2017). After segmentation of the structural MRI T1-weighted images, ROAST builds the three-dimensional tetrahedral mesh model of the head. The segmentation identifies five tissue types: white and gray matter of the brain, cerebrospinal fluid, skull, and scalp, and assigned them different conductivity values: 0.126 S/m, 0.276 S/m, 1.65 S/m, 0.01 S/m, and 0.465 S/m respectively. ROAST uses finite element methods (FEM, #Logan et al. 2007#) to find the electric potential distribution under 1 A/m2 current density injected into the frontal stimulation electrode. The resulting electric potential distribution was calibrated to correspond to the current injection used in the device (Thymatron 900 mA, MECTA 800 mA). These procedures resulted in a voxel-wise EF distribution map in each individual. Further processing was performed by FreeSurfer version 5.3, and Quarc (Holland and Dale 2011) was used for unbiased estimation of subcortical and cortical volume change. 96 ROIs were identified and volume change between baseline and end of the ECT treatment was calculated. We also calculated the mean EF in each ROI. In the ROI based analyses, we used Bonferroni corrected statistical threshold ($p<0.0005$).

Results: There was a strong correlation between EF and volume increase in amygdala and hippocampus both sides ($p<0.0005$) respectively. These correlations were even stronger when we multiplied EF with the number of ECT (cumulative dose). Due to the asymmetry of the dose distribution of the RUL ECT, this correlation was present on both sides with different scales. In line with our previous reports, volume changes, however, did not correlate with clinical improvement (Oltedal et al. 2018). In a separate analysis, we found that EF correlated with clinical improvement in the cingulate cortex only (voxel-wise analysis, FDR corrected $p<0.05$), but no volumetric changes were identified in this region.

Conclusions: The direct electrical distribution of ECT is tightly linked with MRI brain changes in the hippocampus and amygdala. While EF is likely causative in these volume changes, volume changes fail to mediate clinical effect. Volume change is either neutral in these regions or responsible for memory side effects, which needs to be verified in future studies with neurocognitive measures. Based on our results EF exerts its clinical effect at the cingulate cortex. Overall this is an encouraging biological validation of the electrical field modeling technique which could lead to new insights in personalized neuromodulation.

Keywords: Neurostimulation, Depression, Brain MRI, ECT, Electrical Field Modeling

Disclosure: Nothing to disclose.

M110. Discovery of Central Autonomic Dysregulation Mechanisms in Major Depression and Translation of a Novel Neuromodulation Technique for its Treatment

Ronald Garcia, Klara Mareckova, Arielle Stanford, Jessica Stowell, Laura Holsen, David Gitlin, Riccardo Barbieri, Vitaly Napadow, Jill Goldstein*

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States

Background: Cardiac autonomic dysregulation in response to negative stressful stimuli has been implicated in the comorbidity of major depression (MDD) and cardiovascular disease (CVD). We previously argued that this maladaptive physiological response is associated with abnormalities in the development of specific regions in the stress response circuitry (hypothalamus, amygdala, hippocampus, anterior cingulate cortex, orbital and medial PFC, and brainstem regions) that are morphologically and functionally sexually dimorphic and associated with vulnerability for sex differences in MDD and CVD risk. In a previous functional magnetic resonance imaging (fMRI) study we demonstrated the differential and greater negative impact of depressed mood on brain activity deficits and connectivity between stress circuitry regions in women than men (specifically hypothalamus and amygdala with orbital and hippocampal regions). We have now extended this work by investigating sex differences in the associations of these fMRI findings with peripheral autonomic dysregulation (i.e., reduced parasympathetic cardiac tone) in response to negative affective stimuli (Discovery phase). These results were then used in a second study to guide the evaluation of a novel, non-invasive, respiratory-gated auricular vagus afferent nerve stimulation (RAVANS) technique for transcutaneous vagus nerve stimulation (tVNS) on the modulation of the above brain regions and peripheral parasympathetic activity in 20 women with active recurrent MDD (Translational phase).

Methods: Discovery phase: The sample consisted of 50 subjects (28 females, 22 males), ages 45.5±5.0 years, spanning a range from healthy to major Axis I diagnoses to ensure depressed mood variability. fMRI data were acquired on a Siemens Tim Trio 3 T MRI scanner (TR=2000 ms, TE=40 ms, slice thickness 5 mm). The fMRI task consisted of presentation of images adapted from the International Affective Picture System, comprising a mild visual stress challenge. Average parameter estimates (percent signal change values) and task-related connectivity values (beta weights of psychophysiological interaction regressors) in significant target clusters (negative vs. neutral) were extracted. The relationship between stress response circuitry activity and connectivity and cardiovagal activity [percent change in high frequency power of heart rate variability (HFn)] in response to negative affective stimuli was evaluated using GLM analyses, including interactions with depressed mood and sex.

Translational phase: Twenty women (30.3±4.7 yrs) with recurrent MDD and in an active episode were included. fMRI data were acquired on a Siemens Tim Trio 3 T MRI scanner (TR=1250 ms, TE=33 ms, slice thickness 2 mm). Women attended two imaging visits within one-week (to ensure early follicular timing across sessions) in which they were exposed to a visual stress challenge that preceded and followed expiratory-gated (eRAVANS) or inspiratory-gated (iRAVANS) stimulation. Stress response circuitry areas evaluated in the discovery phase were used for region of interest group-level analyses with non-parametric permutation tests (eRAVANS vs iRAVANS). In addition, a GLM analysis evaluated effects on cardiovagal modulation (HFn) and depressive symptoms [Beck Depression Inventory (BDI)].

Results: Discovery phase: Significant relationships between reduction of cardiovagal activity and activation of hypothalamus ($p=0.001$) and amygdala ($p=0.02$) during exposure to negative images were observed in women (and not men) with high depressed mood. Analyses also revealed that only women (and not men) with high depressed mood exhibited low connectivity between hypothalamus and right orbitofrontal cortex associated with low cardiovagal activity (lower HFn change) in response to negative affective stimuli ($p=0.001$).

Translational phase: Significantly greater activation of nucleus tractus solitarii and raphe nuclei were observed during stimulation with eRAVANS compared to iRAVANS ($p<0.01$). In addition, a significant greater activation of anterior cingulate and orbitofrontal cortices as well as deactivation of hypothalamus were observed during the stress task (post vs pre RAVANS) when comparing eRAVANS to iRAVANS ($p<0.01$). Furthermore, a significant acute reduction in BDI values (28.1±6.9 vs 19.9±9.1, $p<0.01$) and increase in cardiovagal output (HFn: 43.3±9.3 vs 52.2±10.6, $p<0.01$) were observed after eRAVANS, with no significant differences after iRAVANS.

Conclusions: The discovery phase in this set of analyses revealed mood and sex-dependent interactions in the association between stress response circuitry activity deficits and reduced cardiovagal modulation in response to negative affective stimuli. In particular, women with depressed mood showed greater inability to regulate brain activity and cardiac autonomic tone during negative emotional arousal than men. These results provide a window into a pathway for understanding sex differences in the comorbidity of MDD and CVD. Subsequently, results from the translational phase evaluating RAVANS tVNS in women with recurrent MDD demonstrated that this neuromodulatory therapeutic approach effectively modulated the stress response circuitry with acute beneficial effects on mood and autonomic regulation. This discovery-translational research design suggests a novel neuromodulatory application to the treatment of comorbid MDD and CVD in women.

Keywords: Major Depression Disorder, Stress Response Circuitry, Cardiac Autonomic Tone, Transcutaneous Auricular Vagus Nerve Stimulation (taVNS), Sex Differences

Disclosure: Nothing to disclose.

M111. Neurotransmitter Sensing via Aptamer-Field-Effect Transistors

Abstract not included.

M112. CSF Acetylcholinesterases: Relationship to Peripheral and CSF Pro-Inflammatory Cytokines in Late-Life Major Depression

Nunzio Pomara, Davide Bruno, Jay Nierenberg, Chelsea Reichert, Minnie Fu, Katherine Brundage, Henrik Zetterberg, Kaj Blennow*

Nathan S. Kline Institute/New York University School of Medicine, Orangeburg, New York, United States

Background: Increased levels of peripheral and CSF pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-8 have been reported in depressive disorders, including late life major depression (LLMD), and these elevations may interfere with patients' responses to conventional antidepressants. However, findings from meta-analyses that examined inflammatory biomarkers in depression, including pro-inflammatory cytokines, also indicate that the results of these studies are conflicting, suggesting that elevations of pro-inflammatory cytokines may occur in some depressed individuals but not others. Thus, there is a need to elucidate clinical and biological factors that may contribute to these differential effects. Several lines of evidence suggest that an increase in cholinergic activity produced by administration of cholinergic agonists such as cholinesterase inhibitors results in a significant attenuation of cell-mediated immune responses, such as those evoked in endotoxin-induced sepsis and other inflammatory conditions. These anti-inflammatory effects of acetylcholine (ACh) have been shown to be mediated by activation of efferent vagal pathways and α-7 nicotinic ACh receptors on macrophages and other inflammatory cells. It has also been suggested that activation of the cholinergic anti-inflammatory reflex can be triggered by localized elevations in peripheral cytokines via vagal afferents or by elevations in circulating cytokines that enter the brain via the circumventricular organs or via active transport across the blood-brain barrier.

Interestingly, reductions in peripheral butyrylcholinesterase (BChE) activity have been described as one of the earliest manifestations of acute systemic inflammation. These reductions have been associated with decreased release of pro-inflammatory cytokines and better survival, suggesting that a compensatory cholinergic anti-inflammatory response occurs in systemic inflammation. In a preclinical experiment, a single intraperitoneal injection of the lipopolysaccharide endotoxin in rats resulted in significant decline in brain acetylcholinesterase (AChE) and BChE activity consistent with possible upregulation of the central cholinergic anti-inflammatory response. However, the status of the cholinergic system in the context of cytokine changes in individuals with long-standing depression has never been examined. This gap in the literature prompted us to examine peripheral and CSF pro-inflammatory cytokine levels (IL-6, IL-8, TNF-α, IL-1b) in LLMD, a disorder associated with increased risk for Alzheimer's disease (AD) and their relationship to CSF AChE and BChE activity.

Methods: 91 participants, aged 60 years and older completed a 3-year longitudinal study. All subjects were cognitively-intact at screening and had a) no evidence of dementia, b) a Mini-Mental State Exam score of at least 28, and c) no gross MRI abnormalities other than white matter hyperintensities. Baseline CSF was obtained from 44 older adults (27 with LLMD and 17 healthy controls). Plasma pro-inflammatory cytokines levels (IL6, IL8, IL1b) and CSF BChE, AChE, and pro-inflammatory cytokines were determined using commercial kits as per manufacturers' instructions. Nonparametric Mann-U Whitney test and Spearman's correlations were run.

Results: CSF BChE was lower in people with LMDD compared to controls (Mann-Whitney U Test $p = .02$). There was no significant difference between groups for CSF AChE ($p = 0.13$), but a similar trend was observed with lower AChE in the LLMD group.

Plasma Findings. In LLMD, lower CSF BChE ($rho = -.46$, $p = .02$) and AChE ($rho = -.45$, $p = .02$) were associated with higher plasma IL-6. Whereas, in the control group, only lower CSF AChE was associated with higher plasma IL-8 ($rho = -.54$, $p = .03$).

CSF Findings. In the whole group analysis (LLMD and control group), lower CSF BChE was associated with lower CSF IL-8 ($rho = 0.60$, $p < 0.001$). However, only in the control group, lower CSF BChE was associated with lower CSF IL-8 ($rho = 0.62$, $p = 0.008$).

Conclusions: CSF BChE activity was lower in the LLMD group compared to controls. A similar trend was also observed for CSF AChE. Plasma cytokines were inversely correlated with CSF AChE

or BChE in both LLMD and controls. In contrast, CSF AChE and BChE were positively correlated with CSF cytokines. These preliminary findings, if confirmed, are consistent with a possible compensatory upregulation of the central cholinergic anti-inflammatory pathway in response to elevated plasma pro-inflammatory cytokines, especially in LLMD.

Keywords: Late-Life Depression, Vagus, Pro-inflammatory Cytokines, Cholinergic Anti-Inflammatory Response

Disclosure: Nothing to disclose.

M113. A Significant Dose-Effect and Insignificant Sequence Effect of the Prediction of Suicidal Behavior by Interactions Between Immune-Driven Illnesses and TBI

Teodor Postolache, Michael Benros, Lisa Brenner, Olaoluwa Okusaga, Christopher Lowry, John Stiller, Annette Erlangsen*

University of Maryland School of Medicine, Baltimore, Maryland, United States

Background: Inflammation appears to moderate and immune activation may even mediate certain clinical symptoms and functional trajectories in Traumatic Brain Injury (TBI) and was more recently implicated in suicidal behavior. TBI and specific immune mediated clinical conditions (IMCs: infections, allergy and autoimmune) have been previously predictively associated, individually, in Suicidal Self-Directed Violence (SSDV). We now evaluated the effect of interactions between TBI and IMCs in predicting SSDV in a Nationwide, population-based, prospective cohort study, with a special focus on dose-response and temporal sequence effects.

Methods: All 7.22 million individuals- 15 years or older living in Denmark between January 1, 1980, and December 31, 2011, were observed during a 32-year follow-up period, with more than 149 million person-years of follow-up. The relative risk for suicide and SSDV (suicide and attempts) was expressed as Incidence rate ratios (IRRs) and accompanying 95% CIs. History of TBI and infections, allergic disease and autoimmune disease, with stratification for mental illness, were coded using ICD 8 and 10. Data was adjusted for sex, age, and time interval, and was analyzed with Cox regression and multivariable logistic regression. We further analyzed lethal vs. non-lethal SSDV, SSDV using violent vs. nonviolent methods, number of admissions for IMCs and TBI and order of interaction (TBI first vs. IMC first).

Results: There was a significant interaction between TBI and IMCs in predicting SSDV- with synergistic effects for infections and allergy ($p<0001$), and bellow- additive effects for autoimmune disease ($p<0.001$). For infections specifically, while a robust dose-response effect has been identified ($p<0.001$), there was no significant difference in effect size with the sequence of the interaction.

Conclusions: The results support the possible role of inflammation (and IMCs) in predicting severity of TBI, mediating its SSDV risk elevating effects and perpetuating that risk. Preventing and assertively addressing IMCs may significantly lower the SSDV risk after the TBI.

Keywords: Suicide, Depression, Traumatic Brain Injury, Inflammation

Disclosure: Nothing to disclose.

M114. Temperament, Personality, and Risk for Mood Disorder

Tiffany Greenwood, Nancy Downs*

University of California, San Diego, La Jolla, California, United States

Background: Early detection of vulnerability is an important clinical goal that can have a major impact on future quality of life by enabling timely interventions and effective risk management. However, this requires a better understanding of the environmental and genetic influences, as well as latent personality traits that may serve as key indicators of risk prior to the onset of illness. We, and others, have consistently shown that individuals with mood disorder possess temperament and personality traits that are significantly different from healthy controls, even in euthymia. Based on these observations, we recently began a pilot study to develop prediction models based on behavioral, environmental, and genetic risk factors to facilitate the early identification of mood disorders in transition age youth.

Methods: In total, 468 undergraduate students aged 18-25 completed an online, anonymous survey during the first year of the study at one public, west coast university with an undergraduate enrollment of approximately 28,000. The survey used the Patient Health Questionnaire to screen for depression, the Mood Disorder Questionnaire to screen for bipolar spectrum disorders, and the Suicide Behaviors Questionnaire-Revised to screen for suicide risk. Additional questions were included to inform lifetime diagnoses of major depression and bipolar disorder according to DSM criteria. The Temperament Evaluation of Memphis, Pisa, Paris, and San Diego Auto-questionnaire (TEMPS-A) was used to assess lifelong, milder aspects of bipolar symptomatology. The Temperament and Character Inventory (TCI) was included to evaluate additional dimensions of personality according to a psychobiological model. The Hypomanic Personality Scale (HPS) and the Barratt Impulsivity Scale (BIS) were also included.

Results: Of the 441 students with complete mood and personality data, 166 reported no current or lifetime mood symptoms and serve as controls, 54 met criteria for bipolar disorder, and 62 met criteria for depression, 19 of whom also reported significant manic symptoms and are likely bipolar. Additionally, 159 students reported significant mood symptoms but did not meet criteria for a mood disorder due to lack of reported impairment. All temperament and personality traits investigated showed significant group differences. Hypomanic personality, impulsivity, irritable temperament, and novelty seeking were characteristic of individuals with bipolar disorder, while harm avoidance was characteristic of depression. Dysthymic and anxious temperament significantly discriminated healthy controls from those with a mood disorder but did not distinguish bipolar disorder from depression. Only the cyclothymic temperament significantly discriminated between all three groups, with effect sizes of 1.0 and 1.8 for depression and bipolar disorder, respectively, compared with controls. A combination of hypomanic personality and cyclothymic and irritable temperament explained >0.40 of the variance in bipolar disorder.

Conclusions: These results are consistent with those of others in suggesting that temperament and personality traits can be useful in predicting risk for mood disorder, in combination with other factors. It must be noted, however, that these results are based solely on self-report of mood symptoms in the absence of structured clinical interviews. As mood disorders often emerge during adolescence and young adulthood, this stage of development represents a critical point for early intervention. A prediction model based on latent personality traits in conjunction with genetic and environmental risk factors would facilitate this goal.

Keywords: Mood Disorder, Temperament, Personality, Biomarkers for Risk Assessment

Disclosure: Nothing to disclose.

M115. Data-Driven Subtypes of Depression in a Treatment Resistant Cohort

Laura Hack, A. Umair Janjua, Sara Dover, Patricio Riva Posse*

VA Palo Alto MIRECC/Stanford School of Medicine, Palo Alto, California United States

Background: Initial efforts to parse patients with depression into more clinically homogeneous groups were based on observations of differences in symptomatology. Over the past five decades, these efforts have become data-driven. More recently, there has been renewed interest in this area due to the development of the NIMH's Research Domain Criteria as well as advances in machine learning approaches and biomarker measurement. The ultimate goal of this work is the development of a more biologically-based understanding of psychiatric diseases that will foster the selection of personalized treatments. Most work in this area has utilized two broad data-driven person-centered analytic approaches, including finite mixture models, particularly latent class analysis, and clustering methods. Both methods are unsupervised in that the algorithms find patterns in the data without being provided with labels. Analyses with these methods have yielded between 2 and 7 latent classes or clusters of depressed patients. Both methods have consistently identified subtypes based on severity, as well as melancholic and atypical features. To our knowledge, no studies attempting to subtype patients with depression have specifically focused on a treatment resistant population.

Methods: We used data from 319 patients of both sexes who presented for consultation to our Treatment Resistant Depression Center at The Emory Clinic from January 2016 through July 2018. We entered baseline Quick Inventory of Depressive Symptoms (QIDS-SR16) scores into an agglomerative hierarchical clustering algorithm using Ward's method. To determine the optimal number of clusters, we used the R package NbClust, which provides 30 indices, including the standardly used average silhouette method and the gap statistic, and selects the optimal number based on the majority rule. Using ANOVA, we then tested whether subjects within the 3 clusters differed based on severity and type of depressive symptoms.

Results: A 3-cluster solution was identified as optimal by the unsupervised machine learning algorithm and the majority rule. Based on the symptom profiles, we labeled the clusters, or subtypes, as "Severe Melancholic" (N=158, 50%), "Mild Melancholic" (N=126, 39%), and "Atypical" (N=35, 11%). The clusters differed significantly on both severity of depressive symptoms ($F1 = 42.3$, $P = 3.6e\text{-}10$) and symptom type. The "Atypical" cluster had a mean QIDS score of 20.0 with significantly higher scores on the QIDS items "Sleeping too much" ($F1 = 11.5$, $P = 7.7e\text{-}4$) and "Increased appetite" ($F1 = 137.6$, $P < 2e\text{-}16$) as compared to the other clusters. The mean QIDS score for the "Severe Melancholic" cluster was 20.4 with significantly higher scores on "Decreased appetite" ($F1 = 73.6$, $P < 2e\text{-}16$) and "Early morning awakening" ($F1 = 21.4$, $P = 5.5e\text{-}6$), while the mean QIDS for the "Mild Melancholic" group was 13.6.

Conclusions: We present a clustering analysis of depressive symptoms in a group of treatment resistant depressed patients that reveals differences in subtypes based on severity and symptom type. This is consistent with many prior studies using data-driven approaches to parse patients with depression, although, to our knowledge, our study is the first to use a treatment resistant cohort. We plan to test for differences among the subtypes on a variety of sociodemographic and biological measures, which may have implications for personalized interventions.

Keywords: Hierarchical Clustering, Depression Subtypes, Treatment Resistant Cohort

Disclosure: Nothing to disclose.

M116. Genome-Wide DNA Methylomic Differences Between Dorsolateral Prefrontal and Temporal Pole Cortices of Bipolar Disorder

Marin Veldic, Man Choi (Ada) Ho, Stacey Winham, Sebastian Armasu, Caren Blacker, Vincent Millischer, Catharina Lavebratt, James Overholser, George Jurjus, Lesa Dieter, Gouri Mahajan, Grazyna Rajkowska, Eric Vallender, Craig Stockmeier, Keith Robertson, Mark Frye, Doo-Sup Choi*

Mayo Clinic, Rochester, Minnesota, United States

Background: Dorsolateral prefrontal cortex (DLPFC) and temporal pole (TP) are brain regions that display abnormalities in bipolar disorder (BD). DNA methylation is an epigenetic mechanism that is heritable and sensitive to environmental influence and hence has received considerable attention in mood disorder studies. Here we hypothesized that DNA methylomic (DNM) differences in DLPFC and TP may play a role in BD. We investigated the genome-wide DNM differences associated with BD within and between the gray matter of DLPFC and TP. Major depressive disorder (MDD) cases were included to identify BD-specific brain DNM differences.

Methods: Postmortem brains were collected at autopsy at the Cuyahoga County Medical Examiner's Office, Cleveland, OH. All procedures performed were in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards. Subjects meeting DSM-IV criteria for BD or MDD, and controls without a psychiatric diagnosis, were selected for this study. Subjects with neuropathological or neurological disorders were excluded. Tissues were dissected and rapidly frozen in 2-methylbutane on dry ice without fixation and stored at -80°C. Gray matter tissues of DLPFC and anterior TP from 20 BD, 10 MDD, and 10 control subjects were procured. MDD and control subjects were matched to BD subjects according to the group's age and sex distributions, while control subjects were age-and-sex matched to MDD subjects individually. Genomic DNA was extracted from ~40 mg tissue and then subjected to bisulfite conversion. DNA methylation levels were determined by the Illumina 850 K Infinium MethylationEPIC BeadChip. Multivariate analyses (principal component analysis and hierarchical clustering) were performed on top variable probes to detect potential confounding factors. Differentially methylated positions (DMPs) were then identified by the R Bioconductor package limma. Paired comparison was used for between-brain-region comparisons in each group and for MDD-control comparison in each brain region. Statistically significant DMP was considered at adjusted $p<0.05$. Functional enrichment analysis was performed on genes annotated to the lists of significant DMPs that were shared by all groups as well as shared by and distinct to BD and MDD. Pathways were considered statistically significant at Benjamini-Hochberg corrected $p<0.05$.

Results: Multivariate analyses detected no significant associations of methylation profile clusters with arrays, sex, age, postmortem interval, or tissue pH. Between DLPFC and TP, 1601 DMPs in the control group, 11954 DMPs in the MDD group, and 39039 DMPs in the BD group reached statistical significance. Substantial proportions of these DMPs overlapped between groups, indicating that some between-brain-region methylation differences were common to all or some subject groups. The genes associated with DMPs shared by BD and MDD (7709 DMPs) were significantly enriched in seven nervous system-associated pathways; while the genes associated with DMPs distinct to the BD group (29846 DMPs) were significantly enriched in 15 nervous system-associated pathways. The top-ranked pathway was "axon guidance signaling" for both analyses. Pathways enriched only in

the BD-MDD shared list pointed to GABAergic dysregulation, while those enriched in the BD-only list suggested glutamatergic dysregulation and more impacts on synaptogenesis and synaptic plasticity. No significant DMPs were found in any between-group comparisons in DLPFC or TP, and the pathway analyses of the top 100 DMPs in these pairwise comparisons detected no significantly enriched pathway.

Conclusions: We identified DNM differences between DLPFC and TP that were associated with BD and MDD and associated with BD only but absent in controls. These differences were related to genes and pathways involved in axon guidance, glutamatergic and GABAergic neurotransmissions, synaptic plasticity, and neurodevelopmental mechanisms. Our findings imply that a methylation imbalance between DLPFC and TP may contribute to BD symptomology. If so, DNM could prove to be an important target for further investigations of vulnerabilities associated with BD. Limitations of this study include the lack of cell type specificity, inability to differentiate between DNA methylation and DNA hydroxymethylation, small sample size, and unbalanced groups. These important issues should be addressed in additional studies.

Keywords: DNA Methylation, Bipolar Disorder, Postmortem Brain Tissue

Disclosure: Nothing to disclose.

M117. Prophylactic Ketamine Protects Against Fear Overgeneralization

Alessia Mastrodonato, Randy Martinez, Ina Pavlova, Christina LaGamma, Rebecca Brachman, Alfred Robison, Christine Ann Denny*

Columbia University, Research Foundation for Mental Hygiene, Inc., New York, New York, United States

Background: Stress exposure is the main cause of mood disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, some individuals can successfully adapt to stress, which is known as stress resilience. We previously reported that a single injection ketamine, an NMDA antagonist, prior to stress protects against the development of depressive-like behavior and attenuates learned fear in mice. Recently, we have showed that ketamine induces a prophylactic effect by modulating expression of the transcription factor ΔFosB in ventral CA3 (vCA3). In particular, transcriptional inhibition or overexpression of ΔFosB in vCA3 occludes and mimics, respectively, prophylactic ketamine efficacy, suggesting that ΔFosB expression in vCA3 is necessary and sufficient for ketamine prophylactic efficacy. Here, we sought to identify if prophylactic ketamine protects against fear generalization and which neural alterations correlate to fear generalization.

Methods: ArcCreERT2 mice were injected with saline or ketamine (30 mg/kg). One week later, mice were administered a pattern separation (PS) paradigm. After an initial training in the context A, where they received a shock, mice were exposed daily to the aversive context A and to a similar, but safe context B, for 10 days. Mice were then sacrificed, and brains were processed. Whole-brain immunolabeling was utilized in order to identify the neural ensembles (e.g., memory traces/engrams) representing fear generalization.

Results: During PS task, both groups of mice exhibited comparable levels of freezing following one-shock in the aversive context A. However, prophylactic ketamine mice ketamine mice distinguished between the two contexts more rapidly than prophylactic saline mice, froze significantly less in the similar but neutral context B and had significantly higher levels of discrimination between the two contexts. The ketamine prophylactic effect persists up to 6 weeks following a single injection.

Conclusions: Our data indicate that a single prophylactic injection of ketamine may be able to prevent fear generalization and protect against stress-induced psychiatric disorders (e.g., PTSD and depression) in a long-lasting, self-maintaining vaccine-like fashion. Prophylactic ketamine treatment in human subjects and PTSD patients might decrease fear generalization and alter similar neural circuits identified in the mouse studies.

Keywords: Fear Generalization, Ketamine, PTSD

Disclosure: Nothing to disclose.

M118. Absence of QTc Prolongation with Buprenorphine/Samidorphan Combination: A Thorough QT/QTc (tQT) Study in Healthy Volunteers

Hong Lu, Marjie Hard, Robert Kleiman, Wenlei Liu, Tim Bergsma, Arielle D. Stanford, Narinder Nangia, Lisa von Moltke*

Alkermes, Inc., Waltham, Massachusetts, United States

Background: The fixed-dose buprenorphine/samidorphan (BUP/SAM) combination comprises BUP, a μ-opioid receptor partial agonist, and SAM, a novel μ-opioid receptor antagonist optimized for potency and sublingual bioavailability. The efficacy and safety profile of adjunctive BUP/SAM has been demonstrated in patients with MDD with inadequate response to antidepressant therapy. Clinical development routinely includes evaluation for cardiac ventricular repolarization liability. Here we describe the effect of escalating doses of BUP/SAM on the QT interval and other electrocardiographic parameters to characterize the potential for arrhythmia associated with therapeutic and supratherapeutic doses.

Methods: Study 213 (NCT0247930) was a phase 1, randomized, double-blind, placebo (PBO)-controlled, parallel study with a nested crossover of BUP/SAM, positive control (moxifloxacin), and PBO in healthy adults. The study consisted of positive control period 1 (Day 1), a titration period (Days 2 to 13), and positive control period 2 (Day 14). Participants were randomized in a 2:1:1 ratio into Treatment Groups 1, 2, or 3, respectively. Group 1 received moxifloxacin-matched PBO during both positive control periods and BUP/SAM during the titration period, with titration from 0.5 mg/0.5 mg to 8 mg/8 mg. Group 2 received moxifloxacin 400 mg during positive control period 1 and BUP/SAM, then moxifloxacin-matched PBO during the titration period and positive control period 2, respectively. Group 3 received moxifloxacin, then BUP/SAM-matched PBO during positive control period 1 and the titration period, respectively, and moxifloxacin 400 mg during positive control period 2. Pharmacodynamic (PD) electrocardiograms (ECGs) were obtained during a 24-hour observation window using a 12-lead digital (Holter) ECG recorder at baseline (Day −1), and on Days 1, 2, 7, 10, 13, and 14. Blood pharmacokinetic (PK) samples were collected at the end of each PD ECG timepoint starting on Day 1. The primary endpoint, ΔΔQTcF, was the time-matched mean difference between BUP/SAM 8 mg/8 mg and PBO in their respective ΔQTcF, which was the time-matched change from baseline to Day 13. The ΔΔQTcF was evaluated using a linear mixed-effects model. Secondary endpoints included the ΔΔQTcF for BUP/SAM 0.5 mg/0.5 mg (Day 2), 2 mg/2 mg (Day 7), and 4 mg/4 mg (Day 10) doses, as well as heart rate (HR), PR interval, QRS interval, and ECG morphology. PK parameters of BUP, SAM, and their respective metabolites were determined using a non-compartmental method. The relationship between the QTcF effect and plasma concentrations of BUP, SAM and metabolites was analyzed using linear mixed-effects modeling. Adverse events (AEs) were recorded.

Results: Of 128 participants randomized, 111 completed the study. The estimated least squares mean (LSMEAN) ΔΔQTcF ranged from −3.4 to −0.2 msec with all upper bounds of the 2-sided 90% confidence interval (CI) well below 10 msec in the 24 h after BUP/SAM 8 mg/8 mg administration on Day 13 ($P < 0.001$), indicating an absence of QT prolongation. The LSMEAN ΔΔQTcF for the lower doses were −5.4 to 4.4 msec (0.5 mg/0.5 mg), −1.8 to 3.0 msec (2 mg/2 mg), and −3.2 to 1.5 msec (4 mg/4 mg). No values were associated with upper bounds of 90% CIs exceeding the threshold of 10 msec ($P < 0.05$), indicating absence of QT prolongation. The QT assay sensitivity was confirmed with lower bounds of 90% CIs above 5 msec following moxifloxacin administration. Mean changes from baseline for HR, PR interval, and QRS interval during the 24-hour period after BUP/SAM administration relative to PBO were small and not clinically meaningful. Plasma exposures for BUP, SAM, and metabolites appeared to increase in a dose-proportional manner. Linear mixed effects modeling of the plasma concentration-QTc relationships showed positive but shallow slopes for each analyte. The incidence of AEs after up to 12 days of BUP/SAM (53.1%) or matched PBO (40.3%) were similar. No serious AEs or deaths were reported. No participants experienced AEs related to ECG morphology findings.

Conclusions: A daily therapeutic sublingual dose of BUP/SAM 2 mg/2 mg and a daily supratherapeutic sublingual dose of BUP/SAM 8 mg/8 mg did not prolong the QTcF interval above the regulatory threshold of concern. Results indicate that BUP/SAM 2 mg/2 mg does not have an adverse effect on cardiac repolarization. BUP/SAM from 0.5 mg/0.5 mg to 8 mg/8 mg was generally well tolerated in this study.

Keywords: Thorough QT study, Buprenorphine/samidorphan, Negative QT Study, Safety

Disclosure: Alkermes, Inc., Employee

M119. Deconstructing Synaptic and Behavioral Effects of Rapid-Acting Antidepressants With Circuit and Cell Type Specific Resolution

Marco Pignatelli, Leonardo Bontempi, Yocasta Alvarez-Bagnarol, Debora Masini, Carlos Zarate Jr., Michael R. Tadross, Gilberto Fisone, Antonello Bonci*

National Institute on Drug Abuse Intramural Research Program/NIH, Baltimore, Maryland, United States

Background: Preclinical evidence has established that a single sub-anesthetic dose of either (R,S)-ketamine (ketamine) or its metabolite (2 R,6 R)-hydroxynorketamine (HNK) exerts rapid-acting antidepressant effects. While ketamine use is associated with undesirable side effects, such as psychotomimetic effects and addiction liability, HNK exerts its antidepressant actions in mice, while lacking ketamine-related side effects. Whereas ketamine and HNK's primary molecular target is still uncertain, unequivocal experimental evidence shows that synaptic activation of AMPA receptors (AMPARs) is required for their antidepressant effects. Thus, I started investigating whether AMPAR increase in synaptic strength within the Nucleus Accumbens (NAc), a key brain region involved in motivation and hedonic drive, represents the key "therapeutic" neuroadaptation induced by a single sub-anesthetic dose of ketamine or HNK and if the latter condition might underlie their long-lasting antidepressant effects, which notably outlast drug clearance for days.

Methods: In order to deconstruct the synaptic and behavioral effects of ketamine and HNK with circuit and cell type specific resolution, I used the mouse as a model system (7-8 males and 7-8 females for each group for each manipulation that follow), and I first explored whether acute intraperitoneal exposure to saline, ketamine (10 mg/kg) or HNK (10 mg/kg) was affecting the activity of glutamatergic neurons that project to the NAc from ventromedial prefrontal cortex (vmPFC), basolateral amygdala (BLA), paraventricular thalamus (PVT) or ventral subiculum (vSub). Toward this goal, I injected the retrograde tracer, CTb, into the NAc and evaluated projection-specific neuronal activation by looking at the neuronal activity marker, cFos, within CTb-expressing projecting neurons, 1 h post injection. Moreover, I collected brain slices containing the NAc and performed whole-cell recordings from the main population of neurons residing within the NAc (D1 and D2 MSNs), while optogenetically interrogating the main monosynaptic inputs to NAc in mice injected with either saline, ketamine (10 mg/kg) or HNK (10 mg/kg) 24 h earlier. To test whether increased AMPAR function within the NAc was required for ketamine or HNK's rapid-acting antidepressant effects, I delivered the selective AMPAR antagonist, NBQX (40 μM), into the NAc 15 min prior to the forced swim test (FST), a well-described rodent model of behavioral despair, in mice that have been exposed to a systemic injection of either ketamine or HNK24h earlier. Moreover, to determine the postsynaptic sites of action of ketamine and HNK, I employed an intersectional viral approach that allowed me to selectively block AMPAR onto accumbal D1 MSNs or D2 MSNs by means of DART technology. DART (Drugs Acutely Restricted by Tethering) offers an unprecedented opportunity to block AMPAR within genetically specified cells (D1 vs D2 cells). The validated DART AMPAR antagonist, termed YM90K-DART (experimental group) or vehicle (control group), was delivered into the NAc 15 min prior to the FST in animals that have been exposed to a systemic injection of either saline, ketamine or HNK 24 h earlier.

Results: In this study, I found that a single sub-anesthetic dose of either ketamine or HNK leads to the establishment of input-selective synaptic plasticity, in the form of long-term potentiation, within NAc D1 and D2 medium spiny neurons (MSNs). Moreover, by using a contralateral disconnection procedure in combination with DART, I show that the occurrence of input-selective plasticity and postsynaptic recruitment of AMPAR within genetically specified NAc MSNs is necessary and sufficient to ameliorate behavioral aspects ascribed in the context of anhedonia and behavioral despair.

Conclusions: These data will help deciphering the detailed mechanisms of ketamine and HNK's antidepressant action and may lead to novel and safer antidepressant agents with circuit and cell type-selective effects and decreased undesirable side effects, aligned with the spirit of modern precision medicine.

Keywords: Racemic Ketamine and Metabolites, Nucleus Accumbens, Medium Spiny Neuron, AMPA Glutamate Receptors

Disclosure: Nothing to disclose.

M120. The Duration of Antidepressant Effects by Ketamine or the Ketamine Metabolites (2 R, 6 R)-HNK and (2 S, 6 S)-HNK is Extended by Repeated Administration

Caroline Browne, Hildegard Wulf, Janet Clark, Carlos Zarate, Irwin Lucki*

Uniformed Services University of the Health Sciences, Bethesda, Maryland, United States

Background: Major Depressive Disorder (MDD) is one of the leading causes of disability and functional impairment worldwide. Characterized by persistent negative mood and anhedonia, current antidepressant treatments are only modestly effective at producing remission of symptoms. Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist that demonstrates robust

antidepressant effects in treatment-resistant patients at subanesthetic doses within hours of infusion. Unfortunately, the antidepressant effect from a single ketamine treatment lasts for just a few days. However, some recent clinical studies have shown that repeated treatment with ketamine can lengthen the period of its antidepressant effects. The first goal of these studies was to determine whether repeated treatment with ketamine extended the duration of antidepressant-like responsiveness in a rodent model. The second goal of the studies reported here was to corroborate the antidepressant-like effects for (2 R, 6 R)-HNK and (2 S, 6 S)-HNK, two metabolites of ketamine, and to determine whether repeated treatment also extended their period of responsiveness.

Methods: The behavioral effects of RS-ketamine (10 mg/kg, i.p.) and the ketamine metabolites (2 R, 6 R)-HNK and (2 S, 6 S)-HNK (10 mg/kg, i.p.) were compared with saline in 8 - 12-week-old C57BL/6 J mice. Drugs were administered either once or thrice, with injections spaced 48 h apart. Antidepressant-like activity was measured as decreased immobility in the forced swim test (FST). The FST was administered at 24 h, 7- or 14-days post dosing in separate cohorts of mice. The behavioral effects of HNK were also compared with the motoric and analgesic effects of acute ketamine in assays for locomotor activity and analgesia immediately following the same drug delivery regimen used for the FST.

Results: Ketamine and the two ketamine metabolites, (2 R,6 R)-HNK and (2 S,6 S)-HNK, exerted an antidepressant-like response when tested 24 h after injection. The effects of ketamine were maintained up to 7 days only when given repeatedly. Repeated treatment with (2 R, 6 R)-HNK, and (2 S, 6 S)-HNK reduced immobility in the FST when measured at 7 and 14 days following repeated injection. Unlike ketamine, (2 R, 6 R)-HNK and (2 S, 6 S)-HNK were inactive in assays for locomotor activity and analgesia, whereas ketamine produces alterations in motoric activity and transient thermal analgesia

Conclusions: These data confirmed the protracted antidepressant-like activity of ketamine, (2 R, 6 R)-HNK and (2 S, 6 S)-HNK as measured in the mouse FST. Furthermore, repeated treatment extended the duration of antidepressant-like effects for both ketamine and these two metabolites. Finally, in contrast with ketamine's NMDA mediated effects on locomotor activity and analgesia, the metabolites were inactive in those assays. Ketamine, and its metabolites (2 R, 6 R)-HNK and (2 S, 6 S)-HNK, have potential as novel, rapidly-acting antidepressants that may serve to fill an important treatment gap for MDD.

Keywords: Depression, Ketamine, Metabolites

Disclosure: Nothing to disclose.

M121. (2 R,6 R)-Hydroxynorketamine Acts Presynaptically to Rapidly and Selectively Enhance Hippocampal Glutamatergic Transmission

Lace Riggs, Yasco Aracava, Panos Zanos, Jonathan Fischell, Edna Pereira, Edson Albuquerque, Scott Thompson, Todd Gould*

University of Maryland School of Medicine, Baltimore, Maryland, United States

Background: Ketamine is a rapid-acting antidepressant that is promptly converted into several metabolites in vivo, including (2 R,6 R)-hydroxynorketamine (HNK). Preclinical studies have shown that (2 R,6 R)-HNK retains the rapid and sustained antidepressant actions of ketamine but lacks its dissociative-like properties and abuse potential. While N-methyl-D-aspartate receptor (NMDAR) antagonism has long been credited for the antidepressant effects of ketamine, (2 R,6 R)-HNK is one of several compounds to show preclinical antidepressant actions in the absence of NMDAR antagonism. Previous studies suggest that—regardless of their precise mechanism of action—putative rapid-acting antidepressants exert their effects by restoring the balance between excitation and inhibition in affect-regulating synapses. Understanding how (2 R,6 R)-HNK exerts its effects will allow for a fuller appreciation of the diverse mechanisms underlying rapid antidepressant action and will help to promote the development of therapeutic options that possess superior efficacy, safety, and tolerability than what is currently available. In the current study, we examined the acute actions of (2 R,6 R)-HNK on hippocampal excitatory synaptic transmission.

Methods: Ex-vivo slice electrophysiology recordings of field excitatory postsynaptic potentials (fEPSPs) and whole-cell patch clamp recordings of miniature excitatory postsynaptic currents (mEPSCs) were used to examine the effects of (2 R,6 R)-HNK in the CA1 region of the hippocampus. A dual recording configuration was used to assess the effects of (2 R,6 R)-HNK concurrently among subregions of the apical dendritic field, and between hippocampal afferent pathways.

Results: Bath application of (2 R,6 R)-HNK enhanced Schaffer collateral-CA1 fEPSPs in hippocampal slices derived from male and female rats. We found that while the (2 R,6 R)-HNK-induced potentiation is completely eliminated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) blockade, these effects were independent of NMDAR activity. Instead, (2 R,6 R)-HNK enhanced AMPAR-mediated synaptic transmission through a concentration-dependent increase in the probability of glutamate release, which occurs uniformly throughout the dorsal-ventral axis of the hippocampus. Additionally, (2 R,6 R)-HNK increases release probability across dendritic subfields that receive Schaffer collateral innervation, but not when stimulating electrotonically distinct temporoammonic afferents that synapse onto the same CA1 cell population. Whole-cell recordings of hippocampal mEPSCs revealed that (2 R,6 R)-HNK increases the frequency, but not amplitude, of AMPAR-mediated mEPSC events, consistent with a presynaptic site of action.

Conclusions: (2 R,6 R)-HNK augments AMPAR-mediated excitatory synaptic transmission in the hippocampus by acting presynaptically to enhance glutamate release. This suggests that the mechanism underlying the acute effects of (2 R,6 R)-HNK may be distinct from the sustained adaptations in synaptic efficacy that they give rise to, and that are shared among other rapid-acting antidepressant compounds.

Keywords: Depression, Ketamine, Hydroxynorketamine, Hippocampus, Glutamatergic Transmission

Disclosure: Nothing to disclose.

M122. Enhancement of the Firing Activity of Dopamine and Norepinephrine Neurons in Rats Following Repeated Administration of a Subanesthetic Dose of Ketamine

*Chidiebere Michael Iro, Mostafa El Mansari, Pierre Blier**

University of Ottawa Institute of Mental Health Research, Ottawa, Canada

Background: Ketamine is a non-competitive NMDA channel blocker which acts by binding to its PCP site. Clinical studies have repeatedly demonstrated the rapid antidepressant effects of subanesthetic doses of ketamine (within 2 to 24 h post administration) [1,2]. In addition to these, previous studies have shown that there is a rapid enhancement (within 2 h) of ventral tegmental area (VTA) dopamine (DA) and locus coeruleus (LC) norepinephrine (NE) activity following ketamine administration, which is α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-dependent [3,4]. The current study investigated the

presence of these changes 24 h after a single administration, as well as after repeated administration. We hypothesized that the effects of ketamine on these neurons can be prolonged with repeated administration.

Methods: Experiments were performed on male Sprague Dawley rats (250 – 320 g). Rats were anesthetized with chloral hydrate (400 mg/kg intraperitoneal (i.p) and mounted in a stereotaxic frame. Recordings were carried out in the dorsal raphe nucleus (DRN), VTA and LC. Electrophysiological recordings were conducted: a) 24 h after a single administration of ketamine (10 mg/kg; i.p) or b) 24 h after repeated administration of ketamine given thrice weekly for two weeks. Neurons were analyzed for changes in action potential frequency and changes in the percentage of bursts occurring per spike, as well as changes in the number of spontaneously active neurons per trajectory through the VTA.

Results: The previously observed increase in VTA DA neuron activity was absent 24 h after acute administration. However, it was present after repeated administration for two weeks (spikes occurring in bursts: controls 24 ± 4 %, ketamine 32 ± 3 %; p=0.02), as well as an increase in spontaneously active DA neurons per tract (controls: 1.8 ± 0.1, n=61 neurons; ketamine: 3.1 ± 0.6, n=94 neurons; p=0.02; N=5 rats per group). Similar results were obtained for LC NE neurons: there was no change in firing 24 h after a single administration, but an increase after repeated administration (controls: 1.6 ± 0.1 n=49 neurons; ketamine: 2.4 ± 0.1 Hz n=57neurons; p<0.001). No change was observed in the firing activity of DRN serotonin neurons under these conditions.

Conclusions: The present study supports previous findings which show that ketamine can increase the firing activity of NE and DA neurons. However, this was not observed 24 h after a single dose, but present after two weeks of repeated administration. These effects may thus be contributory to the sustained therapeutic actions of ketamine in MDD when given repeatedly.

Keywords: Ketamine, Dopamine, Norepinephrine

Disclosure: Nothing to disclose.

M123. HCN Channel Inhibitor Induces a Rapid and Sustained Reversal of Social Deficit in a Chronic Social Defeat Stress Model of Depression

*Yingbo Zhu, Mary Regis Shanley, Stacy Ku, Carole Morel, Hongxing Zhang, Yuan Shen, Allyson Friedman, Ming-Hu Han**

Icahn School of Medicine at Mount Sinai, New York, New York, United States

Background: Current antidepressant medications for major depressive disorder (MDD) require several weeks to achieve therapeutic effects, and medication optimization takes months to reach treatment efficacy suitable for MDD patients. Such delay for drug efficacy not only prolongs distress and impairment for depressed patients but is also life threatening for suicidal MDD patients. Recent clinical studies, including deep brain stimulation, ketamine and scopolamine therapies, have begun to change the field due to their ability to regulate mood states within minutes to hours. Preclinical studies show that optogenetic control of dopamine neuron activity in the ventral tegmental area (VTA) reward circuit can rapidly regulate social avoidance, a behavioral deficit seen in susceptible mice in the chronic social defeat stress (CSDS) model of depression. Further evidence shows that hyperpolarization-activated cyclic nucleotide-gated (HCN) channels play a key role in the regulation of VTA dopamine neurons, and more recent work supports that HCN channels are involved in mediating ketamine's rapid antidepressant effects. However, it is unknown whether directly targeting HCN channels can achieve ketamine-like rapid and sustained antidepressant efficacy.

Methods: C57Bl/6 J mice were subjected to 10-day CSDS. Those exhibiting depressive-like symptoms (susceptible mice) received a VTA microinfusion or systemic intraperitoneal (i.p.) injection of HCN channel inhibitor cilobradine (DK-AH269). In vitro brain slice recordings were employed to assess HCN-mediated Ih currents and firing rate of VTA dopamine neurons post-cilobradine treatment.

Results: We first show that mice susceptible to CSDS spend significantly less time with a social target as compared to stress-naïve controls and display significantly higher firing activity and increased Ih currents of VTA dopamine neurons when compared to controls. Utilizing this robust model, we further show that bath application of cilobradine in brain slice preparation obtained from susceptible mice significantly reduces Ih currents and dose-dependently decreases pathophysiological firing activity of VTA dopamine neurons. Additionally, our in vivo studies show that acute intra-VTA infusion and systemic administration of cilobradine normalizes social avoidance behavior within one hour. Strikingly, both acute intra-VTA infusion and systemic i.p. injection of cilobradine produce a sustained 13-day duration of treatment efficacy. Moreover, our electrophysiological recording data determined that the pathological hyperactivity of VTA dopamine neurons in susceptible mice was significantly decreased during this 13-day period.

Conclusions: This study provides a new line of evidence that directly targeting HCN channels induces acutely acting, long-lasting antidepressant effects.

Keywords: Major depression, HCN, Ventral Tegmental Area, Rapid Depression Treatment, Ketamine

Disclosure: Nothing to disclose.

M124. AGN-241751, an Orally Bioavailable Positive NMDA Receptor Modulator, Exhibits Rapid and Sustained Antidepressant-Like Effects in Rodents

John Donello, Yong-Xin Li, Pradeep Banerjee, Kirk Bertelsen, Yuan-Xing Guo, Xiao-Lei Zhang, Patric Stanton, Roger Kroes, Amanda Gross, Joseph Moskal*

Allergan, Inc., Irvine, California, United States

Background: Positive modulation of glutamatergic synaptic transmission by N-methyl-D-aspartate receptors (NMDARs) can produce rapid and sustained antidepressant effects. Rapastinel, a positive NMDAR modulator, has been shown to produce rapid and sustained antidepressant effects in animals and MDD patients. However, rapastinel is a tetrapeptide and is administered IV. Therefore, an orally bioavailable compound like AGN-241751 with rapastinel-like pharmacological properties offers distinct advantages over rapastinel for the treatment of depression. In this study, the pharmacological properties of AGN-241751 were characterized in various in vitro and in vivo assays.

Methods: NMDAR activity was measured by a [3 H]MK-801 potentiation assay in membrane extracts prepared from human NR2A-D subtype-expressing HEK cells. NMDA induced intracellular calcium increases with or without AGN-241751 were analyzed with calcium indicator Fluo-4 in cultured rat brain cortical neurons. All test articles were dissolved in Mg2+-free extracellular medium (containing TTX and NBQX) and applied to the cells using a customized rapid drug application system that exhibits a 90% solution exchange time of less than a second. NMDAR mediated synaptic currents (Inmda) and synaptic plasticity were recorded in rat medial prefrontal cortical (mPFC) slices. Pharmacokinetic parameters of AGN-241751 were evaluated in male Sprague

Dawley rats following oral dose administration. Concentrations of AGN-241751 in rat plasma, CSF and brain samples were determined by fit-for-purpose LC-MS/MS method. The antidepressant-like effects of AGN-241751 were tested in the rat forced swimming test (FST).

Results: Relative to the maximal level of glutamate co-agonism by 1 mM glycine, AGN-241751 (1 fM to 0.1 μM) increased [3 H]MK-801 binding by 35% to 78%. Median effective concentration (EC50) values ranged between 0.1 pM at NR2C receptors to 0.6 nM at NR2B receptors. In cultured rat cortical neurons, AGN-241751 and rapastinel exhibited a similar modulation of NMDAR activity, but AGN-241751 was approximately 30X more potent. NMDA (10 μM) produced a small but significant increase in intracellular calcium in the absence of exogenous D-serine or glycine. While AGN-241751 (0.1-1000 nM) alone did not increase intracellular calcium influx, co-application of low concentrations of AGN-241751 (0.3 to 10 nM) with 10 μM NMDA produced ~30% potentiation of the NMDA-induced calcium signal. Similar to rapastinel, the potentiation of NMDAR signaling by AGN-241751 is independent of the NMDAR glycine site. In mPFC, AGN-241751 (20 -100 nM) increased Inmda and enhanced the magnitude of long-term potentiation (LTP).

Following a single oral dose of AGN-241751 in male Sprague Dawley rats, plasma, brain, and CSF concentrations were quantified. AGN-241751's oral bioavailability was >95%, and it demonstrated dose proportional increases in plasma, CSF, and brain exposure up to doses of 10 mg/kg. CSF/plasma ratios were ~0.15. In the rat FST assay, a single oral dose of AGN-241751 (3 - 100 μg/kg) produced a dose-dependent and rapid antidepressant-like effect which lasted for 7-14 days. A single antidepressant dose of AGN-241751 also induced a dose dependent increase in mPFC metaplasticity.

Conclusions: AGN-241751 belongs to a novel class of positive NMDAR modulators that act independently of the glycine site but act as modest glutamate co-agonists. In vitro NMDAR-dependent functional assays demonstrate that AGN-241751 positively modulates NMDARs similar to rapastinel but is significantly more potent (~ 30×). Consistent with its modulation of mPFC NMDARs, AGN-241751 also increases mPFC LTP and metaplasticity. Oral administration of AGN-241751 produces dose dependent increases in plasma, brain, and CSF concentrations which yields dose dependent anti-depressant-like activity. The beneficial properties of AGN-241751 represent a significantly improved therapeutic profile for the development of therapeutics for major depressive disorders.

Keywords: Depression, NMDA Receptor, AGN-241751, Rapastinel, Rapid-acting Antidepressant

Disclosure: Allergan, Inc., Employee

M125. Intrinsic Dopaminergic Activity Underlying Sex-Specific Differences in the Stress Response

*Mary Shanley, Christopher Guevara, Allyson Friedman**

Hunter College, New York, New York, United States

Background: Sex differences in the incidence of depression frequently emerge during adolescence. This suggests that female stress susceptibility may be linked to surges in reproductive hormones that occur during puberty. Interestingly, the β isoform of the estrogen receptor is expressed in a population of mesolimbic dopaminergic neurons in the ventral tegmental area (VTA) which, in males, have been linked to changes in social stress induced depressive behaviors. These VTA neurons exhibit a range of activity modes, varying in frequency and degree of burst firing. In females, in vivo VTA dopamine neuron bursting activity is affected by the phase of the estrous cycle. Functionally, these differences in activity have been shown to contribute to the release of dopamine. Previous work has shown that a single pulse activation of these neurons releases twice as much dopamine in high estrogen females in the VTA- nucleus accumbens (NAc) pathway, compared to both males, and low estrogen females. We explored the physiological role of estrous cycle on dopaminergic regulation, as well as dysregulation, following social stress. We demonstrate that underlying dopamine neuron activity changes are intrinsic neuroadaptations that are driven by the fluctuations in reproductive hormones. Further, we propose that these intrinsic changes in channel function affect the female social stress response.

Methods: We utilized electrophysiological cell-attached and whole-cell recording of VTA neurons from freely cycling female C57BL/6 J mice. We used a series of voltage-clamp protocols, in combination with pharmacological agents, to isolate A-type (fast) and M-type (slow) potassium channel function which influence DA neuron bursting profiles. To determine the effect of estrous cycle hormone fluctuations on neuronal activity we used vaginal cytology and estradiol 17β ELISA measurements to correlate hormone levels with channel function. In in vivo pharmacological experiments, female mice were subjected to local infusions to the VTA of bio-available estradiol or ICI 182,780 (estrogen receptor antagonist) prior to social stress. Mice were then tested on social interaction and novelty suppressed feeding 24 h post-social stress.

Results: The in vitro firing rate of VTA neurons demonstrated minimal variance across the estrous cycle in stress naïve mice. Interestingly, we found significant differences in K+ channel function that correlated with the phases of the estrous cycle. Despite these channel function differences in stress naïve mice we found no influence on social interaction and novelty suppressed feeding behaviors. Conversely, 24 h following an acute social stress, behavioral testing revealed that the estrogen dependent intrinsic differences mediated significant differences in the behavioral responses. Next, we determined that estradiol was in part acting through the VTA by directly infusing either estradiol or an estrogen receptor antagonist into the VTA prior to the social stress and testing 24 h later.

Conclusions: Throughout the estrous cycle the reward system responds differently to salient stimuli, an effect that could increase the probability of social stress inducing dopamine dysregulation. Our findings demonstrate that estradiol modulates VTA neuron physiology, which may contribute to sexual dimorphism in social stress induced depression vulnerability.

Keywords: Acute Stress, Estradiol, Dopamine

Disclosure: Nothing to disclose.

M126. Affective Dysregulation and Dopamine Hypofunction in Female Rodents During the Early Postpartum Period

Millie Rincón-Cortés, Anthony Grace*

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Background: The onset of motherhood is often accompanied by alterations in mood, including anxiety and depressive-like symptoms, in humans and rodents (Fernández et al., 2014; O'Hara et al., 2014). The highest rates of anxiety and depression occur during the first few weeks, months or year postpartum: most new mothers experience mild transient affective dysregulation (i.e. postpartum blues) during the 1-2 weeks postpartum (Pawluski et. al 2017). In accordance, animal models of postpartum depression have also reported time-dependent effects on depressive-like behavior and anhedonia (Brummelte and Galea, 2010), with negative effects being greater in early/mid postpartum

females (Haim et al., 2014). Yet there is little data regarding the neural adaptations that occur in response to parity (i.e. the condition of having borne offspring) and shortly after giving birth that may be associated with these affective changes.

The dopamine (DA) system has traditionally been associated with anhedonia, the inability to derive pleasure from normally rewarding stimuli, and has been repeatedly implicated in the pathophysiology of depression. A causal link between a hypofunctioning DA system (i.e. decreased DA neuron activity) and stress-induced depression-related behaviors (i.e. anhedonia, despair, anxiety) has been demonstrated in animal models (Tye et. al, 2013; Chang and Grace, 2014), with females showing greater effects (Rincón-Cortés and Grace, 2017). However, little is known about the DA system in females following reproductive experience, including postpartum DA function.

Methods: The elevated plus maze (EPM) and the three-chambered social approach test (SAT) were used to compare anxiety-like behavior and social motivation in virgin and postpartum female rats across different timepoints (i.e. 1d-PP, 3d-PP, 1week-PP; n=9-16 per group). A separate cohort of animals was tested during late postpartum (i.e. 22-24d-PP; n=14-18 per group). Single-unit recordings of VTA DA neurons (n=7-12 animals per group) were conducted the day following behavioral testing and 3 parameters were measured: i) the number of spontaneously active DA cells (i.e. population activity or cells/track), ii) basal firing rate and iii) firing pattern (i.e. the percentage of spikes firing in bursts). Comparisons of 3 or more groups were analyzed using one-way ANOVA, whereas comparisons between 2 groups were analyzed using t-tests.

Results: 1d-postpartum female rats exhibited increased anxiety-like behavior in the EPM, as indexed by reduced open arm entries ($p < 0.01$) and time spent in the open arms ($p < 0.001$) compared with virgin or 1wk-postpartum rats. Early (1d-,3d-) postpartum female rats exhibited reduced social motivation ($p < 0.05$), as indexed by decreased social sniff time and fewer number of crossings into the social chamber ($p < 0.05$) compared with virgins. Early (1d-,3d-) postpartum female rats females exhibited an attenuation of VTA population activity, as indexed by a decrease in the number of active DA cells per electrode track, compared with virgin rats ($p < 0.01$) but no differences in firing rate or the percentage of spikes occurring in bursts. At 1-week postpartum, a split was observed in which approximately half the dams exhibited high neurobehavioral dysregulation (i.e. low social motivation, DA hypofunction), suggesting a link between impaired social motivation and attenuated DA function. None of these behavioral or electrophysiological effects were observed in late (22-24d) postpartum female rats compared with virgins.

Conclusions: Collectively, our findings suggest that parity-driven changes in affect and VTA DA neuron activity vary across the postpartum period and that the early postpartum period is a time of enhanced affective dysregulation, which is accompanied by reduced DA activity, in female rats.

Keywords: Postpartum, Dopamine, Mood and Anxiety Disorders, Electrophysiology, Ventral Tegmental Area (VTA)

Disclosure: Nothing to disclose.

M127. Human Experimenter Sex Modulates Mouse Behavioral Responses to Stress and to the Antidepressant Ketamine

Polymnia Georgiou, Panos Zanos, Jaclyn Highland, Carleigh Jenne, Brent Stewart, Danielle Gerhard, Ronald Duman, Todd Gould*

University of Maryland School of Medicine, Baltimore, Maryland, United States

Background: Lack of replicability of experimental results in different laboratories may be due to unexpected experimental variables that are unrecognized, and therefore not appropriately controlled. The sex of the human experimenter is rarely considered as a biological variable that can affect experimental results and is not usually reported or required in the experimental methods. However, there is some evidence that rodents may be able to differentiate the sex of human experimenters who handle them, and this discrimination could have measurable effects on their biological/behavioral responses. In particular, exposure of rodents to the scent of male experimenters was previously shown to result in increased anxiety and stress-induced analgesia in mice compared with an exposure to the scent of female experimenters.

Methods: We investigated the effects if the sex of the experimenter on baseline and stress-induced behaviors in mice, and the reversal of such behaviors by antidepressant drugs. In addition, we assessed the involvement of distinct stress systems on experimenter sex-induced differences on mouse stress-related behaviors. The effects of the sex of human experimenter was also investigated on electroencephalographic (EEG) and biochemical outcomes. All experimental procedures were approved by the University of Maryland, Baltimore Animal Care and Use Committee and were conducted in full accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Results were analyzed by a two-way ANOVA followed by Holm-Sidak post-hoc test when a significant interaction effect was observed.

Results: We show that mice manifest differential behavioral and stress responses to human odors (n=8 experimenters/group; n=16 mice/group). Administration of the antidepressant drug ketamine to mice by male experimenters reversed stress-mediated behavioral responses, while such responses were absent following injection of the drug by a female experimenter (n=4 pairs of experimenters; n=10/group). Similar sex-dependent experimenter effects were identified with the ketamine metabolite (2 R,6 R)-hydroxynorketamine (n=8 experimenters/group; n=16 mice/group), but not with other mechanistically distinct antidepressants (1 pair of experimenters; n=10 mice/group). The nearby presence of a female experimenter was sufficient to block antidepressant actions of male-administered ketamine (1 pair of experimenters; n=10 mice/group). Non-antidepressant behavioral actions of ketamine where present regardless of the sex of the experimenter (1 pair of experimenters; n=10 mice/group). Ketamine administration induced both overlapping and distinct EEG and biochemical profiles dependent upon the sex of the experimenter (n=3 experimenters/group; n=16/group). Manipulation of different mouse stress systems prior to treatment yielded differential responses to male and/or female-administered ketamine (n=5 experimenters/group; n=9-10 mice/group).

Conclusions: We establish that male scent is necessary to induce ketamine's antidepressant effects in some model systems in a manner dependent upon specific stress hormones. Overall, these findings demonstrate the importance of the sex of the experimenter on a subset of experimental outcomes. Our data argue that the sex of the experimenter may affect replicability and should be considered as a potential experimental variable in neuropsychopharmacology research involving rodent behavioral models.

Keywords: Ketamine, Hydroxynorketamine, Reproducibility, Design, Replication, Replication, Sex Differences

Disclosure: Nothing to disclose.

M128. Ovarian Hormones Causally Contribute to the Prophylactic Efficacy of (R,S)-Ketamine and (2 R,6 R)-Hydroxynorketamine in Female Mice

*Briana Chen, Christina LaGamma, Rebecca Brachman, Xiaoming Xu, Shi-Xian Deng, Donald Landry, Christine Ann Denny**

Columbia University, New York, New York, United States

Background: Exposure to stress is a major risk factor for mood disorders, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). However, stress does not universally cause disease. Stress resilience, the ability to adapt to stress without developing psychopathology, varies in individuals. For example, although women experience trauma at significantly lower rates than men, they are twice as likely to develop MDD. We previously reported that a single injection of (R,S)-ketamine prior to stress protects against the onset of depressive-like behavior and buffers against a deleterious fear response in male mice. However, the prophylactic efficacy of ketamine and ketamine metabolites in female mice remain largely unknown. Therefore, the goal of this study was to determine whether prophylactics can be developed for use in females and whether metabolites of (R,S)-ketamine can have the same prophylactic efficacy as their precursor.

Methods: Female 129S6/SvEv mice were administered (R,S)-ketamine, (2 R,6 R)-HNK, or (2 S,6 S)-HNK at various doses 1 week before one of a number of stressors, including contextual fear conditioning (CFC), learned helplessness (LH), and chronic immobilization stress (CIS). Prophylactic efficacy was validated using the forced swim test (FST). In a separate set of experiments, we examined whether sex hormones influenced the efficacy of prophylactic compounds.

Results: We found that (R,S)-ketamine and (2 R,6 R)-HNK, but not (2 S,6 S)-HNK, significantly reduced immobility in the FST compared to saline controls. Interestingly, in females, ketamine was prophylactic at a lower dose than previously shown in males. Moreover, (2 R,6 R)-HNK was prophylactic at a significantly smaller dose and at a faster rate than its precursor (R,S)-ketamine. Moreover, we determined that the prophylactic efficacy of these compounds may be mediated by ovarian-derived hormones.

Conclusions: Overall, these data indicate that (R,S)-ketamine and (2 R,6 R)-HNK are effective prophylactics against a variety of stressors in females and that their sex-specific effects may be modulated by gonadal hormones. To our knowledge, this is the first demonstration that (2 R,6 R)-HNK may possess the same prophylactic properties of its precursor (R,S)-ketamine. Our findings offer insights into the prevention of stress-related impairments in a susceptible population and may further elucidate underlying sex-specific neuropathology contributing to the onset of MDD.

Keywords: Racemic Ketamine and Metabolites, Depression, Sex Differences, Sex Hormones

Disclosure: Provisional Patent, Patent

M129. Cholinergic Innervation of the Hippocampus Regulates Stress-Induced Behaviors

Yann Mineur, Cristiana Pineda, Laura Vanopdenbosch, Ashraful Islam, Tenna Mose, Richard Crouse, David Thompson, Matthew Bentham, Wengliang Zhou, Marina Picciotto*

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Acetylcholine (ACh) acts through multiple cholinergic receptors to regulate neurobiological systems controlling behaviors related to depression, anxiety and stress resilience. Clinical imaging studies suggest that nicotinic acetylcholine receptor (nAChR) occupancy by ACh is increased in the brains of human subjects with major depression or bipolar disorder during a depressive episode. Conversely, blockade of either nicotinic or muscarinic ACh receptors can have antidepressant effects in human subjects and in preclinical models. Stress can increase ACh levels in specific brain areas and alter the activity of acetylcholinesterase (AChE), the primary enzyme degrading ACh. Further, blocking AChE systemically leads to depression-like symptoms in humans and in mouse models, while increasing ACh signaling locally in the hippocampus is sufficient to induce behaviors related to anxiety and depression. Thus, it is critical to determine how the cholinergic innervation of the hippocampus is involved in behaviors related to anxiety, depression, and stress resilience.

Methods: We first examined the changes of AChE (as a proxy for ACh concentration) in several brain regions, including the hippocampus and the medial septum, following restraint stress in mice. We then combined multiple strategies including optogenetics, chemogenetics, immunohistochemistry, pharmacology, and electrophysiology in wild-type and transgenic mice expressing Cre in cholinergic neurons (ChAT-Cre) to determine how modulating the cholinergic neurons of the hippocampus or of the septo-hippocampal pathway could alter physiology and behavior at baseline and in a hypercholinergic model of anxiety- and depression-like states. Most experiments were performed in two independent ChAT-Cre lines (BAC ChAT-Cre and ChAT-IRES-Cre) to account for potential line effects.

Results: Stress had significant region-dependent effects on AChE activity, with the greatest regulation occurring in ventral hippocampus. Few behavioral effects were observed when cholinergic neurons innervating the hippocampus were silenced or activated by infusing AAV-floxed-Gi-DREADD or AAV-floxed-Gq-DREADDs, respectively, into the medial septum of ChAT-Cre mice. However, the increases in stress-related behaviors induced by physostigmine were attenuated by inhibiting ChAT-Cre positive neurons, confirming that cholinergic inputs from the septo-hippocampal pathway are activated in response to stress, and that this pathway mediates the increased anxiety- and depression-like behaviors induced by cholinesterase antagonism. The lack of effect seen following DREADD stimulation of the medial septum in the absence of physostigmine could be due to projections that are not selective for the hippocampus. We therefore activated neurons projecting to the hippocampus selectively via optogenetic stimulation of septo-hippocampal terminals but did not selectively activate cholinergic terminals and found that stimulated mice exhibited less exploration of an anxiogenic environment and more immobility in tests of antidepressant efficacy, along with decreased interaction in a social defeat paradigm. To reinforce that these behavioral changes were due to activation of cholinergic inputs to the hippocampus, a retro-AAV-floxed-Gq-DREADD was infused into the hippocampus of ChAT-Cre mice. Consistent with optogenetic experiments in wild type mice, CNO-treated ChAT-Cre mice exhibited increased anxiety- and depression-like phenotypes and decreased stress resilience. Finally, stimulating the sparse population of ChAT-Cre-positive cells intrinsic neurons in the hippocampus using AAV-floxed-Gq-DREADD increased anxiety-like behaviors, immobility in tests of antidepressant efficacy and interaction in the social defeat paradigm, but only in BAC ChAT-Cre mice. These effects were partially reversed by locally infusing the broad nicotinic antagonist mecamylamine into the hippocampus, suggesting that this effect was nAChR-dependent.

Conclusions: Taken together, these results demonstrate that stress can alter expression of the primary degradative enzyme for ACh, thereby modulating cholinergic signaling in the

hippocampus. Activating ChAT-positive neurons in the hippocampus, or specifically modulating the cholinergic inputs from the medial septum/diagonal bands of Broca, can induce behaviors related to anxiety and depression in the mouse. Conversely, the results also suggest that activating non-hippocampal septal projections could have opposite effects on these stress-related behaviors.

Keywords: Acetylcholine, Hippocampus, Medial Septum, Depression, Stress

Disclosure: Nothing to disclose.

M130. Pilot Study of an Intracranial Electroencephalography Biomarker of Co-Morbid Depression in Epilepsy

Katherine Scangos, Lowry Kirkby, Kristin Sellers, Alia Shafi, Heather Dawes, Andrew Krystal, Edward Chang*

University of California, San Francisco, Sacramento, California, United States

Background: Adult patients with epilepsy have an increased prevalence of major depressive disorder (MDD) and other psychiatric co-morbidities. MDD in epilepsy is associated with worse outcome and quality of life. However, it continues to be underdiagnosed and untreated and further attention to this comorbidity is critical. Intracranial electroencephalography (iEEG) captured during extended inpatient monitoring of patients with treatment-resistant epilepsy who are potential surgical candidates offers a particularly promising method to study MDD networks in adult epilepsy, offering both high temporal resolution and spatial precision. Despite the enormous potential of iEEG, there are no studies to date that examine the neurophysiological signatures of network dysfunction in mood and anxiety disorders in patients with epilepsy. Such studies are critical in order to better understand the etiology of co-morbid MDD and could lead to the development of novel personalized therapies. In this pilot study high-density intracranial electroencephalography (iEEG) in humans was utilized to investigate the neural activity patterns within corticolimbic structures that reflect the presence of co-morbid MDD in epilepsy.

Methods: We examined 24 h of resting state iEEG recordings from a preliminary sample of 14 human subjects undergoing surgical treatment for medication refractive epilepsy. Eight patients (57%) had co-morbid MDD [Patient Health Questionnaire-9 (PHQ-9) ≥10] and 6 had mild/no MDD (no-MDD, PHQ-9 < 10). All patients had neural recordings from 5 brain regions: orbitofrontal cortex, amygdala, hippocampus, cingulate, and insula. Standard iEEG/ECoG pre-processing techniques were used. Continuous waveform transformation using the Morlet transform wavelet method was performed in 30 s intervals to obtain power spectra in 5 standard frequency bands. Relative power was calculated by dividing the power of each frequency band by the total power for each electrode. Principal component analysis was performed on the z-scored mean relative power across 24 h of iEEG recordings and across electrodes within a region and combined across subjects. Stepwise linear and logistic regressions were performed with PHQ-9 score or presence of moderate-severe MDD as the outcome variable respectively, and principle components (PCs) of power in a particular frequency band as the independent variables. A logistic classifier model was used to determine the ability of the biomarker to correctly classify patients with and without MDD. The standard "leave-one-out" cross-validation method provided a preliminary indication of whether results would generalize to an independent dataset.

Results: A forward stepwise linear regression model was significant with 4 PCs accounting for 70% of the variance in the PHQ-9 score ($p = 0.0178$, $R2 = 0.70$, 'leave-one-out' cross-validation: $R2 = 0.25$). PC1 was found to account for the majority of the variance in correlation with the PHQ-9 score ($R2 = 0.29$, $p = 0.046$, coeff $= 0.82$), with the 3 other PCs contributing about equally to the remainder. The 4 PCs were heavily dependent on beta and theta power, with greater MDD symptom severity associated with greater beta power throughout the entire 5 region network, higher subcortical theta power and lower cortical theta power.

A forward stepwise logistic regression model was significant with 2 PC's (PC1,PC2) accounting for the majority of the difference between the MDD and no-MDD groups ($R2 = 0.40$, $p = 0.023$; 'leave-one-out" cross-validation $R2 = 0.17$) with an odds ratio of 1.5 for PC1 and 2.0 for PC2. A logistic classifier model using these two PC's correctly classified 79% of patients (sensitivity 75% and specificity of 83%, leave-one-out cross validation).

Consistent with the results from the PCA analysis, mean beta power across the network was significantly greater by ~14% in the MDD group than in the no-MDD group ($p = 0.009$). Similarly, an analysis of variance revealed a significant group (MDD vs. no-MDD) by location (subcortical, cortical) interaction effect for theta frequency power ($p = 0.0133$, $F(1,66) = 6.13$). Cortical theta power was significantly lower in the depressed group ($p = 0.003$, ttest), while subcortical theta was numerically, although non-significantly, higher in this group. Using these three features alone (mean beta power, subcortical theta power, and cortical theta power) a logistic classifier model correctly classified 12/14 patients correctly (86% accuracy, sensitivity 88%, specificity 83%, leave-one-out cross validation).

Conclusions: In this pilot dataset, we have identified a putative biomarker of co-morbid MDD in medication refractive epilepsy patients that is correlated with the severity of their MDD symptoms and can correctly classify patients with and without MDD with 86% accuracy. This finding is the first of its kind to address circuit level activity within the overlapping circuits involved in epilepsy and co-morbid psychiatric conditions. Further research is indicated to examine what aspects of this activity and its time-course contribute most strongly to the differences observed.

Keywords: Depression, Biomarker, Intracranial EEG, Epilepsy

Disclosure: Nothing to disclose.

M131. Effect of Social Stimulation on Ethanol Intake and Gene Expression in Mice

Lei Yu, Arthur Tomie, Shivani Mehra, Usman Toor, Minjie Bao, Akhila Manthena*

Rutgers University, Piscataway, New Jersey, United States

Background: Social stimulation may play a role in ethanol consumption. There is considerable evidence that socializing stimulates ethanol drinking in humans and in animals. Humans drink more ethanol in the presence of social interactions than in the absence of such interactions. Previous studies in rodents have shown that, when put in social situations, mice change their behavior and drinking habits. Interestingly, we noticed that, although mice display a similar overall pattern of change for social interaction-mediated ethanol consumption, the extent of change in ethanol consumption varies substantially among individual mice, suggesting genetic factors at play. In particular, differences were noted with different gender pairing.

Methods: To investigate the effect of social stimulation on ethanol intake and gene expression, mice were given a free choice of water and ethanol, while in the presence of companion mice of the same or opposite gender.

Results: Some mice drank a significantly higher amount of ethanol than others, depending on the gender pairing of the social companion mouse. Brain tissues were collected, and the steady-state levels of candidate gene messengers were measured. Our results suggest that certain dopamine receptor genes, as well as selected GABA receptor genes, appear to display significant correlation with social stimulation-mediated effect.

Conclusions: Social stimulation plays a role in the extent of free choice ethanol intake. Gender pairing during social stimulation is a factor, and dopaminergic and GABAergic neurotransmission pathway genes appear to be affected.

Keywords: Ethanol, Social, Gender, Gene Expression

Disclosure: Nothing to disclose.

M132. Human-Based Exome Capture Performed in Rhesus Macaques Identifies a GABRA6 Polymorphism That Predicts Individual Differences in Neonatal Imitation Behavior

Ravi Kumar Sindhu, Carlos Driscoll, Qiaoping Yuan, Stephen G. Lindell, Annika Paukner, James Kohler, David Goldman, James Dee Higley, Stephen J. Suomi, Pier Francesco Ferrari, Christina Barr*

National Institute of Health, Rockville, Maryland, United States

Background: We have been examining genetic factors that contribute to variation in the neurobiological systems that influence reward pathways, sociality, impulsivity and stress reactivity, as these systems may also influence alcohol use and addiction vulnerability in modern humans. In order to interrogate these systems, we wanted to sequence the exomes of rhesus macaque subjects that were selected based on variation in temperament. The major advantage of using Whole Exome Sequencing (WES) is that DNA extracted from whole blood can be used without the need for extracting DNA from the tissue of interest. WES allows for the capture of large insertion/deletions and SNPs and is best for either non-synonymous or frameshift mutations. While there are no commercially available reagents for performing WES in nonhuman primates, a human whole exome platform is available.

Methods: Exonic sequences were enriched using the Agilent SureSelect all exon capture array targeting ~38 Mb and were annotated using Ensemble genes, refGene and refSeq xenoRefGene for H. sapiens & M. musculus from UCSC. Sequence alignment was performed using CASAVA, Recalibration & SNP calling using GATK, Annotations, filtering, counts and calculations using custom scripts, and visualizations using R. Missense variants' functionalities were inferred using Polyphen. PolyPhen posterior probability scores associated with false positive rate (FPR) below 5% are characterized as 'probably' damaging and those below 10% are determined to be 'possibly' damaging under the HumDiv classifier model. Focusing on candidate genes relating to risk for alcohol use disorders (1536 marker Addictions Array, LNG), we identified a number of non-synonymous SNPs, some of which were predicted to be "damaging" or "potentially damaging" by in silico analysis (PolyPhen). Among these was a SNP in the GABARA6 gene, a gene confined in its expression to the cerebellum and which has known roles in alcohol response in both rodents and humans.

Given a putative role of the cerebellum in mirroring behavior, we wanted to determine if Tyr28Phe genotype predicted individual differences in neonatal imitation. On postnatal days 1-14, infants were presented with two different stimuli: 1) a lipsmacking gesture (LPS) which is a common affiliative gesture in macaque and consists of the rapid opening and closing of the mouth; and 2) a nonsocial control condition (a white plastic disk with black/red or green/yellow orthogonal stripes slowly rotated clockwise and counter-clockwise). The neonatal imitation study was conducted on nursery-reared infants, raised at the Laboratory of Comparative Ethology at the National Institutes of Health in eight cohorts between 2007 and 2014. All procedures described below adhered to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the NICHD Animal Care and Use Committee.

Results: The human exome capture kit was effective for sequencing rhesus macaque exomes. Using this approach, we obtained good coverage at capture sights. Also bearing on the validity of the SNP detection pipeline, the transition/transversion ratio of human and macaque SNPs was non-random (2:1). We observed approximately 25,000 missense variants, among which was a nsSNP in the GABRA6 gene.

We found that GABRA6 genotype predicted the degree to which infant macaques imitated the behavior of a human caregiver. Carriers of the 28Phe allele exhibited higher levels of lip-smacking imitation (an affiliative gesture in macaques) than did infants homozygous for the ancestral allele ($P < 0.01$).

Conclusions: We used a human capture kit to effectively sequence the genome of rhesus macaques, which are 25 mya diverged from humans. In so doing, we identified a damaging nsSNP in the GABRA6 gene. Studies in humans and rodents have demonstrated that variation at the GABRA6 gene predicts individual difference in alcohol response. As the GABRA6 gene, which encodes the α6 subunit, is highly expressed in cerebellar granule cells, it is not surprising that functional variation at this gene influences alcohol-induced ataxia. One other system that is under control by the cerebellum and that is also reduced in its function in various psychiatric disorders is the mirror neuron system. The cerebellum is involved in the action-perception mechanism and is likely linked to imitative behaviors and probably other social cognitive skills. Notably, some motor impairments in children with autism -and their limited capacity to build an internal motor representation of actions- are thought to be based on a motor loop between the traditional parietal-premotor mirror circuit and the cerebellum. Here, we demonstrate that a non-synonymous SNP at the GABRA6 gene predicts individual differences in neonatal imitation behavior in rhesus macaques. This might suggest that functional variation at GABRA6 in humans could moderate risk for psychiatric and neurodevelopmental disorders.

Keywords: Whole Exome Sequencing, GABRA6, Next Generation Sequencing, Alcoholism

Disclosure: Nothing to disclose.

M133. Regional Brain Creatine Relates to Cognitive Function: A Multi-Voxel 1H-MRS Study in First Episode Psychosis and Clinical High Risk for Psychosis

Jeremy Watts, Sofia Chavez, Cory Gerritsen, Huai-Hsuan Tseng, Michael Kiang, Michael Bagby, Romina Mizrahi*

University of Toronto, Centre for Addiction & Mental Health, Toronto, Canada

Background: Brain energy metabolism is thought to be disrupted in schizophrenia and despite evidence that brain energy systems, such as creatine-phosphocreatine, are involved in cognition and are altered in schizophrenia, few in vivo studies have investigated the relationship between regional brain creatine and cognitive deficits in schizophrenia.

In vivo imaging studies in psychosis report lower rates of phosphocreatine formation in first episode psychosis (FEP). Further, development of neuropathologies of brain metabolism may precede the onset of frank psychotic symptoms, as observed

in individuals at clinical high risk of developing psychosis (CHR). We aim to investigate regional brain creatine and cognition in psychosis by measuring neurocognitive performance and regional total creatine+phosphocreatine (hereafter, 'creatine') levels using 1H-magnetic resonance spectroscopy (1H-MRS) in 114 participants comprising FEP, CHR and healthy controls (HC).

Methods: FEP patients (n=31) and CHR (n=43) were excluded if concurrent diagnoses better explained the symptoms for psychotic disorders or CHR criteria. HC (n=40) had no past or current DSM IV axis I disorder. All participants underwent 1H-MRS scans for one or more of the five regions of interest, for a total of 388 individual voxels.

Single voxel 1H-MRS spectra were obtained using a 3 T scanner and a standard sequence using point-resolved spectroscopy. Voxels were positioned on the left hippocampus, left dorsal caudate, left dorsolateral prefrontal cortex (DLFPC), bilateral supragenual anterior cingulate cortex (sgACC) and bilateral PMC. Binary voxel masks were applied to segmented T1 images in order to correct metabolite concentrations for tissue composition.

We used the Repeatable Battery for the assessment of neuropsychological status; 'RBANS') to assesses immediate and delayed memory, attention, visuospatial ability and language. Participants were antipsychotic-free at the time of the study except for six FEP patients and ten CHR taking antipsychotic drugs at low doses (i.e., below 100 mg chlorpromazine equivalents).

Data were analyzed using a generalized linear model with effect of group, creatine and their interaction, with RBANS total score as the dependent variable. Interactions were followed by between-group contrasts of regression β values. Main effects were followed up by a GLM for RBANS subscales.

Results: Our preliminary analysis found that lower creatine in PMC was associated with lower total cognitive scores ($F(1,53) = 13.669$, $p = .001$) and interacted with group ($F(2,53) = 8.873$, $p = .0005$) such that creatine was more strongly associated with total cognitive score in HC ($\beta = 11.32$; $p = .027$) and FEP ($\beta = 15.54$; $p = .01$) as compared to CHR ($\beta = -0.27$). In contrast to observations in PMC, total cognitive scores were not significantly associated with creatine in hippocampus ($F2,61 = 0.278$, $p = .759$), striatum ($F(2,59) = 0.286$, $p = .752$), DLPFC ($F(2,95) = 0.185$, $p = .832$), or sgACC ($F(2,96) = 0.261$, $p = .771$).

Lower PMC creatine was associated with poorer immediate memory ($F(1,53) = 8.873$, $p = .0005$), and this effect differed by group ($F(2,53) = 8.873$, $p = .0005$) such that creatine was more strongly associated with immediate memory score in HC ($\beta = 10.89$; $p = .009$) and FEP ($\beta = 21.21$; $p = .0003$) compared to CHR subjects ($\beta = -4.42$). Lower PMC creatine was significantly associated with better visuospatial ability ($F(1,39) = 8.607$, $p = .006$) across all groups, and this effect did not differ between groups. No associations were observed between creatine and other cognitive domains in PMC or other regions.

Conclusions: Preliminary results of this study support a role for PMC total creatine levels in overall cognition and immediate memory in HC and FEP but not in CHR. This result is in line with the PMC's high basal energy consumption and its role as a major network hub involved in memory. That these effects were not observed in CHR may result from the high clinical heterogeneity of this group. Thus, the primary result of this study suggest that the domain of immediate memory may be particularly sensitive to total creatine levels in the PMC.

Keywords: psychosis, clinical high risk for psychosis, Cognition, imaging, energy metabolism

Disclosure: Nothing to disclose.

M134. Imaging Alpha7 Nicotinic Acetylcholine Receptors in PTSD: Preliminary Findings and Sex Differences

Ansel Hillmer, Irina Esterlis, Maggie Davis, David Matuskey, Henry Huang, Richard Carson, John Krystal, Kelly Cosgrove*

Yale University School of Medicine, New Haven, Connecticut, United States

Background: Posttraumatic stress disorder (PTSD) affects over 7% of Americans, yet the underlying neurochemical factors are poorly understood, and limited pharmacotherapies are available. The α7 nicotinic acetylcholine receptor (nAChR) is present on glutamatergic neurons connecting the medial prefrontal cortex (mPFC) with the amygdala and hippocampus. These receptors modulate plasticity in these important circuits implicated in PTSD. Here, we aimed to measure α7 nAChRs in PTSD and controls with positron emission tomography (PET) brain imaging, with a focus on possible sex effects in people with PTSD.

Methods: Study participants included eleven individuals (5 females, 6 males) with a SCID-5 diagnosis of PTSD and 6 age-matched healthy control males. Data collected from all subjects included MRI and PET scans and mood and PTSD symptom assessments. Individuals with PTSD exhibited moderate to severe PTSD symptomatology (PCL-5 Scores: females = 52±7; males = 53 ±16). The α7 nAChR specific radioligand [18 F]ASEM was injected as a 338±55 MBq bolus. Imaging data and metabolite-corrected arterial blood samples were collected for 120 min. α7 nAChR availability was indexed by the total distribution volume (VT), estimated using multilinear analysis in brain regions of amygdala, hippocampus, and mPFC. Cohen's d effect sizes were estimated for comparisons among three groups: males with PTSD, females with PTSD, and male controls.

Results: For all regions, group average VT values followed the rank order of: PTSD males < PTSD females < control males. When comparing PTSD males with PTSD females, medium effect sizes of 0.7, 0.7, and 0.5 were observed in amygdala, hippocampus, and mPFC, respectively. Comparing PTSD males with control males revealed very large effect sizes of 1.6 and 1.2 in amygdala and hippocampus, with a moderate effect size of 0.6 in mPFC. We did not observe any associations between receptor availability and symptom severity in any of the groups.

Conclusions: These preliminary findings suggest altered α7 nAChR availability in men with PTSD. Although a healthy control female comparison group is not available at this time, our data suggest possible sex differences in α7 nAChR availability in brain regions associated with emotional processes. Work is ongoing to determine the role of α7 nAChR in PTSD, specifically by sex.

Keywords: PTSD, Alpha-7 Nicotinic Acetylcholine Receptor, PET Imaging, Sex Differences

Disclosure: Nothing to disclose.

M135. Fiber Cluster Topography Analysis of the Pattern of Structural Connectivity in Frontostriatal Circuitry in Healthy Subjects

James Levitt, Fang Zhang, Mark Vangel, Marek Kubicki, Martha Shenton, Lauren O'Donnell*

VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Brockton, Massachusetts, United States

Background: Alterations in brain connectivity may underlie neuropsychiatric conditions such as schizophrenia or autism. We here assess the pattern of structural connectivity between the

prefrontal cortex (PFC) and striatum in 100 healthy subjects (HSs) from the Human Connectome Project (HCP); age: 22 to 35; sex: 46 females and 54 males. We propose a novel method, using fiber clustering of dMRI tractography to assess the pattern of frontostriatal structural connectivity, which allows us to quantify the degree of pattern deviation from a topographic, parallel, arrangement.

Methods: To enable the identification of fiber tract parcels from the prefrontal cortex (C) and the striatum (S), we used a data-driven fiber clustering atlas (Zhang et al, 2018) that allows for a whole brain tractography parcellation into 2000 fiber clusters according to the white matter (WM) anatomy (i.e., fiber geometric trajectory). Then, fiber clusters of interest (i.e., from C to S) from the whole brain WM were identified according to their connected anatomical brain regions. We studied multiple Freesurfer PFC regions including orbital, lateral and medial PFC regions and the caudate. We identified 17 fiber clusters that connect C and S. To quantify the topographical relationship of these fiber clusters, we measured the mean distances between the endpoints of the fiber clusters within the prefrontal cortex (i.e., cortical distance) and the mean distances between the endpoints of the corresponding fiber clusters terminating in the striatum (i.e., striatal distance).

Results: We plotted the data in 2 ways. First, we generated a plot (not shown) based on the 17 fiber clusters (with 136 pairs of fiber clusters, yielding 136 data points), showing the relationship between the cortical distances and the corresponding striatal distances of the obtained fiber cluster pairs that connect the prefrontal cortex and the caudate. A 2-term exponential model was fit to the data points which was superior to a linear model. We showed that the PFC-striatal WM streamline projection pattern was non-linear, which was driven by the results from 10 cluster pairs. Certain clusters, for example cluster 6, representing a cluster originating in pars orbitalis PFC, were significantly over-represented in these 10 cluster pairs. Second, we generated plots (not shown) for each of the 17 cluster pairs. For each cluster, we fit a least squares line for predicting striatal distance from cortical distance, for the distance from that cluster to each of the other 16. Then we performed two-tailed binomial tests for the smaller of the number of 16 points with striatal < cortical distance and the number with cortical < striatal. Adjusting for the 17 comparisons, clusters 6 and 8 (both originating in pars orbitalis PFC), and cluster 10 (originating from both medial and lateral orbitofrontal PFC) showed significant deviation from chance with striatal < cortical, i.e., in a convergent, non-parallel, pattern (adjusted p-value 0.009). Further, clusters 1 (originating in rostral middle frontal gyrus PFC) and 7 (originating in lateral orbitofrontal PFC) trended towards significance (adjusted p-value = 0.071), again, in a convergent, non-parallel, pattern.

Conclusions: Using dMRI fiber cluster topography analysis in HSs, we show that the PFC projection pattern between the PFC and the striatum deviates from a topographic, parallel, organization, due to convergence, driven by specific anatomic clusters, in particular, those emanating from orbital and lateral PFC. This approach will allow us to test for variation in the pattern of frontostriatal structural connectivity in other neuropsychiatric conditions such as schizophrenia and autism.

Keywords: Diffusion Weighted Imaging, Frontostriatal Circuitry, Brain Structural Connectivity

Disclosure: Nothing to disclose.

M136. The Effects of Acute Dopamine Depletion on Resting-State Functional Connectivity and Striatal Glutamate in Healthy Humans

Fernando Caravaggio, Yusuke Iwata, Alex Barnett, Shinichiro Nakajima, Carol Borlido, Eric Plitman, Yukiko Mihashi, Julia Kim, Philip Gerretsen, Ariel Graff*

Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Background: Understanding the interplay between the neurotransmitters dopamine and glutamate in the striatum has become the highlight of several theories of neuropsychiatric illnesses, such as schizophrenia. However, it is unclear how acute dopamine depletion in healthy humans may affect the functional connectivity of the striatum and glutamate concentrations therein.

Methods: Sixteen healthy participants (8 female, age [mean ± SD] = 27.4 ± 9.3) participated in the study. Participants provided both resting-state MRI (rsMRI) and 1H-MRS scans (3 T GE Discovery MR750; 8-channel head coil) before and after acute dopamine depletion. Dopamine depletion was induced by oral metyrosine intake over 25 h (64 mg/kg over 24 h).

Results: Metyrosine administration resulted in increased self-reported fatigue ($t(15)=-3.66$, $p=0.002$) and reduced vigor ($t(15)=3.95$, $p=0.001$). Compared to baseline, dopamine depletion reduced functional connectivity between the caudate and medial prefrontal cortex, as well as between the ventral tegmental area and hippocampus. However, acute dopamine depletion did not alter striatal glutamate concentrations measured with 1H-MRS.

Conclusions: Acute dopamine depletion in healthy humans may reduce the functional connectivity between the dorsal striatum and prefrontal cortex. This work has important implications for theorizing about neurochemical alterations in neuropsychiatric diseases and, in turn, our understanding of the functioning of the basal ganglia in humans.

Keywords: Dopamine, Resting State Functional Connectivity, Resting-state fMRI, 1H-MRS, Glutamate

Disclosure: Nothing to disclose.

M137. Increasing Minority Participation and Diversity in ACNP Meetings and Membership: 2018 Status and Recommendations

Jack Henningfield, Lawrence Brown, Sandra Comer, Albert Garcia-Romeu, Dorothy Hatsukami, Debra Furr-Holden*

Johns Hopkins University School of Medicine, Bethesda, Maryland, United States

Background: This poster will provide an update on data-based evaluation of progress, issues, and thinking on efforts to increase underrepresented minority (URM) membership, annual meeting attendance, and participation in committees since the Henningfield et al. poster presented at the 2016 ACNP meeting. The core premises remain the same as discussed in the 2016 poster and are consistent with ACNP organizational goals and values. Namely, that neuropsychopharmacology science, its application in disease prevention and medicine, and drug regulation and policy, should address and benefit the diversity of the population, and that increasing its own diversity will support these goals. The 2016 poster included data from the College on Problems of Drug Dependence (CPDD) which, through, its UnderRepresented Populations (URPop) committee, shares these same core goals with ACNP. It was proposed then that both ACNP and CPDD might

be more effective in promoting underrepresented minority representation through more active collaboration, and indeed increased communication and sharing of ideas between ACNP and CPDD since 2016 has been helpful in addressing these issues. Adopting epidemiological approaches to data collection was discussed to better understand minority participation in ACNP and CPDD and guide interventions to increase participation.

Methods: Most surveys by ACNP and CPDD address the following specific populations of priority to enhance diversity: "African American", "American Indian or Alaskan Native", and "Hispanic". Some surveys have also counted "Asian", and "other". These surveys have also included "Caucasian" or "white" and "male" and "female" gender. The most recent ACNP data represent racial and gender self-identification by ACNP members in 2017.

Neither organization systematically collects information reflecting potential barriers to participation or information that might guide the development of more effective inclusion strategies by the organizations and external funders such as the National Institute on Drug Abuse. A novel approach that was piloted at the 2016 meeting will also be conducted at the 2018 meeting to extend the expert poll to ACNP meeting visitors to the poster.

Results: The most recent data from ACNP are from its 2017 membership poll, whereas the most recent CPDD data are from a poll of meeting participants following its 2017 annual meeting. Although using somewhat different approaches, the overall data are remarkably similar in population representation. Specifically, African Americans represented 0.7% of ACNP members and 2.5% of CPDD meeting participants who responded to the poll (note it appears that approximately 25% of CPDD attendees responded to the poll – a more accurate estimate should be available for the poster); Hispanic self-identification was 3% of ACNP members and not counted by CPDD but may have been included among the 7.7% who self-identified as "other"; Pacific Islander self-identification was 0.1% of ACNP members and 0.3% of CPDD attendees; Asian self-identification was 8% of ACNP members and not counted by CPDD but may have been included among the 7.7% who self-identified as "other". Caucasian/white self-identification was 79% of ACNP members and 82% of CPDD attendees who responded to the poll.

Gender self-identification indicated that approximately 28% of ACNP members are female, and 60% of those who responded to the CPDD meeting poll were female (again note that only about 25% of meeting attendees responded to the CPDD poll).

Conclusions: Gender self-report data suggest promising trends for women with their ACNP membership increasing from approximately 5% in the early 1990s to approximately 28% in 2017. Although the CPDD estimates for meeting participation are limited by low poll response rates, the self-identification of approximately 60% of meeting participants as female are also encouraging. In contrast, racial self-identification data are far from acceptable in absolute numbers and trends for African American, Hispanic, and Pacific Islander/Native American individuals. As will be discussed in the poster, the filling of all available minority travel awards indicates that these programs are functioning at least to ensure some level of minority participation in meetings that would otherwise likely be lacking without such programs. However, the limited membership data available for CPDD and trends in membership based on ACNP data do not support the conclusions that these programs are substantially contributing to the diversification of membership for either organization.

Clearly more needs to be done and done more rapidly as neither organization is keeping pace with emerging trends in racial ethnic makeup of the US. Unfortunately, neither organization is currently utilizing modern epidemiologically-based surveillance methods to capture the true diversity of meeting participants and membership beyond crude historical census-based types of categories, nor is either organization collecting the kinds of qualitative data vital to better understand the barriers and provide a data-based foundation for more effective interventions to increase diversity. The poster will include such ideas for going forward, and its poll to be conducted at the meeting is expected to provide additional options for consideration by ACNP and CPDD.

Keywords: Racial Ethnic Minority, Epidemiology, Ethical Issues

Disclosure: Pinney Associates, Consultant

M138. Practical Experiences in Advanced Data Discovery: The Databridge for Neuroscience Project

*Howard Lander, Arcot Rajasekar, Jessica Turner, Lei Wang**

Northwestern University Feinberg School of Medicine, Chicago, Illinois, United States

Background: The DataBridge for Neuroscience (DBfN) project is an NSF funded effort to introduce the benefits of advanced data discovery to the Neuroscience community. In this pilot project, we exploited the technical capabilities of the DataBridge to provide discoverability to a collection of clinical data sets housed in the SchizConnect (http://schizconnect.org/) virtual archive.

Methods: We exploited existing work in harmonization of the data sets to create an actionable RDF ontology representing relationships among entities represented in the data sets. Next, we used the ontology to create a DataBridge "signature" for each data set. We then selected the well-known Hammings Distance algorithm for our similarity measure. Finally, we used the DataBridge to perform a pairwise comparison among the selected corpus of SchizConnect data to produce a searchable similarity matrix.

Results: The project produced several versions of an owl formatted ontology representing a data harmonization for research instruments utilized by studies in the SchizConnect archive. These are available at http://maven.renci.org/ontologies/. The project also produced searchable matrices representing estimates of the underlying relationships among the studies.

Conclusions: The pilot project succeeded in the basic objective of applying the DataBridge to a small set of Neuroscience data. The produced matrices seem "reasonable" to domain experts. Further evaluation will require larger amounts of data.

Keywords: Data Sharing, Deep Indexing, Data Discovery, Data Similarity, Open Neuroscience

Disclosure: Nothing to disclose.

M139. Inaccurate Prescribing Warnings in Electronic Medical Record Systems: Results From an American Society for Clinical Psychopharmacology Membership Survey

Katharine Phillips, Leslie Citrome*

Weill Cornell Medical College, Cornell University; New York-Presbyterian Hospital; Alpert Medical School of Brown University, New York, New York, United States

Background: Electronic prescribing is becoming widespread. All states allow it, some states require it, and many institutions now mandate electronic prescribing. Many electronic prescribing systems use computerized decision support algorithms that give automated warnings or alerts at the time of prescribing if a potential prescribing error is identified -- for example, regarding dosing or contraindications. Some studies suggest that electronic prescribing alerts may reduce prescribing errors and can be clinically useful, but others caution that the warnings may have

substantial limitations and that clinicians often consider them clinically irrelevant. Harmful unintended consequences of such prescribing alerts have been described. Despite this topic's importance, few studies have examined the accuracy of automated prescribing warnings in electronic prescribing systems; to our knowledge no study has focused primarily on the accuracy of systems regarding prescribing of psychotropic medications. To examine this issue, we surveyed members of the American Society for Clinical Psychopharmacology (ASCP) regarding automated warnings generated by electronic prescribing systems.

Methods: The authors developed a 30-item survey that obtained information about prescribers' experience with prescribing warnings in electronic medical record prescribing systems. The survey included questions on respondent and practice characteristics, electronic prescribing systems used, perceived errors in automated electronic prescribing warnings, ability to override prescribing warnings, and related questions. The survey was hosted by Survey Monkey, a free online survey tool, and was sent to all current active ASCP members (n=1223). Summary statistics were calculated.

Results: A total of 118 ASCP members from 33 states completed the survey (9.6% response rate). A majority of respondents (56.8%) were age 55-74; 72.4% were male. An electronic prescribing system was used by 78.0% of respondents; 15.9% used more than one system. Overall, respondents used a total of 31 different electronic prescribing systems. Use of such a system was mandatory in the state, institution, or practice setting of 43.2% of respondents. Regarding the number of electronic prescriptions written in a year, about one third wrote more than 900. Among those who electronically prescribe, 83.1% reported that their electronic prescribing system provides automated warnings if the system detects a potentially problematic prescription. Among these individuals, one third believed that their system has provided incorrect warning information, and one third of this latter group believed that warnings were inaccurate 50% of the time or more. Types of information in prescribing alerts that clinicians considered inaccurate were: dosing range (54.2% of respondents), drug interactions (50%), contraindications (41.7%), dosing frequency (37.5%), dosing time (12.5%), indications (12.5%), and other (8.5%). Examples of erroneous prescribing alerts included: the maximum daily dose of fluoxetine is 40 mg/day, fluoxetine should not be combined with clonazepam, three doses a day of venlafaxine XR 37.5 mg exceeds the recommended maximum dose of one a day, prescribing bupropion and fluoxetine concurrently is contraindicated, aripiprazole is contraindicated for patients ages 6 through 18, and SSRIs are contraindicated for patients under age 18. Among respondents who perceived some warnings to be inaccurate, 95.8% stated that their system allows them to explain their rationale for the prescription or to override the warning, thereby enabling them to prescribe the desired medication despite the warning. However, a majority (76.2%) reported being unable to alert the system that the warning was incorrect. Regarding the burden of managing inaccurate prescribing data alerts, only 4.2% indicated that such warnings were not at all burdensome; 45.8% reported slight burden, 45.8% reported moderate burden, and 4.2% reported severe burden.

Conclusions: These results indicate that a substantial proportion of prescribing clinicians with an interest in psychopharmacology believe that their electronic prescribing system has provided incorrect prescribing warnings. It is particularly puzzling and problematic that some warnings do not reflect product labeling information – for example, regarding maximum dose or contraindications. Such errors potentially have profound consequences. For example, the erroneous warning that SSRIs and aripiprazole are contraindicated for children and adolescents may cause inadequate treatment of potentially life-threatening conditions in this age group. It is also concerning that most respondents reported being unable to alert the system about the inaccuracy of a prescribing warning. Nonetheless, automated electronic prescribing alerts are potentially useful; a limitation of our survey is that it did not assess the perceived usefulness of alerts or the balance of perceived benefits versus perceived risks. Other limitations include the low survey response rate and the small number of responses for some questions. We also do not know whether all alerts considered erroneous were actually erroneous. Additional studies of this topic are needed, especially given increasing use of electronic prescribing and potentially detrimental clinical consequences of inaccurate prescribing warnings.

Keywords: Clinical Psychopharmacology, Prescribing, Electronic Prescribing Warnings

Disclosure: Nothing to disclose.

M140. Kappa Opioid System Regulates Motivation to Pursue a Cold Environment

*Manish Madasu, Tayler Sheahan, Jordan McCall, Ream Al-Hasani**

St. Louis College of Pharmacy/ Washington University in St. Louis, St. Louis, Missouri, United States

Background: The kappa opioid system plays a critical role in the modulation of motivated behaviors, which regulate disease states such as depression and addiction. Importantly, kappa opioid receptors are well known to have analgesic efficacy despite the induction of negative affect. A role for KOR has been well elucidated in decreasing sensitivity to heat, however less is known about their role in cold sensation. Studies have demonstrated that transient receptor potential (TRP) A1 channels facilitate the perception of noxious cold at the level of dorsal root ganglia (DRG), where expression of KOR has also been reported. Here we investigate the role of the KOR in motivation to pursue cold environments and whether the presence/activation of TRP channels modulates such an effect.

Methods: To measure cold responsivity, we used the cold plate and cold plantar tests. For the cold plate we habituated male WT mice in plexiglass boxes for 1 h prior to treatment with: 1) U50 (5 mg/kg, i.p.), 2) norBNI (KOR antagonist,10 mg/kg, i.p.), 3) saline (10 ml/kg, i.p.). Post-treatment mice were placed on the cold plate for 5 minutes and nocifensive response was calculated. For the cold plantar assay, 30 mins following saline (10 ml/kg) or U50 (10 mg/kg) administration, we acclimated male and female WT mice on a glass plate and applied a cold stimulus to the hind-paw and measured the latency to withdraw from the cooled glass. We assessed the role of KOR in the motivation to purse hot or cold environments using an operant plantar thermal assay. To determine the calcium dynamics, we cultured DRG neurons from WT mice and treated the cultures with a TRPA1 agonist, mustard oil (MO) (100 μM), U50 (10 μM), and a combination of both at 1, 3, 5 mins respectively and quantified the change in the intensity of the Ca2+ indicator.

Results: Mice injected with KOR agonist U50 showed a significant potentiation in the number of jumps on the cold plate compared to controls. U50-induced nocifensive responses were attenuated in mice injected with norBNI. In the cold plantar assay, the latency to withdraw the hindpaw to cold stimulus appeared to decrease in males, but not in females. Mice showed increased motivation to avoid the cold environment when injected with U50. In the calcium imaging experiments, simultaneous application of MO, and U50 yielded a potentiated Ca2+ response, while U50 alone failed to elicit a calcium response, suggesting crosstalk between receptors.

Conclusions: Here we show that activation of KOR not only increases cold sensation in male and female mice, but these mice

are actively motivated to avoid the cold environment. We further show that KOR mechanism of action is likely in conjunction with TRPA1 as the Ca2+ response is potentiated when both are activated. These findings reveal a distinct role for KOR in motivation to pursue a cold environment suggest a role for KOR in physiological and pathological cold transduction and cold-triggered pain.

Keywords: Kappa Opioid Receptors, Transient Receptor Potential (TRP) A1, Temperature Regulation, Motivation

Disclosure: Nothing to disclose.

M141. Cortical Involvement in RMTg-mediated Aversive Signaling

Elizabeth Glover, E. Margaret Starr, Wesley Wayman, John Woodward, L. Judson Chandler*

University of Illinois at Chicago, Chicago, Illinois, United States

Background: The rostromedial tegmental nucleus (RMTg) is a small GABAergic nucleus that exerts inhibitory control over midbrain dopamine neurons. Exposure to aversive stimuli is associated with enhanced activity within the RMTg and activation of the RMTg facilitates aversive responding. The medial prefrontal cortex (mPFC) provides input to the RMTg and activity within this region has also been implicated in many of the same endpoints. However, little is known about the anatomy and function of this projection.

Methods: To better characterize the density of mPFC input to the RMTg anatomically, the distribution and number of tracer labeled neurons was assessed in adult male Long-Evans rats injected with the retrograde tracer cholera toxin B (CtB) into the RMTg (n=6). To determine the functional role of the mPFC-RMTg projection, we measured the behavioral response to stimulation of mPFC terminals in the RMTg using in vivo optogenetics in combination with real-time place preference (n=5-7/group). In addition, we quantified cFos induction in RMTg-projecting mPFC neurons following exposure to neutral and aversive stimuli (n=6-9/group). Finally, we evaluated stimulus-induced plasticity in RMTg-projecting mPFC neurons by measuring evoked firing following exposure to aversive stimuli in both male and female Long-Evans rats using whole-cell patch-clamp slice electrophysiology (n=4-6/group). Data were analyzed using t-tests and ANOVAs where appropriate.

Results: Rats sacrificed two weeks following CtB injection into the RMTg exhibited dense cell body labeling throughout the entire medial and orbital walls of the PFC as well as the entire rostrocaudal extent of the region. Labeling was restricted primarily to layer V of the mPFC, though a small number of cells were also consistently observed in the deepest portion of layer VI. Quantification of CtB labeled neurons relative to NeuN labeling found that approximately 14.21% ± 0.38 of layer V prelimbic neurons projected to the RMTg – a proportion that is substantially greater than many other subcortical projections from the prelimbic cortex including the amygdala, ventral tegmental area, and periaqueductal gray. Stimulation of RMTg-projecting mPFC inputs produced significant avoidance behavior, the magnitude of which was similar to that produced by stimulation of lateral habenula inputs to the RMTg ($p \leq 0.01$) indicating that activation of this pathway can induce aversive responding. Rats presented with a shock or a tone predictive of shock exhibited a significant increase in cFos expression in RMTg-projecting mPFC neurons compared to rats exposed to neutral stimuli ($p \leq 0.05$). In addition, exposure to a single episode of 10 consecutive foot shocks resulted in a significant decrease in the frequency of evoked firing in RMTg-projecting prelimbic neurons compared to unshocked controls ($p \leq 0.0001$).

Conclusions: Together, these results uncover a remarkably dense projection from the mPFC to the RMTg that drives behavioral responding to aversive stimuli. We further reveal significant plasticity as a result of exposure to aversive stimuli. Alterations within this neural circuit may be critically involved in neuropsychiatric illnesses associated with disruption of the balance between signaling of rewarding and aversive outcomes including addiction and mood disorders.

Keywords: Aversion, RMTg, mPFC

Disclosure: Nothing to disclose.

M142. fMRI-Measured Brain Network Connectivity Changes After Acute Cannabis Challenge

Michael Stevens, Nicolas Ward, Erwin Boer, Diana King, Catherine Boyle, Ashley Bullock, Vince Calhoun, Godfrey Pearlson*

Yale University School of Medicine, Hartford, Connecticut, United States

Background: The timecourse of acute cannabis effects on brain function and how these changes relate to behavior is important for understanding the ways in which marijuana use might confer public health risk or therapeutic benefit. One of the least understood phenomena is how cannabis alters the way in which widely-distributed brain regions co-engage to form functional neural networks underlying task performance. Here, we used functional connectivity analyses to describe how complex network characteristics were changed by smoking cannabis and how those changes evolved over the course of several hours.

Methods: As part of an ongoing NIDA-funded study (R01DA038807), fMRI data were collected from 15 regular marijuana users after administering NIDA herbal 13.4% THC, 5.9% THC, or placebo cannabis via a paced inhalation protocol using a vaporizer. On each visit, participants were given the drug/placebo by 9:00 a.m., then underwent fMRI 3 separate times post-dose in a randomized, double-blind design. All participants were scanned at 0.5 h following dosing, but the other two fMRI sessions occurred either at 2.5 h, 4 h, or 5.5 h after drug use in a counter-balanced design that provided a greater number of timepoints at which to observe whether the effects of the drug had resolved. Two fMRI task probes were used that prior research has validated are sensitive to both neural and behavioral effects of smoked cannabis -- A time estimation task and a cognitive set shifting paradigm. fMRI BOLD timeseries were prepared for analysis using Human Connectome Project protocols, then examined using graph theory-based connectivity metrics to characterize connectivity abnormalities after drug dosing relative to placebo. A repeated-measures ANOVA identified brain regions with linear or curvilinear changes in the degree of connectivity strength over time for all 391 cortical and subcortical HCP parcels. For any HCP parcel-localized effect $p<.05$ or less, we inspected mean plots to understand the profile of regional connectivity abnormalities relative to placebo over time.

Results: Linear effects that met the $p<.05$ significance threshold had eta-squared effect sizes ranging from 0.32 to 0.60 (mean 0.42) for the time estimation task, and from 0.35 to 0.53 (mean 0.49) for the set shifting task (all "large" effects). Network connectivity abnormalities induced by cannabis showed evidence of task-dependency. Most network connectivity changes observed immediately after cannabis inhalation during set shifting task performance took the form of excessive cortical connectivity, whereas there was widespread evidence for hypo-connectivity soon after dosing on the time estimation task. No brain regions

were commonly impaired across both tasks. The most notable finding was that brain connectivity remained abnormal compared to placebo 5.5 h after cannabis use. While the majority of initial abnormalities had waned by 2.5 h, evidence emerged that regional connectivity disturbances seen immediately after using cannabis then "overshot" their baseline levels after several hours. That is, by 5.5 h many regions showing cortical hyper-connectivity became hypo-connected, or vice versa. There also were brain regions that failed to show any initial difference from placebo in their local connectivity strength, but that over time showed more connectivity changes.

Conclusions: These preliminary study findings suggest that cannabis does not simply have a localized effect in regions with high density of CB receptors, but rather it can induce persistent, widespread effects on functionally-integrated neural networks. This effect appears not only to be context-specific, but also to be biphasic over time, with initial abnormalities changing dramatically after a few hours to a longer, persistent state with quantitatively and qualitatively different connectivity abnormalities. These findings prompt different possible interpretations. One possibility is that the immediate effects of cannabis on network connectivity might reflect the limited duration of acute intoxication. Another is that the network abnormalities that emerge later reflect a form of neural compensation for the initial brain connectivity impairment. There were more examples of late-occurring "overshoot" abnormalities than quickly-waning network connectivity disturbances, raising questions about the nature and effect of these longer-lasting brain network effects of cannabis use. These different classes of drug-induced effects on distributed brain function suggest future functional neuroimaging research should consider lengthier periods of post-drug recovery when attempting to understand how cannabis-induced brain changes might influence cognition and behavior.

Keywords: Cannabis Use, Functional Connectivity, fMRI, Drug Response

Disclosure: Nothing to disclose.

M143. Critical, Sex-Dependent Impacts of a Vasopressin Model of Preeclampsia on Neurodevelopment and Behavior in Mouse Offspring

Serena Gumusoglu, Akanksha Chilukuri, Salma Haider, Sabrina Scroggins, Jeremy Sandgren, Dark Santillan, Donna Santillan, Justin Grobe, Hanna Stevens*

University of Iowa Carver College of Medicine, Iowa City, Iowa, United States

Background: Preeclampsia is an often severe, gestational hypertensive condition linked to abnormal child neuropsychiatric outcomes (e.g. autism spectrum disorder, learning delays). This connection between preeclampsia and offspring neurodevelopment is poorly understood. One unique animal model of preeclampsia involves continuous maternal administration of arginine vasopressin (AVP) throughout pregnancy. This exposure results in pregnancy-specific hypertension, proteinuria, and an altered inflammatory profile in dams and offspring. Here, we examine critical impacts of this model of preeclampsia exposure on neurodevelopment and behavior in mouse offspring.

Methods: C57Bl/6 J mouse dams were implanted with a subcutaneous osmotic minipump (Alzet), filled with AVP or saline (24 ng/hr), 3 days prior to mating. Juvenile and adult offspring were tested for behavioral phenotypes using the Y-Maze, rotarod, social approach, and elevated plus maze assays (n=12-14 per group per sex). Offspring brains were collected embryonically and postnatally to examine cortical morphogenesis histologically (n=4-6 per group per sex per age). Additionally, RNA from embryonic cortical tissues (n=4 per group per sex) was extracted and sequenced (Illumina HiSeq 4000). Reads were pooled across two lanes (approximate depth: 30,000), aligned and summed using Kallisto, and then statistically compared and analyzed using Sleuth. Hits were functionally annotated and analyzed for enrichment of functional clusters/pathways using PANTHER and DAVID. Differences that survived correction for multiple comparison were validated with qPCR.

Results: Preeclampsia-exposed adult males exhibited increased anxiety-like behavior and social approach while adult females exhibited impaired procedural learning and working memory. Despite these sex differences, preeclampsia-exposed male and female offspring showed similar volume reductions in dorsal forebrain and cortical plate late in embryonic and early in postnatal development only. Interestingly, preeclampsia-exposed offspring also exhibited compensatory increases in embryonic cell packing density, maintaining the same total number of dorsal forebrain cells and preserved cortical layers. RNAseq analyses of embryonic anterior cortex revealed a single gene differentially expressed by preeclampsia exposure across males and females—ebf2—which was upregulated and plays a critical role in cortical neurogenesis. Sex-specifically, 49 genes were differentially-expressed by preeclampsia exposure in male offspring (select GO pathways: translation, transcriptional regulation) and 31 in females (GO pathways: development, signal transduction). Of the top five altered genes in male embryonic cortex—gdf1, capn11, slc26a4, fgf15, and tfap2d—three have been implicated in cortical patterning, neuronal differentiation, and neurogenesis. Of the top five altered genes in female embryonic cortex—cped1, gprc5c, postn, lox, and mrc1—four are implicated in development and response to injury.

Conclusions: Within an AVP-based model of preeclampsia, we found that exposed offspring exhibited sex-specific deficits in behavior. Corticogenesis was disrupted across both males and females, with altered development of neuronal precursors and upregulation of the cortical neurogenesis regulating gene, ebf2. Sex-specific alterations in embryonic cortex with preeclampsia exposure most significantly disrupted genes implicated in processes of protein translation in male embryonic brain while female offspring showed the most substantial alterations in signal transduction genes. The origins of sex differences in corticogenesis and behavior were not apparent, but they suggest distinct pathways by which preeclampsia may disrupt brain development.

Keywords: Neurodevelopment, Pregnancy, Hypertension, RNA Sequencing, Animal Models

Disclosure: Nothing to disclose.

M144. Developmental Exposure to Pyrethroid Pesticide Causes an Autism-Related Phenotype and Dopamine System Alterations in Mice

James Burkett, Rachel Branco, Rohan Dhamsania, Emily Winokur, Shannon Gourley, Gary Miller*

Emory University Rollins School of Public Health, Atlanta, Georgia, United States

Background: Pyrethroids are a class of pesticide whose use has broadly expanded in recent years, as it is considered the "safe" alternative to harmful organophosphates and organochlorides. Recent epidemiological studies, however, have suggested that residential exposure to pyrethroid pesticides during pregnancy increases the risk of Autism Spectrum Disorders (ASD) in the unborn child. Our lab's previous work has shown that developmental exposure to the pyrethroid deltamethrin, in doses

considered safe by the EPA, causes an ADHD-related phenotype and disruptions in the dopamine system in mice.

Methods: In this study, we exposed multiple independent cohorts of female mice (total N=60) to a low dose of deltamethrin (3 mg/kg PO Q3D) during pre-conception, pregnancy and weaning. We tested the offspring on a broad behavioral battery representing all three diagnostic domains of ASD, as well as related symptoms and comorbid disorders.

Results: Consistent with our prior publications, we found evidence of hyperactivity and repetitive behaviors. In addition, we found decreased ultrasonic vocalizations, increased rigidity, and learning deficits. No deficits in social behavior were found. We also found increased striatal dopamine, increased dopamine transporter, and other dopamine-related disruptions.

Conclusions: Additional studies are urgently needed to determine whether exposure to this common class of pesticides contributes to ASD diagnosis in humans.

Keywords: Neurodevelopmental Disorders, Toxins, Autism Spectrum Disorders, Pesticides

Disclosure: Nothing to disclose.

M145. Larger Numbers of Glial and Neuronal Cells in the Periaqueductal Gray Matter of μ-Opioid Receptor Knockout Mice

Abstract not included.

M146. Increased Calcium Influx in Response to Activity in Human Induced Pluripotent Stem Cell-Derived Neural Progenitors Lacking Fragile X Mental Retardation Protein

*Ulla-Kaisa Peteri, Venkat Swaroop Achuta, Maija Castrén**

University of Helsinki, Helsinki, Finland

Background: The absence of FMR1 protein (FMRP) results in fragile X syndrome (FXS) and disturbed FMRP function is implicated in several forms of human psychopathology. FMRP is essential for normal neurogenesis and functional maturation of synapses and neuronal networks. Exaggerated group 1 mGluR function is found to be a fundamental abnormality in FXS. Responsiveness of FXS neurons is increased and correlates with hyperarousal, sensory hypersensitivity, and susceptibility to epilepsy in the FXS phenotype. We have functionally characterized differentiating mouse and human FXS neural progenitors at the early stage of differentiation [1]. The studies have revealed enhanced differentiation of glutamate-responsive cells and augmented intracellular calcium responses to activation of mGluR in FXS progenitors. Increased responses to activity promoted us to explore the role of L-type voltage-gated calcium (Cav) channels in altered differentiation of FXS progenitors.

Methods: Human neural progenitors were differentiated in neurospheres from four FXS iPS cell lines and three control cell lines that are previously characterized [1,2]. Mouse neural progenitors were generated from the brain of wild type and Fmr1 knockout mice. We used fura2-AM based calcium imaging to study intracellular calcium responses and RT-PCR for expression studies and to confirm results of the Affymetrix array analysis.

Results: We observed augmented responses to depolarization with high extracellular calcium in both human and mouse neural progenitors. Nifedipine treatment prevented the increase in calcium influx indicating that L-type Cav channels contributed to the exaggerated responses in FXS progenitors. Ratio of the pore-forming alfa1 subunits of the L-type channel/T-type channel expression was increased and correlated with enhanced differentiation of FXS progenitors, but no significant changes were detectable in the expression of single subunits. Transcriptome analysis of human iPS cell-derived FXS progenitors revealed alternative splicing of the CAST gene that encodes calpastatin, suggesting contribution of cytoplasmic factors to augmented intracellular calcium responses.

Conclusions: Our results show a critical role for increased calcium influx through L-type Cav channels in FXS progenitors and address impact of altered calcium homeostasis during neuronal development in FXS brain.

Keywords: Voltage-Gated Calcium Channel, Fragile X Syndrome, Neural Progenitor Cells, Calcium, In Vitro Neuronal Differentiation

Disclosure: Nothing to disclose.

M147. Genetic Variants of OCD Phenotypes and Comorbid Conditions

Vera Nezgovorova, Nichole Rigby, John Battles, David Krause, Naomi Fineberg, Michael Van Ameringen, Eric Hollander*

Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, United States

Background: Obsessive-compulsive disorder (OCD) is characterized by recurrent and intrusive thoughts, impulses or images (obsessions) that cause discomfort and are accompanied by repetitive behaviors (compulsions) to alleviate discomfort. OCD is often associated with significant psychiatric comorbidity which is frequently underdiagnosed and undertreated. Comorbid disorders include mood and anxiety disorders as well as obsessive-compulsive spectrum disorders (OCSDs), including anorexia nervosa, bulimia nervosa, binge-eating disorder, BDD, compulsive shopping, kleptomania, pathological gambling, intermittent explosive disorder, hypersexual disorder, tic disorder and autism spectrum disorders. Comorbidity in OCD may influence treatment decisions and may require specific pharmacotherapy augmentation. The Genecept Assay® (Genomind, King of Prussia, Pennsylvania) provides information to clinicians that can be used for personalized treatment decisions on psychotropic medications based on individual patient's genetic, pharmacokinetic and pharmacodynamic profile. It also might help to develop management strategies for different OCD comorbidities, influencing treatment selection.

Methods: We evaluated 130,629 patients (61.09% female) who underwent the Genecept Assay phenotyping protocol. 1,882 patients (1.44%) had OCD as the primary diagnosis and 2,763 patients (2.12%) had OCD as comorbid diagnosis. All patient data was deidentified for analysis purposes. DNA sample collection occurred as part of the patient's standard of treatment. Consent to perform the Genecept Assay was obtained by study physician. All analyses were performed using R software, v.3.3.3 (R Foundation for Statistical Computing, Vienna, Austria). We performed a descriptive analysis of the studied cohort data using nonparametric tests and logistic regression analysis while controlling for comorbid depressive disorders, bipolar disorders, ADD/ADHD, anxiety and panic disorders phenotypes.

Results: In the studied cohort, 21.79% of patients with primary OCD diagnosis were diagnosed with comorbid depressive disorder, 19.29% with anxiety, 14.24% with ADD/ADHD, 3.77% with panic disorders, 3.13% with bipolar disorder and 1.75% with PTSD. Over 80% of patients with OCD were reported as Caucasian, and over 20% were between 15-19 years old. Patients with primary OCD diagnosis had significantly higher frequencies of comorbidities with depressive disorders and ADD/ADHD, as compared to patients without an OCD-related diagnosis

($p<0.05$). Comorbid OCD and bipolar disorders phenotypes were associated with COMT, OPRM1 and GRIK1 genotypes. Comorbid OCD and depressive disorders phenotypes were associated with OPRM1 and CYP3A4/5 genotypes ($p<0.05$). Comorbid OCD and ADD/ADHD were associated with MC4R and 5HT2C genotypes ($p<0.05$). Comorbid OCD and panic disorders were associated with CACNA1C genotypes ($p<0.05$). Comorbid OCD and anxiety were associated with CYP3A4/5 variants in OCD patients ($p<0.05$).

Conclusions: Our analysis constitutes a first attempt to use the Genecept assay to elucidate genetic profiles in OCD patients and relate these to comorbidities and treatment response. Although more research is needed, a personalized approach for management of treatment-resistant OCD cases associated with mental health comorbidities based on common gene variants could potentially improve patients' quality of life and reduce treatment costs. Future studies of sequential next steps in treatment-resistant OCD management including use of gene variants as predictors of response to personalized treatments are needed.

Keywords: Obsessive-Compulsive Disorder (OCD) Phenotypes, Genecept Assay, Pharmacogenomics, Obsessive-Compulsive Spectrum Disorders (OCDS), Personalized Medicine

Disclosure: Nothing to disclose.

M148. Pharmacokinetic and Pharmacodynamic Properties of the Investigational AMPA Receptor Positive Allosteric Modulator TAK-653 After Single and Multiple Rising Doses in Healthy Volunteers

Mahnaz Asgharnejad, Stephen Zicha, Lin Xu, Don Cheng, Sergio Iadevaia, Andy Dorner, Venketesha Murthy, Emiliangelo Ratti*

Takeda Development Center Americas, Inc., Cambridge, Massachusetts, United States

Background: Antagonism of the N-methyl-D-aspartate (NMDA) receptor by ketamine at subanesthetic doses to patients with treatment-resistant depression (TRD) is associated with rapid onset of antidepressant effects. This antidepressant action appears to be mediated via increased levels of brain-derived neurotrophic factor (BDNF) and increased mammalian target of rapamycin (mTOR) signaling. This effect can be replicated by the activation of post-synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors downstream of NMDA inhibition. Activation of AMPA receptors triggers increases in BDNF release; raising BDNF levels has been described as a potential biomarker of antidepressant activity. Therefore, selective activation of AMPA receptors can be considered a novel mechanism for antidepressant effect. We have discovered TAK-653, a selective and potent AMPA positive allosteric modulator that was efficacious in nonclinical models of depression. In this study, we describe the results from the first-in-human study with TAK-653 where we tested the safety and tolerability in a single rising dose (SRD) and multiple rising dose (MRD) settings in healthy volunteers. In addition, for a preliminary understanding of the antidepressant potential of TAK-653, plasma and serum BDNF levels were measured to determine if TAK-653 has any effect on this depression-related biomarker.

Methods: This study (NCT02561156) was a randomized, double-blind, placebo-controlled, combined SRD and MRD in healthy volunteers. Subjects with a history of or a risk factor for seizures were excluded. The study enrolled 8 subjects (6 active and 2 placebo) per cohort in 6 SRD and 5 MRD cohorts. Each cohort was orally administered TAK-653 in tablet form sequentially to ensure adequate safety and tolerability before administering the next dose level. In SRD cohorts, a single dose of TAK-653 (0.3, 1, 3, 5, 9, or 18 mg) or matching placebo was administered on Day 1 (fasting conditions) followed by safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) assessments. The starting doses were selected based on predicated human PK and no-observed-adverse-effect level in preclinical species. In MRD cohorts, a single dose of TAK-653 (0.3, 1, 3, 6, or 9 mg) or matching placebo was administered on Day 1 followed by 5-day safety, tolerability, PK, and PD assessments. TAK-653 was then administered once daily (QD) for 13 days. In the 3 mg MRD cohort, a single cerebrospinal fluid (CSF) sample was collected from each subject on Day 12 to estimate average central concentrations of TAK-653 at approximately steady state. Safety assessments were treatment-emergent adverse event (TEAE) monitoring; vital signs; safety laboratory tests, electrocardiograms, and electroencephalograms; and the Columbia-Suicide Severity Rating Scale.

Results: TAK-653 was safe and well tolerated in all cohorts. All TEAEs were considered mild or moderate. No dose relationship in the incidence of any TEAEs was observed in either SRD or MRD cohorts.

TAK-653 was absorbed rapidly in plasma after SRD or MRD administrations of TAK-653 tablet formulation under fasted conditions. TAK-653 plasma concentrations generally reached maximal levels within median 1.25 to 5 h after dosing. Mean Cmax ranged from 3.63 to 126 ng/mL following single doses ranging from 0.3 to 18 mg, and from 7.86 to 243 ng/mL following repeated QD doses ranging from 0.3 to 9 mg. Mean overall drug exposure during the dosing interval (AUC24) ranged from 151 to 4598 h*ng/mL for QD doses of 0.3 to 9 mg. Observed interindividual variability was low to moderate (coefficient of variation <45%) for both Cmax and AUC. TAK-653 accumulation after QD dosing was 3- to 4-fold, which is consistent with its 33.1 to 47.8 h half-life. The mean CSF/plasma ratio of TAK-653 was 0.056, which is similar to the unbound plasma concentration.

Plasma BDNF values were extremely variable and prone to factors such as hemolysis and differences in time sitting on ice. Since it is well known that platelets are a source of BDNF in the blood, only serum values were analyzed. In the SRD part of the study, only the 3 mg dose caused a significant 40% increase in serum baseline-normalized BDNF that was maintained for up to 96 h postdose. All the other doses caused a transient ~25% decrease in BDNF levels that recovered to baseline levels after 12 h. The increase in BDNF with the 3 mg dose of TAK-653 was not replicated in the MRD part of the study. None of the other dose levels had any significant elevation compared to baseline levels of BDNF.

Conclusions: TAK-653 was well tolerated in healthy subjects at all doses tested, both in the SRD and MRD cohorts. Exposure to TAK-653 was approximately dose proportional. Because of its long half-life, 3- to 4-fold accumulation of TAK-653 was observed after QD administration. The comparable TAK-653 concentration between CSF and unbound plasma suggests its rapid brain penetration. Although BDNF is hypothesized to be a potential biomarker of antidepressant activity, measuring serum levels in healthy volunteers, who had normal levels of BDNF, did not detect an increase in BDNF (PD activity of TAK-653). This was likely due to a ceiling effect as well as the fact that BDNF levels are not reduced, as they are in TRD patients.

Keywords: TAK-653, treatment-resistant depression, AMPA receptor, positive allosteric modulator, antidepressant effect

Disclosure: Nothing to disclose.

M149. Neurophysiological Correlates of Sensorimotor Cortex in Humans Affected by Fragile X Syndrome

Ernest Pedapati, Craig Erickson, Lauren Ethridge, John Sweeney, Donald Gilbert*

Cincinnati Children's Hospital, Cincinnati, Ohio, United States

Background: Hyperarousal and other abnormalities in cortical excitability have been well documented in animal and slice models of Fragile X syndrome (FXS). However, the degree that these abnormalities are present, including any clinical correlates, in humans with FXS in the sensorimotor cortex remains an open question in the literature.

Methods: Edit per original abstract feedback for review: We have now collected 22 affected Fragile X subjects and are currently recruiting healthy controls. We anticipate by the meeting in December we will have approximately 15 -20 control subjects completed for a robust comparison. This includes TMS data as well as resting EEG data.

Original abstract submission:

We present early analysis of 14 males affected by full mutation Fragile X Syndrome with historical match controls. The primary technique is paired pulse transcranial magnetic stimulation (TMS) presented with data resting state 128-lead EEG data and behavioral when available.

Results: We have completed analysis on 14 subjects with a short interval cortical inhibition (SICI) of 0.75 +/- SD 0.59 and intracortical facilitation (ICF) of 1.26 +/- 0.49. Of particular interest, we have identified that ICF is highly correlative with EEG resting alpha power (-0.783, $p = 0.013$).

This pilot data represents a small sample without adequately matched controls. TMS measures indicate variability within the FXS population, with early indication of correlation with resting state theta and gamma power.

Conclusions: We apologize for the rather preliminary nature of this abstract but anticipate a more complete set of data with recruited matched controls by December 2019.This study provides feasibility and initial evidence to encourage further investigation into the sensorimotor cortex to complement ongoing investigations of the sensory cortex in humans and sensorimotor physiology in animal models. The quantification and correlation of these deficits to identify individual sources of variability can aid in the development of physiological biomarkers, which may differentiate endotypes of disease or speed drug discovery.

Keywords: TMS, Fragile X Syndrome, Quantitative Electroencephalography (qEEG)

Disclosure: Nothing to disclose.

M150. Inflammatory Biomarkers and Anxiety Traits in the Development of Persistent Post-Traumatic Headaches Following Mild Traumatic Brain Injury in a Patient Cohort: A Pilot Study

Smriti Iyengar, Jie Xie, Youngsok Kim, Jared Smith, Christopher Carey, Hyun Kang, Jonathan Saxe, Kelly Naugle, Fletcher White*

Indiana University School of Medicine, Carmel, Indiana, United States

Background: Post traumatic headache (PTH) is the most frequent symptom following head injury/traumatic brain injury (TBI), manifesting both as a new-onset headache as well as a worsening of preexisting headache. The International Classification of Headache Disorders (third edition, ICHD-3 beta) defines PTH as a secondary headache with no defining clinical characteristics, that starts within 7 days of injury. If headache persists for greater than 3 months' duration it is considered to be persistent. PTH is frequent and common in both military and civilian populations. PTH appears to be more likely to develop following mild TBI (concussion) compared with moderate or severe TBI (with a prevalence of 47–95%). Although PTH is highly prevalent, the underlying mechanisms leading to PTH and its maintenance are less clear. Sensitization of the trigeminal pain network may be one mechanism underlying the chronification of PTH following head injury. Inflammatory mediation of peripheral and central sensitization has also been implicated. Persistent activation of peripheral immune cells which give rise to a network of immune-to-brain signaling may influence behavior following trauma. Thus, the purpose of this prospective pilot study was to evaluate inflammatory biomarkers at 1-week, 1 month and 4 months post injury, with a view to predict the persistence of post-traumatic headaches at 4 months post injury in mTBI patients.

Methods: Adult mTBI patients recruited from a Level I Emergency Department Trauma Center completed study sessions at 1-week (visit 1), 1 month (visit 2) and 4-months post mTBI (visit 3). Peripheral blood mononuclear cells (PBMCs) derived from individual PTH patients and sex and age matched controls were evaluated for primed innate immune responses to lipopolysaccharide (LPS) stimulation of PBMCs in vitro. Resultant supernatant samples were assayed using ELISA for the presence of IL-10, IL-1□, TNF□ and the chemokine CCL2. Participants also completed (1) a 0-10 numeric pain rating scale (NRS) to measure average intensity of headache pain; (2) the Center for Epidemiologic Studies (CES-D) depression scale with cutoff scores of 16 and greater for identifying risk for depression; (3) the State-Trait Anxiety Inventory (STAI) for anxiety symptoms. Patient-derived cytokine protein levels were correlated with pain severity and anxiety and depression states, at visits 1, 2 and 3. Patients with self-report of previous concussion events and use of long-term pain medications were excluded. Over the counter NSAIDS or Tylenol was allowed for episodic use but not on days of assessments.

Results: A total of 11 of 16 patients completed all tests and visits. Overall, in 8 of the 11 patients, headache persisted at Visit 3 (4 months after the mTBI incident) while in 3 patients there was no persistence of headache at Visit 3. Across individual patients, trends suggested that: (1) Patients showed high elevations in CCL2 levels at visit 1 that persisted in several patients at visit 3 and these patients had ongoing headaches at visit 3. (2) IL-1b levels showed increases at visit 1 and persisted in several patients at Visit 3. (3) TNFa levels showed no significant increases in any patient. (4) Increases in IL-10 and headache persistence were variable. One patient with elevated IL-10 levels on visit 3 did not report headache, while headache persisted at Visit 3 in one patient with IL-10 increases at visit 3 and in one patient with IL-10 increase at visit 1. (5) Anxiety traits stayed steady or showed only slight decreases in patients who had persistent headaches, but showed decreased traits in two of three patients that showed no headache at Visit 3. (6) Depressive symptoms were variable with regards to persistence of headache at visit 3 e.g., two patients with no depressive symptoms still had persistent headache at visit 3, three patients with decreasing depression had persistent headaches at Visit 3, three patients with steady or increased depressive symptoms had persistent headache, while three patients with no headache had decreasing depressive symptoms at Visit 3.

Conclusions: This pilot study suggests that persistent headache occurred in 8 of 11 mTBI patients. Overall, increases in the chemokine CCL2 and persistence of anxiety traits appeared to be associated with persistence of headache in mTBI patients. These observations need further confirmation in a clinical study with larger cohorts of mTBI patients.

Keywords: Chronic Pain, Inflammation, Biomarker

Disclosure: Nothing to disclose.

M151. Effects of Selective Melatonin MT2 Receptor Ligands in the Treatment of Neuropathic Pain: Modulation of Descending Brainstem Antinociceptive Pathways and Opioid Interactions

Abstract not included.

M152. Biased Signaling Agonists of D3R Modulate D1R-D3R Crosstalk in Levodopa Induced Dyskinesia

Abstract not included.

M153. Blast Exposure in Veterans and an Animal Blast Model Reveal Inter-Related Acute and Chronic Blood-Brain-Barrier Disturbances Associated With Chronic Neuropathology

Elaine Peskind, James Meabon, Aric Logsdon, William Banks, C. Dirk Keene, Desiree Marshall, Donna Cross, Todd Richards, Daniel Perl, Cynthia Mayer, Abigail Schindler, Murray Raskind, David Cook*

VA Puget Sound Health Care System, Seattle, Washington, United States

Background: We have reported structural and functional brain neuroimaging abnormalities in Iraq and Afghanistan war Veterans > 4 years after their last blast mild traumatic brain injuries (mTBI) [1,2]. In an mTBI mouse model of repetitive blast mTBI we have demonstrated region-specific blood-brain-barrier (BBB) disruption in brain regions vulnerable to chronic blast mTBI neuropathology [3–5]. Collectively, these findings raise the possibility that early-occurring BBB disruptions (which often resolve in <24 h), may trigger latent pathologic processes that give rise to chronic neuropathology. To address this possibility, we have found evidence of: (i) blast-induced peripheral immune cell infiltration into the mouse brain, (ii) distinct microglial/macrophage neuropathology in both mice and postmortem brains from Veterans with blast-related mTBI in cerebrospinal fluid (CSF) from Veterans with blast mTBI (iii) chronically elevated immune cell chemo-attractant proteins, as well as (iv) liver-derived circulating peripheral proteins.

Methods: Blood and CSF were collected from 55 Iraq/Afghanistan Veterans with blast mTBIs (mean 21, range 1-102) and 22 deployed Veterans with no lifetime history of TBI. CSF and plasma proteins were measured using a validated MesoScale platform assays. Postmortem brain tissue was accessioned from 3 mTBI Veterans and 3 controls. Male 3-4-month-old C57Bl/6 mice received blast exposure using a shock tube that accurately models battlefield-relevant blast exposure in mice [3–5]. To measure BBB disruption in mice, brain concentrations of peripherally injected [99Tc]-albumin, which does not normally cross the BBB, were measured in blast and sham control animals. Well-established flow cytometry methods were used to measure blast-induced brain infiltration of CD3+/CD4 + T-cells and CD45hi/Ly6C/6+ monocytes in mice.

Results: In mice, within 24 h after blast, CNS [99Tc]-albumbin levels in the pons/medulla had returned to normal (sham control levels), but the BBB again reopened with significantly abnormal entry of radiolabeled albumin into the pons/medulla ($p<0.05$). Importantly, 3 days post-TBI is a time frame previously established as a key temporal window for peripheral immune cell infiltration that subsequently abates over days. In keeping with this we found that repetitive blast exposure also caused a significant elevation in T-cell and peripheral monocyte infiltration into the pons/medulla ($p<0.006$, $p<0.018$). While it is not possible to perform such experiments in our living mTBI Veteran cohort, we found that Monocyte Chemo-attractant Protein 1 (MCP-1) and Macrophage-Derived Chemokine (MDC) were elevated in CSF from mTBI Veterans compared to deployed controls ($p\leq0.05$ and $p\leq0.058$, respectively, one-tailed). MCP-1 and MDC are well-characterized chemokines that mediate trafficking of monocytes, T-cells, and other peripheral immune cells into the brain. In addition, serum amyloid A (SAA), a protein produced selectively by the liver and released into the circulatory system, was elevated in CSF from mTBI Veterans versus deployed controls ($p<0.058$). In mice we found distinctive, clustered IBA1+ microglia/macrophages in the brainstems of blast exposed mice ($p<0.001$) compared to controls. Prompted by this finding, we also examined pons and medulla of postmortem brains from Veterans with blast-related mTBI and found very similar appearing IBA1+ and CD68+ clustered microglia/macrophages.

Conclusions: These data indicate that disturbed BBB function contributes to both short and long term neuroimmune-related neuropathologic and structural abnormalities associated with blast exposure and implicate the importance of interactions between the CNS and peripheral immune systems in the pathologic cascades triggered by blast exposure.

All experimental protocols in animal studies were approved by the VA IACUC and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

These data indicate that disturbed BBB function contributes to both short and long term neuroimmune-related neuropathologic and structural abnormalities associated with blast exposure.

All experimental protocols in animal studies were approved by VA IACUC and were conducted in accordance with NIH Guide for Care and Use of Laboratory Animals.

Keywords: TBI, Blast, CSF Biomarkers, Animal Models, Neuropathology

Disclosure: Nothing to disclose

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M154. Drug Metabolizing Enzyme Associations With Response to Agents Used in Neuropsychopharmacology

Abstract not included.

M155. RDoC Working Memory Constructs Spanning Levels From Disability to Structural MRI

Robert Bilder, Agatha Lenartowicz, Jesse Rissman, Sandra Loo, Jean Baptiste Pochon, Holly Truong, Kristen Enriquez, Carrie Bearden*

Semel Institute for Neuroscience & Human Behavior, Los Angeles, California, United States

Background: The Research Domains Criteria (RDoC) initiative identified a series of constructs including "working memory," each of which is putatively specified by features at different levels or "units of analysis" including genetic, molecular, cellular, physiological, neurocognitive, and symptom levels. Specification of these constructs implies causal links between levels of analysis, but so far, most research has examined only two levels at a time, and the nature of associations of findings across multiple levels of analysis remains sparse. Further, most studies have focused on examining individuals from a discrete diagnostic group in comparison to relevant control groups, but this design may be suboptimal if the aim is to identify transdiagnostic characteristics that will better identify future diagnostic markers and targets for treatment. We ascertained relevant samples and examined them using MRI, EEG, neurocognitive, symptom, and disability assessments putatively relevant to the RDoC Working Memory domain.

Methods: To avoid biases associated with recruiting diagnostic groups, we examined two groups of individuals comprising both men and women: (1) Care-Seeking (CS, n=106) individuals from the community, recruited through clinics and clinical web-sites, if they were seeking help for the way they were thinking or feeling; and (2) Non-Care-Seeking (NCS, n=44) individuals from the same community, who were not seeking care and had not done so within the year preceding enrollment. All participants had the same battery of clinical, cognitive, EEG and MRI assessments. Clinical assessments included MINI 7.0 neuropsychiatric interview, multiple symptom rating scales, and the WHODAS 2.0 disability assessment. The neurocognitive tests on working memory included both "complex multifactorial" measures (e.g., Digit Span, Letter-Number Sequencing, Symbol Span, Spatial Addition, Automated Operation Span) and "cognitively specific" measures (e.g., Lateralized Change Detection [LCD], Spatial Working Memory Capacity [SCAP], Dot Pattern Expectancy [DPX], Switching Stroop Color Word [SSCW], Recent Negatives [RN], Delayed Face Recognition [DFR]). We acquired EEG during an eyes open/eyes closed rest condition, and during 4 of our cognitive tasks (LCD, DPX, SCAP, and DFR). MRI measures included: structural MRI (sMRI) acquired using MPRAGE sequences; fMRI measures at rest from which graph theory metrics of functional connectivity were extracted; and fMRI in an activation paradigm using the DFR task to identify load-sensitive effects at supra-capacity levels of span. We used a combination of dimension reduction strategies and general linear models to examine both the structure of measures within levels of analysis and relations across levels of analysis.

Results: CS and NCS groups were well matched on age, sex, personal and parental education, but the CS group had lower personal and family income. The CS group had more categorical mental disorders than the NCS group, the most prominent of which were current Major Depressive Disorder in 50% of CS compared to 21% of NCS, and Anxiety Disorders in 25% of CS compared to 14% of NCS). Psychotic disorders were found in 7.5% of CS and 0% of NCS individuals. Disability and symptom data were explained by 6 or 7 factors comprising "generalized psychopathology", "depression-anxiety", "psychoticism", "agitation-mania", and "somatic concern." Neurocognitive data were best explained by models comprising "general cognitive ability", "complex span", "relational-long term encoding/retrieval", "goal maintenance", "interference control", and "storage capacity." Disability was well explained by the clinical measures, which accounted for 75% of variance in WHODAS scores. Neurocognitive, EEG, and MRI measures did not add to the prediction of disability beyond clinical assessments, and among the more "basic" measures most did not share more than 5% of the variance in functional disability, but sMRI measures did account for 13% of the variance in disability, and total gray matter volume alone explained 7% of variation in disability across groups. In contrast, there were more robust associations among neurocognitive, EEG and MRI variables, with typical multivariable associations sharing 10% of variance between sets of variables within each level.

Conclusions: The results suggest that "multi-level" models of RDoC dimensions face several challenges, including limits in the strength of associations across levels. While we observed relatively robust associations of basic indicators like total gray matter volume reduction with the severity of disability, this effect was not obviously mediated via EEG, fMRI or cognitive measures. There do exist patterns of association among neurocognitive, EEG and fMRI measures that may define meaningful functional neuroanatomic dimensions, but so far their relations to higher level symptoms, syndromes, and disability remain less clear.

Keywords: Neurocognitive Functioning, Disability, Research Domain Criteria (RDoC), EEG, MRI

Disclosure: Nothing to disclose.

M156. Effects of Transcranial Infrared Stimulation on Neural Information Flow in Healthy Volunteers

Elisa Kallioniemi, Tyrell Pruitt, Xinlong Wang, Mustafa Husain, Hanli Liu*

University of Texas Southwestern Medical Center, Dallas, Texas, United States

Background: Transcranial infrared brain stimulation (TIBS) is a novel non-invasive neuromodulation method which uses high power infrared light to alter neural activity via intracellular metabolism. So far, TIBS has been observed to induce changes in neural activity and behavior. For instance, in healthy controls TIBS has been shown to change both reaction time and emotional state. Furthermore, some evidence exists that TIBS might have therapeutic effects in neurological and psychiatric disorders. Therefore, in this study our aim was to gain more understanding on how TIBS affects the neural function in healthy volunteers.

Methods: We measured thirty healthy volunteers (24=males, age range 21-30 years). The protocol included both an active and sham TIBS. Each participant underwent both conditions which were separated by 14 days to avoid any potential after effects from TIBS. In both conditions, the stimulation was given with the same FDA approved laser (Model CG-5000 Laser, Cell Gen Therapeutics LLC, Dallas, TX, USA). In the sham condition, a black cap was inserted in between the laser aperture and the participant to prevent any infrared light exiting from the device. TIBS was administered at a wavelength of 1064 nm for 11 minutes and was targeted to the right forehead just below the Fp2 electrode. This target was chosen, as previous studies have shown TIBS to enhance cognitive performance when targeted here. The order of the conditions was randomized, and the participants were blind to whether they got active or sham TIBS at each session. Throughout the experiment, the participant and the researcher wore protective goggles.

To evaluate the neural effects of TIBS, we acquired high-density electroencephalography (EEG) with 64-active electrodes using the BioSemi ActiveTwo EEG system (BioSemi BV, Amsterdam, Netherlands). EEG was recorded with a sampling frequency of 256 Hz and the ground and reference electrodes were located near the inion. The measurement contained three EEG parts: a 2-min baseline, an 8-min laser stimulation and a 3-min post-stimulation period.

The offline processing of EEG data was done using the EEGLAB toolbox and custom Matlab scripts. Effects of TIBS on EEG activity were evaluated with Granger causality test on the correlation coefficients between EEG data at each electrode with a custom RStudio script. Granger causality measures the directional information flow, i.e., flow of EEG activity, between EEG electrodes and can thus, estimate how TIBS influences the information

processing in a resting brain. Granger causality was evaluated at the alpha frequency band. Information flow estimates with Bonferroni corrected p-values smaller than p=0.05 were considered.

Results: Active TIBS was able to significantly ($p \leq 0.05$) alter the information flow in the alpha band of a resting brain. During TIBS, information spread from the frontal areas to the right premotor cortex. Interestingly, TIBS also caused information to flow from the left hemisphere to the right premotor cortex. No changes in sham condition were observed. Instead, the information flow in the sham condition resembled of that observed in the default mode network. This network is the basic functional network measured in a resting brain when the brain is not under the influence of any intervention.

Conclusions: TIBS is a promising neuromodulation method able to alter neural information flow (EEG activation) in a resting brain. Furthermore, TIBS was found to be safe and feasible in healthy volunteers.

Keywords: Neuromodulation, Infrared, EEG

Disclosure: Nothing to disclose.

M157. Elucidation of the Role of Serotonergic IL-1R Signaling in the CNS

Paula Gajewski-Kurdziel, Elizabeth Potts, Matthew Robson, Nicole Baganz, Xaioyu Lui, Ning Quan, Randy Blakely*

Florida Atlantic University, Jupiter, Florida, United States

Background: Serotonergic circuits are involved in many complex behaviors where dysfunction is believed to support multiple neuropsychiatric disorders, including anxiety, depression, autism, and schizophrenia. Although often treated monolithically, serotonergic projections arise from subpopulations of neurons that ultimately confer specific behavioral outcomes following activation. One subpopulation of serotonergic neurons that has drawn recent attention, but for which little is understood, are those that support the transduction of peripheral immune system activation into changes in discrete behaviors. Prior RNA expression studies suggest non-uniform expression of the interleukin 1 receptor (IL-1R), indicating that specific pathways dictate the serotonergic contributions to the behavioral actions of the inflammatory cytokine IL-1β (Okaty et al., 2015). Additional evidence points to a subpopulation of serotonergic neurons in the dorsal raphe interfascicular region that respond to stimulation of the peripheral immune system, suggesting that disruptions in immune system function could have effects on serotonergic neurotransmission (Hollis et al., 2006). Furthermore, peripheral administration with the bacterial mimetic, lipopolysaccharide (LPS), results in rapid, significant increases in activity of the serotonin transporter, supporting serotonergic neurons as a mediator of the CNS and behavioral actions of peripheral immune system activation (Zhu et al., 2010). Here we report evidence that serotonergic IL-1Rs mediate the responsiveness of serotonergic neurons to peripheral immune activation and contribute significantly to CNS IL-1β production.

Methods: Until recently, detection of expression of IL-1Rs at the protein level has proved difficult, and as such IL-1R modulated 5-HT circuits have remained poorly defined. Using transgenic mouse lines in which we specifically eliminate IL-1Rs in serotoninergic neurons or restore serotonergic expression of IL-1Rs on an IL-1R knockout (KO) background, we explored both the serotonergic distribution and the role of serotonergic IL-1Rs in mediating immune-system related changes. To assess whether the peripheral immune system's effects on serotonergic neurons are mediated by IL-1Rs, we acutely administered LPS (0.2 mg/kg i.p.) or saline to adult (8-12 wks) male ePet1:Cre:IL-1Rflx/flx or ePet1:Cre:IL-1Rr/r mice. One cohort was then sacrificed by transcardial perfusion with PBS and 4% PFA one hour after treatment, followed by brain extraction and post-fixation of the brain in 4% PFA for 24 h before being moved to PBS until sliced on a compresstome at 100 µm. Slices containing dorsal raphe were immunolabeled with 5-HT (Immunostar #20079, 1:1000) and cFos (Abcam #ab190289, 1:5000) and cleared using an established glycerol gradient (Selever et al., 2011), with cell counts obtained by a blinded observer. Another cohort was sacrificed by rapid decapitation one hour after treatment, followed by dissection of the midbrain and hippocampus, which were processed for RNA isolation. qPCR was conducted using the Taqman gene expression assay, with Taqman probes for 18 S (HS99999901) and IL-1β (Mm00434228). Additionally, in vivo chronoamperometry was utilized to determine the effect of local IL-1β (2 ng) on 5-HT clearance in wild type mice.

Results: We have gathered evidence to support the existence of subsets of serotonergic neurons that express IL-1Rs, with enrichment evident in the dorsal and lateral subsections of the dorsal raphe, and with the capacity to respond to IL-1β via IL-1Rs. Acute treatment with LPS (0.2 mg/kg) caused an upregulation of IL-1β expression in the midbrain of wildtype mice as monitored by qPCR. A constitutive KO of IL-1Rs completely eliminated midbrain IL-1β expression after LPS treatment. Strikingly, selective elimination of IL-1Rs in 5-HT neurons also significantly reduced LPS-mediated increases in IL-1β. Additionally, re-expression of IL-1Rs in 5-HT neurons on a constitutive KO background significantly rescued LPS-induced IL-1R expression in the midbrain, effects also seen in the hippocampus. Our initial studies demonstrate that the same acute treatment with LPS increases serotonergic neuronal activation as measured by cFos, and in mice that lack serotonergic expression of IL-1Rs, the number of cFos-positive 5-HT neurons is significantly decreased. Finally, local application of IL-1β in the CA3 subregion of the hippocampus resulted in increased 5-HT clearance.

Conclusions: These data provide the first evidence, to our knowledge, of 5-HT neurons as contributing significantly to CNS immune activation, specifically IL-1β induction, in response to peripheral immune system activation. Our anatomical studies point to a subset of 5-HT neurons with high IL-1R expression that we propose contribute significantly to IL-1β induction and LPS induced 5-HT neuron activation. Our current efforts are aimed at determining requirements for serotonergic IL-1R expression for the physiological and behavioral actions of IL-1β, elucidating the projections and inputs of IL-1R expressing 5-HT neurons, and establishing the necessity of serotonergic IL-1R expression for IL-1β driven behavioral responses. We see the broader significance of our work as elucidating a mechanistic connection between observations of elevations in inflammatory markers in psychiatric disorders and the role played by 5-HT in modulating circuits that support disease risk.

Keywords: Serotonin, Immune System, Interleukin 1beta, Central Nervous System

Disclosure: Nothing to disclose.

M158. Individual-Level EEG Connectomics Reveals Differential Functional Connectivity Patterns in Different Subtypes of Resting-State

*Jacob Van Doorn, Rael Cahn, Arnaud Delorme, Olusola Ajilore, Alex Leow**

University of Illinois at Chicago, Chicago, Illinois, United States

Background: As part of a study on the effects of different techniques of meditation on electroencephalographic (EEG)

activity, this pilot study aimed to determine EEG functional brain connectivity signatures in two forms of resting state activity among nonmeditators by leveraging computational connectomics.

Methods: Overview: EEGs were recorded from individuals without prior meditation experiences, who were instructed to observe and focus on their breathing or engage in emotionally neutral autobiographical thinking as a form of mind wandering for twenty minutes each. Functional connectomes of each individual were formed using weighted phase lag index (WPLI). For each individual, dynamic EEG connectomes as a function of time were then analyzed using a recently developed state-space manifold learning procedure, the Graph Dissimilarity Embedding procedure (GDE), followed by visualization via Minimum Spanning Tree (MST) and Isomap dimensionality reduction. Due to the intra-individual nature of the recovered state-space manifold, we then devised a permutation testing procedure to determine whether these two 'subtypes' of resting exhibit statistically significant differences.

Subject recruitment: 32 healthy control subjects of both sexes were recruited and data collection took place at the Meditation Research Institute in Rishikesh, India. Subjects were compensated and reimbursed for travel, accommodation, and meals. The project was approved by the local Indian ethical committee and the IRB of the University of California San Diego. Control subjects were chosen for inclusion in this study based on age and gender and their absence of a meditation practice. For the "meditation condition," they were instructed to focus on the sensation of their breath for the duration of the recording period ("keep paying attention to the sensations of the breath, both of the inhalation and the exhalation. If your mind starts to wander, please bring it back to your breath.")

Data collection and preprocessing: We recorded data using a 64 + 8 channel Biosemi Active-Two amplifier system and a 10–20 Headcap standard 64-channel cap from the same company. Using external electrodes, we also recorded right and left mastoid electrodes as well as vertical and horizontal electrooculogram (EOG) by placing two periocular electrodes above and below the left eye and two electrodes at both the left and right outer canthi. Data processing was done using the EEGLAB open source software version 12 running on Matlab R2009b under a Linux operating system. EEG data were first referenced to the right mastoid and down-sampled from 1024 Hz to 256 Hz. The first 10 minutes of the meditation block (MED) are considered a preparatory period helping to relax and deepen the meditation practice. Subjects practiced breath awareness throughout the whole MED block. For consistency, we kept the length of the Instructed Mind-Wandering block (IMW) equal to the length of the meditation block. When analyzing the data, we compared the last 10 minutes of the breath-focused MED block to the last 10 minutes of the IMW block. We then applied a high-pass filter at 1 Hz using an infinite impulse response (IIR) filter with a transition bandwidth of 0.3 Hz and an order of 6. We automatically removed portions of the signal presenting non-stereotyped artifacts using EEGLAB's pop_rejcont function. The data were first segmented in 1-second epochs with 0.5-second overlap. Segments of 8 contiguous epochs in which the 0–10 Hz frequency band and the 35–128 Hz frequency band had an amplitude higher than 17 and 14 decibels respectively were labeled as artifactual. We used this rejection procedure to ensure that artifact rejection was uniform for all subjects. Rejection of low-frequency segments helped remove signals related to head and body movements. Rejection of high frequency activity helped reject data portions of muscular activity. The data was then checked visually for any potential remaining artifact. We then manually identified and removed bad electrodes (from 0 to 18 bad electrodes per subject, average of 5 electrodes removed per subject).

Results: 16 subjects out of 32 were included for analysis based on the number of good electrodes after preprocessing (usable number of electrodes 53 to 70). After computing the dynamic EEG connectomes associated with each resting subtype (the connectome at each time point is an electrode x electrode x frequency 3D matrix; frequency range 2-110 Hz) we constructed individual-level GDE, yielding the pairwise geodesic between two connectomes. GDE, visualized by both MST and Isomap, show qualitative separation between the two states. Using the average inter-class geodesic minus the average intra-class geodesic as the test statistic we sampled the null distribution (i.e. connectomes do not differ between states) by randomly assigning all connectome labels (to either MED or IMW). Using this procedure, we demonstrated significant connectome differences between MED and IMW in all of 16 participants (p-value < 0.001) and an effect size ranging from 10 to 120 standard deviations.

Conclusions: In sum, our pilot analyses suggested distinct differential EEG functional signatures between these two forms of resting state activity – instructed mind wandering and meditative engagement with the sensations of the breath.

Keywords: Connectomics, Electroencephalography, Resting State Functional Connectivity

Disclosure: Nothing to disclose.

M159. A Randomized, Double-Blind, Placebo-Controlled Crossover Trial of the NMDA Receptor Antagonist Memantine in People Receiving Chronic Prescription Corticosteroid Therapy: Effects on Hippocampal Subfields and Memory

E. Sherwood Brown, Alexandra Kulikova, Erin Van Enkevort, Alyson Nakamura, Elena Ivleva, Nicholas Tustison, Jared Roberts, Michael Yassa, Changho Choi, Alan Frol, David Khan, Miguel Vazquez, Traci Holmes, Kendra Malone*

University of Texas Southwestern Medical Center, Dallas, Texas, United States

Background: Corticosteroid excess is associated with decreases in memory performance and hippocampal volume in humans as well as in animal models. In animal models, the CA3 region of the hippocampus appears to be particularly sensitive to the effects of stress or corticosteroids, although changes in the CA1 region are also reported. Hippocampal changes with corticosteroids, such as dendritic shortening, in animal models are prevented by NMDA-receptor antagonists. In this report, the effect of the NMDA receptor antagonist memantine on memory and hippocampal subfield volume was examined in people receiving chronic prescription corticosteroid therapy.

Methods: Outpatient adults receiving chronic oral corticosteroid therapy were randomized to memantine and placebo for 24 weeks each using a crossover design with a four-week washout period between treatment conditions. Declarative memory was assessed using the Hopkins Verbal Learning Test (HVLT) and structural magnetic resonance imaging (MRI) was obtained at baseline and after each medication condition. Neuroimaging was performed on Philips 3 T scanner at the Advanced Imaging Research Center, UT Southwestern Medical Center. Sagittal T1–weighted MPRAGE scans (TE/TI/TR=3.8/875/1360 ms, 256×256×160 mm3 field of view, 160 slices, voxel size 1 ×1 ×1 mm3) were collected and used for hippocampal subfield segmentation. The segmentation was performed using a consensus labeling approach with multi-spectral atlas-based registration based on a well-validated atlas composed of T1 and T2-weighted high-resolution structural scans from cognitively normal subjects that were manually labeled using a highly reliable anatomical protocol used in prior published work for segmentation of hippocampal subfields. To propagate a weighted consensus labeling from the expertly labeled atlas set to the

study scans, we spatially normalized the atlas set to the study scans and applied the joint label fusion technique. Advanced Normalization Tools (ANTs) package was used for both spatial normalization and consensus-based labeling (i.e., joint label fusion). First, the intra-subject atlas T1/T2 rigid transforms were calculated. To minimize total number of deformable registrations, a "pseudo-geodesic" approach to align the data was used. This required construction of an optimal T1-weighted template representing the average shape/intensity information of the T1 component of the atlas set. Deformable transformations between each T1-weighted image of the study cohort and the T1 atlas template were calculated. Transformation between the atlas labels and unlabeled study cohort image was then computed by concatenating the T1 atlas /T2atlas rigid transformation, the T1atlas /T1 template deformable transformation, and the T1 template/and T1subject deformable transforms. Once the atlas set was normalized to the unlabeled subject, regional labeling was determined using weighted averaging where the weighting takes into account the unique intensity information contributed by each atlas member. After visual quality assessment to confirm the output of the labeling procedures, voxels within the labeled regions were counted and multiplied by the voxel resolution to calculate volumes in cubic millimeters. Utilizing a mixed-model approach, structural data were examined by an ANOVA, and memory was assessed with a multi-level longitudinal model.

Results: A total of 46 participants (n=28 women) were randomized and received memantine and placebo. The majority of participants were receiving chronic corticosteroid therapy to prevent renal transplant rejection. The mean dose of corticosteroid therapy was 7.6±6.4 mg/day and the mean duration was 58.8 ±67.3 months. The mean age of the participants was 43 years. Controlling for baseline volume, the left DG/CA3 region was significantly larger (~ 2%) following 24 weeks of memantine as compared to placebo (p=0.011). A trend in the same direction was observed with the right CA1 subfield (p=0.055). HVLT scores did not differ significantly between the memantine and placebo conditions. Memantine was well tolerated.

Conclusions: Memantine was associated with a larger CA3/DG volume than placebo when given to corticosteroid-treated patients. The findings translate preclinical research on the ability of NMDA receptor antagonists to block the effects of corticosteroids on the hippocampus. Furthermore, the findings suggest memantine may have potential as a neuroprotective agent in people receiving prescription corticosteroids therapy or with elevated levels of endogenous cortisol.

Keywords: corticosteroids, Hippocampal subfields, Memory, Memantine, Corticosteroids

Disclosure: Otsuka, Grant, Allergan, Advisory Board

M160. Cerebellar [18 F]FDG Uptake is Positively Correlated With Time Elapsed Since Blast-Related Mild Traumatic Brain Injury in Veterans

Garth Terry, Mark Muzi, Donna Cross, James Meabon, Murray Raskind, David Cook, Elaine Peskind*

VA Puget Sound Health Care System and University of Washington, Seattle, Washington, United States

Background: Blast-induced mild traumatic brain injury (mTBI) is the "signature injury" of the wars in Iraq (OIF) and Afghanistan (OEF). Blasts account for 70-88% of mTBIs sustained in OEF/OIF, with affected Servicemembers usually experiencing multiple blast mTBIs. Even years after returning from deployments, many Veterans with blast-related mTBI report postconcussive cognitive symptoms, behavioral symptoms, and somatic symptoms, leading to substantial disability and interference with job and family relationships.

Our group's initial [18 F]FDG-PET study in a sample of 12 male OIF Veterans with mTBI and 12 cognitively and medically healthy community controls (7 male, 5 female) demonstrated a consistent pattern of less [18 F]FDG uptake in infratentorial structures and medial temporal cortex in mTBI Veterans compared to the controls. In our follow-up study of 33 Veterans with blast mTBI and 16 deployed control Veterans with no lifetime history of mTBI, voxelwise analysis demonstrated hypometabolism in bilateral parietal lobes, left somatosensory cortex, and right visual cortex, as well as in parahippocampus for Veterans with 20 or more blast mTBI. There was a strong correlation between glucose metabolism in the cerebellum and number of blast exposures.

We sought to identify if our prior findings are present in our much larger cohort, and assess if hypometabolism previously described is affected by time since injury.

Methods: The local institutional review boards approved all procedures and all the participants provided written informed consent before enrollment into the study. Veterans with blast-related mTBI (n=79; average blast mTBI exposures 22), with history of military deployment and no lifetime history of any TBI (n=29), and community controls with no history of TBI or deployment (n=12) underwent thorough history and clinical characterization as part of our ongoing longitudinal study. A standard clinical 15-minute PET acquisition was performed 60 minutes after injection 8-10 mCi of [18 F]FDG on either a GE Advance scanner or Philips Gemini PET/CT, and data underwent OSEM reconstruction. Three 5-minute frames were averaged following motion correction, smoothed 8×8×8 mm, and transformed directly into MNI standardized space using SPM12. Individual images were scaled for intensity using a VOI applied to parenchyma, yielding fractional uptake (unitless) as the measured value in PMOD. The AAL VOI library (119 regions) was applied for regional analysis, and data tested with 2-sided t-test with Bonferroni correction of multiple comparisons ($p<0.004$). Replication regression analysis of blast x fractional uptake in the cerebellum was conducted with a priori $p<0.05$. Images were separately analyzed on a voxelwise basis using SPM12 with 6 mm smoothing in the nonparametric toolbox (SnPM) which implements a single tailed test, with age as a covariate, and adjusted significance value (pFWE-corrected<0.05, equivalent to t-score >5).

Results: Compared to deployed or community controls, Veterans with mTBI demonstrated less fractional uptake in areas of frontal and temporal cortex, and greater fractional uptake in deep gray of globus pallidus and putamen by both VOI and voxelwise analysis and correction for multiple comparisons (left globus pallidus p<5×10-10). Similar to our previous finding, fractional uptake in cerebellum (specifically, regional cerebellum 7-9 and vermis 6-9) was negatively correlated with log transformation of number of blast mTBI (i.e., more blast exposures was associated with less [18 F]FDG uptake; vermis7 r2=0.09, p<0.008). However, fractional uptake was positively correlated with time since last blast mTBI (i.e., individuals imaged at longer intervals after exposure had greater [18 F]FDG uptake; left cerebellum9 r2=0.20, p<0.00003).

Conclusions: Veterans with history of blast mTBI demonstrate less fractional [18 F]FDG uptake in cortex and cerebellum compared to individuals with no history of TBI, and greater fractional uptake in regions of basal ganglia. Fractional uptake in cerebellum was negatively correlated with number of blast mTBI exposures, and was positively correlated with time elapsed since blast exposure.

Keywords: Mild Traumatic Brain Injury, fluorodeoxyglucose, Positron emission tomography, combat veteran

Disclosure: Nothing to disclose.

M161. Impact of Resiliency Training on Mental Health Symptoms and Resting State Connectivity for First-Semester College Students

Robin Aupperle, Elisabeth Akeman, Tim McDermott, Masaya Misaki, Ashley Clausen, Namik Kirlic, Lisa Cromer*

Laureate Institute for Brain Research, Tulsa, Oklahoma, United States

Background: College students experience substantially higher rates of anxiety and depression (30% prevalence) than the general population, which can have deleterious effects on academic progress and success (Ibrahim et al., 2013; Regehr et al., 2013). This highlights the importance of identifying preventative interventions that can be used widespread across college campuses. Given the known time of stressor onset and high risk for experiencing mental health symptoms, university settings also offer a unique opportunity for development, evaluation, and widespread dissemination of programs targeting anxiety and depression. While meta-analyses indicate that cognitive-behavioral (CBT) or mindfulness interventions can be beneficial for college students, these have often been long (13-14 session) interventions (Conley et al., 2015). The current project sought to identify the potential mental health benefits a brief, scalable intervention delivered during college orientation classes. In addition, we aimed to identify potential neurobiological mechanisms (neural connectivity) for the resiliency training, thus informing further refinement of intervention targets or personalized medicine approaches.

Methods: A total of 126 undergraduate students completed four weeks of resiliency training as part of orientation classes during the first semester of college (73 female). Training focused on value identification, goal-building, mindfulness, and the growth mindset. A sample of 126 students from orientation classes that did not receive training and who were matched on baseline depression scores were identified as the comparison group (83 female). All participants complete NIH PROMIS® anxiety and depression measures and the Connor-Davidson Resilience Scale pre and post training and at the end of the semester (e.g., "finals week"). The Frieburg Mindfulness Inventory (FMI) and a cognitive-behavioral skills questionnaire were completed pre, weekly during training, and post training. A subset of participants (23 training; 17 no-training) completed functional magnetic resonance imaging (Discovery MR750 3 T) with a seven-minute resting state scan (96×96 matrix, 2×2mm2 in-plane resolution, 35 axial slices, 2000ms TR, 207 volumes, SENSE factor R=2). Linear mixed models were used to examine training by time interaction effects on self-report survey scores (covarying for gender and college [e.g., Arts and Sciences, Engineering]). Connectome-wide association analysis was conducted voxel-wise with resting-state fMRI data using multivariate distance matrix regression (MDMR) based on the Euclid distance matrix. MDMR offers a data-driven methodology for identifying regions for which connectivity with the rest of the brain is impacted by conditions of interest (Shehzad et al., 2014), which included the time by training effect in the current study. To correct for multiple comparisons, permutation testing was utilized to identify the required cluster size (896 mm3) for voxel-wise $p < .005$.

Results: Resiliency training resulted in significant reductions in depression symptoms compared to the control group ($F(2,452) = 4.08$, $p = .018$), with effects most robust at the end of the semester ($t = -2.85$, $p = .005$; Cohen's $d = .26$). There were also trend effects on anxiety ($F(2,448) = 2.51$, $p = .083$). This was accompanied by within-training improvements in mindfulness ($F(6,1151) = 6.89$, $p < .001$) and cognitive-behavioral skills ($F(6,1147) = 4.91$, $p < .001$) but not resilience ($F(2,44) = .77$, $p = .464$). MDMR analysis of resting connectivity scans revealed regions of the bilateral dorsolateral prefrontal cortex (dlPFC; BA 9), left precuneus (BA 31), and left superior parietal cortex (BA 40) in which whole-brain connectivity was impacted by training.

Conclusions: Results indicate that a brief, four-session resiliency training course that is incorporated into first-semester undergraduate classes can have a significant, beneficial impact on mental health over the first semester of college. Changes in cognitive-behavioral and mindfulness-based skills may be important psychological mechanisms for the observed benefits, while self-beliefs regarding one's resilience may be more difficult to change. Such resiliency training may also lead to changes in whole-brain connectivity within regions involved in executive function and decision-making (dorsolateral PFC), attention processing (superior parietal), and self-relevant processing (precuneus). These findings have implications for how colleges may approach the problem of rising mental health concerns and offer insights into potential mechanisms of preventative-based resiliency programs.

Keywords: resilience, Depression, Functional MRI (fMRI), Cognitive Behavioral Therapy

Disclosure: Nothing to disclose.

M162. How Does Electroconvulsive Therapy Suppress Self-Injurious Behavior Associated With Intellectual and Developmental Disabilities

*Alec Stepanian, Melissa Staley, Cindy Jiang, Sanmit Adhikari, Andrew Chang, Jay Baraban, Irving Reti**

Johns Hopkins University, Baltimore, Maryland, United States

Background: Electroconvulsive therapy (ECT) is highly effective for suppressing severe intractable self-injurious behavior (SIB) in many patients with intellectual and developmental disabilities (IDD). However, in contrast to depressive patients who respond to ECT and can typically be successfully weaned off ECT with the aid of antidepressant medications, IDD patients with SIB remain dependent on long-term frequent maintenance ECT, often starting at a young age, the long-term effects of which are unknown. Accordingly, it is important to learn more about why ECT is effective in these patients in order to generate long-term effective non-convulsive treatments.

It is not known why IDD patients being treated with ECT for SIB seem to have a different pattern of response from depressive patients being treated with ECT. However, it suggests that ECT's antidepressant mechanism of action may be different from the ECT response mediating suppression of SIB. Moreover, we have found that the GABAergic agonist class of drugs, benzodiazepines (which do not act as antidepressants), are sometimes effective in suppressing SIB in IDD patients, especially when they have concomitant intermittent catatonia, which occurs frequently. These observations raise the possibility that ECT may act through the GABAergic system to mediate suppression of SIB in IDD. In fact, numerous lines of evidence suggest that ECT enhances GABAergic tone, including increased cortical GABA concentration following a course of ECT.

Methods: To further characterize how ECT suppresses SIB in IDD, we are using mouse models that display stereotyped excessive self-grooming, mimicking the SIB seen in IDD. We are using the conditional knockout mouse, Viaat-Mecp2-/y, which displays Rett Syndrome phenotypes, excessive self-grooming and reduced GABA levels in the forebrain (Chao et al, 2010). We have found that over the course of a week following a single electroconvulsive seizure (ECS), excessive self-grooming progressively declines in these mice reaching significant suppression between days three and five, before returning to baseline by day eight after treatment (Chang et al., 2016). We are also using a

genetically distinct line of mice that also displays stereotyped excessive self-grooming, namely the Shank3B-/- mice (Peca et al., 2011), but that does not demonstrate the GABA dysfunction observed in Viaat-Mecp2-/y mice. In addition to monitoring self-grooming following ECS in these mice, we are also monitoring both tissue and extracellular GABA levels in the cortex, hippocampus and striatum, the latter by in vivo microdialysis and high-performance liquid chromatography (HPLC).

Results: In contrast to the Viaat-Mecp2-/y mice, where stereotyped self-grooming was quite sensitive to ECS, we have found that ECS does not suppress the excessive self-grooming of Shank3B-/- mice one, three or five days after either a single ECS or after three ECS treatments spaced 48 h apart.

In ongoing studies, we are monitoring extracellular GABA levels in the striatum before and after ECS by microdialysis and HPLC. In a mixed cohort of Shank3B-/- and wild-type mice, we found that after an initial spike in GABA levels following implantation of the microdialysis probe, levels come down quickly and stabilize within about 30 minutes. In preliminary results in this mixed cohort we have found that ECS appears to produce a marked increase in GABA release in the striatum within 30 minutes of a seizure.

We have also begun monitoring GABA levels by immunohistochemistry and in preliminary results have observed more intense GABA cell body staining in the striatum of wild-type mice euthanized 60 minutes after ECS compared with mice exposed to sham stimulation.

Conclusions: We have found differing responses of stereotyped excessive self-grooming to ECS in two genetically distinct mouse models, namely the Viaat-Mecp2-/y and Shank3B-/- lines. Whereas the excessive self-grooming of the Viaat-Mecp2-/y mice is suppressed by a single ECS, ECS is not effective in the Shank3B-/- line. These data raise the possibility that the response of GABA levels to ECS may differ between these two mouse models, which we are presently assessing. In particular, GABA release following ECS may be more marked in Viaat-Mecp2-/y than in Shank3B-/- mice. These studies could help shed light on how ECT suppresses SIB associated with IDD. They may also shed light on why some of these patients may respond better to ECT than others.

Keywords: Self-Injurious Behavior, Electroconvulsive Therapy, GABA, Mouse Models

Disclosure: Nothing to disclose.

M163. Delineating the Hippocampal Circuitry Underlying Pair Bonding in Prairie Voles

*Jayme Temple, Michaela Best, Hannah Dougherty, Zoe Donaldson**

University of Colorado Boulder, Boulder, Colorado, United States

Background: Pair bonds are long-lasting social attachments that form between mating partners. While pair bonding is common among humans, the majority of mammals, including laboratory rats and mice, do not exhibit this trait. Instead, socially monogamous prairie voles, which form life-long pair bonds, provide an excellent model for studying attachment in adults. To date, the study of pair bonding in prairie voles has focused on neuromodulatory systems, including oxytocin, vasopressin, dopamine and endogenous opiates, while the specific neural circuits that modulate attachment remain largely unexplored. The ventral hippocampus has been implicated in regulation of emotions and social memory across a variety of rodent species. Thus, we asked whether the ventral hippocampus is required for a selective partner preference, a behavioral indicator of pair bonding.

Methods: We used ibotenic acid to bilaterally lesion the ventral hippocampus in female prairie voles. After two weeks of recovery, estrogen-primed females were paired and mated with a male. Twenty-four hours later, we performed a partner preference test.

Results: Animals with sham injections spent significantly more time huddled with their partner than a novel individual ($n = 6$, $p = 0.002$), indicating that they had formed a bond. In contrast, animals with ventral hippocampal lesions did not spend more time huddled with their partner ($n = 10$, $p = 0.45$).

Conclusions: Our data indicates that an intact ventral hippocampus is required for partner preference. However, because lesions result in permanent tissue disruption, it remains unclear whether an intact hippocampus is required for preference formation, expression of an existing bond, or both. Likewise, it is unclear which neuronal subsets within this region modulate partner preference. Thus, our ongoing work is examining the specific role of different hippocampal projections during pair bond formation versus expression. This research will provide a novel dissection of the role of hippocampal systems in pair bonding behavior, potentially providing valuable insights into how disruption of these circuits contributes to social deficits.

Keywords: Pair Bond, Hippocampus, Social Behavior, Prairie Voles

Disclosure: Nothing to disclose.

M164. Altered Functional Connectivity of the Spatial Network in Children With Nonverbal Learning Disability, Specific Learning Disability in Reading, and Typically Developing Children

Amy Margolis, Sarah Banker, David Pagliaccio, Lauren Thomas, Rachel Marsh*

Columbia University Medical Center/NYSPI, Brooklyn, New York, United States

Background: Nonverbal Learning Disability (NVLD) is characterized by deficits in visual-spatial processing in contrast to strengths in verbal reasoning, whereas reading disorder is characterized by deficits in verbal reasoning and strengths in spatial processing. The current study compared resting state functional connectivity of the spatial network among children with NVLD, children with reading disorder (RD), and typically developing (TD) children. We hypothesized that children with NVLD would have altered connectivity within the spatial network relative to the other groups, consistent with the phenomenology of the disorder.

Methods: Resting State fMRI data (rsfMRI) were acquired from 86 children. Thirty-six children were excluded for excessive motion (less than 5 minutes of usable data with FD < 0.5 mm), leaving a total of 54 children in the analysis (15 TD, 19 NVLD, 20 RD). Using the CONN toolbox, we performed ROI-ROI analyses among 12 seeds of a spatial network previously defined by Arnold [Journal of Cognitive Neuroscience, 26(2), 380 (2014)] and evaluated group differences while controlling for age, sex, and mean motion. We evaluated associations between network connectivity and functional impairment on the Child Behavior Checklist across all subjects while controlling for age, sex, mean motion, and diagnostic group.

Results: Two ROI-ROI connections in the spatial network showed significant group differences. Connectivity from left posterior cingulate (PCC) to right retrolimbic area (RA) was reduced in children with NVLD relative to typically developing children and children with RD. Across all children, such connectivity was inversely associated with internalizing problems ($b=-14.550$, $t=-2.741$, $p=0.009$), social problems ($b=-6.438$, $t=-2.331$ $p=0.024$), thought problems($b=-9.904$, $t=-2.575$, $p=0.013$), and total problems ($b=-12.408$, $t=-2.338$, $p=0.024$), and positively associated with school competence ($b=7.307$, $t=2.110$, $p=0.040$).

Connectivity from left PCC to right cerebellum was reduced in children with NVLD and children with RD relative to TD children. Given that both clinical groups showed reduced connectivity relative to TD children, the two groups were combined for behavioral analyses. Connectivity from left PCC to right cerebellum was positively associated with activities competence (b=19.37, t=2.02, p=.05) and total competence (b=16.0, t=1.99, p=.05).

Conclusions: Reduced cortico-cortical connectivity characterized children with NVLD and associated with behavioral impairment consistent with NVLD but not RD (internalizing and social problems) pointing to the specificity of these findings to NVLD. Altered connectivity in the spatial network may contribute to the psychological deficits that accompany NVLD, perhaps providing a novel target for treatment.

Reduced cortico-cerebellar connectivity characterized both groups of children with learning disabilities and associated with reduced competence in activities including sports, hobbies, and chores, possibly reflecting the motor deficits often reported in both NVLD and RD. In addition, reduced cortico-cerebellar connectivity associated with their overall sense of competence, possibly reflecting a domain general phenomenon experienced by children with learning disabilities. Such findings of reduced connectivity between the default mode network (PCC) and cerebellum in children with learning disabilities provide direction for future studies of children with learning disabilities.

Keywords: Learning Disability, Resting State Functional Connectivity, Visuospatial Ability

Disclosure: Nothing to disclose.

M165. Stress and the Brain's Hemodynamic Response: A New Perspective on Stress Response Regulation in Humans

Immanuel Elbau, Immanuel Elbau, Benedikt Brücklmeier, Manfred Uhr, Janine Arloth, Darina Czamara, Victor Spoormaker, Michael Czisch, Klaas Enno Stephan, Elisabeth Binder, Philipp Sämann*

Max Planck Institute of Psychiatry, Munich, Germany

Background: Ample evidence links dysregulation of the stress response to risk for psychiatric disorders. Yet, we lack an integrated understanding of mechanisms that are adaptive during the acute stress response but potentially pathogenic when dysregulated. One mechanistic link emerging from rodent studies is the interaction between stress effectors and neurovascular coupling, a process that adjusts cerebral blood flow according to local metabolic demands.

Methods: Here we use functional magnetic resonance imaging in healthy humans (two cohorts, together spanning n=98, ~ 50 % female) during an acute psychosocial stress intervention and parallel multi-level assessment of the stress response (on the endocrine, autonomous nervous system and subjective experience level) to investigate the effect of stress on shape-characteristics of the brain's hemodynamic response function (HRF). The HRF models how local neural activity elicits cerebral blood flow changes and reflects several biophysical processes including neurovascular coupling.

Results: We show that acute psychosocial stress rapidly impacts the peak latency of the hemodynamic response function (HRF-PL) in temporal, insular and prefrontal regions in two independent cohorts of healthy humans. These latency effects occurred in the absence of amplitude effects and were moderated by regulatory genetic variants of KCNJ2, a known mediator of the effect of stress on vascular responsivity. Further, hippocampal HRF-PL correlated both with cortisol response and genetic variants that influence the transcriptional response to stress hormones and were associated with risk for major depression.

Conclusions: We conclude that acute stress modulates hemodynamic response properties as part of the physiological stress response and suggest that HRF indices could serve as endophenotype of stress-related disorders.

Keywords: Acute Stress, Functional MRI (fMRI), Hemodynamic Response Function, Neuroendocrine Responses, Neurovascular Coupling

Disclosure: Nothing to disclose.

M166. Sexual Dimorphic Effects of Restraint Stress on Anxiety and Recency Memory, Limbic System Activation and Synaptic Plasticity

*Aggeliki Velli, Kleanthi Chalkiadaki, Aikaterini Chatzaki, Kyriaki Sidiropoulou**

University of Crete, Heraklio, Greece

Background: Sex differences are present in several neuropsychiatric disorders. Women are more vulnerable to anxiety disorders and major depression while men exhibit worse cognitive symptoms in several psychiatric disorders, such as schizophrenia. A common environmental factor that precipitates or worsens the pathology of the above disorders is stress. Stressor exposure affects men and women differentially (Bangasser et al, 2017, Physiology and Behavior). However, we do not understand the neurobiological mechanisms involved. Our aim in this work was to investigate the sexual dimorphic effects of stress on males and females on the function of the prefrontal cortex (PFC), the amygdala and the hypothalamus.

Methods: Adult male and female were initially subjected to two hours of restraint stress (RS), or left in their home-cage (NR), and then tested in the light-dark test (after 5 min), followed by the temporal order object recognition (TOR) test (1 h later) (n=9 for male NR, n=8 for male RS, n=9 for female NR and n=8 for female RS). In the light-dark test, mice were placed in the dark compartment of chamber and they were allowed to explore both the dark and the light compartments for 5 min. In the TOR task, mice are allowed to explore two identical copies of object A for 5 min and after 25 min two identical copies of object B for another 5 min. In the test session (25 min after the last one), mice were allowed to explore object A (old object) and object B (recent object). The mice brains were removed immediately after the end of the TOR test and prepared for immunofluorescence detection of the c-Fos protein. Brain regions of the limbic system, including the PFC, the amygdala, the hypothalamus and the dentate gyrus, were analyzed for the number of c-Fos-expressing cells. In a different cohort of animals, field excitatory postsynaptic potentials (fEPSPs) were recorded in PFC layer II, using the brain slice preparation, following the 2 h restraint stress. Tetanic stimulation resulted in long-term synaptic potentiation (LTP) of the fEPSP. All experiments were approved by the Institutional Animal Care and Use Committee of the University of Crete and were conducted in accordance with the European Union ethical standards. Statistical significance was ascertained by two-way ANOVA or t-test.

Results: When mice were tested in the light-dark test, RS resulted in significant differences in the latency to exit the dark side (two-way ANOVA, $F(3, 32) = 3.4$, $p=0.03$). Significant effects were observed both in the stress variable (NR vs RS) and the sex*stress interaction. Post-hoc LSD tests showed that the latency of female RS mice was significantly longer compared to female NR mice (p=0.004), male NR mice (p=0.02) or male RS mice (p=0.03). In the TOR task, male and female NR mice, as well as female RS mice, spent significantly more time exploring the recent object

compared to the older object (t-tests, p=0.03, p=0.01, p=0.02, respectively), indicating that mice in these groups could successfully discriminate the temporal order of object presentation. However, there was no significant difference between recent and old object exploration in male RS mice (p=0.3), demonstrating that male RS mice exhibit impaired recency memory.

Expression of restraint stress-induced c-Fos expression was examined in the cingulate cortex, the prelimbic cortex, the dentate gyrus of the hippocampus, the amygdala and the hypothalamus of RS male and female mice. Fos expression was enhanced in all of the above regions in RS female and male mice, compared to their respective NR mice. Fos expression was enhanced in female RS mice, compared to male RS mice, as well as compared to male and female NR mice in the cingulate cortex, the hypothalamus and the amygdala (4 brains in each groups tested so far, two-way ANOVA, F(3,13)=4.1, p=0.02, F(3,13)=3.5, p=0.04, F(3,13)=3.8, p=0.03, respectively).

In addition, electrophysiological recordings in the PFC showed that both adult male and female NR mice could enhance the fEPSP response following tetanic stimulation, thus, resulting in LTP (Konstantoudaki et al, 2018, Journal of Neurophysiology). However, LTP (measured at 35-50 min post tetanic stimulation) in the PFC was significantly reduced in male RS (n=5) compared to male NR (n=6), female RS mice (n=5), and female NR mice (n=7) (two-way ANOVA, F(3, 20)=3.8, p=0.02).

Conclusions: Restraint stress results in enhanced anxiety in female mice only and reduced recency memory in male mice. These behavioral effects are due to enhanced amygdala activation in female stressed mice and reduced LTP in the PFC of male stressed mice, respectively.

Keywords: Prefrontal Cortex, Amygdala, Hypothalamus

Disclosure: Nothing to disclose.

M167. Inhibition of the Endocannabinoid Anandamide Degradation Restores Stress-Mediated Impairments of Contextual Fear Memory Extinction and Hippocampal In Vivo Long-Term Synaptic Plasticity

Maria Morena, Roberto Colangeli, Andrei S. Nastase, Alessia Santori, G. Campbell Teskey, Matthew Hill*

University of Calgary, Calgary, Canada

Background: It is well established that stress has a profound impact on memory functions and the endocannabinoid system is a crucial modulator of stress-related behavioral responses.

Acute stress reduces hippocampal endocannabinoid anandamide (AEA) levels and impairs long-term potentiation (LTP) at CA3-CA1 synapses in the hippocampus.

Studies have shown that direct cortical input to the CA1 through the temporoammonic (TA) pathway is required for long-term synaptic plasticity and memory formation.

Based on this evidence, we examined the effects of acute stress on cued and contextual fear memory dynamics and on long-term synaptic plasticity at the TA-CA1 synapses in the dorsal hippocampus and the role of AEA in modulating these effects.

Methods: To test the effects of stress on fear memory dynamics, male adult Sprague Dawley rats were subjected to a forced swim stress 30 min before being tested for fear memory recall/extinction training in either an auditory or contextual fear conditioning paradigm (n = 11-12 per group). To test the effects of stress on synaptic plasticity, different groups of animals were subjected to the forced swim stress and anesthetized for in vivo extracellular field recordings at TA-CA1 synapses (n = 5-8 per group). To examine the role of AEA in the modulation of stress effects on fear memory and plasticity, separate cohorts of rats received either bilateral intra-CA1 injections of the AEA hydrolysis inhibitor URB597 30 min before the acute stress and tested for contextual fear memory dynamics, or systemic URB597 injections before the forced swim stress and then anesthetized for in vivo extracellular field recordings (n = 5-10 per group). All experimental procedures were in compliance with protocols approved by the University of Calgary Animal Care Committee and guidelines from the Canadian Council on Animal Care.

Results: Our results show that acute stress given before fear memory recall/extinction training session did not affect memory dynamics in the cued fear conditioning paradigm, but strongly reduced contextual fear memory recall, as rats in the stress group showed a marked reduction of freezing behavior when re-exposed to the fear conditioning context 24 h after conditioning, as compared to their control group (p = 0.03). Moreover, the exposure to the forced swim stress robustly impaired the acquisition of contextual fear memory extinction, as shown by increased freezing levels in stressed rats during the extinction recall session as compared to the non-stressed control group (p = 0.01). Consistently with these behavioral results, in vivo extracellular field recordings also revealed that acute stress strongly impaired LTP at TA-CA1 synapses. Very interestingly, pharmacological inhibition of AEA hydrolysis reverted the detrimental effects of stress on both fear memory extinction and LTP.

We are currently investigating possible mechanisms underlying such effects.

Conclusions: Our results show that acute stress impairs the acquisition of contextual, but not cued, fear memory extinction and this might be likely mediated by the stress-induced suppression of long-term synaptic plasticity at TA-CA1 synapses in the dorsal hippocampus. Moreover, pharmacological inhibition of AEA degradation completely reverts these stress impairing effects.

Taken together, our results shed light on the mechanisms underlying stress detrimental effects on memory and synaptic plasticity, opening the avenue to investigate new potential endocannabinoid-based tools to treat stress-related psychopathologies, such as Post-Traumatic Stress Disorders.

Keywords: Endocannabinoids, Fear Extinction, Long Term Potentiation, Hippocampus, Acute Stress

Disclosure: Nothing to disclose.

M168. Differential Valuation and Learning From Social and Non-Social Cues in Borderline Personality Disorder

Abstract not included.

M169. Imaging the Endocannabinoid System in Borderline Personality Disorder: A [11 C]-CURB Positron Emission Tomography Study

Nathan Kolla, Shelley McMain, Pablo M. Rusjan, Sylvain Houle, Michael Bagby, Karolina Karas, Christine Wang, Romina Mizrahi, Isabelle Boileau*

University of Toronto, Toronto, Canada

Background: Borderline personality disorder (BPD) is a poorly understood psychiatric condition with few biomarkers to guide development of novel treatments. Peripheral abnormalities of the endocannabinoid system have been described in BPD, but central measures have not yet been investigated. We used the novel radiotracer [11 C]-CURB and positron emission tomography (PET) to quantify levels of fatty acid amide hydrolase (FAAH) in multiple brain regions. FAAH is an enzyme that degrades anandamide

(AEA), an endocannabinoid that binds to CB1 receptors with high affinity. We hypothesized that FAAH would be elevated in the prefrontal cortex (PFC) and amygdala of BPD relative to healthy controls.

Methods: Twenty females with BPD and 20 healthy subjects were recruited. All of the BPD participants were medication-free. None had a comorbid major depressive episode. All were currently self-harming. None of the healthy controls had a psychiatric history. All study participants screened negative for illicit substance use and were non-smokers. Each participant underwent one [11 C]-CURB PET scan and a proton density magnetic resonance imaging scan for coregistration. Scans were analyzed as previously described (Kolla et al, 2016). Subjects were also genotyped for a common polymorphism that affects binding of FAAH. For the primary hypothesis, PET data were analyzed using multivariate analysis of variance (MANOVA) with PFC and amygdala FAAH levels as the dependent variables and diagnosis and genotype as fixed factors. Effects in each region, analyzed by univariate ANOVA, were considered significant after Bonferroni correction ($p < 0.025$).

Results: MANOVA revealed that BPD individuals had greater FAAH binding in the PFC relative to controls ($p = 0.019$). There was no significant difference in amygdala FAAH levels between groups ($p = 0.13$). Among the BPD patients, there was a positive correlation between resentment scores on the Buss-Durkee Hostility Inventory and FAAH levels in the PFC ($r = 0.53$, $p = 0.019$).

Conclusions: This study is the first to report an elevation of FAAH in any psychiatric condition. To the best of our knowledge, it is also the only PET study of BPD since 2016. Results indicate that the endocannabinoid system is altered in BPD. Elevated levels of FAAH could lead to lower AEA levels, resulting in lower CB1 receptor neurotransmission. Increased FAAH may play a role in specific BPD symptomatology, as PFC FAAH levels were positively correlated with a measure of anger. Our results suggest that FAAH inhibitors could be tested for their utility in treating BPD with high anger.

Keywords: Borderline Personality Disorder, Positron Emission Tomography Imaging, Endocannabinoid System, Fatty Acid Amide Hydrolase, Anger

Disclosure: Nothing to disclose.

M170. Exploring Familial Relationships Between Borderline Personality Disorder and Autism and Asperger's Spectrum Disorders: New Perspectives for Treatment

Valerie Porr, Nicolette Mallios, Isak Leon, Da Ae Ban, Fauve Arthur*

TARA for Borderline Personality Disorder Association, New York City, New York, United States

Background: BPD has a lifetime prevalence rate of 5.9%. It is characterized by impairment in interpersonal functioning, poor empathy and problems with trust and intimacy. People with BPD have been found to be hyper-vigilant, rejection sensitive, negatively biased and self-referential. They have difficulties in both cognitive and emotional empathy. Autism, characterized by social and communication difficulties, narrow interests and repetitive behaviors, has an estimated prevalence of 1%, predominately in males. Very few studies have examined the relationship between these disorders. People with BPD and ASD have difficulties with interpersonal relationships and in understanding, regulating and responding to emotions their own and others. These disorders seem to overlap in difficulty processing facial expressions, high sensory sensitivity, and difficulty in mentalizing. Hofvander found a 68% overlap between ASD and personality disorder (42 out of 62) while Ryden found 6 out of 41 BPD subjects (14.6%) met criteria for ASD. Lugnegard found 26 out of 54 (48%) ASD subjects had at least one personality disorder. In a 2017 study of the Overlap Between ASD and BPD, Dudas (2017), found that people with BPD have as high levels of autistic traits as people with ASD. He suggests that some ASD in females with BPD is not easily detected, perhaps owing to their "apparent competence." This study highlights the frequent misdiagnosis of these disorders. No study to date has looked at the incidence of BPD and ASD in family members nor on the cognitive and social behaviors within the two populations.

Methods: TARA developed an online survey, Exploring the relationship between BPD, Autism Spectrum Disorder and Asperger's Syndrome, to determine if there is a relationship between these two greatly misunderstood disorders. A literature review of Borderline Personality Disorder, Autism Spectrum Disorder and Asperger's syndrome was conducted to gain an in depth understanding of the symptoms or traits characteristic of each disorder. The survey included questions pertaining to social cognition, cognitive deficits, sensory processing disorder, and learning disorders such as ADHD and Dyslexia. We sought to identify symptoms that overlap between all three disorders and those specific to each. We then developed a symptom scale expressed in layman's terms regarding the following categories: social interactions, cognition, perception, experiencing emotions, and biologically based reactions. The survey was posted on the TARA4BPD website. The survey responses were predominantly from the BPD community. There were 322 responses to the survey.

Results: The survey results found 130 people identified themselves as having BPD; 27% of them identified as having Autism themselves or in a family member (1 out of 4). Out of 322 (N) responders, 48 participants reported having Autism in self and family, representing 15% of the autism survey population. Out of 322 responders, 94 participants reported having Asperger's in self and family, representing 29% of the ASD survey population. Of these 94 participants, 57 participants, reported having a relative with BPD or 61% of the ASD survey population. Of 205 people who had BPD within their family, 58% had a relative with Autism while 75% had a relative with ASD. Of 205 people with BPD family members, 16% had a child with Autism, 20% had a child with ASD; 12% had a niece/nephew with Autism, !2 % of their niece/nephews reported having ASD. In the case of siblings, 5% of BPD family had a sibling with autism and 10% had an ASD siblings. We also found interesting results for sensory processing disorder, dyslexia, ADHD, auditory disorder.

Conclusions: The relationships between BPD and Autism Spectrum Disorders is a neglected area of research. TARA's online survey was available to the public and therefore cannot be compared to a study done in a clinical setting with reliable clinical assessments. Despite these shortcomings, our preliminary findings seem to point to an apparent relationship between these disorders. Our extensive experience with family members of those with BPD has led us to believe that there are early signs of BPD in young children, such as emotional and sensory hypersensitivity, social interaction problems, concrete/rigid thinking, difficulty in facial recognition, early sleep dysregulation, and problems with empathy. These early signs are generally ignored or trivialized by most pediatricians and child psychiatrists. These symptoms overlap with ASD symptoms. As early intervention training with Autistic/Asperger children has been shown to be effective, early recognition of similar BPD symptoms might benefit from similar training.

Keywords: Borderline Personality Disorder, Autism, Asperger's Spectrum Disorder

Disclosure: Nothing to disclose.

M171. Effectiveness of an Emotional Working Memory Training in BPD

Annegret Krause, Julia-Caroline Walther, Susanne Schweizer, Stefanie Lis, Martin Bohus, Christian Schmahl*

Leiden University, Leiden, Netherlands

Background: Borderline Personality Disorder (BPD) is a severe mental disorder, characterized by emotion dysregulation, interpersonal problems, and stress-related cognitive disturbances. While several specialized evidence-based treatments exist, waiting times are often long and affective symptoms persist after successful treatment completion. Online trainings targeted at specific BPD symptoms, such emotion dysreguation and interpersonal distubances, may be cost-effective add-on interventions for individuals waiting for treatment. Findings from previous research in healthy individuals suggests that an 'Emotional Working Memory Training' (EWM), developed by Schweizer and colleagues [1], may show beneficial effects on affective-cognitive control. This computerized training involves different dual-n-back-tasks with emotional distractors (pictures, words) and increasing difficulty (adaptive testing). So far, no study has tested the effectiveness of this EWM training in BPD: The purpose of this study was to evaluate its effects on working memory and emotion regulation capacities in BPD.

Methods: In a randomized control trial, 60 female BPD patients were assigned to either an EWM training group (dual-n-back-task with emotional distractors, n=30) or a placebo training (feature match WM task, n=30). Training duration and success were recorded online. Before the training (T1) and after 26-day training (T2), participants performed two tasks measuring cognitive control of disturbing emotional material: 1) an adapted Sternberg working memory paradigm (with vs. without emotional pictures as distractors), and 2) an emotion regulation (cognitive re-appraisal) task. Behavioral performance and heart rate variability (HRV) were assessed as outcome measures before and after the training and evaluated within/between groups, using a repeated measure analysis of variance design.

Results: After the training (T2), both training groups showed significant improvements in working memory during the Sternberg Task compared to T1 ($F(1,46)=5.73$, $p=0.021$, $\eta^2=.11$). In the Emotion Regulation task, patients who had performed the EWM training showed significantly better down-regulation of negative emotions at T2 compared to T1, in comparison to the Placebo Training group (interaction effect: $F(1,40)=11.33$, $p=0.002$, $\eta^{22}=0.16$). In addition, significant correlations between training success and lower arousal ratings ($r= -.585$, $p=0.003$, $R^2=.34$) as well as higher HRV ($r= -.577$, $p=0.005$, $R^2=.33$) during the Emotion Regulation task were observed in the EWM training group (but not in the Placebo group). Results were similar for completers and intent-to-treat.

Conclusions: These novel un-published findings provide preliminary evidence for a beneficial effect of an Emotional Working Memory training on emotion regulation capacities in BPD. Computerized trainings, such as the EWMt, may be a cost-effective add-on intervention, e.g., for patients who are on the waiting list for a treatment. More research is needed to evaluate whether these effects can be replicated in larger samples. Future studies may further improve the acceptance of the training in the EWM group. Further implications for the clinical setting and future research are discussed.

Keywords: Borderline Personality Disorder, Working Memory, Emotional Regulation, Heart Rate Variability, Computerized Cognitive Training

Disclosure: Nothing to disclose.

Reference:

1. Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D. & Dalgleish, T. (2013). Training the emotional brain: improving affective control through emotional working memory training. Journal of Neuroscience, 33(12), 5301–5311. doi:10.1523/JNEUROSCI.2593-12.2013.

M172. Cortical RNA Profiles of Adult Offspring of Prenatal Restraint Stressed (PRS) Mouse Dams Identifies Differentially Expressed Genes

Dennis Grayson, Erbo Dong, Eleonora Gatta, Vikram Saudagar, Jeff Dunn, Alessandro Guidotti*

University of Illinois at Chicago, Chicago, Illinois, United States

Background: Prenatal or early life exposure to adverse events including stress, infection, malnutrition, hormones, and the use of illicit drugs, may have a profound effect on adult brain structure and function. Mice born from dams stressed during pregnancy (PRS mice), manifest various behavioral and biochemical endophenotypes when they reach adulthood. The behavioral endophenotypes include hyperactivity, stereotypic and compulsive behaviors, abnormal social interactions, prepulse inhibition, fear conditioning, object recognition, and hypersensitivity to NMDA receptor blockers.

Methods: Pregnant dams were subjected to daily episodes of restraint stress (45 min, 3 times daily with bright light) from days 7 through birth. Control dams were left in their cages. Following birth, pups were kept with their moms and were allowed to nurse. After weaning, mice were group housed and left alone until early adulthood (90 days) at which time, animals were sacrificed and the prefrontal cortex (PFC) was dissected. RNA was isolated from the prefrontal cortices of 5 PRS and 5 non-stressed (NS) mice. RNA quality was determined using an Agilent Bioanalyzer and all samples had a RIN greater than 7.5.

RNA-seq libraries were prepared using the TruSeq Stranded mRNA Library Prep Kit (Illumina) at the High-Throughput Sequencing Unit of the Roy J. Carver Biotechnology Center, University of Illinois. Quantity and size distribution of each library was observed using an Agilent 2100 Bioanalyzer using the High Sensitivity DNA kit. Pooled libraries were sequenced as single-end 100 nt reads on two lanes for 101 cycles using an Illumina HiSeq2500 platform using a TruSeq SBS sequencing kit. FastQ files were evaluated for read quality and trimmed. TopHat2 was used to align sequences to the mouse genome. Raw gene counts were then analyzed in R using STAR in edgeR. 5,084 genes without at least 1 count per million mapped reads in at least 3/6 samples were removed from analysis, leaving 13,936 genes. TMM normalization (20) was used to correct for any RNA composition bias and differential expression between N and S groups was tested using a replicate-paired design and a generalized linear model appropriate for count-based data. Principle Components Analysis showed a clustering of samples into two well separated groups. voom transformed values and weights were tested for differential expression using an empirical Bayes method. For gene ontology, gene symbols and fold change for all mRNAs with adjusted $p< 0.05$ were submitted to ConsensusPathDB, DAVID, and Gene Set Enrichment Analysis (GSEA).

Results: There were a total of 1,619 differentially expressed (DE) genes in the FC of adult (PD80) PRS mice at an adjusted p value ≤ 0.05. Of these significantly different RNAs, 665 were increased and 955 were decreased relative to the NS samples. The volcano plot, shows the relationship between the statistical test p-values and the log10 (Fold Change) of the difference in expression between PRS samples and NS groups. Differentially Expressed (DE) genes (with adjusted p values < 0.05) were analyzed using gene

ontology software. When these transcripts were input into DAVID, top annotation terms included ribosome, mitochondrial function, immune system, and response to stress. Many of these were predominantly up- or down-regulated. For example, of the 63 genes associated with ribosomal proteins, all were down-regulated in PRS mice relative to NS mice. Similarly, of the 125 genes associated with the DAVID term Mitochondrion, 111 mRNAs were decreased while only 13 were increased. The ribosomal protein mRNAs significantly different in PRS mice are shown, as are those mRNAs encoding proteins linked to mitochondrial function and oxidative phosphorylation. We've validated and replicated many genes associated with each functional gene category.

Conclusions: Our data support the hypothesis that prenatal stress induces long-lasting changes in gene expression in the prefrontal cortex of mice. Many of the genes that exhibit altered expression profiles are likely associated with the observed behavioral anomalies. The reduced expression of genes associated with ribosomal proteins are likely responsible for the recently noted reduction in dendritic spines on prefrontal cortical neurons in PRS mice and may be associated with the spine loss observed in psychiatric disorders. Numerous studies have linked the gene ontology terms mitochondrial function and immune process with schizophrenia (SZ) and autism spectrum disorder (ASD). We looked for overlap between our DE genes (FDR<0.05) and genes associated with SZ, ASD, and bipolar disorder (BP). We found a pronounced overlap (73 genes) between our DE genes and genes associated with SZ. There were 20 DE genes that overlap with ASD associated genes and 10 genes that are also altered in BP. Collectively, offspring of PRS mice exhibit behavioral and molecular endophenotypes that are reminiscent of the endophenotypes associated with various psychiatric disorders.

Keywords: Prenatal Stress, Mouse Model, Epigenetics, Schizophrenia

Disclosure: Nothing to disclose.

M173. Stimulus-Specific Adaptation and Deviance Detection in Primary Auditory Cortex of the Awake Non-Human Primate

*Tobias Teichert**

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Mismatch negativity is the key biomarker of altered short-term memory function and/or predictive coding in schizophrenia. Mismatch negativity has been sub-divided into two components, stimulus-specific adaptation and deviance detection. Deviance detection, i.e., increased neural activity to stimuli that violate expectations, can facilitate the identification of informative events in the environment. Stimulus-specific adaptation is a complementary process that reduces responses to repeated stimuli that are less likely to be informative. While stimulus-specific adaptation can most likely be explained by short-term presynaptic plasticity, it remains unclear how the brain computes expectations and deviations from expectation required for deviance detection. Efforts to understand the underlying neural mechanisms of deviance detection have been hampered by the fact that it has not been observed in the non-human primate, an important model system.

Methods: To better understand the phenomenology of mismatch negativity in the monkey we recorded neural responses in primary auditory cortex (A1) of two awake macaque monkeys while they listened to 50 ms long 60 dB SPL loud pure tone bursts presented in the context of a modified roving standard paradigm. The transition probabilities between different tones in the paradigm were manipulated to create a regular condition in which time and identity of upcoming tones was predictable and a random condition in which it was not.

Results: Following standard conventions, deviance detection was operationalized as stronger responses for deviants in the regular compared to the random condition. Based on this definition both animals exhibited deviance detection in addition to stimulus-specific adaptation. This is the first report of deviance detection in this species. Deviance detection was found in supra-granular, granular and infra-granular layers. Deviance detection was present in the first wave of cortical activity (20-45 ms) and was even stronger in a later period from 70 to 125 ms. Deviance detection was observed independent of the stimulus-onset asynchrony over the entire range of values tested (250 to 8000 ms). We present a computational model that can explain key aspects of deviance detection using a simple yet effective local circuit architecture and biologically realistic synaptic function.

Conclusions: In addition to stimulus-specific adaptation, primary auditory cortex of the macaque monkey also exhibits deviance detection. This finding suggests a closer homology between the two species than previously assumed, thus paving the way for additional studies to dissect the neural mechanism. The delayed timing of deviance detection relative to stimulus-specific adaptation suggests that it might be fed back from higher auditory regions.

Keywords: Mismatch Negativity, Deviance Detection, Macaque Monkey, Auditory Short-Term Memory, Primary Auditory Cortex

Disclosure: Nothing to disclose.

M174. Identification of Functional Role of Medial Prefrontal Cortical Neurons Co-Expressing D1 and D2 Receptors

*Clementine Quintana, Jivan Khlghatyan, Jean-Martin Beaulieu**

University of Toronto, Toronto, Canada

Background: The D2 receptor (Drd2) is a direct or indirect target of antipsychotics and mood stabilizers. Medial prefrontal cortical (mPFC) functions of Drd2 are of interest, considering the involvement of cortical dopamine in cognitive functions and emotional processing in schizophrenia and mood disorders. However, low mRNA expression of Drd2, selectivity of antibody, drug and reporter systems has prevented the specific detection and study of Drd2 expressing neurons. To overcome previous technical limitations hindering reliable mapping of Drd2 neurons particularly in cortex we used a TRAP (Translational Ribosome Affinity Purification) approach using mice expressing a Cre activated RiboTag, specifically in Drd2 positive cells (Drd2+ cells). These mice allow for a highly sensitive detection of Drd2+ cells and provide the possibility to perform cell-specific translational profiling to identify the molecular determinants of Drd2+ cells in mPFC. Interestingly, this model allows for the detection of other dopamine receptors, such as Drd1, in mPFC Drd2 cells+.

Methods: To investigate the impact of co-expression of Drd2 and Drd1 in mPFC neuronal function, we used somatic CRISPR/Cas9 mediated knockout and chemogenetic modulation revealing their involvement in the regulation of behaviors. Immunohistochemistry and translational profiling were used to identify the molecular determinants of Drd2+ cells in mPFC. To investigate behavioral regulation, we used CRISPR/Cas9 and DREADD approaches modulating directly Drd2+ cells activity in mPFC in adult mouse brain.

Results: By extraction of mRNA binding HA tagged ribosome in mPFC Drd2 cells+ we observed the co-expression of various GPCRs in Drd2+ neurons. Interestingly, expression profiling revealed a high level of Drd1 mRNA expressed in Drd2 cells+ in

cortical neurons. This was confirmed by an immunofluorescent analysis showing a high density of Drd2 cells+ that co-express D1 receptor in cortical layer II and V. Ultimately, using different approaches, we modulated directly the protein synthesis or the activity of these neurons to reveal their involvement in behavioral regulation.

Conclusions: This comprehensive analysis of mPFC Drd2 neurons provides indications for its functional implications in healthy and disease conditions. Heterogeneity of dopamine receptor expression in mPFC has to be taken into consideration during pharmacological intervention and assessment of functional and behavioral data.

Keywords: D1 Dopamine Receptors, Dopamine 2 Receptor, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

M175. Enhanced NGR/p75/KAL9 Signaling Influences Dendritic Morphogenesis in a Schizophrenia-Relevant Manner

Melanie Grubisha, Zachary Wills, Susan Erickson, Cassandra Helmer, Gregg Homanics, Peter Penzes, Robert Sweet*

University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, United States

Background: Kalirin (KAL) is a Rho GEF that is highly involved in regulation of cytoskeletal morphology within dendrites. The KAL9 isoform activates RhoA downstream of p75 when p75 interacts with Nogo receptor (NGR). This NGR/p75/KAL9 complex acts to restrict dendritic morphogenesis. Increased levels of Nogo mRNA as well as elevated levels of KAL9 protein have been described in schizophrenia, suggesting enhanced activity of this pathway may contribute to the impairments in dendritic morphogenesis in disease. We evaluated a missense mutation in KALRN (KALRN-PT), located near the RhoA GEF in KAL9, and found that it acts as a gain of function mutation for RhoA activation. We hypothesized that enhanced activity in the NGR/p75/KAL9 pathway impairs dendritic morphogenesis in pyramidal cells (PCs) across development.

Methods: RhoA activation assays were performed using transient expression of a RhoA sensor in in vitro dissociated cortical cultures overexpressing either KALRN-WT or KALRN-PT. CRISPR/Cas9 gene editing was used to insert the human KALRN-PT mutation at the endogenous locus of the C57/Bl6J strain. Golgi staining was performed on cortical sections from 4 and 12-week old mice encompassing primary auditory cortex (A1), and full dendritic reconstructions of A1 Layer 3 PCs were performed in NeuroLucida software. Spine density analyses and cortical volume measurements were performed on Golgi stained material using StereoInvestigator software.

Results: KALRN-PT confers enhanced RhoA activation compared to KALRN-WT. L3 PCs from A1 in homozygous KALRN-PT mice demonstrate reduced dendritic length and complexity at 12-weeks, but not at 4-weeks. There is no observed change in spine density along secondary apical dendrites between 12-week old KALRN-WT and KALRN-PT mice. Similarly, there is no significant change in cortical volume between genotypes at 12-weeks, although KALRN-PT mice showed a trend towards a 5-6% volume reduction ($p=0.24$).

Conclusions: The increased RhoA activity arising from the PT mutation results in increased NGR/p75/KAL9 signaling and subsequently leads to reduced dendritic length and complexity in L3 PCs in A1 in early adulthood. Interestingly, this change is not present during the pre-adolescent period and presumably emerges during adolescence, consistent with the timing of onset of clinical symptoms of schizophrenia in humans. This change in dendritic structure is not accompanied by any statistically significant change in spine density or cortical volume, suggesting that KALRN-PT provides a useful model for isolating mechanisms of impaired dendritic morphogenesis as they relate to schizophrenia.

Keywords: Auditory Deficits in Schizophrenia, NGR/p75, Dendritic Morphogenesis

Disclosure: Nothing to disclose.

M176. Increased Protein Insolubility in Brains From a Subset of Patients with Schizophrenia

*Leslie Nucifora, Matthew MacDonald, Brian Lee, Matthew Peters, Alexis Norris, Benjamin Orsburn, Kun Yang, Kelly Gleason, Russell Margolis, Jonathan Pevsner, Carol Tamminga, Robert Sweet, Christopher Ross, Akira Sawa, Frederick Nucifora**

Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

Background: The mechanisms leading to schizophrenia are likely to be diverse. However, there may be common pathophysiological pathways for subsets of the disease. In the present study, we hypothesized that disruption of protein quality control can lead to protein insolubility for a subset of patients with schizophrenia.

Methods: Prefrontal cortex or superior temporal gyrus from autopsy brains provided by the University of Pittsburgh, University of Texas Southwestern, and Harvard were subjected to cold sarkosyl fractionation, separating proteins into soluble and insoluble fractions. All pellet samples were analyzed to quantify insoluble protein levels and ubiquitin reactivity, normalized to total homogenate protein. We then performed mass spectrometry analysis to identify the contents of the insoluble pellets. The potential biological relevance of the detected proteins was assessed using Gene Ontology Enrichment Analysis and Ingenuity Pathway Analysis.

Results: A subset of patients with schizophrenia showed an increase in protein insolubility and ubiquitination in the insoluble protein fraction. Mass spectrometry of the insoluble fraction revealed that cases with increased insolubility and ubiquitination showed a similar pattern of peptide clustering by principal component analysis plot and heatmap analysis. The proteins that were significantly altered in the insoluble pellet were enriched for terms relating to axon target recognition as well as nervous system development and function.

Conclusions: This study suggests a pathological process related to protein insolubility for a subset of patients with schizophrenia. Understanding the molecular mechanism of this subtype of schizophrenia could lead to a better understanding of the pathways, circuitry, and symptoms seen in some patients with major mental illness and could lead to improved nosology and novel therapeutic targets.

Keywords: Protein Insolubility, Ubiquitination, Schizophrenia

Disclosure: Nothing to disclose.

M177. Laminar- and Cell Type-Specific Transcriptomic Analysis of Electron Transport Chain Complexes in the Prefrontal Cortex of Schizophrenia Subjects

Jill Glausier, John Enwright, Dominique Arion, David Lewis*

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Accumulating evidence indicates that a key mitochondrial function, ATP synthesis via oxidative

phosphorylation (OXPHOS), is lower in the prefrontal cortex (PFC) of schizophrenia subjects. Pathway analyses of transcriptome data from PFC layers 3 and 5 pyramidal cells, and layer 3 parvalbumin (PV) interneurons, indicate electron transport chain (ETC) and OXPHOS as top affected gene pathways. Despite the abundance of data indicating less ATP production via OXPHOS, the nature of these alterations in the disease is unknown. Two distinct mechanisms can affect OXPHOS: cellular demand for ATP and dysfunction of the ETC complexes. The first mechanism regulates the level of ATP produced by OXPHOS in mitochondria in response to cellular energetic demands, whereas the second mechanism impairs OXPHOS production of ATP in mitochondria. Determining which of these mechanisms, lower energetic demand or impaired energetic capacity, contributes to disease findings is paramount since each possibility carries very different implications for therapeutic targets.

Lower cellular ATP demand and impaired OXPHOS have different effects on the expression levels of ETC complexes. Synthesis of ATP via OXPHOS only occurs upon demand, and the most energetically-demanding processes involve support of neuronal action potentials and synaptic signaling. Accordingly, persistent decreases in neuronal firing lowers ATP demand, eliciting a correlated reduction in the expression of ETC complexes in these cells. Thus, if ATP demand is lower in PFC layers 3 and 5 pyramidal cells and layer 3 PV interneurons, then we would expect to find lower expression of ETC complexes of similar magnitude within each cell population. Impaired OXPHOS, on the other hand, has an unequal effect on the expression of ETC complexes, and preferentially affects cells with high firing and energy demands. For example, PV interneurons have substantially higher firing rates and ATP demand than pyramidal cells. Accordingly, perturbations of OXPHOS enzyme function, including induction of oxidative stress by a variety of experimental manipulations, preferentially affects PV cells. Thus, if OXPHOS is dysfunctional, then we would expect to find a larger reduction in the levels of ETC complexes in PV relative to pyramidal cells and non-correlated changes in the expression of ETC complex expression in each cell population. To distinguish between these alternatives in schizophrenia, we compared transcript expression levels of each ETC complex in layers 3 and 5 pyramidal cells and layer 3 PV interneurons.

Methods: We used microarray data from previous reports of gene pathways altered in schizophrenia. Briefly, frozen tissue sections containing PFC area 9 from 36 matched pairs of schizophrenia and unaffected comparison subjects were stained with thionin for Nissl substance to identify pyramidal cells or labeled using immunoperoxidase for aggrecan to identify PV cells. Pyramidal and PV somata were dissected using a Leica laser microdissection (LMD) system. Transcriptome profiling was performed by microarray using Affymetrix GeneChips specific to the human genome. A Z-score was calculated for each subunit comprising an ETC complex (Complex I: 37 subunits, Complex II: 4 subunits, Complex III: 9 subunits, Complex IV: 10 subunits, Complex V: 16 subunits), then all subunit Z-scores within a complex were averaged to obtain a composite Z-score for each subject.

Results: Expression levels of all five ETC complexes were 14-21% lower in layer 3 pyramidal cells, 17-22% lower in layer 5 pyramidal cells, and 4-27% lower in layer 3 PV cells of schizophrenia subjects relative to unaffected comparison subjects. The expression levels among ETC complexes within all three cell populations was highly correlated in unaffected comparison subjects (layer 3 pyramidal cells: mean r=0.9; layer 3 PV cells: mean r=0.8; layer 5 pyramidal cells, mean r=0.7), and these correlations were completely retained in all three cell populations in subjects with schizophrenia.

Conclusions: Our laminar- and cell type-specific transcriptomic analyses indicate that expression of all five ETC complexes is not more affected in PV cells relative to pyramidal cells, and that correlated expression across ETC complexes is preserved in the disease state. Together, these data suggest that lower measures of OXPHOS likely reflect lower ATP demand, and not impaired OXPHOS capacity, in the PFC of subjects with schizophrenia.

Keywords: Postmortem Brain Tissue, Parvalbumin Neurons, Oxidative Phosphorylation, Schizophrenia, Pyramidal Cell

Disclosure: Nothing to disclose.

M178. Comprehensive Analysis of Regional Specific RNA-Editing Differences in Brain Across the Lifespan of Normal Subjects and Individuals With Schizophrenia

HyeonJin Cho, Tae Young Hwang, Carrie Wright, Jae-Kyung Won, Emily Burke, Andrew Jaffe, Thomas Hyde, Joel Kleinman, Daniel R. Weinberger, Joo Heon Shin*

Lieber Institute for Brain Development, Baltimore, Maryland, United States

Background: RNA editing is a co/post-transcriptional process that alters the nucleotide sequence of primary transcripts. ADAR (adenosine deaminases acting on RNA) enzymes catalyze A-to-I RNA editing by deamination of adenosine, converting stable A:U base pairs to less stable I:U mismatches. These RNA sequence alterations also often influence structure as well as recoding of amino acids. Especially in the mammalian nervous system, it has been shown that RNA editing contributes to the function of diverse neuronal receptors and immune-homeostasis, suggesting that abnormalities in RNA editing are involved in several pathological conditions including psychiatric diseases. Indeed, previous studies have shown multiple links between RNA editing and certain human brain disorders, including schizophrenia, mood disorder, autism and Alzheimer's disease. However, these studies have been limited by small sample sizes and have largely only evaluated a limited number of editing sites. To better understand the relationship between schizophrenia and A-to-I RNA editing in an unbiased way, we compared RNA editing profiles of a large number of postmortem neurotypical brain samples and samples with schizophrenia using RNA-seq data of several brain regions.

Methods: We used RNA-seq data from 254 control and 184 schizophrenia from dorsolateral prefrontal cortex (DLPFC), 319 control and 133 schizophrenia from hippocampus (HIPPO), which were generated by BrainSeq Consortium and also from the dentate gyrus (DG) of the hippocampal formation isolated by laser capture microdissection from 93 control and 75 individuals with schizophrenia. We profiled 4,282 editing sites previously identified in DLPFC human postmortem brain data set that had high median numbers of sequencing reads in our current sample and were associated with genes. We calculated editing ratios for each site by dividing the number of alternate sequence counts with the total number of counts (both reference matching and alternate) that were filtered with multiple quality controls in the RNA-editing pipeline.

For each brain region, a linear regression analysis was performed to compare editing ratios of each site between the diagnostic groups using the empirical Bayes method of the Bioconductor Limma package in R. RNA-seq quality metrics, as well as age and gender were included as covariates. In addition, multi-dimensional scaling (MDS) components determined from genotype data were included in the models for each region to account for the ethnic diversity of our samples. Significance values were corrected for multiple testing using the Benjamini Hocheberg method and a threshold of 0.05 was used to determine significance.

Results: No editing sites had significantly different ratios between the diagnostic groups for the DG and the HIPPO;

however, 17 sites were significantly different for the DLPFC, one of which was identified as a candidate risk gene in the current GWAS in PGC2 loci about its relationship with schizophrenia.

Conclusions: Previous studies suggest a link between editing rates of glutamate receptor subunits and serotonin 2 C receptor subtype in schizophrenia, but these studies have had limited sample sizes and have not performed global assessments of other editing sites. Furthermore, previous work has often not accounted for possible effects of age, race, gender and RNA quality on ADAR editing rates. We plan to perform targeted re-sequencing for validation of the discovered sites to confirm the differences in ADAR editing. Further research is necessary to better understand how the differences in editing rates between the diagnostic groups of these editing sites may influence the function of these genes and their potential role in pathogenesis of schizophrenia.

Keywords: A-to-I RNA-editing, Schizophrenia, Adenosine Deaminases Acting on RNA

Disclosure: Nothing to disclose.

M179. A Missense Mutation in SLC39A8, a Manganese Transporter Linked to Schizophrenia, is Associated With Specific Changes in Plasma N-Glycosylation

Robert Mealer, Richard Cummings, Mark Daly, Sylvain Lehoux, Jordan Smoller*

Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts, United States

Background: Recent Genome Wide Association Studies (GWAS) identified a strong association between the disorder and a missense mutation (A391T) in the zinc/manganese transporter SLC39A8 ($p < 8\times10\text{-}15$). Manganese (Mn) is a critical cofactor for many enzymes including certain glycosyltransferases; enzymes that attach sugar molecules to proteins and lipids to regulate their function. Patients with severe mutations in SLC39A8 (not A391T) present with symptoms of a type II congenital disorder of glycosylation, and treatment with Mn or precursors of galactosylation reverses deficient transferrin glycosylation and some clinical phenotypes. The purpose of our study is to determine the link between the SLC39A8 A391T missense mutation linked to schizophrenia and the glycosylation pathway.

Methods: Using the Partners Biobank, a biorepository of 80,000 samples linked to the electronic medical record and genomic data, we optimized a search algorithm with 65% accuracy to identify patients with schizophrenia. After confirming the diagnosis via chart review, controls and patients with schizophrenia were stratified into groups based on SLC39A8 genotype, and samples of serum and plasma were obtained from the Biobank for study. Levels of Mn and Zn were measured in serum using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Plasma N-glycans were release by PNGaseF cleavage, permethylated, and purified prior to analysis using MALDI-TOF.

Results: We confirm that the A391T mutation results in decreased serum manganese with no effect on zinc. Analysis of plasma N-glycans shows a reduction in high molecular weight structures by ~25% ($p<0.05$) in A391T mutation carriers, suggesting reduced activity the Mn-dependent enzyme β(1,4)-galactosyltransferase. Analysis of plasma N-glycans from patients with schizophrenia independent of SLC39A8 genotype identified a 20% increase in fucosylation and 30% reduction of sialylation relative to controls, though these modifications can also be affected by inflammation, environmental exposures, and medications that may be present in the disease group. Investigation of a subset of individuals with schizophrenia and the A391T mutation are ongoing.

Conclusions: We demonstrate that plasma N-glycosylation is altered in individuals harboring the SLC39A8 A391T mutation and hypothesize that similar changes in the developing brain result in the increased risk of developing schizophrenia in mutation carriers. We also find changes in the plasma N-glycans of individuals with schizophrenia, though the significance of these differences are yet to be determined. We ultimately hope to develop a scalable blood biomarker of risk based on genetics, Mn levels, and glycosylation patterns, in addition to generating novel insights in the neurodevelopmental changes that underlie schizophrenia.

Keywords: N-Glycosylation, Schizophrenia Genetics, SLC39A8

Disclosure: Nothing to disclose.

M180. Inhibition of Brain and Liver Kynurenine Aminotransferase II Activity by N-Acetylcysteine in Rodent, Pig and Human

*Korrapati Sathyasaikumar, Tonali Blanco-Ayala, Robert Schwarcz**

Maryland Psychiatric Research Center, Baltimore, Maryland, United States

Background: Kynurenic acid (KYNA), a metabolite of the kynurenine pathway of tryptophan degradation, is increasingly understood to play an important role in the mechanism(s) underlying normal and abnormal cognitive processes, most likely by acting as an antagonist of α7 nicotinic and NMDA receptors. Specifically, elevated KYNA levels are detrimental in psychiatric diseases such as schizophrenia. KYNA is synthesized from its immediate precursor kynurenine - either by non-enzymatic oxidation or through irreversible enzymatic transamination by kynurenine aminotransferases. In the mammalian brain, kynurenine aminotransferase II (KAT II) is the principal enzyme responsible for the neosynthesis of rapidly mobilizable KYNA. KAT II therefore constitutes an attractive target for pro-cognitive interventions (Schwarcz et al., 2012). N-acetylcysteine (NAC), a brain-penetrant drug with pro-cognitive efficacy in humans, including individuals with schizophrenia, has been proposed to exert its actions by increasing the levels of the endogenous antioxidant glutathione (GSH) in the brain (Steullet et al., 2016). We now examined a possible alternative mechanism of NAC action, namely KAT II inhibition.

Methods: Using a well-established procedure (Sathyasaikumar et al., 2011), we first tested the effect of NAC on KAT II activity in liver and brain tissue homogenates from mice, rats, pigs and humans in vitro. Next, we investigated the ability of NAC to affect the activity of pure human recombinant KAT II protein. Finally, we examined the effect of NAC on the neosynthesis of KYNA in vivo using microdialysis in the medial prefrontal cortex (mPFC) of unanesthetized adult rats. To this end, NAC (20 mM) was locally applied by reverse dialysis for a period of 6 h. 120 min after starting the perfusion, kynurenine was administered systemically (50 mg/kg, i.p.) while NAC perfusion continued for the remaining 4 h. In separate animals, NAC (500 mg/kg, i.p.) was administered systemically 120 and 60 min before the peripheral administration of kynurenine.

Results: In all tissue homogenates, NAC inhibited KAT II activity with IC50 values in the high micromolar to the low millimolar range. Using human recombinant KAT II, NAC inhibited enzyme activity with an IC50 of ~500 μM, while GSH was approximately 40 times less potent (IC50 >20 mM). In vivo, NAC reduced the de novo production of KYNA from its immediate precursor kynurenine by ~45% and ~50%, respectively, in the two experimental paradigms used.

Conclusions: Our results raise the possibility that NAC exerts its neurobiological effects at least in part by reducing cerebral KYNA levels via KAT II inhibition.

Keywords: Cognition, Kynurenine, Kynurenic Acid, Schizophrenia, N-acetylcysteine

Disclosure: Nothing to disclose.

M181. Interaction Between Anticholinergic Medication Burden and Treatment Effects of Targeted Cognitive Training in Schizophrenia Patients Mandated to Long-Term Locked Inpatient Care

Yash Joshi, Michael Thomas, Andrew Bismark, William Hochberger, Emily Treichler, Melissa Tarasenko, John Nungary, Laura Cardoso, Alexa Sison, Juan Molina, Neal Swerdlow, Gregory Light*

University of California, San Diego School of Medicine, San Diego, California, United States

Background: Targeted cognitive training (TCT) is an emerging computerized intervention aimed at remediating auditory information processing deficits in schizophrenia (SZ). TCT increases the fidelity of low-level auditory discrimination in SZ through adaptive and intensive exercises in a durable way and is associated with improved psychosocial outcomes. The underlying brain circuitry which mediates TCT-gains is thought to depend on appropriate brain cholinergic signaling. While patients with SZ are known to be vulnerable to elevated anticholinergic load stemming from psychotropic medications, the relationship between brain cholinergic signaling in the context of TCT trials conducted in a treatment-refractory SZ population has not been well characterized. Here we report findings from a randomized clinical trial investigating the effectiveness of TCT in SZ patients mandated to long-term locked inpatient care and the interaction of anticholinergic burden on treatment effects.

Methods: Patients with SZ were randomized to treatment as usual (TAU) or treatment as usual + TCT. No significant differences were present in demographic, clinical or cognitive variables at baseline. The Anticholinergic Cognitive Burden Scale (ACCBS) was used to calculate anticholinergic burden using medication administration records. Auditory discriminability, cognitive functioning and symptoms scores were assessed at baseline and after a full course of TCT. Data were analyzed using linear mixed effects models. No group differences in ACCBS scores were present at baseline or follow up. Both groups had similar total antipsychotic load.

Results: TCT improved auditory discriminability ($d=0.6$), verbal learning and memory ($d=0.8$), and positive symptoms ($d=-0.6$). Baseline ACCBS score negatively correlated with change in verbal learning (TAU, $r=-.61$, $p<0.02$; TCT, $r=0.14$, NS) and auditory discriminability (TAU, $r=-.53$, $p<0.05$; TCT, $r=0.41$, NS) in TAU but not TCT group.

Conclusions: TCT improved auditory discrimination, cognitive functioning and symptoms in SZ patients in locked residential care. Anticholinergic burden negatively correlated with measures of auditory discrimination and cognition in the TAU group, but not in those receiving TCT. These data suggest that patients with SZ who experience a high anticholinergic burden can benefit from TCT. These results also imply that TCT may protect against anticholinergic-burden associated impairment in SZ. Future studies are needed to identify strategies that optimize brain cholinergic signaling in SZ to better support or augment cognitive training in SZ patients.

Keywords: Computerized Cognitive Training, Cholinergic System, Human Clinical Trial, Auditory Deficits in Schizophrenia, Psychotropic Medications

Disclosure: Nothing to disclose.

M182. Influence of Olanzapine Dosing and History of Cannabis Use on Treatment Response in Acute Schizophrenia

Dagmar Koethe, David Meyrath, Carola Schaefer, Cathrin Rohleder, F. Markus Leweke*

Brain and Mind Centre, The University of Sydney, Camperdown, Australia

Background: In acute schizophrenia higher dosages of antipsychotics are often administered early and previous cannabis use is most common. The influence of the early antipsychotic dosage and/or cannabis use in response to treatment are not well investigated. Here, we performed a clinical trial starting with a low dose of olanzapine with controlled increase where needed. Thereby, we studied the impact of olanzapine dosage and previous cannabis use on clinical response and plasma olanzapine.

Methods: To address these questions, we analyzed the data from a 6-week clinical trial in 37 acute schizophrenia patients. Olanzapine was stepwise increased by 2.5 mg/day weekly from 5 mg/day up to 15 mg/day based on an improvement of symptoms to the previous week (BPRS improvement >2, no increase). 18/37 patients received additional oxcarbazepine (1,500 mg/day) with no significant effect on plasma levels or improvement of symptoms. The history of cannabis use and psychopathology (PANSS) were assessed. Previous cannabis use was determined by self-report (no ($n=13$; NC), moderate ($n=6$; MC), and high ($n=16$; HC) cannabis use.

Results: Patients were in average 29.5 ys, 23/14 male/female, 62% smokers. Average decrease in tPANSS to baseline was 25.4 ±23.0 (MV±SD). The mean maximum dose of olanzapine during the trial was 9.85±3.3 mg/day. 24/37 patients received a maximum dose of ≤10 mg/day of olanzapine, 7/37 remained on the initial dose of 5 mg/day. Cannabis history did not influence response, but HC use was associated with lower olanzapine plasma levels.

Conclusions: In this design, 65% of patients benefited from low dose olanzapine. The effects of pharmacological treatment were independent of previous cannabis use although the latter influenced olanzapine plasma levels significantly. Our results suggest that initial low dose treatment in acute schizophrenia is justified and does not lead to a less favorable outcome seems to justify the low-dose start of olanzapine in acute schizophrenia where possible.

Keywords: Cannabis Use, Psychosis, Treatment Response, Olanzapine, Clinical High-Risk State For Psychosis

Disclosure: Nothing to disclose.

M183. KarXT, a Combination of the M1/M4 Cholinergic Receptor Agonist Xanomeline and Trospium for the Treatment of Psychosis and Cognitive Impairment in Schizophrenia: Phase I Studies

Stephen Brannan, Andrew Miller, Steven Paul, Alan Breier*

Karuna Pharmaceuticals, Boston, Massachusetts, United States

Background: Xanomeline is a M1 /M4 preferring muscarinic agonist that has demonstrated antipsychotic and pro-cognitive effects in both schizophrenia (Shekar, et al, 2001) and Alzheimer's disease (Bodick et al, 2007). However, its peripheral cholinergic side effects, including nausea, vomiting and diarrhea, have prevented its continued clinical development. A previous Phase I

clinical trial demonstrated that the addition of trospium, a peripheral cholinergic receptor antagonist that does not cross the blood brain barrier, to xanomeline substantially improved its tolerability by reducing peripheral cholinergic side effects (nausea, vomiting, diarrhea, excess sweating and salivation). We now report the results of a Phase 1, multi-dose safety study aimed at optimizing the combination of xanomeline with trospium using a new BID co-formulation.

Methods: 69 healthy volunteers participated in the phase 1 multiple ascending dose (MAD) study of KarXT. Objectives included: assessing the PK characteristics of the new proprietary BID co-formulation (and comparing results to the two components given separately) and to explore the tolerability of higher doses of both xanomeline and trospium respectively. The study design was comprised of a 2-day titration period of either placebo or a KarXT dose of 50 mg xanomeline + 20 mg trospium followed by a 5-day treatment period. The doses (all BID) assessed were: xanomeline 100 mg, 125 mg and 150 mg in combination with trospium 20 mg or 40 mg. For comparing cohorts, tolerability assessment was focused on the pre-specified cholinergic adverse events of nausea, vomiting, diarrhea, excessive sweating and salivation; Safety and tolerability were also assessed using spontaneous reports of adverse events, labs, vital signs, Bristol stool scale, pupillometry and saliva volume.

Results: The 2-day titration of 50/20 was well tolerated in all cohorts. Doses of 100 and 125 BID of xanomeline were also well tolerated when paired with 20 mg and 40 mg BID of trospium, respectively. Across the cohorts, cholinergic adverse events were correlated with xanomeline dose. Increasing trospium dose ameliorated cholinergic events, and lead to the observance of some anticholinergic adverse events as cohorts tested on 40 mg trospium BID reported some signs of anticholinergic effects (i.e., dry mouth), particularly in the cohort receiving 125 mg BID of xanomeline. The total number of subjects reporting cholinergic adverse events (ChAEs) in cohorts on xanomeline of 100 mg (39%) or 125 mg (33%) was similar to that seen in the KarXT arms in the previous KAR-001 study (34%). Most ChAEs occurred within the first few days of starting or increasing the study drug. The majority of these TEAEs at 100 mg and 125 mg xanomeline-dose levels were mild and transient in nature, with only a few adverse event reports lasting more than 3 h in the 100/20 mg cohort.

None of the cohorts showed meaningful changes in orthostatic heart rate or obvious differences in BP between placebo and KarXT compared to placebo. All cohorts receiving KarXT showed placebo-adjusted increases in mean resting HR in subjects, consistent with past studies with xanomeline where short-term increases in resting heart rate were observed that normalized to baseline over time. Both trospium and xanomeline exposures (AUCs) and variability were comparable to KAR-001 where the compounds were given using separate formulations.

Conclusions: The new KarXT co-formulation performed well in humans and will be carried forward in future studies with KarXT. A range of combination doses was identified for further investigation and xanomeline-doses equivalent to, and higher, that what demonstrated efficacy in previous xanomeline clinical studies will be carried forward into a planned Phase II study in schizophrenia. Longer terms studies will provide further data around the safety and tolerability of KarXT. Importantly, the tolerability observed in this healthy volunteer study may not be representative of schizophrenia patients, who tolerate currently marketed antipsychotic medicine better than healthy volunteers. No new safety signals were reported in the present study. The timing and duration of AEs were related to peak drug levels (Cmax) and suggest that there is a potential for increased tolerability over time. In addition, all AEs rapidly ameliorated to baseline levels upon dosing discontinuation. Consistent with our previous studies, KarXT is substantially better tolerated than xanomeline alone.

Keywords: Short-Term Clinical Studies, Schizophrenia Novel Treatment, Muscarinic Acetylcholine Receptor, Advantages of The Combination Of Therapies

Disclosure: Karuna Pharmaceuticals, Employee

M184. Maintenance of Long-Term Clinical Stability in Patients With Schizophrenia Converted From Oral Antipsychotic Medications to Monthly Extended-Release Risperidone (RBP-7000)

James Graham, John Csernansky, Maurizio Fava, John Newcomer, Anne Andorn, Sunita Shinde, Gilbert Muma, Christian Heidbreder*

Indivior Inc., Richmond, Virginia, United States

Background: RBP-7000 (risperidone in ATRIGEL® Delivery System) is a once-monthly, extended-release depot formulation recently approved for the treatment of schizophrenia in adults. RBP-7000 delivers clinically relevant plasma levels of risperidone on the first day of use without requiring loading or supplemental dosing. The efficacy, safety and tolerability of RBP-7000 were established in an 8-week, double-blind, placebo-controlled trial (NCT02109562) conducted in adults with acute exacerbation of schizophrenia. Maintenance of clinical stability was examined in the open-label study reported here.

Methods: This 52-week, Phase III, open-label study (NCT02203838) included completers ("rollovers") from the previously conducted 8-week double-blind study, as well as de novo patients with a DSM-IV-TR diagnosis of schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total score ≤70. Rollover patients—those who had received 2 injections of placebo or RBP-7000 (90 mg or 120 mg) in the double-blind study—received 11 additional injections of RBP-7000 120 mg in the current study. De novo patients, who were required to be on oral antipsychotic treatment prior to enrollment, received up to 13 injections of RBP-7000 120 mg after titration or conversion to oral risperidone (3 or 4 mg/day). Mean changes from Baseline to end of study in PANSS total score, PANSS Positive, Negative, and General Pathology subscale scores, and Clinical Global Impression-Severity of Illness (CGI-S) score were summarized descriptively. No statistical testing was performed for this open-label study. As the primary objective of this study was long-term safety (results reported elsewhere), all analyses of clinical outcome data (secondary objective) were conducted using the safety population, defined as all those who received ≥1 dose of open-label RBP-7000 120 mg.

Results: Of 500 patients in the safety population (rollover, n=92; de novo, n=408), a total of 234 (46.8%) completed the study. Most patients were male (67.8%) and black/African-American (70.8%), with a mean age of 45.1 years. De novo patients were stable at enrollment [mean (SD) PANSS total score = 58 (8.3)] and remained stable throughout the study [mean (SD) change from Baseline to end of study = -0.4 (8.7)]. Rollover patients continued to show improvement in PANSS total score for the duration of the trial (baseline to end of treatment): placebo, -20.2 (15.6); RBP-7000 90 mg, -12.5 (15.5); RBP-7000 120 mg, -10.9 (13.2). PANSS subscale scores generally remained stable throughout the study among de novo patients, with mean (SD) changes from Baseline of -1.3 (3.3) for PANSS Positive Scale, 1.3 (3.6) for PANSS Negative Scale and -0.4 (5.0) for PANSS General Psychopathology Scale. CGI-S scores remained stable throughout the study for both rollover and de novo patients. Decreases in each PANSS subscale scores were observed in each rollover group, including those who had received placebo in the double-blind study: mean (SD) changes from Baseline on the PANSS Positive Scale score were -7.8 (5.5), -3.7 (4.1) and -3.7 (3.5) among those

previously treated with placebo, RBP-7000 90 mg or RBP-7000 120 mg, respectively. For the PANSS Negative Scale score, mean (SD) changes from Baseline were -4.0 (5.9), -4.1 (4.6) and -0.9 (3.8) for placebo, RBP-7000 90 mg and RBP-7000 120 mg, respectively. For the PANSS General Psychopathology Scale score, mean (SD) changes from Baseline were -8.3 (7.0), -4.7 (9.0) and -6.4 (7.9) for those previously treated with placebo, RBP-7000 90 mg or RBP-7000 120 mg, respectively.

Conclusions: In de novo patients, efficacy measures remained stable over 12 months of treatment once treatment with RBP-7000 120 mg was initiated. Additionally, rollover patients from the double-blind study continued to improve over the course of this long-term open-label study. While pre-study antipsychotic medications and dose equivalents varied among the de novo patients included in this study, the results strongly suggest that RBP-7000 120 mg is associated with maintenance of clinical stability.

Keywords: Antipsychotic, Schizophrenia, Extended-Release Depot, Clinical Stability, Positive and Negative Syndrome Scale

Disclosure: Indivior, Employee

M185. Effects of Roluperidone on Two Dimension of the Negative Symptoms Factor Score: Reduced Emotional Experience and Expression

Philip Harvey, Jay Saoud, Michael Davidson, Remy Luthringer*

Miller School of Medicine, University of Miami, Miami, Florida, United States

Background: Everyday functioning is impaired in people with schizophrenia, with these impairments spanning domains of vocational, social, and everyday activities. Recent research has suggested that negative symptoms (NS) can be considered in terms of two different dimensions: diminished expression (expressive deficit) and reduced experience (experiential deficit). Expression includes displays of facial affect (referred to as blunted affect), reduced vocal inflection, and reduced vocal output. Experience includes the motivation to engage in potentially pleasurable activities and the subjective experience of enjoyment when engaging in reinforcing activities. Reduced experience has also been referred to as reflecting avolition and apathy, as a descriptor of the observable consequences of deficits in experience.

Roluperidone, a compound with high affinities for 5 HT2A and sigma2 receptors, has previously shown superiority over placebo on improving NS in prospectively designed study in patients with schizophrenia. The objective here is to explore the effect of roluperidone compared to placebo, on the 2 domains of the Negative Symptoms Factor Score (NSFS): Reduced Experience and Expression in patients with stable symptoms of schizophrenia.

Methods: This was a multi-national Phase 2b trial that enrolled 244 patients diagnosed with schizophrenia who were symptomatically stable for ≥ 3 months prior to entering the trial and had baseline scores ≥ 20 on the NS subscale of the PANSS. Patients were randomized to daily monotherapy with roluperidone 32 mg, roluperidone 64 mg, or placebo in a 1:1:1 ratio. The primary endpoint was the PANSS negative symptom score based on the 5-factors (pentagonal) model. The Mixed-Effect Model Repeated Measure (MMRM) was used for analyzing the 2 domains of NSFS.

Results: All enrolled patients (N=244) were Caucasian, and 137 (56%) were male. Median age was 41 years and range from 18 to 60. The 3 treatment groups were balanced on all demographic and illness-related baseline characteristics. Completion rates for randomized patients in this 12-week study were as follows: roluperidone 62 mg = 69%, roluperidone 32 mg = 69% and placebo = 65%.

The NSFS mean scores at baseline were 25.0 ± 3.98 for the placebo group, and 25.2 ± 4.00 for the 2 roluperidone groups. Both doses of roluperidone were superior to placebo on both domains: Experience ($p \leq 0.006$ for the 32 mg; $p \leq 0.001$ for the 64 mg) with persistent significant superiority beginning at Week 2 for the 64 mg dose and at Week 8 for the 32 mg dose. Expression ($p \leq 0.003$ for the 32 mg; $p \leq 0.001$ for the 64 mg) with similar persistent significant superiority.

Conclusions: While both doses of roluperidone improved negative symptoms and showed good tolerability in stable schizophrenia patients, the post hoc analysis reported here found the drug to work on all aspects of negative symptoms as quantified by the PANSS in general, as well as the reduced emotional experience and reduced emotional expression subscales recently empirically derived from the PANSS.

Keywords: Negative, Symptoms, Expression, Experience, Schizophrenia

Disclosure: Minerva Neurosciences, Employee

M186. Reduction in Peripheral C-Reactive Protein Levels With Canakinumab Administration is Related to Reduced Positive Symptom Severity in Patients With Schizophrenia and Inflammation

Thomas Weickert, Cynthia Shannon Weickert*

University of New South Wales, Randwick, Australia

Background: Schizophrenia is characterized by positive and negative symptoms and cognitive impairments that are related to functional disability. All present approved treatments targeting small molecule neurotransmitter receptors are limited in their effectiveness and leave many patients with residual symptoms and debilitating side effects. Psychotic symptoms, cognitive impairment, and treatment response are variable in schizophrenia, highlighting heterogeneity in the etiology and presentation of the illness. Thus, there is a critical need for novel treatments targeting subgroups related to underlying biology that can be identified by biomarkers. We have shown that a substantial subgroup (approximately 40%) of people with schizophrenia can be distinguished by inflammation in both peripheral blood and in brain, e.g., the cytokine interleukin 1-beta (IL-1β) is elevated in schizophrenia. IL-1β mRNA and protein levels are significantly increased in serum, plasma, white blood cells, cerebrospinal fluid and brain tissue in chronically ill patients with schizophrenia and in first episode psychosis. Inhibition of excessive immune response is possible by interrupting the cascade of cytokine responses which can be achieved by administering canakinumab: an approved human anti-interleukin 1β monoclonal antibody that interferes with the bioactivity of IL-1β. For the approved indications, canakinumab is effective for up to 4 to 8 weeks following a single injection. However, the extent to which adjunctive IL-1β blockade by canakinumab can reduce peripheral markers of an overactive immune system (e.g., high sensitivity C-reactive protein: hsCRP) and bring about amelioration of psychotic symptoms in schizophrenia is unknown.

Methods: We conducted a randomized, placebo-controlled, double-blind, parallel group trial of the monoclonal antibody canakinumab to block IL-1β in schizophrenia. Twenty-seven chronically ill patients with schizophrenia or schizoaffective disorder who had elevated peripheral inflammation markers (IL-1β, IL-6, hsCRP and/or neutrophil to lymphocyte ratio) were randomized to a one-time subcutaneous injection of canakinumab (150 mg) or placebo (normal saline) as an adjunctive treatment to their usual antipsychotic. Peripheral hsCRP levels were measured at baseline (prior to injection) and at 1, 4 and 8 weeks after a

single injection of canakinumab or placebo. Positive and Negative Syndrome Scale scores were assessed at baseline and at 4 and 8 weeks after injection of canakinumab or placebo.

Results: Separate t-tests comparing canakinumab or placebo treatments at weeks 1, 4, and 8 to baseline showed significant reductions in peripheral hsCRP levels at all time points (all p's < .02) in the canakinumab treatment group only. There were no significant changes in hsCRP levels in the placebo group. Based on separate t-tests, we also found a significant reduction in positive symptom severity scores at week 8 ($p = 0.05$) in the canakinumab group and at week 4 ($p = 0.02$) in the placebo group. There was a trend for low peripheral hsCRP levels to be strongly correlated with low positive symptom severity scores ($r = .57$, $p = .07$) only at week 8 in the canakinumab treatment group only. There were no significant reductions in negative or general psychopathology symptom severity scores in either canakinumab treatment or placebo groups. Given that canakinumab was administered via subcutaneous injection, all participants were compliant and the dropout rate (at only 7%), was low.

Conclusions: Preliminary results from our clinical trial suggest that blockade of the cytokine IL-1β by the monoclonal antibody canakinumab can significantly reduce peripheral hsCRP serum levels and that these reductions may be related to a reduction in positive symptom severity in chronically ill patients with schizophrenia who received adjunctive canakinumab. It is important to note that the groups were selected such that only those patients who initially display elevated peripheral markers of inflammation were recruited. The effects of canakinumab on the reduction of peripheral hsCRP would potentially be of benefit to general health in schizophrenia. The relatively strong relationship between the effects of canakinumab on the biological marker hsCRP and positive symptom severity after 8 weeks of treatment supports the effect of canakinumab on positive symptom severity. Given that treatment with a monoclonal antibody is a novel and substantial advance in the potential treatment of psychotic symptom severity in schizophrenia, future studies should consider increased and/or top-up doses with longer follow up assessments to confirm the benefit of adjunctive canakinumab treatment in schizophrenia.

Keywords: Schizophrenia Novel Treatment, Positive Symptom Factor, Antibody, Inflammation, IL-1b

Disclosure: Nothing to disclose.

M187. Replicated Associations Between Common Variants and Neurocognitive Functioning in Adult- And Childhood-Onset Schizophrenia

*Tim Bigdeli, Keith H. Nuechterlein, Catherine Sugar, Kenneth L. Subotnik, Thomas Kubarych, Michael Neale, Kenneth Kendler, Robert Asarnow**

UCLA, Los Angeles, California, United States

Background: The aggregation of neurocognitive deficits among both the non-psychotic first-degree relatives of adult- and childhood-onset schizophrenia patients suggests that there may be a common etiology for these deficits in childhood- and adult-onset illness. Our comprehensive assessment of a wide range of neurocognitive domains in adult- and childhood-onset schizophrenia families yielded comparable estimates of familial transmission for some dimensions, as well as preliminary evidence of partially divergent multifactorial architectures for attention, working memory, and verbal learning. However, whether specific genetic factors influencing these neurocognitive domains have comparable effect sizes in adult- and child-onset schizophrenia is not known.

Methods: The Consortium on the Genetics of Schizophrenia (COGS) single nucleotide polymorphism (SNP) chip includes 1,536 common variants and provides excellent coverage of 94 functionally relevant genes including AKT1, CHRNA7, COMT, DAO, DAOA, DISC1, DTNBP1, ERBB4, GRM3, GSK3B, NOS1AP, NRG1, PAFAH1B1, PPP3CC, PRODH, RELN, and RGS4. Using the COGS custom array, we genotyped probands and relatives from the UCLA Family Study (N=458), including N=109 from 39 childhood-onset schizophrenia families, N=148 from 67 adult-onset schizophrenia families, and N=201 from 66 age-matched community control pedigrees. We used the variance-component association module of MERLIN (v1.1.2) to test for association between SNPs and empirically derived composite scores representing attention, working memory, verbal learning, verbal retention, and memory for faces.

Results: We attempted replication of selected genotype-phenotype associations based on analogous neurocognitive assessments reported by Greenwood et al. (2011) and established an experiment-wide multiple-testing threshold based on 15 a priori hypotheses (P<10e-3). We successfully replicated associations between the verbal learning factor and GRIN2B and NRG1 in adult- and childhood-onset schizophrenia, respectively; and replicate an association between working memory and GRID2 in both adult- and childhood-onset schizophrenia. Associations between variants in ERBB4 and verbal learning were successfully replicated in our analysis of childhood-onset schizophrenia but fell short of our experiment-wide significance threshold in the adult-onset analysis (P<0.001). Comparing observed directions of allelic effects for significant gene-trait associations from Greenwood et al., we observed the greatest degree of consistency with adult-onset schizophrenia findings for the verbal learning factor (P=0.0195). Comparing association results for childhood- and adult-onset schizophrenia, we observed an excess of same-direction effects for the verbal learning factor (P<0.01).

Conclusions: We successfully replicate several previously reported associations between neurocognitive performance and biologically relevant loci in adult- and childhood-onset schizophrenia. While diverging evidence of replication in adult- and childhood-onset analyses may reflect limited statistical power to detect associations, the observed pattern of findings may also reflect their partially divergent multifactorial architectures.

Keywords: Childhood-Onset Schizophrenia, Genetic Association Study, Neurocognitive Functioning, First Episode Schizophrenia

Disclosure: Nothing to disclose.

M188. Abnormal Effective Connectivity During Eye Gaze Processing in Schizophrenia

Open Board.

M189. Engagement of the Temporo-Parietal Junction and Posterior Superior Temporal Sulcus (TPJ-PSTS) by Naturalistic Stimuli in Individuals at High-Risk for Developing Schizophrenia

Gaurav Patel, Nahian Chowdhury, Juan Sanchez-Peña, Cheryl Corcoran, Daniel Javitt*

Columbia University, New York, New York, United States

Background: Deficits in social functioning are a major cause of psychosocial disability in schizophrenia patients (SzP). Many of the brain networks involved in social functioning have nodes in the temporoparietal junction and posterior superior temporal sulcus (TPJ-pSTS), which may act as an integrative hub for the cognitive

processes underlying social functioning. This region has previously been shown to only be engaged by naturalistic stimuli requiring integration of information over long time-scales (>30 seconds). This integration in the TPJ-pSTS has recently been shown by Lerner et al. 2018 to be disrupted in patients with first episode schizophrenia. It remains unclear, however, whether this disruption is the result of the development of schizophrenia or precedes its onset.

To answer this question, we examined the engagement of TPJ-pSTS and other cortical areas by a naturalistic auditory stimulus in individuals at high risk for developing schizophrenia (CHR) compared to a sample of healthy controls (HC) and chronic schizophrenia patients (SzP). CHRs in our sample are individuals who already have some positive symptoms and meet criteria for Attenuated Positive Symptom Syndrome (APSS). Subjects listened to a 7-minute radio story ("Pieman", adapated from Lerner et al. 2011) while BOLD-fMRI data was collected. They also listened to scrambled versions of this story, scrambled by paragraph, sentence, and word. We then compared the intersubject correlation (ISC) of these areas between the three populations.

We predicted that, like the first-episode patients, the SzP in our sample would demonstrate integration deficits in the TPJ-pSTS as compared to the HC. For CHRs, we predicted that the ISC for these areas would be between that of HCs and SzPs.

Methods: 12 CHRs, 19 SzPs, and 16 HC performed the Pieman task while BOLD-fMRI data were collected. CHR patients met criteria for attenuated positive symptom syndrome (APSS, >=1 positive symptom >= 1×/week in the past month) with worsening of positive symptoms ≥1 pt in the past year as rated by the SIPS/SOPS. SzPs met DSM-IV criteria for schizophrenia or schizoaffective disorder. HCs were age matched to the SzPs and CHRs and did not meet criteria for any major DSM-IV Axis 1 disorders. Subjects lay in the NYSPI 3.0 T GE MR750 MRI while listening to the Pieman stimuli through noise insulated headphones; subjects were simply instructed to passively listen to the story. A separate BOLD run of about 7.5 minutes was collected for each stimulus. BOLD-fMRI data were collected with a Human Connectome Project (HCP) compatible functional sequence: a multi-band fMRI sequence with a TR=850 ms and a spatial resolution of 2 mm isotropic and were processed with the HCP processing pipelines. Additional processing was performed to remove spurious artifacts related to movement and other sources, including global signal regression and censoring of high movement frames with a framewise displacement >.2 mm. Parcels from Gordon et al. 2014 were used to parcellate the time-series data from each subject. ISC was then calculated for each parcel by correlating the timecourse of activity evoked by the Pieman stimuli to the average of all of the HCs for each parcel. HCs were correlated to a leave-one-out average of all other HCs. These individual ISC maps were then used to calculate the significance of ISC for each group and for the pairwise comparison of each group.

Results: As expected, HCs demonstrated significant ISC of TPJ-pSTS, mid and anterior STS, and auditory cortex in both hemispheres ($p<.0001$). In addition, anterior medial prefrontal default mode areas in both hemispheres also demonstrated significant ISC. Also, as expected, SzPs demonstrated significantly decreased ISC of posterior TPJ parcels corresponding to the default mode network as well as a number of STS areas in both hemispheres, along with anterior medial prefrontal default mode areas ($p<.05$). CHRs, however, largely resembled the ISC pattern of HCs as opposed to SzPs, with significantly stronger ISC in TPJ-pSTS, mid/anterior STS, and dorsomedial prefrontal cortex compared to SzP. Only anterior-medial prefrontal cortex demonstrated any significantly decreased ISC in CHRs vs. HCs ($p<.05$).

Conclusions: In the present study, we have found that engagement of the TPJ-pSTS and other cortical areas by a naturalistic stimulus is largely similar in CHRs vs. HCs, even though this sample of CHRs has already begun to experience some positive symptoms. This suggests that the onset of schizophrenia causes some degeneration of the integrative functions in the TPJ-pSTS and other cortical areas. Our findings not only demonstrate the utility of using naturalistic stimuli to study psychiatric disorders, but also helps to establish a timeline for the cortical changes that accompany the onset of schizophrenia.

Keywords: Language, Functional MRI (fMRI), Default Mode Network (DMN)

Disclosure: Pfizer Inc, Employee

M190. Translational Studies of Neuroscience-Informed Cognitive Training in Schizophrenia

Rogerio Panizzutti, Gerson Guercio, Linda Scoriels, Melissa Fisher, Sophia Vinogradov*

Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Background: Cognitive impairments are related to deficits in primary auditory and visual sensory processes in schizophrenia. These impairments can be remediated by neuroscience-informed computerized cognitive trainings that target auditory and visual processes. However, it is not clear which modality results in more transfer of benefits to non-trained tasks and clinical outcomes. In this study, we investigated the impact of training auditory or visual cognitive processes in parallel experiments with schizophrenia subjects and mice model of schizophrenia.

Methods: Seventy-nine schizophrenia participants were randomly assigned to either 40 h of auditory or visual computerized training. Auditory and visual exercises were chosen to be dynamically equivalent and difficulties increased progressively during the training.

Results: Participants who received the visual training showed significant improvements in global cognition compared to the auditory training group. The visual training significantly improved attention and reasoning and problem-solving, while the auditory training improved reasoning and problem-solving only. Schizophrenia symptoms improved after training in both groups, whereas quality of life remained unchanged. Interestingly, there was a correlation between attention and schizophrenia symptoms improvements for the visual training group. In mice, auditory training induced improvements in the pre-pulse inhibition of the startle response.

Conclusions: We conclude that the visual training and the auditory training are differentially efficient at remediating cognitive deficits and symptoms of clinically stable schizophrenia patients. Cognitive training can also induce transfer of benefits to untrained tasks in an animal model of schizophrenia.

Keywords: Cognition, Schizophrenia Novel Treatment, Computerized Cognitive Training

Disclosure: NeuroForma, Stock / Equity

M191. Emotion Identification Bias in Youths With Psychosis-Spectrum Symptoms From the Philadelphia Neurodevelopmental Cohort

Sunny Tang, Lauren White, Tyler Moore, Ran Barzilay, Monica Calkins, Raquel Gur, Ruben Gur*

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Individuals with psychosis-spectrum (PS) disorders and clinical risk are more likely to exhibit an attribution style that is biased toward perceiving hostility and external causality. Biased attribution style in PS is associated with increased persecutory

ideations and impaired functioning. We examine whether PS youths over-identified threat-related emotions in an emotion recognition task compared to non-PS youths.

Methods: The Philadelphia Neurodevelopmental Cohort is a large non-clinical sample including 9,292 youths aged 8 – 21 years who underwent structured evaluation of psychiatric symptoms and a computerized neurocognitive battery (CNB). The CNB includes the Penn Emotion Identification Task (ER40) where participants are asked to identify the emotion corresponding to 40 faces (angry, fearful, happy, sad, or neutral). Accuracy, speed, and efficiency (combination of accuracy and speed) were collected. A bias score for misidentifying faces as being threat-related (angry or fearful) was calculated in contrast with bias toward non-threat-related emotions (happy, sad, neutral). Scores were standardized and adjusted for age where appropriate. Linear and logistic regressions were used.

Results: PS youths were less accurate for threat ($p = 0.003$, Std β Coef = -0.01), nonthreat ($p < 0.001$, Std β Coef = -0.29) and overall items ($p < 0.001$, Std β Coef = 0.05) when covarying for sex and socioeconomic status. There were no sex by threat or nonthreat accuracy interactions. Accounting for overall poorer performance, efficiency in identifying non-threat items was more impaired in PS ($p = 0.007$, Std β Coef = -0.01), but efficiency in identifying threat items was preserved ($p = 0.37$, Std β Coef = 0.004). Accounting for overall accuracy, PS youths were also more likely to score correctly for angry faces ($p = 0.04$, Std β Coef = 0.009); this was also true when comparing accuracy on angry faces to a dimensional measurement of psychosis severity ($p = 0.02$, Std β Coef = 0.02). Increased threat bias ($p < 0.001$, β Coef = 1.8 ×10-4) but not bias toward non-threat emotions ($p = 0.12$, β Coef = -8.5 ×10-5) was correlated with older age; both were correlated with male sex, and not related to race or socioeconomic status. Greater overall cognitive impairment ($p < 0.001$, Std β Coef = 0.009) and use of an illicit substance ($p = 0.02$, Std β Coef = 0.009) were correlated specifically with greater threat bias and were not related to bias toward non-threat emotions.

Conclusions: Youths with PS symptoms perform worse on both threat and nonthreat emotion items. When accounting for overall differences in performance, threat-related emotion identification is relatively preserved in PS. Threat bias is correlated with older age, male sex, poorer overall cognitive performance and substance use. Effect sizes are generally small. Future directions include replication in a sample with more severe psychosis spectrum pathology and specifically in young people who endorse threshold and subthreshold persecutory ideations.

Keywords: Clinical High-Risk State for Psychosis, Social Cognition, Facial Emotion Processing, Early Illness Schizophrenia, Threat Faces

Disclosure: Nothing to disclose.

M192. White Matter Integrity and Verbal Memory Performance in Schizophrenia Compared to Healthy Controls: Differences Between Episodic Memory and Working Memory

Leticia Czepielewski, Clarissa Gama*

Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Background: Cognitive impairments are core symptoms in schizophrenia. Among them, memory deficits seem to be strongly related to several outcomes, such as psychosocial functioning and accelerated aging. Nevertheless, the neurobiological mechanisms associated with memory dysfunction are still unclear. One hypothesis would be related to white matter microstructural abnormalities, since neuronal connectivity underlies cognitive processing. More specifically, uncinate fasciculus, cingulum cingulate and angular bundles, and superior longitudinal fasciculus-temporal terminations seem to be relevant to memory performance. They connect the medial temporal lobe to other cortical regions and the cingulate to the prefrontal cortex. Therefore, we aimed to study the relationship between white matter integrity in relevant tracts using diffusion tensor imaging (DTI) and episodic memory and working memory in individuals with schizophrenia (SZ) compared to healthy controls (HC).

Methods: This was a cross-sectional study. We included 100 participants, 43 individuals with SZ that were medicated according to guidelines and stable for at least 6 months, and 57 unaffected individuals. All participants were informed about study procedures and signed consent before assessment. Research protocol was conducted in accordance with the Helsinki Declaration. The Institutional Review Board approved the study protocol. Participants underwent cognitive assessment with Hopkins Verbal Learning Test for episodic memory and Letter-Number Sequencing subtest from WAIS-III for working memory. Diffusion tensor imaging was performed on a Philips Achieva 1.5 T scanner. We performed linear regression models separately for patients and controls with the sum of left and right fractional anisotropy (FA) of the abovementioned relevant tracts predicting memory performance, controlling for age, sex, and years of education.

Results: Individuals with SZ had worse episodic and working memory performances compared to HC ($t(96) = 7.088$, $p < .001$ and $t(97) = 4.614$, $p < .001$, respectively), however groups did not show differences among FA of white matter tracts ($p > .05$). Episodic memory was not significantly predicted by uncinate fasciculus, cingulum-cingulate bundle, cingulum-angular bundle, and superior longitudinal fasciculus-temporal terminations FAs in both HC and SZ. Working memory was not significantly predicted by uncinate fasciculus, cingulum-cingulate bundle, and superior longitudinal fasciculus-temporal terminations FAs. However, cingulum-angular bundle showed a significant main effect predicting working memory in SZ ($t = 2.303$, $p = .027$, Beta = .307; model: $F = 5.209$, $p = 0.002$, R2Adj = .286), but not in HC ($t = .383$, $p = .704$, Beta = .046; model: $F = 7.369$, $p < .001$, R2Adj = .329).

Conclusions: Decreased white matter integrity in cingulum-angular bundle, which are fibers that connect frontal, parietal and temporal lobes, was related to worse working memory performance in schizophrenia. This highlights the importance of neuronal connectivity abnormalities to higher-order cognitive processes in psychosis. The cingulum microstructure is described as being related to cognitive control and executive function, and thus could be a focus for new therapeutic strategies focusing on cognitive symptoms.

Keywords: Verbal Episodic Memory, Working Memory, Diffusion Tensor Imaging (DTI)

Disclosure: Nothing to disclose.

M193. Integrated EEG-fMRI Analysis of Reward Processing During Slot Machine Play in Schizophrenia

Susanna Fryer, Brian Roach, Judith Ford, Michael Jacob, Daniel Mathalon*

University of California, San Francisco, San Francisco, California, United States

Background: Negative symptoms of schizophrenia, such as anhedonia and amotivation, signal an absence of typical hedonic and motivational outputs, and may reflect underlying alterations in the way the brain processes rewarding stimuli. The goal of this study was to directly combine neuroimaging modalities to enable a more comprehensive assessment of spatial (fMRI) and temporal

(EEG) features of reward-related brain responses to help characterize reward processing dysfunctions in schizophrenia.

Methods: EEG and fMRI were recorded in separate sessions while participants (patients with schizophrenia (SZ)=50; healthy controls (HC) = 45) completed the same slot machine gambling task. The reward positivity (RewP), an event-related potential reflecting reward outcome evaluation, was measured from the EEG data by creating a difference wave of wins – losses from a time window established in the literature by prior meta-analysis (Sambrook and Goslin, 2015). Reward-related spatial activations contrasting brain responses to wins vs. losses were modeled using standard voxelwise parametric methods. Next, these EEG and fMRI signals of interest were entered into a Joint Independent Components Analysis (jICA) to establish how task-specific temporal patterns in EEG related to spatial fMRI activation patterns, and to interrogate group differences in the relationship between these electrophysiological and hemodynamic reward-related signals.

Results: RewP (gain – loss) event-related potentials and fMRI activations to rewards vs. losses were equivalent across SZ and HC groups. Joint analysis revealed two components of interest showing distinct patterns of association between EEG and fMRI signals. First, a component that reflected the temporal signature of the RewP in the EEG domain (peaking between 250-300 ms) showed strong, but equivalent, covariation in both groups with fMRI activations from regions including bilateral anterior cingulate, insula, and distributed visual cortex. Second, a later evaluative component (peaking ~400 ms) distinguished the groups, with patients showing significantly weaker co-activation, relative to HCs, who showed strong, positive covariance with activations in regions including bilateral brodmann area 39, and left brodmann areas 6 and 40 (p=.03).

Conclusions: These data suggest that even in the context of our slot machine paradigm, which intentionally placed minimal demands on decision making and response planning, early reward evaluation signals appear preserved in schizophrenia, but abnormalities emerge at later stages of reward evaluation that likely reflect more extensive and/or higher-order processing of reward outcome information.

Keywords: Prediction Error, Early Illness Schizophrenia, Fronto-medial Negativity, Theta

Disclosure: Nothing to disclose.

M194. Spite Sensitivity and Persecutory Ideation in a Transdiagnostic Sample of Patients: An fMRI Study of Social Decision-Making Under Uncertainty

Angus MacDonald, Rebecca Kazinka, Danielle Pratt, Anita Kwashie, Saaraa Ameri, Krista Wisner, Sylia Wilson*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Persecutory ideation is a psychiatric symptom with devastating consequences. Recently, the neural mechanisms underlying persecutory ideation have been examined using decision-making tasks amenable to neuroimaging, such as the Minnesota Trust Game, that make it possible to distinguish between rational concerns about others' selfishness versus concerns about others' spitefulness. To evaluate the relationship between persecutory ideation and suspicious decision-making, we examined decision-making during fMRI in a sample of patients recruited for early-episode psychosis.

Methods: To date, the two-player social decision-making task, Minnesota Trust Game (MTG), has been completed by a transdiagnostic sample of patients (N=28) during fMRI at 3 T. By varying financial risk and the partners' temptation to defect, MTG provides a psychometric function that differentiates suspiciousness (fear of a partner being spiteful when the partner would lose from defection) from rational mistrust (fear of a partner being selfish because the partner gains from defection). We examined persecutory ideation symptoms, trusting behaviors and brain activation in cognitive control, mentalizing and reward networks.

Results: Individuals who reported more persecutory ideation tended to be less trusting in the suspiciousness condition, but not the rational mistrust condition. The manipulation of financial risk by partner's temptation to defect was associated with differential activity in the lateral orbitofrontal cortex (OFC) and nucleus accumbens (NAcc). Bilaterally, greater OFC activity was associated with increasing risk in the suspiciousness condition. This pattern was also observed in the medial frontal cortex (anterior default mode network, or DMN) and posterior cingulate (posterior DMN). Greater NAcc activity was associated with decreased risk, but only in the rational mistrust condition. Patients reporting more persecutory ideation showed less activity in posterior DMN as risk increased (r=-0.40, p≤.04).

Conclusions: Using a novel paradigm in a transdiagnostic sample, we demonstrated the utility of studying spite sensitivity to advance neuroscientific understanding of persecutory ideation. We replicated previous behavioral findings using this task and have found a similar set of regions sensitive to interpersonal risk and reward as previously reported. While future analyses will examine the crucial hypothesis that dysfunctional synchrony between top-down executive and midline affective networks increase risk for persecutory ideation, the current findings highlight to role of mentalizing networks, such as the default mode network, in these symptoms.

Keywords: Persecutory Ideation, Early Psychosis, Reward-Based Decision-Making, Paranoia

Disclosure: Nothing to disclose.

M195. Intra-Individual Cognitive Variability in Psychosis Spectrum Disorders: Association With Structural Brain Measures

David Roalf, Raquel Gur, Andrew Crow, Ruben Gur*

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Neurocognitive deficits are a core feature of psychosis {Goldman-Rakic, 1994 #320; Andreasen, 1997 #321; Harvey, 2006 #322}, are strong predictors of functional outcome {Harvey, 2006 #322}, and are associated with alterations in brain structure {Shepherd, 2012 #287} and function {Gur, 2010 #323}. Hence, recent neurocognitive studies have focused on individuals at clinical high-risk (CHR) for developing psychosis. The profile of neurocognitive deficits in CHR largely mimics the pattern seen in psychosis {Carrion, 2015; Brewer, 2005; Brewer, 2006; Gur, 2015}, and recent evidence suggests there may be little progression of these deficits in CHR individuals after conversion to psychosis {Carrion, 2015}. As such, cognitive deficits likely confer vulnerability to developing psychosis making them a salient marker of incipient illness. Yet, the preponderance of neurocognitive research has emphasized group differences in mean neurocognitive performance. This approach largely ignores intra-individual variability (IIV) in neurocognitive performance, which likely confers unique predictive information about cognitive functioning beyond mean performance {Jensen, 1992 #318; Hultsch, 2004 #334; MacDonald, 2006 #319}

In general, IIV reflects within-person fluctuations on a trial-by-trial basis {MacDonald, 2006 #319}. The inability to maintain consistent responding across tasks is associated with difficulty in tuning cortical circuitry and in the failure to optimize signal-to-

noise in prefrontal/anterior cingulate cortex {MacDonald, 2009 #39} and distinct control networks in the brain {Fair, 2007 #432}. This disruption in communication may be associated with loss of gray matter (GM) or disorganization of white matter (WM) {MacDonald, 2006 #319}, which are typically disrupted in psychosis and in CHR. Yet, there is limited investigation of IIV in individuals at-risk for developing psychosis and associated structural brain phenotypes.

Methods: Young adults and adolescents were recruited into one of two groups: 1) Psychosis Spectrum (PS; n=32), which included clinical high-risk youth and those meeting criteria for DSM-IV psychotic disorder; and 2) Typically Developing (TD) youth who were symptom free, without an Axis II Cluster A diagnosis or a family history of psychosis (n = 28). All individual underwent neurocognitive testing the Variability Toolbox. The Variability Toolbox (see Figure 1) is a set of eight computerized tasks designed to measure variability in reaction time during neurocognitive performance (~35 minutes). This Toolbox is specially designed to index patterns of moment-to-moment inconsistency during speeded cognitive testing. The tasks include: Simple Motor Reaction Time, Attention & Working Memory (2 tasks), Simple and Complex Choice Reaction Time, Simple and Complex Processing Speed and Abstract Matching. Most individuals also underwent 3 T MRI, which include T1-weighted imaging and diffusion-weighted imaging.

Results: Overall, PS performed more poorly than TD in accuracy ($F(1,53) = 13.44$, $p < .001$, $\eta 2 = .16$) and speed ($F(1,53) = 5.93$, $p = .018$, $\eta 2 = .06$) measures. IIV was significantly higher across all tasks in PS as compared to TD. ($F(1,53) = 10.59$, $p = .002$, $\eta 2 = .21$). The largest IIV effects were found in simple reaction time and processing speed, followed by complex processing speed and reasoning. Small (Pearson rs = 0.25), but positive associations between IIV and diffusion-weighted scalar measures were also found, particularly within the corpus callosum.

Conclusions: Our work indicates that youth with psychosis spectrum symptoms exhibit subtle, but significant, abnormalities in cognitive performance variability (IIV). Preliminary associations between IIV and brain white matter organization suggest important association, particularly within the corpus callosum. Given the clinical evidence implicating abnormal neurodevelopment in the pathogenesis of schizophrenia, and the potential utility of cognitive and neuroimaging measures to predict illness vulnerability, this approach holds promise for understanding neurodevelopmental contributions to psychosis pathophysiology. These abnormalities may reflect aberrant brain development that predisposes an individual to the illness, and quantification of these features will likely enhance our ability to detect those truly at risk for developing psychosis.

Keywords: Cognition, Clinical High Risk for Psychosis, Diffusion Tensor Imaging (DTI)

Disclosure: Nothing to disclose.

M196. Interaction Between Neurological Soft Signs, Extrapyramidal MotorSymptoms and Antipsychotic Medication in Schizophrenia Spectrum Disorders

Dusan Hirjak, Stefan Fritze, Fabio Sambataro, Alina Bertolino, Cristina Topor, Katharina Kubera, Robert Christian Wolf*

The Central Institute of Mental Health, Mannheim, Germany

Background: In the last two decades, neurological soft signs (NSS) have garnered increasing attention in neuroimaging research on genuine motor abnormalities (GMA) in schizophrenia spectrum disorders (SSD). However, the majority of these studies examined patients receiving antipsychotic treatment and therefore it still remains unclear whether NSS levels might have been confounded by antipsychotics. Here, we address the question whether NSS scores are associated with extrapyramidal motor symptoms (EPMS) and antipsychotic treatment in SSD?

Methods: A comprehensive motor assessment was performed to examine NSS and EPMS by means of standardized instruments in 105 patients with SSD. Antipsychotic dose equivalence estimates were determined by the classical mean dose method (doses equivalent to 1 mg/d olanzapine). Relationships between NSS, EPMS and antipsychotic medication were determined using correlational analysis and multiple linear regression analyses.

Results: NSS and EPMS scores were not significantly associated with olanzapine equivalents. NSS were not significantly associated with other EPMS scales (p=0.003; Bonferroni-corrected for multiple comparisons). There was a significant association between NSS motor coordination and global parkinsonism (p=0.002, Bonferroni-corrected for multiple comparisons).

Conclusions: Our results support the view that NSS and the majority of EPMS are not significantly modulated by antipsychotic medication in SSD. The significant relationship between NSS and global parkinsonism supports the genuine rather than medicationdependent origin of particular motor symptoms in SSD.

Keywords: Schizophrenia, Neurological Soft Signs, EPMS, Antipsychotic Medication

Disclosure: Nothing to disclose.

M197. Brain Insulin Resistance and Altered Brain Glucose are Related to Memory Impairments in Schizophrenia

Andrea Wijtenburg, Dimitrios Kapogiannis, Stephanie Korenic, Roger Mullins, Joyce Tran, Frank Gaston, Maja Mustapic, Elliot Hong, Laura Rowland*

Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland, United States

Background: Memory impairments are among the most robust cognitive impairments observed in schizophrenia (SZ) and are related to functional outcome. Altered brain glucose (Glc) metabolism has been associated with memory dysfunction, and studies in SZ show lower Glc metabolism using PET. Glc hypometabolism in Alzheimer's disease (AD) is associated with insulin resistance (IR), which is believed to be an underlying cause of the illness. Recent work has identified biomarkers of neuronal-specific IR in the setting of AD by isolating blood exosomes of neuronal origin and measuring levels of phosphorylated insulin signaling effector molecules. Complementary to exosome IR biomarkers, measures of brain Glc levels may provide further insight into brain Glc metabolism. Currently, magnetic resonance spectroscopy (MRS) is the only non-invasive technique that does not use ionizing radiation to study cerebral Glc. In this study, we examine the relationships between biomarkers of brain IR, brain Glc levels using MRS, and memory function in SZ.

Methods: Twenty-two adults with SZ and 24 healthy controls participated in this study. Verbal and visual spatial memory were assessed using the HVLT and BVMT from the MATRICS battery. We isolated exosomes from fasting plasma samples and enriched them for neuronal origin with immunoprecipitation for neuronal cell adhesion molecule L1-CAM. We quantified insulin signaling markers Akt, pAkt (phosphorylation of the Ser473 residue), GSK3B, pGSK3□ (phosphorylation of the Ser9 residue), p70S6K and pp70S6K (phosphorylation of the Thr421/Ser424 residue). Participants were scanned on a Siemens Trio 3 T MR system (Erlangen, Germany) using a 32-channel phased array head coil housed at the CBIR. A short TE PR-STEAM sequence (TR/TE=2000/6.5 ms, 128 excitations, VOI ~ 24 cm3) was used to acquire Glc data from the

occipital cortex. Spectra were analyzed with LCModel and were corrected for the proportion of gray matter, white matter, and CSF within the voxel using in-house Matlab code. T-tests with significance set at $p<0.05$ were performed to examine group differences, and correlation analyses were performed to examine relationships between brain IR, brain Glc, and memory function.

Results: Exosome biomarkers, Akt and p70S6K, showed trends for being lower in adults with SZ compared to controls ($p = 0.097$ and $p = 0.112$, respectively). MRS Glc was higher in adults with SZ compared to HC ($p = 0.002$), and BVMT and HVLT scores were lower in adults with SZ compared to HC ($p = 0.002$ for both). Correlation analyses revealed several trend-level relationships only in adults with SZ such that MRS Glc was correlated with exosome biomarkers p70S6K ($r = -0.432$, $p = 0.095$), and pGSK3β ($r = -0.477$, $p = 0.062$), as well as with BVMT scores ($r = -0.448$, $p = 0.071$). Exosome biomarker p70S6K was correlated with HVLT ($r = 0.541$, $p = 0.017$). There were no significant relationships between exosome biomarkers, MRS Glc, and memory in HC.

Conclusions: Our results suggest that higher levels of brain Glc, reflective of poor glucose utilization, and brain IR are evident in schizophrenia. For the first time, we show that MRS Glc and brain IR biomarkers are related to each other, as well as with memory impairments in SZ. Therefore, brain IR may play a role in the pathogenesis of memory dysfunction in SZ, and treatments targeting brain IR may be useful in alleviating memory deficits in SZ.

Keywords: Schizophrenia, Brain Insulin Resistance, Magnetic Resonance Spectroscopy, Exosomes of Neuronal Origin, Memory Function

Disclosure: Nothing to disclose.

M198. Effects of Acute Olanzapine Exposure on Central Insulin-Mediated Regulation of Whole Body Fuel Selection and Feeding

Abstract not included.

M199. Clinical, Neurocognitive, and Genetic Characteristics of Youths at Familial High Risk for Psychosis

Jerome Taylor, Nana Asabere, Monica Calkins, Tyler Moore, Sunny Tang, Rose Xavier, Daniel Wolf, Laura Almasy, Ruben Gur, Raquel Gur*

Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States

Background: Youth with a first-degree relative with psychosis (FHR-P) are at increased risk for psychosis. FHR-P youth also have increased psychopathology and cognitive deficits compared to other youth. In this study, we sought to characterize clinical, neurocognitive, and genetic features of FHR-P youths in the Philadelphia Neurodevelopmental Cohort (PNC).

Methods: For 8,929 youths, ages 8-21, the PNC assessment included the Family Interview for Genetics Studies (FIGS) Screen and the FIGS Psychosis Supplement if the Screen found that first-degree relatives of the youth had symptoms that could possibly be due to psychosis. Familial high risk for psychosis (FHR-P) status was based on the FIGS done with the youth and caregiver, and we compared youths with (i.e. FHR-P) and without family histories of psychosis.

Results: Family history of psychosis was reported for 5.6% (n=500) of youths. FHR-P youths had lower global assessment of functioning scores ($p<0.001$), increased mood, psychotic, externalizing, and anxious symptoms (all $p<0.001$) and similar neurocognitive scores relative to youths without a family history of psychosis. FHR-P youths were also more likely to be African-American, Hispanic, live in lower SES neighborhoods, and have trauma experiences (all $p<0.001$); however, functioning and clinical differences persisted after adjusting for these factors. Similar impairments were seen in FHR-P youths, whether the reported family history was a schizophrenia spectrum disorder, psychosis due to substance abuse or medical causes, or psychotic symptoms without a clear etiology. In a subsample of Caucasians (n=4,433), FHR-P youth had higher polygenic risk scores for schizophrenia (PRS) ($p=0.02$), and FHR-P status predicted psychopathology and functioning in youths even after adjusting for PRS.

Conclusions: Self- and caregiver-reported family history of psychotic symptoms is an important risk factor for greater psychopathology and poorer functioning. We also found that FHR-P youths tended to live in more adverse environments and had increased genetic loading for psychosis, but these did not fully account for the clinical impairment. Given that FHR-P youth have increased risk for developing psychiatric disorders, future research should study FHR-P youth longitudinally to identify mechanisms by which familial psychosis impacts outcome and characterize both risk and resiliency factors for developing severe mental illness.

Keywords: Polygenetic Risk Score, Children and Adolescents, Psychosis Risk

Disclosure: Nothing to disclose.

M200. Associations Among Prenatal History, Postnatal Brain Development, and Psychosis Risk in the Initial ABCD Data Release

*Kevin Dowling, Eren Sipahi, Gianni Petrozzino, Hamdi Eryilmaz, Ezra Susser, Joshua Roffman**

Massachusetts General Hospital, Charlestown, Massachusetts, United States

Background: Convergent evidence implicates the fetal milieu in postnatal brain development and risk for serious mental illness, but longitudinal and mechanistic studies are needed to develop tractable early interventions. The Adolescent Brain Cognitive Development (ABCD) study, a longitudinal multi-site investigation of clinical, cognitive, and brain imaging data, provides a new opportunity to relate prenatal history to risk for psychotic and other emergent symptoms in youths through MRI measures of neurodevelopment. Following the initial release of baseline data, we related obstetrical history to psychosis spectrum symptoms and cortical thickness at age 10 in the ABCD cohort.

Methods: Baseline data from n=3,785 participants (age mean/SD 10.0/0.6 years, 47% female) were included in the present analysis. We excluded 739 participants whose structural scans failed the ABCD quality control pipeline or who were missing data. Included participants were enrolled across 20 US-based sites and scanned on one of 5 3 T magnet platforms. Obstetric history questionnaires were administered to the primary caregiver. Psychotic spectrum symptoms were measured using the Prodromal Questionnaire – Brief Child version (PQ-BC) and participants were grouped according to total distress score percentile (1-50, 51-60, 61-70, 71-80, 81-90, 91-99 %ile). Covariates of interest included maternal age, planned/unplanned pregnancy, vaginal/caesarian delivery, single/multiple live births, presence of pregnancy or birth complications, birth before/after 37 weeks' gestation, and sex of child. Potential confounders also included in the model were caregiver education and income; child's age, race, and ethnicity; and presence of a parental partner and any older sibling. Ordinal regression determined whether dependent variables predicted psychosis grouping, controlling additionally for study

site. Cortical thickness measurements were derived from standardized T1 scan data; global mean thickness was the primary outcome, and for post hoc analyses, the cortex was divided into 12 bilateral parcels based on genetic correlation of surface area (Chen et al, 2012). General linear models examined the relation of dependent variables to cortical thickness, including any significant predictors of psychosis grouping from the previous ordinal regression analysis, as well as scanner type.

Results: C-section (p=.003), younger maternal age (p=.004), unplanned pregnancy (p=.008) and pregnancy complications (p=.02) independently predicted increased psychosis scores after controlling for all other covariates. Of these, only unplanned pregnancy associated with reduced global cortical thickness (p=.016); further, pregnancy planning status interacted significantly with psychosis group to influence cortical thickness (p=.032), with strongest effects of unplanned pregnancy on reduced thickness in the 61-70 and 81-90 %ile psychosis groups (p<.05). Post hoc testing of regions-of-interest indicated significant interactive effects of unplanned pregnancy and psychosis group on thickness in bilateral posterior/lateral and superior temporal cortex, left dorsomedial frontal cortex, left precuneus, right inferior parietal cortex, right anterior/medial temporal cortex, and right pars opercularis.

Conclusions: While echoing previous associations of obstetric complications to psychosis risk, the present results newly relate psychosis spectrum symptoms in youth to unplanned pregnancy. Further, they suggest that the well-established relationship between thinner cortex and psychosis risk may be modified by pregnancy planning status. Importantly, pregnancy planning and related maternal health decisions are complex, reflecting multiple behavioral and biological determinants, and specific mediating factors on brain development and psychosis remain to be elucidated. Other potential limitations include retrospective obstetrical history and unrecognized confounders. However, future data releases from ABCD will provide the opportunity to replicate and test longitudinal associations among the prenatal milieu, postnatal brain development, and psychosis risk.

Keywords: Early Psychosis, Cortical Thickness, ABCD Study, Pregnancy

Disclosure: Nothing to disclose.

M201. Phenome Wide Association Study (PheWAS) of Schizophrenia Risk Genes and Associated Diagnosis in Patients From the Mount Sinai Biome Database

Whitney McFadden, Laura Huckins, Andrew Chess, Eli Stahl, Marie Verbanck, Lisheng Zhou*

The Mount Sinai Hospital, New York, New York, United States

Background: Schizophrenia is a complex neuropsychiatric disorder that presents with psychosis, paranoid ideation, hallucinations, and flat affective symptoms. Large well powered Genome Wide Association Studies (GWAS) have identified over 255 genome-wide significant loci that confer associated risk for disease, however their function is poorly understood. In addition, the complexity of phenotypes is not fully captured and heterogeneity in clinical presentation can make our understanding of genetic risk and specific function of risk loci unclear.

Phenome-wide association studies (PheWAS) help us to identify unbiased genetic associations with traits and diagnoses to better understand disease mechanisms and discover variants that confer risk for multiple diseases with similar underlying genetic causes. Conversely to GWAS, which compare allele frequencies between very well defined 'cases' and 'controls', PheWAS seeks to understand the impact of a given genotype, across all phenotypes within our medical system. For example, we might ask which traits and disorders occur in individuals with a specific schizophrenia-associated genotype, or differences in expression of a schizophrenia risk gene in relevant tissues.

These analyses can identify other disorders and traits affected by schizophrenia risk variants and genes and could provide clues to their biological mechanisms and functions.

Here, we ran PheWAS on well-studied schizophrenia-associated genes and tested for disease associations in a large metropolitan biobank.

Methods: We used electronic health records (EHRs) and genotyping information from the Mount Sinai BioMe biobank. We applied "prediXcan" to impute genetically regulated gene expression (GREX) across multiple tissue types for 11,094 patients in BioMe that had genotypic and EHR records available at the time. By modeling genetically regulated gene expression in multiple tissues, we can observe relevant disease affected tissues without having to sample the tissues from patients. We separated biobank individuals into three groups, according to self-defined ancestry; European American (n=1,349), Hispanic American (n=3,083), and African American(n=2,252). We ran our PheWAS analysis separately for each population-specific group, and meta-analyzed results across groups using an inverse-variance based approach in metal.

We defined traits and disorders within our biobank according to ICD9 codes. We included only traits or disorders occurring in at least 20 individuals within our biobank. Individuals with missing data (i.e. no history of a specific diagnosis) were treated as controls. In total, we tested 1,358 ICD9 codes.

Our initial PheWAS analysis includes two sets of genes. First, 15 validation genes were used to establish consistency with previous PheWAS studies. Second, we tested five well-studied schizophrenia risk genes (FURIN, SNAP91, CLCN3, TSNARE1, CNTN4), identified in the CommonMind Consortium (CMC) post-mortem brain transcriptome analysis.

We applied two thresholds for multiple testing. First, a gene-specific threshold, correcting for all ICD9 codes tested only. Second, an experiment-wide threshold, correcting for all genes and all ICD9 codes tested.

Results: We first tested 15 genes with strong, replicating associations from PheWAS in other biobanks. In line with these previous studies, our PheWAS results revealed robust gene-endophenotype associations with diabetes, psoriasis, Crohn's and rheumatoid arthritis. CMC derived genes reveal 12 associations reaching our per-gene threshold (p<8.4e-07), including SNAP91 with hearing loss (ICD9 389 p=5.2e-5) and CLCN3 with alcoholism (ICD9 317, 317.1 p<8.2e-5). SNAP91 reaches experiment wide significance with hearing loss (p=5.2e-5).

Conclusions: The results we present here are the first stage of our analysis, applying PheWAS to psychiatric risk genes. As such, our results constitute a proof-of-concept: that PheWAS studies are a promising approach for studying psychiatric risk genes. We believe that PheWAS provides the opportunity to study the impact of psychiatric risk genes in the general public; this will lead to a deeper understanding of the biological mechanisms underlying these diseases.

To date, we have validated a small subset of risk genes from the CMC study. Our next steps will incorporate schizophrenia and bipolar disorder risk genes from our recent large scale PrediXcan studies. We hypothesize that schizophrenia risk genes are associated with diagnoses and endophenotypes that have common mechanistic foundations.

Keywords: Human Genetics, DNA Sequencing, Multiplex Families, Schizophrenia, Bipolar Disorder, Genetics, Genome Wide Association Study

Disclosure: Nothing to disclose.

M202. Convergent Phenotypic and Genomic Analyses of Symptom-Level Data in the Multi-Ancestry Genomic Psychiatry Cohort (GPC) Study of Schizophrenia

Tim Bigdeli, Jacquelyn Meyers, Helena Medeiros, Roseann Peterson, Jorge Valderrama, Giulio Genovese, Conrad Iyegbe, James A. Knowles, Kenneth Kendler, Carlos Pato, Michele Pato, Nina Schooler, Ayman Fanous*

SUNY Downstate Medical Center, Brooklyn, New York, United States

Background: Schizophrenia is a complex and clinically heterogeneous syndrome, with individual patients varying widely in terms of symptomatic presentation, course, outcome, and severity. Whether categorical subtypes describe variation in clinical features is unclear, and subtype specifiers were removed from DSM-5 given a lack of corroborating field evidence. Dimensional constructs such as positive, disorganization and negative, and affective symptoms represent alternative conceptualizations of demonstrated clinical significance. However, the potential promise of clinical features in the prediction of course, outcome, and response to treatment has not yet been realized. Defining dimensional constructs with large data bases and linking these constructs to genetic information represents an important step in achieving this goal.

Methods: We performed exploratory factor analysis (EFA) of symptom-level endorsement and interviewer rating data for N > 10,000 schizophrenia and schizoaffective disorder patients from the Genomic Psychiatry Cohort (GPC). The GPC is a large cosmopolitan sample of newly ascertained cases and screened controls with considerable representation of African and Latino ancestries. Participants enrolled as probable cases were interviewed by mental health professionals using the Diagnostic Interview for Psychosis and Affective Disorders (DI-PAD), a semi-structured clinical interview incorporating questions developed for the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al. 1994). Genome-wide single nucleotide polymorphism (SNP) data was available for 7,289 cases with complete DI-PADs, and we constructed polygenic risk scores using summary statistics from the Psychiatric Genomics Consortium (PGC) study of schizophrenia (PGC Schizophrenia Working Group, 2014).

Results: Our EFA yielded a six (6) factor model representing delusions, hallucinations, and depressive, manic, disorganized and negative symptoms. We retained items with loadings of 0.4 or greater in a subsequent confirmatory factor analysis (CFA), which indicated good model fit (RMSEA = 0.043; SRMR = 0.040; CFI = 0.943). Next, we tested for associations between individual-level factor scores and polygenic risk of schizophrenia; we observed the strongest evidence of association for a combined negative/disorganized symptom factor in African-American participants (n = 3181) (R2 = 0.40%; P = 1.02×10e-4), successfully replicating our previous finding for European participants from the PGC study (n = 8000) (R2 = 0.39%; P = 6.39×10e-9).

Conclusions: These analyses represent the largest empirical analysis of symptom-level clinical data for schizophrenia to date. In polygenic risk scoring analyses, we generate trans-ancestry replication support for an association between negative/disorganized symptom severity and increased polygenic burden, showing a similar relationship between a dimensional construct and polygenic risk in African-American and European participants with schizophrenia Ongoing analyses seek to further parse associations between clinical heterogeneity and polygenic risk of schizophrenia, bipolar disorder, and depression.

Keywords: DNA, Whole-Genome, Sequencing, Schizophrenia, Negative Symptoms, Diversity, Clinical Subtypes

Disclosure: Nothing to disclose.

M203. Polygenic Risk Scores and Cognitive Performance Before and After Antipsychotic Treatment in First Episode Psychosis

Jeffrey Bishop, Bin Guo, Scot Hill, James Stevenson, Leah Rubin, Sarah Keedy, Rebekka Lencer, James Reilly, Konasale Prasad, Vishwajit Nimgaonkar, Matcheri Keshavan, Baolin Wu, John Sweeney*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Cognitive performance before and after antipsychotic treatment in psychotic disorders vary across individuals. Untreated patients early in their course of disease with little prior treatment exposure studied before and after treatment may be useful in identifying genetic and pharmacogenetic relationships.

Methods: We examined 95 untreated first episode patients (65% male, age 23.5+/- 6.9, schizophrenia n=69 bipolar disorder with psychotic features n=16 and, major depressive disorder with psychotic features n=10) who had little to no prior antipsychotic exposure in a 6-week pharmacogenomic study of antipsychotic treatment response. Risperidone was the preferred antipsychotic (n=67) with others chosen as secondary options when clinically preferred. Participants were genotyped using the Affymetrix Genome-Wide Human SNP Array 6.0 followed by imputation using the 1000Genomes reference panel. Polygenic risk scores (PRS) were computed based on the most recent GWAS summary data for schizophrenia (SCZ), major depressive disorder (MDD) and bipolar disorder (BD) from the Psychiatric Genomics Consortium (PGC). We divided the data into two groups for analysis (European n=46 and Non-European n=49) and calculated the PRS for SCZ, MDD and BD under 10 different p-values thresholds (p = 0.5, 0.1, 0.05, 0.01, 10-3, 10-4, 10-5, 10-6, 10-7, 5*10-8). Cognitive performance was assessed with a neuropsychological battery including the California Verbal Learning Test, Digits forward/back, digit symbol, Trails A/B, and verbal fluency. A composite cognition z-score (CogZ) was computed for each participant using performance on these measures relative to demographically matched controls. CogZ before treatment and changes after 6 weeks of antipsychotic therapy were examined as quantitative traits. We then fitted models with PRS, using the largest R^2 across different p-value cutoffs for each disease state. PRS were modeled individually and together along with genetic ancestry and dose (posttreatment only) in relation to CogZ before and after 6 weeks of antipsychotic treatment. The significance of R^2 was calculated based on 1000 permutations for each outcome.

Results: PRS for SCZ, but not MDD or BD, were negative predictors of cognitive performance before treatment (p < 0.01), but not change after 6 weeks of antipsychotic therapy in Caucasians. SCZ PRS accounted for a maximum of 25% of the variance in CogZ before treatment in Caucasians using the Caucasian-derived PRS (permutation p<0.001), but only 2% of the variance in non-Caucasians (p=0.90). Collectively examining SCZ +MDD+BD PRS in relation to CogZ did not significantly improve prediction models compared to SCZ alone.

Conclusions: To our knowledge this is the first examination of PRS for psychiatric illnesses in relation to cognitive performance in untreated first episode psychosis. Our findings indicated that higher SCZ PRS were strongly and negatively associated with cognition before treatment are important given the relatively lower or absence of association of PRS with cognition in schizophrenia in previous studies of chronically treated patients. This may indicate that genetic factors are important determinants of cognition early in illness while the relative importance of disease progression or treatment may increase as illness progresses to reduce cognition-genetics associations. Additionally, that the genetic determinants of cognition change after treatment may differ from those related to disease risk. The lack of

association of PRS with cognition in non-Caucasian participants underscores the racial specificity of these PRS measures which were developed from large Caucasian study cohorts.

Keywords: Antipsychotic-Naïve First-Episode Schizophrenia, Polygenic Risk Score, Treatment-Response

Disclosure: Nothing to disclose.

M204. Identification and Prioritization of Gene Sets Associated With Schizophrenia Risk by Co-Expression Network Analysis in Human Brain

Abstract not included.

M205. Identification of a Novel Neuropeptide in Mammalian Brain Using a Ribosome Profiling and Peptidomic Approach

*Ravi Tharakan, Simion Kreimer, Ceereena Ubaida Mohien, Joelle Lavoie, Robert Cole, Koko Ishizuka, Akira Sawa, Leslie Nucifora**

Johns Hopkins School of Medicine, Batimore, Maryland, United States

Background: Intracellular communication in the central nervous system (CNS) is chemically mediated. Neurotransmitters composed of amino acids and their metabolites were first identified as these chemical communication agents. Later, evidence emerged that numerous peptides also serve as messengers in the brain. Neuropeptides are now recognized as the largest and most diverse signaling molecule in the CNS.

Neuropeptides are 3 – 100 amino acids residues in length and act as neurotransmitters, neuromodulators, hormones or growth factors. They have been implicated with a myriad of physiological and behavioral processes. The antagonist to one of the first neuropeptides discovered, neurokinins A and B, has been approved by the Food and Drug Administration for treatment of chemotherapy-induced emesis and has also shown clinical efficacy in the treatment of major depression. This exemplifies the important role of neuropeptides and their receptors with respect to psychiatric disease and the potential for new therapies.

Although neuropeptides possess increased structural complexity, binding affinity, and selectivity compared to the smaller classical neurotransmitters, their concentration levels are much lower in the brain. This makes detection of novel neuropeptides using traditional proteomic methods developed for the detection of larger globular proteins challenging. Continued neuropeptide discovery necessitates the development of proteomic methods with increased sensitivity.

Methods: Peptide extraction was performed on whole brain from black 6 male mice. Capture and detection of extracted peptides was achieved by integration of an online strong cation exchange (SCX) separation into a nanoRPLC-MS/MS system. A combined approach utilizing ribosome profiling method and mass spectrometry-based peptidomics were utilized for the identification of the novel peptide. TMT labeling was used to detect peptide abundance over the course of mouse adolescence.

Results: In this study, we introduce and validate a new methodology for neuropepetide discovery in mammalian brain. This methodology utilizes a combined ribosome profiling and mass spectrometry-based peptidomics approach with sufficient sensitivity to observe low abundance signaling neuropeptides. Using this framework, we have identified a novel neuropeptide in mouse whole brain. The peptide was also detected in two independent cultured brain cells confirming that the peptide is derived from brain and not contamination of peripheral blood. Insignificant changes in expression levels of this neuropeptide was observed over the course of adolescence. An examination of the expression of the underlying transcript using the BioGPS database, indicates highest expression of this transcript in mouse brain when compared to other tissues. The highest expressing brain regions include the dorsal root ganglia, hypothalamus, and amygdala. The hypothalamus and amygdala have roles in the regulation of behavior, suggesting a potential functional role for this peptide as a behavior regulating neuropeptide.

Conclusions: This study reports a novel neuropeptide in mammalian brain that has been identified utilizing a combined ribosome profiling and peptidomic approach. Although we have yet to identify its functional role, it has been previously detected in peripheral tissue and serves as a component of the mRNA decapping complex (D'Lima et al., 2016). Continued efforts into neuropeptide discovery and the understanding of their functional roles in mammalian brain may provide insight into psychiatric disease.

Keywords: Neuropeptides, Ribosome Profiling, Peptidomics, Mass Spectrometry

Disclosure: Nothing to disclose.

M206. Indices of Neuro-Inflammation in the Superior Temporal Gyrus in Chronic Schizophrenia

Margaret Niznikiewicz, Elsiabetta DelRe, Kevin Spencer, Hiu Liao, Simone Merugulama, Paul Nestor, Robert McCarley, Nicolas Bolo, Alexander Lin*

Harvard Medical School, Brockton, Massachusetts, United States

Background: Schizophrenia (SZ) is associated with both glial abnormalities and with neuro-inflammation. In the current study, we have used resting state magnetic resonance spectroscopy (rs-MRS) to investigate myo-inositol, a marker of glial proliferation, choline, a marker of demyelination, and glutathione, a marker of neuro-inflammation, in the three voxels of left and right superior temporal gyrus (STG), given its involvement in schizophrenia pathology and medial anterior cingulate cortex (ACC), given its role in SZ symptomatology and prior reports of neuro-metabolite abnormalities in this region in first episode SZ (FESZ). While metabolites in the medial prefrontal cortex, ACC and medial temporal gyrus have been examined in both chronic SZ (CSZ) and FESZ, we are not aware of published reports of metabolic abnormalities in the STG in either CSZ or FESZ. Based on existing literature, no group differences were predicted in CSZ in ACC, and higher levels of glutathione (GSH), myo-inositol (mI) and choline (Cho) were predicted in the STG in CSZ group as reflective of neuroinflammation.

Methods: Fourteen CSZ patients and 14 healthy controls (HC) matched for age and gender were tested. Myo-inositol, choline and glutathione levels were acquired using short echo spectroscopy (TR/TE=2000/30, PRESS, 128 avgs, 24 cm3) at 3 Tesla (Siemens Skyra, 32 channel head coil). All metabolite values were corrected for the intra-voxel content (white and gray matter and cerebrospinal fluid) for each voxel and for each subject individually and metabolite concentrations were obtained (LCmodel). For all metabolites including GSH, were fitted with CRLB <20%. ANOVA was used to examine myo-inositol, choline, and glutathione in the left and right STG with group as a between factor, and region (left and right STG) as a within factor. One-way ANOVA was used to examine the metabolite levels in the ACC. In addition, correlations were conducted between white matter volume for each voxel and each metabolite in both subject groups. All analyses were corrected for age.

Results: Group differences were observed in the STG bilaterally but not in the ACC for glutathione ($p=0.037$), myo-inositol ($p=0.035$) and choline ($p=0.006$). All three metabolite levels were

higher in the CSZ group relative to HC group. Both myo-inositol and choline in the left STG were negatively correlated with the white matter volume in the left STG in HC but not in the CSZ group (myo-inositol: HC: r=-0.62, p=0.018; CSZ: r=-0.29, p=0.36; choline: HC: r=-0.65, p=0.012; CSZ: r=-0.3, p=0.32).

Conclusions: These results suggest that both neuroinflammatory processes and microstructural glial abnormalities were present in CSZ in the STG voxel while they were not evident in the ACC. The lack of correlations of both choline and myo-inositol with the STG white matter underscores the presence of neuropathological processes in the STG in the CSZ group. The findings of the presence of the neuro-inflammatory and glial integrity marker abnormalities in the left STG offer novel evidence for the role of this brain region in the pathology of schizophrenia. Differences in the profile of abnormalities in neuro-metabolites dependent on the stage of illness, and the voxel examined, have been reported in several studies focusing on FESZ and CSZ (Jellen et al., 2018). The absence of group differences in the ACC in this clinical group is in line with previously published studies (Jellen et al., 2018) and suggests that the profile of abnormalities in neuro-metabolites may dependent on the stage of illness and the voxel examined.

Keywords: Neurochemistry, Schizophrenia, Choline, Myo-Inositol, STG

Disclosure: Nothing to disclose.

M207. Neural and Behavioral Effects of Oxytocin Administration During Theory of Mind in Schizophrenia and Matched Controls

Lize DeCoster, Lisa Lin, Joshua Woolley, Daniel Mathalon*

San Francisco Veterans Affairs Medical Center, San Francisco, California, United States

Background: Social cognitive impairments, including theory of mind (ToM), in schizophrenia more strongly predict functional outcomes than psychotic symptoms or non-social cognitive deficits. Despite their clinical importance, current medications do not improve these deficits. The current study investigated the hypothesis that oxytocin, a neuropeptide implicated in social behavior, would normalize neural abnormalities in schizophrenia during ToM, and that this normalization would mediate improvement in ToM behavior.

Methods: In this cross-over, double-blind, placebo-controlled functional magnetic resonance imaging study, a single dose of 40 IU of oxytocin was administered via nasal spray to male schizophrenia patients (n = 23) and healthy controls (n = 25). Participants completed two ToM tasks in the scanner, the False belief and Person description tasks.

Results: During both tasks, on placebo day, schizophrenia was associated with reduced accuracy, hypo-activity in the rTPJ, and hypo-connectivity between the rTPJ and medial prefrontal cortex (mPFC) compared to healthy controls. Oxytocin, relative to placebo, significantly increased accuracy (Belief I FBT: M=75.54%, SD=14.29%; Thought in PDT: M=82.95%, SD=7.98%) and rTPJ activation for ToM but not control stories in schizophrenia. Furthermore, a significant positive correlation was found between oxytocin-induced increases in rTPJ activity and accuracy (Belief in FBT: r-=.44, p=0.04). Oxytocin also significantly improved connectivity between rTPJ and mPFC in schizophrenia.

Conclusions: Schizophrenia is associated with reduced rTPJ activity during ToM. Oxytocin improved rTPJ activity in schizophrenia during ToM, and this improvement predicted behavioral improvement. rTPJ activity during ToM might be a potential neural target for the treatment of social cognitive deficits in schizophrenia.

Keywords: Theory of Mind, Oxytocin, Schizophrenia, Functional Magnetic Resonance Imaging, Right Temporo-Parietal Junction

Disclosure: Nothing to disclose.

M208. Striatal Connectivity in Breakthrough Psychosis on Antipsychotic Maintenance: Preliminary Results From the BAMM Study

Jose Rubio, John Kane, Christina Fales, Todd Lencz, Anita Barber, Anil Malhotra*

Feinstein Institute for Medical Research, Glen Oaks, New York, United States

Background: Despite antipsychotic drugs being highly efficacious in preventing relapse in psychosis, (1) approximately 15% of treatment adherent patients do relapse during the maintenance phase. (2) This phenomenon is known as "breakthrough psychosis on antipsychotic maintenance medication" (BAMM). (3) The biological mechanisms of psychotic relapse in treatment adherent individuals are poorly understood.

Recent data from our own and other groups indicate that individuals with greater treatment response to antipsychotics demonstrate lower striatal functional connectivity before treatment onset as compared with poor responders. Furthermore, symptom improvement has been associated with increases in specific striatal connections (4-6). This literature suggests that the striatum would be involved in the pathophysiology of psychosis responsive to antipsychotics, whereas poor responders could have extra-striatal pathophysiology.

The purpose of the "BAMM Study" is to generate hypotheses on the striatal connectivity status for individuals with psychosis who have a history of response to antipsychotics yet fail to maintain such response despite confirmed continuous treatment with long acting injectable (LAI) antipsychotics.

Methods: The BAMM study aims to compare the functional connectivity between subjects with BAMM and antipsychotic non-adherent controls using resting state functional magnetic resonance imaging. The BAMM group consists of subjects with a psychotic disorder treated with LAI antipsychotics and history of clinical response to that trial confirmed by collateral, that present with acute psychotic symptoms at the time of the scan (defined as ≥4 in BPRS in at least one of the psychotic items). The control group consists of subjects with a psychotic disorder and history of good treatment response to antipsychotics who are non-adherent yet acutely psychotic (≥4 in BPRS in at least one of the psychotic items) at the time of the scan. Drug adherence status is confirmed with antipsychotic serum level determination, and history of previous treatment resistance or clozapine treatment excludes subjects from study participation. For these preliminary analyses we studied group differences in connectivity maps of striatal seeds as in Di Martino et al. (7). For this, data were preprocessed using the Human Connectome Project pipeline and cleaned with the ICA-FIX procedure, which removed motion artifacts and nuisance variables (white matter and CSF signal), but not global signal. Outputs from this procedure underwent high pass (0.01 Hz), and low pass (0.01 Hz) filtering. Time-series for each striatal seed were extracted and correlated with those of voxels in the whole brain. The resulting z-transformed maps for each subject were then used in the group analysis in FSL. Given the exploratory nature of these analyses, we used very low thresholds (voxelwise z=1.64, with cluster threshold p=0.10). Two-sample t-tests were run to compare group differences in clinical variables.

Results: Within 5 months, analyzable imaging data for 8 BAMM and 9 control subjects has been collected. The mean age of this sample was 39.4 (SD=13.3) years in the BAMM group and 35.4 (11.6) in the control group. Two subjects (25%) were male in the BAMM group compared with 3 (33.3%) in the control group. The number of previous hospitalizations was 4.9 (SD=3.0) in the BAMM group, compared with 3.3 (SD=1.9) in the control group. Mean duration of illness was 10.7 (SD=7.0) years for the BAMM group compared with 8.0 (SD=4.3) for the control group. The clinical global impression severity score was 4.75 (SD=1.1) in the BAMM group and 4.9 (SD=0.6) in the control group. The BPRS total score was 43.0 (SD=6.5) for the BAMM group, and 42.7 (SD=6.2) for the control group, while the psychotic subcomponent score (sum of score of the items "unusual thought content", "hallucinations", and "conceptual disorganization") was 11.5 (SD=2.7) and 14.9 (SD=2.9) respectively. The BAMM group had been treated in average over a year with a LAI antipsychotic with mean dose of 1.4 (SD=0.6) defined daily doses (standard defined daily dose=1) and had received their last dose a mean of 11.0 (SD=7.3) days before the scan. No group differences were found in the clinical variables between groups. No group differences were found in the functional connectivity of any of the 6 bilateral striatal seeds compared with the rest of the brain between the BAMM and the control group.

Conclusions: The preliminary analyses of the first 17 participants of the BAMM study did not find group differences in striatal connectivity between subjects with confirmed antipsychotic adherence who relapsed versus controls who were non-adherent with antipsychotics at the time of relapse. If these results stand through the completion of the study, they will serve to motivate the hypothesis that the pathophysiology of relapse in antipsychotic adherent individuals is mediated through extra-striatal mechanisms. However, given the limited power to detect group differences with this sample, further collection of data is required.

Keywords: Psychosis, Relapse Biomarkers, Medication Adherence, Striatal Pathways, Resting State Functional Connectivity

Disclosure: Lundbeck, Consultant

M209. Activation of Internal Performance Monitoring Circuitry is Reduced in Psychosis Spectrum Youth

*Tess Levinson, Greer Prettyman, Theodore Satterthwaite, Lauren White, Tyler Moore, Monica Calkins, Kosha Ruparel, Raquel Gur, Ruben Gur, Daniel Wolf**

University of Pennsylvania, Wynnewood, Pennsylvania, United States

Background: Self-directed performance monitoring is a critical contributor to cognitive performance and general functioning and is impacted by a variety of psychiatric symptoms and personality traits. We have previously shown that ventral striatum (VS) activates more strongly to correct than incorrect responses during cognitive tasks where no explicit feedback is required, and that this "intrinsic reinforcement" response is reduced in schizophrenia. Here we examined this phenomenon in youth from the Philadelphia Neurodevelopmental Cohort (PNC) performing a working memory fMRI task and related it to a reaction time measure of performance monitoring and to psychosis spectrum status. We hypothesized that VS would respond to internal correctness monitoring while classic "salience network" regions such as dorsal anterior cingulate cortex (ACC) and anterior insular cortex (AIC) would reflect internal error monitoring. We expected that both behavioral and imaging measures of performance monitoring would be reduced in youth with subclinical psychosis spectrum features.

Methods: A sample of 951 youths ages 8-21 from the PNC (227 typically developing, TD; 285 psychosis spectrum, PS) were included. 3 T fMRI BOLD data from the n-back working memory task was examined, focusing on the hardest (2-back) level and comparing fMRI response to correct vs. incorrect trials. fMRI analysis focused on a priori ROIs in VS, ACC and AIC, along with whole-brain voxelwise analyses. Behavioral performance monitoring was assessed in a separate out-of-scanner task without feedback (progressive matrices, PMAT), by correlating across trials within each participant the item-wise reaction time (RT) and difficulty (based on item-response theory analysis).

Results: Across the full sample, a strikingly selective pattern was observed for correct vs. incorrect trials, despite the fact that no accuracy information was provided during the task. As expected, VS showed robust correct>incorrect responses (peak Z=10.6), with positive responses to correct and negative responses to incorrect. In contrast, ACC and AIC showed the opposite pattern with robust incorrect>correct differential activation (peak Z's: ACC -13.9, AIC -14.2), although activating to both correct and incorrect trials. This accuracy monitoring pattern did not simply reflect greater task activation on correct trials: VS was not robustly task activated, task-active regions ACC and AIC were more activated for errors, and other strongly task-activated working memory regions such as dorsolateral prefrontal cortex and posterior parietal cortex did not show robust differences between correct and incorrect trials. Correct-vs-incorrect responses in VS were only weakly correlated with the ACC and AIC responses (r=-0.05), suggesting distinguishable circuitry for correctness vs. error processing. In the out-of-scanner PMAT, RT was slower for items that were more difficult providing evidence of internal performance monitoring; the average RT-difficulty correlation was r=0.39 across all participants. This RT-difficulty correlation measure was significantly correlated with VS correct>incorrect fMRI responses (r=0.16, p<.0001). This correlation was stronger than that seen for overall performance on the out-of-scanner cognitive battery (r=.09), slightly stronger than the relationship seen for accuracy in the fMRI working memory task itself (r=.14), and not accounted for by either of these. Older age was associated with both greater VS correct>incorrect activation and with greater PMAT performance monitoring but did not explain their association. Compared to TD youth, PS showed reduced correct>incorrect VS responses, and reduced AIC incorrect>correct responses (cluster-corrected p <0.05 within regions showing differential correct vs. incorrect response), without significant group differences in ACC incorrect>correct activation. Across all participants, there was a small but significant correlation between reduced VS correct>incorrect activation and greater negative/disorganized symptoms (r=-0.07, p=0.04), and trends for externalizing symptoms and global psychopathology (r's=0.06, p's=0.1); no specific symptom correlations were significant in the PS group alone. In a subset of PS (n=81) with self-report data for subjective experience in the cognitive battery, there was a significant correlation between VS correct>incorrect activation and caring about doing well on the tasks and finding them interesting (r's=0.27,0.28; p's=0.01).

Conclusions: We provide evidence for both error monitoring and correctness monitoring involving distinct brain regions, occurring in the absence of accuracy feedback. We further show a reduction of this internally-generated feedback or monitoring response in psychosis spectrum youth. This impairment likely has multiple contributors, including various symptoms associated with particular disorders as well as trans-diagnostic characteristics such as low motivation and impulsivity. Further work is needed to disentangle these contributors and develop a better understanding of the bidirectional relationship between cognitive performance and aspects of psychiatric syndromes or personality that are not typically considered "cognitive". Addressing such features through pharmacological or non-pharmacological

interventions could facilitate cognitive rehabilitation and efforts to improve social, academic and occupational function.

Keywords: Psychosis Risk, Functional MRI (fMRI), Ventral Striatum, Error Processing

Disclosure: Nothing to disclose.

M210. Neurite Orientation Dispersion and Free Water Alterations in Unmedicated Patients With Schizophrenia are Not Affected by Short Term Treatment With Risperidone

Nina Kraguljac, Thomas Anthony, Frank Skidmore, William Monroe, Jon Marstrander, David White, Meredith Reid, Adrienne Lahti*

University of Alabama at Birmingham, Birmingham, Alabama, United States

Background: Advanced diffusion imaging analytics are designed to provide more specific characterization of white matter microstructure, but only few studies have taken advantage of these techniques in schizophrenia. Results are suggestive of altered neurite morphology and neuro-inflammation as pathophysiological processes in the illness, but because all studies enrolled medicated patients, it is not clear to which extent these alterations can be attributed to antipsychotic medication effects as opposed to intrinsic illness characteristics.

The goal of this study was to apply NODDI to investigate white matter neurite configuration and extracellular free water content in unmedicated patients with schizophrenia and to assess the effects of six weeks treatment with risperidone on these measures.

Methods: We enrolled 42 unmedicated patients (thirty were medication-naïve) with schizophrenia in a longitudinal trial with risperidone. Symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS). We obtained diffusion weighted images before medication was started, and after six weeks of treatment. Healthy controls matched 1:1 on age, gender, and parental socioeconomic status were also scanned twice six weeks apart. 30 diffusion sampling directions spanning the whole sphere were acquired twice and concatenated (in plane resolution 2.2 mm, slice thickness 2.2 mm, b-value 1000 s/mm2, 5 b0 images). After visual inspection of raw images we used TORTOISE for correction of bulk motion, eddy currents and susceptibility artifacts using a single interpolation step in DIFF_PREP. Gradient tables were rotated along with motion correction. To obtain a summary measure of motion, the root-mean-square (RMS) was calculated both for absolute (RMSabs) and relative (RMSrel) movement. For estimation of extracellular free water and orientation dispersion index maps, we used the NODDI toolbox. To spatially normalize diffusion images, we implemented an optimized non-linear image registration using a modified version of 3dQwarp in AFNI. To assess whole brain voxel-wise group differences and changes over time in diffusion indices used AFNI's 3dttest++ (age, sex, and RMSrel as covariates) with clustsim, a bootstrapping method used to correct for multiple comparisons.

Results: Mean age of patients was 26.62 years, 62% of subjects were male. Of the 42 patients included here, 33 completed the study. At baseline, voxelwise analyses demonstrated decreased orientation dispersion in the posterior limb of the internal capsule, and whole brain analysis revealed a trend level increase extracellular free water in patients compared to controls. Longitudinal analyses showed no changes in whole brain extracellular free water or orientation dispersion in healthy controls over time, and no changes in patients after six weeks of treatment with risperidone.

Conclusions: Our results demonstrate circumscribed fiber geometry alterations in the posterior limb of the internal capsule and a trend-level whole brain extracellular free water increase in unmedicated patients, indicating that reported alterations in advanced diffusion indices are not merely a confound of antipsychotic treatment. Furthermore, we found no overall changes of diffusion indices after treatment but did report a positive relationship between change in extracellular free water and medication dose at endpoint.

Keywords: Diffusion Weighted Imaging, Schizophrenia, Antipsychotic Treatment

Disclosure: Nothing to disclose.

M211. Dopamine Receptor Density and White Mater Integrity: 18F-Fallypride Positron Emission Tomography and Diffusion Tensor Imaging Study in Healthy and Schizophrenia Subjects

Monte Buchsbaum, Serge Mitelman, Bradley Christian, Brian Merrill, Bradley Buchsbaum, Jogeshwar Mukherjee, Douglas Lehrer*

University of California, San Diego, San Diego, California, United States

Background: Dopaminergic dysfunction and changes in white matter integrity are among the most replicated findings in schizophrenia. A modulating role of dopamine in myelin formation and white matter integrity has been proposed in animal models and healthy human brain but has not yet been systematically explored in schizophrenia.

Methods: We used diffusion tensor imaging and 18F-fallypride positron emission tomography in 19 healthy and 25 never-medicated schizophrenia subjects to assess the relationship between gray matter dopamine D2/D3 receptor Binding Potential and white matter fractional anisotropy in each diagnostic group. MANOVA comparisons of the groups have previously been published. Patients were neuroleptic naïve or almost neuroleptic naïve, negative for drugs of abuse on urine screen on the scan day. The groups were approximately matched on handedness (16/19 right handed in the healthy group and 23/25 in the patient group (chi-square 0.65, $p=0.41$) One patient had an earlier diagnosis of alcohol abuse and patients with other comorbidity were excluded. Analysis of Functional NeuroImages (AFNI) regions of interest were acquired for 42 cortical Brodmann areas and subcortical gray matter structures, as well as stereotaxically placed in representative white matter areas implicated in schizophrenia neuroimaging literature. Four separate frame images were collected for fallypride and the odd and even frames separately quantified using the same algorithm in a second sample to confirm highly significant reliability (0.8-0.9 correlations) for cortical and subcortical regions.

Results: Healthy subjects displayed an extensive pattern of predominantly negative correlations between 18F-fallypride binding across a range of cortical and subcortical gray matter regions and fractional anisotropy in rostral white matter regions (internal capsule, frontal lobe, anterior corpus callosum). Positive correlations tended to cluster at the dorsal white matter regions closer to the cortex and predominated only in the temporal white matter. These patterns were disrupted in subjects with schizophrenia, who displayed significantly weaker overall correlations, as well as comparatively scant numbers of significant correlations with the internal capsule and frontal (but not temporal) white matter, especially for dopamine receptor density in thalamic nuclei. Permutational analysis was used to confirm correlation coefficient matrix differences between groups.

Conclusions: Dopamine D2/D3 receptor density and white matter integrity appear to be interrelated phenomena, and their decreases in schizophrenia may stem from dysregulation of dopaminergic impact on axonal myelination.

Keywords: Positron Emission Tomography Imaging, dopamine, fluorodeoxyglucose

Disclosure: Nothing to disclose.

M212. Reduced Stress-Induced Dopamine Release in Medial Prefrontal Cortex in Chronic Cannabis Users at Clinical High Risk for Psychosis

Christin Schifani, Jens Pruessner, Huai-Hsuan Tseng, Naren Rao, Abanti Tagore, Alan A. Wilson, Sylvain Houle, Pablo M. Rusjan, Romina Mizrahi*

Centre for Addiction and Mental Health, Toronto, Canada

Background: Dopamine hyperactivity in striatum is associated with psychotic symptoms and both stress and cannabis are risk factors for the development and relapse to psychosis. We have previously reported that subjects at clinical high risk for psychosis (CHR) exhibit a higher striatal dopamine response to acute stress compared to healthy volunteers and that chronic cannabis use blunts this response. However, it is unknown if this abnormal dopamine response to stress and cannabis extends to the prefrontal cortex (PFC), a brain region involved in regulating cognition and stress response, and how it relates to symptoms and cannabis use history. Therefore, we investigated the effect of acute psychosocial stress on PFC dopamine signaling in CHR with and without chronic cannabis use using [11 C]FLB457 positron emission tomography (PET) and a validated stress challenge.

Methods: Thirty-three participants matching in demographics completed two [11 C]FLB457 PET scans (14 CHR without cannabis use, 8 CHR chronic cannabis users (CHR-CU) and 11 healthy volunteers), one while performing a Sensory Motor Control Task (control) and another while performing the Montreal Imaging Stress Task (stress). Binding potential (BPnd) was estimated using the Simplified Reference Tissue Model. Dopamine release was defined as percent change in BPnd between control and stress scans (ΔBPnd). To assess the physiological stress response, saliva samples were taken throughout the scans and cortisol levels (AUCi) determined. The salivary cortisol response was defined as difference in AUCi between control and stress scans (ΔAUCi). Furthermore, attenuated psychotic symptoms were assessed before and after each PET scan session using an abridged version of the Scale of Prodromal Symptoms (SOPS). Drug history was assessed using a semi-structured interview.

Results: Our preliminary analysis revealed that stress-induced dopamine release (ΔBPnd) was significantly different between groups in medial PFC ($F(2,30)=5.40$, $p=0.010$) with CHR-CU exhibiting lower ΔBPnd compared to CHR (Bonferroni-corrected $p=0.008$) but not compared to healthy volunteers (Bonferroni-corrected $p=0.29$). Similarly, salivary cortisol response was significantly different between groups ($F(2,29)=5.08$, $p=0.013$) with CHR-CU exhibiting lower ΔAUCi as compared to CHR (Bonferroni-corrected $p=0.018$) but not compared to healthy volunteers (Bonferroni-corrected $p=1.0$). Furthermore, CHR-CU participants were observed to have increased attenuated psychotic symptoms following the stress task as compared to their score before the stress task (paired t-test; $t=4.58$, $df=7$, $p=0.0025$). The attenuated psychotic symptoms following the stress task were negatively associated with ΔBPnd in medial PFC (ß=-1.49, $SE=0.71$, $F(1,18)=4.44$, $p=0.049$) and dorsolateral PFC (ß=-1.70, $SE=0.59$, $F(1,18)=8.43$, $p=0.009$) in the combined high-risk sample (CHR and CHR-CU) when controlling for group, suggesting that high-risk participants with more severe attenuated psychotic symptoms had lower PFC dopamine release in response to the stress task. Moreover, in CHR-CU participants, length of chronic cannabis use was negatively associated with stress-induced dopamine release in medial PFC, when controlling for current weekly cannabis use (β=-0.19, $SE=0.57$, $F(1,5)=10.89$, $p=0.021$), suggesting that participants with longer chronic cannabis use had lower medial PFC dopamine release in response to the stress task.

Conclusions: These findings provide first evidence of an altered response to stress in PFC dopamine signaling in CHR cannabis users which is directly related to attenuated psychotic symptoms and cannabis use history. This study is especially relevant in the light of the global trend to legalize cannabis, as it highlights the effects of chronic cannabis use on cortical dopamine function in high-risk youth.

Keywords: Cannabis, Positron Emission Tomography, Dopamine, Prefrontal Cortex, Clinical High Risk for Psychosis

Disclosure: Nothing to disclose.

M213. Cerebellar Theta-Frequency Transcranial Pulsed Stimulation Increases Frontal Theta Oscillations in Patients With Schizophrenia

*Krystal Parker**

University of Iowa, Iowa City, Iowa, United States

Background: Cognitive dysfunction is a pervasive and disabling aspect of schizophrenia without adequate treatments. A recognized correlate to cognitive dysfunction in schizophrenia is attenuated frontal theta oscillations. Neuromodulation to normalize these frontal rhythms represents a potential novel therapeutic strategy. Here, we evaluate whether noninvasive neuromodulation of the cerebellum in patients with schizophrenia can enhance frontal theta oscillations with the future goal of targeting the cerebellum as a possible therapy for cognitive dysfunction in schizophrenia

Methods: Using transcranial pulsed current stimulation (tPCS), a non-invasive transcranial direct current that can be delivered in a frequency specific manner, we targeted the midline cerebellum with a single 20-minute session of theta frequency stimulation in 9 patients with schizophrenia (cathode on right shoulder with delta frequency as a control for frequency specific effects). EEG signals from midfrontal electrode Cz were analyzed before and after cerebellar tPCS while patients estimated the passage of 3 and 12 second intervals.

Results: Theta oscillations were significantly larger following theta frequency cerebellar tPCS in the midfrontal region which was not seen with delta frequency stimulation. As previously reported, patients with schizophrenia showed a reduction in accuracy estimating 3 and 12 second intervals as compared to control subjects. Timing accuracy was not modified by theta or delta frequency cerebellar tPCS.

Conclusions: These results suggest that theta frequency cerebellar tPCS may modulate task-related oscillatory activity in the frontal cortex in a frequency-specific manner. This finding warrants further investigation to evaluate whether a full treatment course of cerebellar stimulation may impact cognitive performance and thus have therapeutic implications for schizophrenia.

Keywords: Cerebellum, Transcranial Direct Current Stimulation, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

M214. The Effect of Ethnicity and Immigration on Treatment Resistance in Schizophrenia

Abstract not included.

M215. Preclinical and Early Clinical Pharmacological Profile of Basmisanil, a GABA-A α5 Receptor Negative Allosteric Modulator, Currently in a Phase 2 Clinical Trial for Cognitive Impairment Associated With Schizophrenia

*Maria-Clemencia Hernandez, Jörg Hipp, Michael Hoener, Robert Comley, Michael Derks, Frederic Knoflach, Sian Lennon-Chrimes, Nicholas Seneca, Gerhard Trube, Theresa Ballard-Yardy, Rodolfo Gasser, Tania Wallace, Eric Prinssen, Daniel Umbricht**

F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background: Genetic and pharmacological studies have demonstrated the importance of the GABA-A alpha5 subunit-containing receptors in cognitive processes. Here we describe the preclinical and early clinical pharmacological profile of basmisanil, a potent and highly selective negative allosteric modulator of GABA-A alpha5 receptors, which currently is in Phase 2 clinical development for the treatment of cognitive impairment associated with schizophrenia.

Methods: Radioligand binding and voltage-clamp electrophysiology experiments were conducted in vitro on GABA-A receptors expressed in HEK293 cells and Xenopus oocytes to demonstrate binding and functional selectivity for the GABA-A alpha5 vs. alpha1/2/3 subunit-containing receptors. Cognitive effects were assessed in rats and monkeys using the Morris water maze and the object retrieval task, respectively. Pro-convulsant and anxiogenic potentials were evaluated in mice and rats. In vivo receptor occupancy was determined using [3 H]-RO0154513 in rats and [11 C] RO0154513 in a PET study conducted in 10 healthy volunteers at 3 timepoints: baseline, 3, and 9 h following 1 of 4 doses of basmisanil (2×15, 2×60, 3×130, 3×1250 mg). A separate EEG study in 12 volunteers measured at baseline, midazolam (5 mg), and 14 days of basmisanil treatment (240 mg, bid).

Results: Basmisanil bound to recombinant human GABA-A alpha5 receptors with 5 nM affinity and with more than 90-fold selectivity versus alpha1, alpha2, and alpha3 subunit-containing receptors. At saturating binding concentrations, basmisanil inhibited the GABA-induced current in cells expressing GABA-A alpha5 yet had little or no effect at the other receptor subtypes. In vivo, basmisanil exhibited concentration-dependent occupancy of GABA-A alpha5 receptors and reversed diazepam-induced impairment of spatial learning of rats in the Morris water maze. Basmisanil also significantly improved performance in the object retrieval task in non-human primates. At plasma concentrations shown to improve cognition, basmisanil lacked anxiogenic and proconvulsive activity in rodent paradigms.

In human, the PET study demonstrated basmisanil selective GABA-A a5 target engagement, mainly in temporal and frontal cortical regions, nucleus accumbens and amygdala, consistent with known expression patterns of this receptor. A tight exposure-occupancy relationship was observed, providing an excellent basis for dose selection for clinical trials. In addition, Basmisanil showed modulation of large-scale brain function reflected in characteristic changes of EEG spectral power, in particular power increase in theta to alpha, and decrease in beta frequency ranges at dose associated with ~90% occupancy. This EEG signature was qualitatively opposite to that of midazolam, a non-selective positive allosteric modulator of GABA-A receptors. Importantly, Basmisanil was safe and well tolerated, and no treatment-emergent epileptiform abnormalities were observed.

Conclusions: These data suggest basmisanil is a promising candidate drug with a unique pharmacological and safety profile for further clinical testing in conditions associated with associated cognitive impairment such schizophrenia.

Keywords: GABA-A receptors, Cognition, Schizophrenia, Pharmacology, PET Imaging

Disclosure: F. Hoffmann - La Roche, Employee, Stock / Equity

M216. Persistent Firing in Parvalbumin-Expressing Inhibitory Interneurons of the Neocortex: A Newly Discovered Property With Potential Implications for Psychopathology

Brian Theyel, Rachel Stevenson, Barry Connors*

Brown University, Providence, Rhode Island, United States

Background: A basic property of axons involves their ability to propagate action potentials in both orthodromic ("forward") and antidromic ("backward") directions, e.g. (Brain Res Rev. 21:42, 1995). While spikes are typically generated in axon initial segments and propagate orthodromically, in certain cases spikes have been observed initiating in distal regions of axons and their terminals before propagating antidromically; these are often called 'ectopic' action potentials. Recently, ectopic spiking has been demonstrated primarily in NPY-expressing interneurons of the hippocampus (Nat Neurosci. 14:200, 2011), whereas few parvalbumin (PV)-expressing interneurons generated ectopic spikes.

Methods: To investigate ectopic spiking behavior in cortical interneurons we used standard whole-cell patch clamp techniques to patch neurons in layers 2/3 or 4 of orbitofrontal or somatosensory cortex in 300 micron slices. 5 male and 17 female PV-Cre x Ai14 mice, postnatal day 20 to 35 were used. Statistical analyses are pending completion of experiments.

Results: We have observed that a large majority (>95%) of PV+ cells in neocortex (both orbitofrontal cortex and primary somatosensory cortex) are not only capable of generating ectopic action potentials after they've been sufficiently activated but do so in varying patterns for up to tens of seconds. We also found that somatostatin positive interneurons and even a few pyramidal cells were capable of rare, sparse ectopic spiking, but only after intense stimulation unlikely to occur in vivo. PV+ cells, often referred to as "fast-spiking" interneurons, had a much lower initiation threshold for ectopic spikes, requiring a few hundred spikes over the course of tens of seconds, and often (~75% of the time) fired trains of ectopic action potentials rather than just one or a few.

Conclusions: PV+ cells generate strong inhibition in excitatory cells and other interneurons, and they play a key role in generating network gamma rhythms, so ectopic spiking may have significant implications for network activity and cognitive processing. Several studies have demonstrated abnormalities in PV+ interneurons in schizophrenia (J Neurosci, 29:8, 2344-2354; Trends Neurosci, 35(1), 57-67) and autism spectrum disorder (PLoS One, 10(3), e0119258; Mol Psychiatry, 20(10), 1161-1172). Our future work will focus on whether ectopic spiking behavior changes in PV+ interneurons of animal models of both disorders.

Keywords: GABAergic Interneurons, Cortical Circuit Function, Schizophrenia, Cortical Circuit Function, Autism, Inhibition

Disclosure: Nothing to disclose.

M217. Plasma Nitrite is Associated With Dyslipidemia in Medicated Obese Schizophrenia Patients

Olaoluwa Okusaga, Dietmar Fuchs, Teodor Postolache*

MEDVAMC/Baylor College of Medicine, Houston, Texas, United States

Background: Obesity and cardiovascular disease (CVD) are highly prevalent in patients with schizophrenia leading to premature death, with 15–20 years shorter life expectancy than the general population. Obesity and CVD are related to antipsychotic medication use. We recently linked plasma nitrite (NO2-) a metabolite of nitric oxide (NO), to obesity and components of metabolic syndrome including dyslipidemia, in a non-psychiatric sample but this association has not been evaluated in schizophrenia. We have now assessed the relationship between plasma NO2-, body mass index (BMI) and plasma lipids in a sample of medicated patients with schizophrenia.

Methods: Methods: 106 medicated patients with schizophrenia were recruited. Body mass index (BMI), fasting plasma NO2-, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), neopterin (a marker of immune activation/inflammation) and cotinine (a metabolite of nicotine) were measured in all the participants. Non-HDL Cholesterol (NHDL-C) was calculated by subtracting HDL from TC. The patients were categorized into normal weight (BMI 18.5 to <25) and overweight/obese (BMI >25) groups. T-test compared plasma NO2- between the two groups. Pearson's and partial correlations (adjusting for age, sex, race, education, cotinine, and neopterin) between NO2-, BMI and plasma lipids were calculated in the total sample and in the two patient groups (i.e. normal weight and overweight/obese) respectively.

Results: Plasma NO2- did not differ between normal weight and overweight/obese patients (geometric mean 21.38μmol/L vs 23.98 μmol/L, p=0.398) and there was no correlation between NO2- and BMI. In the unadjusted analysis, plasma NO2- correlated positively with TC, TG, LDL and NHDL-C but negatively with HDL in the total sample but only TG correlated with NO2- in the adjusted analysis. In the unadjusted subgroup analyses, NO2- correlated with TG and NHDL-C in normal weight and overweight/obese groups but also with TC and HDL in the overweight/obese group. In the subgroup analyses, the only correlation that withstood adjustment for potential confounders was between NO2- and TG (partial r= 0.75, p=0.001) and this was only in the overweight/obese group.

Conclusions: The observed correlation between NO2- and TG observed in the total sample is probably driven by this association in the overweight/obese group since no such association was found in the normal weight group. Elucidation of the link between antipsychotic medication-related obesity, dyslipidemia, metabolic syndrome and plasma NO2- may lead to novel treatments to reduce premature death from CVD in patients with schizophrenia.

Keywords: Nitrites, Obesity, Dyslipidemia, Schizophrenia, Antipsychotics

Disclosure: Nothing to disclose.

M218. Neural Mechanisms Underlying Higher Rates of Psychotic and Mood Symptoms in Females With Schizophrenia

Laura Tully, Ana-Maria Iosif, Mary Blendermann, Lauren N. Zakskorn, Anna K. Moody, Bryn M. Ritter, Raisa Rahim, Amanda Guyer, Cameron Carter*

University of California, Davis School of Medicine, Sacramento, California, United States

Background: Females with schizophrenia (SZ) report more psychotic and mood symptoms. Further, in females, psychotic symptom severity relates to mood symptom severity, indicating a link between psychosis and emotional responses not observed in SZ males. One potential mechanism is cognitive control of emotion (CCoE): the self-regulation of emotions and their influence on behavior, mediated by a frontal-limbic network involving the lateral and medial prefrontal cortices and amygdala. Sex differences in CCoE in healthy individuals have not been examined, nor have relationships to sex differences in SZ symptomatology. This study seeks to identify sex differences in the frontal-limbic network during CCoE and their relationship to symptoms in females with SZ.

Methods: During fMRI, participants complete the Social Evaluation Task (SET), in which participants react to or down-regulate their emotional responses to negative social evaluation (NSE) and self-report their negative emotion on a 1-to-5 scale (1=not at all negative; 5=very negative). Participants also complete psychosocial symptom assessments and measures of emotion regulation (cognitive emotion regulation questionnaire [CERQ], the emotion amplification and reduction scales [TEARS]), internal attribution styles (Internal, Personal and Situational Attributions Questionnaire [IPSAQ]), and perspective taking (interpersonal reactivity index [IRI]). At time of submission, 21 healthy (11 female) and 17 SZ (10 female) participants have completed the study. We used independent sample T tests ($p < 0.05$ two-tailed) to conduct preliminary behavioral analyses of differences in reactivity to and regulation of NSE within group (HC females vs. HC males; SZ females vs. SZ males) and within sex (HC females vs. SZ females; HC males vs. SZ males). Effect sizes are reported as standardized mean differences.

Results: Preliminary behavioral results on the SET suggest that compared to healthy males (n=10), healthy females (n=11) demonstrate greater reactivity to (standardized mean difference = 1.45) and greater regulation of (standardized mean difference = 1.18) NSE (ps < 0.05). Preliminary data in SZ participants were in the same direction, although differences did not reach statistical significance: Compared to SZ males (n=7), SZ females (n=10) demonstrate greater reactivity to (standardized mean difference = 0.66) but reduced regulation of NSE (standardized mean difference = -0.30) (ps > 0.05). Preliminary within-sex comparisons indicate the following: Compared to healthy females, SZ females demonstrate a non-significant pattern of reduced reactivity to (standardized mean difference = -0.32; $p < 0.05$) but significantly reduced regulation of NSE (standardized mean difference = -1.64; $p = 0.001$). Compared to healthy males, SZ males demonstrate a pattern of lower reactivity (standardized mean difference = -0.33) and similar regulation of NSE (standardize mean difference = -0.03); differences were not significant (ps < 0.05). Preliminary whole-brain fMRI results demonstrate healthy controls activate expected regions of the frontal-limbic network during CCoE, including the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC) ($p < 0.001$ uncorrected, $k = 10$ voxels).

Conclusions: Females may be more reactive to NSE, and SZ females may have impaired regulation of NSE compare to healthy females and SZ males. Future analyses will examine associated frontal-limbic activity and relationships with symptoms and psychosocial measures. This work directly examines how sex as a biological variable contributes to individual differences in the symptomatology of SZ and could inform the development of sex-specific treatments.

Keywords: Emotion Regulation, Cognitive Control, Early Psychosis

Disclosure: Nothing to disclose.

M219. Elevated TNFα Levels in Males but Not in Females in Cerebrospinal Fluid of Patients With Schizophrenia

Juan Gallego, Robert McNamara, Emily Blanco, Santiago Castaneda, Todd Lencz, Anil Malhotra*

Weill Cornell Medical College, White Plains, New York, United States

Background: Elevated levels of pro-inflammatory cytokines have provided evidence in support of the inflammatory hypothesis of schizophrenia. Most studies of cytokines in schizophrenia have reported cytokine levels in peripheral blood and some have used cerebrospinal fluid (CSF). However, most of these studies have not examined the impact of sex on cytokine levels in detail. Prior studies with non-psychiatric patients have described a potential protective effect of estrogens in inflammatory conditions such as multiple sclerosis. Whether this effect is also present in schizophrenia is unclear, but it could partially explain better outcomes observed among females with this disorder as compared to males with schizophrenia, including a later onset of the illness and an overall better prognosis. Therefore, our aim was to study the relationship between sex and a panel of cytokines in cerebrospinal fluid of patients with schizophrenia and healthy volunteers.

Methods: Thirty-three patients with schizophrenia-spectrum disorders and 23 healthy volunteers underwent a lumbar puncture. 15-25 cc of CSF were obtained from each subject. CSF cytokine (IL-1β, IL-2, IL-4, IL-6, IL-8, TNFα) concentrations were determined in duplicate by enzyme-linked immunosorbent assay (ELISA) and a high-sensitivity MilliplexTM Multiplex kit (HSTCMAG-28SK-06, Millipore, Billerica, MA) per manufacturer's instructions. Raw cytokine values were log-transformed. Comparisons in cytokine levels between groups were performed using either t-tests for normally distributed variables or Wilcoxon rank-sum tests for non-normally distributed variables. Logistic regression analyses were conducted using subject type (patient vs. control) as the dependant variable and age, sex and cytokines as the independent variables.

Results: The mean age was 36.6 years (SD=11.7) in patients and 38.1 years (SD=10.1) in controls. 24/33 (72.3%) of the patients and 14/23 (60.1%) of the healthy volunteers were male. Patients in the SSD group were clinically stable and taking antipsychotic medications. In males, levels were statistically significantly higher in patients vs. controls for TNFα (mean=6.88 pg/ml [SD=3.08] vs. 3.44 pg/ml [2.03], p=0.0004]) and IL-4 (12.21 pg/ml [8.91] vs. 6.65 pg/ml [3.98], p=0.02). There were no significant differences in IL-6 (9.65 pg/ml [2.89] vs. 8.96 pg/ml [2.09], p=0.42) or IL-8 (48.88 pg/ml [10.97] vs. 47.07 pg/ml [10.52], p=0.67). In females, none of the cytokines studied were statistically significantly different between patients and controls. Multivariate logistic regression analysis stratified by sex and adjusting by age showed that TNFα was significantly associated with schizophrenia (OR=9.7 [95% CI: 2.2-42.0], p=0.003) in the male group. In contrast to the findings from the bivariate analysis, IL-4 was dropped from the model due to a p-value >0.05. In females, there were no significant associations between cytokines and schizophrenia.

Conclusions: TNFα, a pro-inflammatory cytokine and a key participant in the acute phase response of the inflammatory cascade, is elevated in CSF of male patients with schizophrenia but not in females. IL-4 levels were also significantly higher in patients in bivariate analysis but were not significant in multivariate regression analysis. Other cytokines studied did not show this sex effect and were not differently found in patients vs. controls despite prior studies having reported elevated levels of other proinflammatory cytokines such as IL-6.

Keywords: Cerebrospinal Fluid, TNF-Alpha, Cytokines, Psychosis

Disclosure: Nothing to disclose.

M220. The Prism Project: A Quantitative Approach to Neuropsychiatry

Celso Arango, Amy Bilderbeck, Gerard Dawson, Brenda Penninx, Nic Van der Wee, Inge Winter-van Rossum, Bernd Sommer, Alex Schubert, Hugh Marston, Niels Jongs, Martien Kas*

Hospital Gregorio Marañon, Madrid, Spain

Background: Current nosology for the diagnosis of neuropsychiatric disorders, such as Schizophrenia and Autism, separates each into non-overlapping diagnostic categories. This separation is not based on their underlying etiology but on convention-based clustering of qualitative symptoms of the disorder. While these diagnostic categories are sufficient to provide the basis for general clinical management, they do not describe the underlying neurobiology that gives rise to individual symptoms. The ability to precisely link these symptoms to underlying neurobiology would not only facilitate the development of better treatments, it would also allow physicians to provide patients with a better understanding of the complexities and management of their illness.

Methods: The PRISM project focuses on schizophrenia (SZ), Alzheimer's disease (AD), and major depression (MD), disorders that share in part common symptomatologies, including social withdrawal and certain cognitive deficits, such as attention, working memory and sensory processing. Innovative technologies (e.g. EEG, cognitive tasks, (f)MRI, smartphone monitoring, genetics and epigenetics) are used to deep phenotype clinical cohorts of SZ and AD patients. These data is then combined with existing clinical data sets from major European and global disease cohorts. The aim is to derive a set of quantifiable biological parameters from these data that allow to cluster and differentiate SZ, AD and MD patients who are, or are not, socially withdrawn.

Results: One of PRISM objectives is to identify quantitative biological parameters that allow assessment of social withdrawal levels across different neurological and psychiatric diagnosis. Preliminary analysis, using self-rated minus researcher-rated WHO-DAS scores, revealed that Alzheimer ($p < 0.001$) and schizophrenia ($p = 0.049$) patients score significant lower based on the WHODAS score, suggesting that the patients are overestimating their levels of social activities. Using objective BEHAPP smartphone monitoring (Mulder et al., 2018), initial analysis indicated that Alzheimer patients spent significantly ($p = 0.001$) more time at home as compared to healthy controls (BEHAPP analysis was corrected for age).

Conclusions: These results will inform future clinical trials assessing negative symptoms such as social withdrawal in different brain disorders. The use of self rated assessments does not seem to be valid based on preliminary results from our study using a digital monitoring.

Keywords: Dimensions of Psychosis, Social Withdrawal, Alzheimer's Disease, Endophenotypes, Diagnostic Boundaries

Disclosure: Acadia, Advisory Board, Ambrosetti, Advisory Board, Gedeon Richter, Consultant, Janssen Cilag, Consultant, Lundbeck, Advisory Board, Otsuka, Consultant, Roche, Advisory Board, Servier, Consultant, Shire, Consultant, Schering Plough, Consultant, Sumitomo Dainippon Pharma, Advisory Board, Sunovion, Advisory Board, Takeda, Advisory Board

M221. Deficient Hippocampal Novelty Response and Habituation in Early Psychosis

Suzanne Avery, Baxter Rogers, Maureen McHugo, Kristan Armstrong, Neil Woodward, Jennifer Blackford, Stephan Heckers*

Vanderbilt University Medical Center, Nashville, Tennessee, United States

Background: Deficits in hippocampal function are among the most consistent and replicable findings in schizophrenia. There is evidence that deficits in hippocampal function also exist at the earliest stages of psychotic illness, although in a subtler form, suggesting hippocampal function may be a useful model for psychosis staging. However, functional markers sensitive to hippocampal pathology, such as interneuron loss and progressive excitatory/inhibitory imbalance, are needed. Animal models have linked novelty response and habituation of neural signal—the decrease in response to repeated sensory stimuli—with neural excitatory/inhibitory balance, suggesting the temporal dynamics of hippocampal response may be a sensitive marker of neuropathology. We previously showed that hippocampal habituation is reduced in chronic schizophrenia. Here we investigate whether hippocampal habituation deficits can also be detected during the earliest stages of psychotic illness.

Methods: We measured hippocampal activity in 65 early psychosis patients (< 2 years illness) and 70 healthy control participants using fMRI. Novelty response and habituation to repeated face and object images were computed for the anterior and posterior hippocampus separately. Analysis of variance tested for between-group differences by stimulus type. Effects of gender were examined and correlations with memory, cognitive, and clinical symptoms were performed.

Results: Early psychosis patients had lower novelty response to faces in the anterior hippocampus compared to control participants (FWE corrected $p = .04$) but did not show altered habituation to faces. In contrast, in response to objects, early psychosis patients showed reduced habituation in the anterior hippocampus compared to control participants (FWE corrected $p = .003$) but did not show altered novelty response. There were no associations between hippocampal response and gender, years of education, IQ, cognitive function, or current clinical symptoms.

Conclusions: These results provide evidence that both hippocampal novelty response and habituation are deficient in the early stage of psychosis. Hippocampal deficits were specific to stimulus type, suggesting examining the combination of social and nonsocial information may elicit a clearer model of pathophysiology. Importantly, our results provide preliminary evidence that deficits in hippocampal temporal response may progress with illness, although longitudinal studies are necessary. These findings further our understanding of the pathophysiology of schizophrenia and suggest a possible model for illness progression.

Keywords: First Episode Psychosis, Habituation, Novelty Response

Disclosure: Nothing to disclose.

M222. Maternal Immune Activation Disrupts Cortical Catecholamine Systems and Induces Cognitive Impairment in Offspring

*Blanca Perez del Palomar, Jorge E. Ortega, J. Javier Meana, Jordan McCall**

Washington University in St. Louis, St. Louis, Missouri, United States

Background: Schizophrenia is a chronic and disabling mental disorder with an early onset. Cognitive deficits start early and are present together with classical schizophrenia symptoms. The dorsolateral prefrontal cortex (DLPFC) is the main anatomical pathway modulating cognitive activities and is critical for executive function. Interestingly, the postsynaptic alpha-2A adrenergic receptors located on pyramidal cells of the DLPFC that maintain basal cognitive activity, seem to be underactive in schizophrenic patients. Importantly, one of the most significant environmental risk factors for the development of schizophrenia is prenatal exposure to infection. Indeed, maternal immune activation (MIA) in animals produces behavioral and neurochemical aberrations considered relevant in models of schizophrenia. The aim of this study was to evaluate cortical adrenergic function in an MIA model of schizophrenia.

Methods: We used an MIA model mimicking prenatal viral infection by the administration of Polyinosinic:polycytidylic acid (Poly(I:C)) to pregnant dams (7.5 mg/kg i.p., gestational day 9.5). We evaluated cognitive impairments of adult offspring by the novel-object recognition test (NORT) in the presence and absence of either the alpha-2 agonist (guanfacine 0.1 mg/kg i.p.) or the alpha-2 antagonist (MK-912 0.05 mg/kg i.p.). In addition, we used microdialysis to measure extracellular dopamine and norepinephrine (NE) concentrations in prefrontal cortex (PFC). To determine the sufficiency of increased PFC noradrenergic tone in reversing the MIA-induced cognitive impairment, we selectively manipulated this projection in vivo. To do so, we genetically targeted channelrhodopsin-2 to only locus coeruleus noradrenergic (LC-NE) neurons and used local photostimulation to increase LC-NE terminal activity in the PFC following MIA.

Results: MIA offspring have activity-dependent and transporter-dependent alterations in release of both dopamine and norepinephrine in the PFC. These mice also showed decreased novel object discrimination in the NORT compared with controls, demonstrating a cognitive deficiency. Interestingly, both the alpha-2A adrenergic receptor agonist (guanfacine) and the alpha-2C adrenergic receptor antagonist (MK-912) were able to reverse that behavioral deficiency in the Poly (I:C) offspring. However, neither compound appears to alter monoamine levels in the PFC of Poly (I:C) mice.

Conclusions: Together these results suggest that noradrenergic tone is important for regulating cognitive function in the Poly (I:C) model of maternal immune activation. The cognitive impairment produced by MIA in offspring could be related to both pre- and postsynaptic alterations in the adrenergic receptors in the PFC that control cognitive processes. Future work will use whole-cell electrophysiology to determine these mechanisms. This approach provides a promising translational animal model for the study of cognitive dysfunctions present in schizophrenia.

Keywords: Schizophrenia-Like Behavior, Locus Coeruelus, Alpha2 Adrenergic Receptors

Disclosure: Nothing to disclose.

M223. Somatostatin Interneurons Facilitate Hippocampal-Prefrontal Synchrony and Prefrontal Spatial Encoding During Working Memory

Atheir Abbas, Marina Sundiang, Britt Henoch, Mitchell Morton, Scott Bolkan, Alan Park, Alexander Harris, Christoph Kellendonk, Joshua Gordon*

Columbia University/New York State Psychiatric Institute, New York, New York, United States

Background: Working memory, a critical cognitive function, is impaired in schizophrenia and other psychiatric disorders including bipolar disorder, unipolar major depression, autism, and attention deficit hyperactivity disorder. Current treatments, however, do not effectively treat cognitive impairments despite their contribution to poor functioning in psychiatric illness. Thus, elucidating the neural basis for cognitive symptoms in psychiatric disorders may inform new treatment strategies which address cognitive deficits and reduce the impact of disease on functioning.

Methods: To address these gaps, we used the light-activated proton pump Arch3.0 to selectively silence prefrontal PV or SOM

interneurons in the medial prefrontal cortex of mice performing the delayed non-match to sample T-maze test of spatial working memory. We simultaneously recorded neural activity in the medial prefrontal cortex (mPFC) and other brain areas known to be involved in working memory, including the dorsal and ventral hippocampus (dHPC and vHPC), and mediodorsal thalamus (MD). We used measures of synchrony such as pairwise phase consistency (PPC) to characterize the functional connectivity between these various structures.

Results: We found that inhibiting SOM interneurons during the sample epoch of the task significantly impaired working memory accuracy when the delay length was 60 seconds. SOM silencing during the sample epoch of the working memory task was associated with a decrease in coherence between mPFC and HPC theta oscillations and a decrease in phase locking, as measured by pairwise phase consistency, between mPFC neurons and vHPC and dHPC theta oscillations. The normal ventral HPC to mPFC directionality of synchrony was also disrupted. SOM inhibition during the sample epoch was also associated with impaired spatial encoding within the mPFC. Inhibiting PV interneurons had no effect on synchrony, directionality, mPFC spatial encoding, or working memory accuracy.

Conclusions: The evidence we present is consistent with SOM interneurons supporting spatial encoding during working memory by facilitating hippocampal-prefrontal synchrony. These findings suggest that interneuron dysfunction may contribute to cognitive deficits in schizophrenia by disrupting long range synchrony between the hippocampus and prefrontal cortex.

Keywords: Somatostatin, Parvalbumin Interneurons, Working Memory, Hippocampal-Prefrontal, GABAergic Interneurons

Disclosure: Nothing to disclose.

M224. Ethnicity and Training in Medical Providers is Associated With Implicit Biases Related to the Treatment of Psychotic and Mood Disorders

*Jose Flores, Amalia Londono Tobon, Jerome Taylor, Michael Bloch**

Yale Child Study Center, New Haven, Connecticut, United States

Background: Mounting research revealing widespread implicit associations within the medical professionals may affect patient diagnosis and treatment. We studied whether self-reported ethnicity effects implicit associations regarding the diagnosis and treatment of psychotic/mood disorders using a sample of national providers.

Methods: Three different IAT tasks were presented to participants. The reaction time (RT) was measured to calculate D-scores as participants paired pictures of black/white faces with words/terms related to psychotic disorders vs. mood disorders (Task 1), non-compliance vs. compliance (Task 2), and antipsychotic medications vs. antidepressants (Task 3). Linear regression was used to estimate multivariable change in continuous D-scores. Dichotomized D-scores using a threshold absolute value $= |0.35|$ was used for logistic regression; such D-scores are considered implicit associations of moderate strength to estimate the odds of having a moderate or strong association. For D-scores $>+0.35$, the reference group was White providers. The same dichotomization was performed on the negative side of the D-score distribution, but the reference group was changed to Black providers. The main predictor was self-reported ethnicity of a provider (a categorical variable with 5 subgroups: Asian, Black, Hispanic, White, and other). Adjustment for multivariable models was performed using selected control variables: provider's age, sex, region of the USA, and reported childhood socioeconomic position (SEP). SEP was measured by asking providers to rank their childhood SEP compared to the rest of their community using a 10-step ladder.

Results: Compared to Black providers, White providers had significantly lower D-scores implying stronger associations of black faces with psychotic disorders (or white faces with mood disorders, D=-0.27, P<0.001), pairing of black faces with poor compliance (or white faces with compliance, D=-0.31, P<0.001) and black faces with antipsychotics (or white faces with antidepressants, D=-0.17, P<0.05). Medical students had lower D-scores (implying less biased pairing of black faces with psychotic disorders compared to Board certified psychiatrists). In logistic regression, compared to White providers, black providers had 54% lower odds of having strong implicit associations scores pairing black faces with psychotic disorders, 74% lower odds of having strong associations pairing black faces with non-compliance, and 81.6% lower odds of strongly pairing black faces with anti-psychotics. We found no significantly increased odds by Black providers paring white faces with psychosis (vs. mood disorders), poor-compliance (vs. compliance) or anti-psychotics (vs. antidepressants).

Conclusions: This study found strong implicit associations indicating a propensity for White providers to pair black faces with psychotic disorders, poor compliance, and with anti-psychotics. Medical students show scores that imply more neutral associations compared to higher levels of training. This preliminary data suggests increased diversity in providers may mitigate potential bias in diagnosis and prescription for the treatment of psychiatric disorders.

Keywords: Psychotic Disorders, Mood Disorders, Diversity

Disclosure: Biohaven Pharmaceutics, Grant, Therapix Biosciences, Grant, Jansssen Pharmaceuticals, Grant, Neurocrine Biosciences, Grant

M225. Context-Associated Cocaine Use During Adolescence: Effect on Context-Induced Reinstatement During Adulthood

*Jennifer Gerena, Aneesh Bal, Doris Olekanma, Rachel Butler, Shangari Varatharajan, Mansi Verma, Amy Arguello**

Michigan State University, East Lansing, Michigan, United States

Background: Cocaine use disorders are characterized by a high risk of repeated relapse following periods of abstinence. Relapse can occur following exposure to stressful events, explicit drug cues or environmental contexts that were previously associated with drug taking. The neural mechanisms contributing to these strong drug-context-associations have been investigated using adult rodent models of relapse. Drug use is often initiated at adolescence and therefore it is important to understand how drug taking during this critical developmental window may affect drug-seeking behavior during adulthood. Previous research has shown that rats which self-administered cocaine during adolescence display increased drug-primed and stress-induced (but not cue-induced) reinstatement of drug-seeking behavior as adults. The role of contextual stimuli in this phenomenon is unknown; therefore, we aim to examine whether cocaine-context associations formed during adolescence can evoke drug-seeking behavior during adulthood. Additionally, we examined whether single or pair-housing conditions would influence context-induced reinstatement.

Methods: Male, sprague-dawley rats (Envigo, postnatal day 30 (P30) on arrival), received jugular catheterization surgery at P35-37. Following surgery and recovery, rats were either pair or single housed. At P40-42, rats began self-administration training (distinct contextual environment, FR1 schedule of reinforcement, minimum of 10 days) followed by extinction training (separate, distinct context, minimum 7 days). Drug-seeking behavior (i.e. active lever

presses) was examined during a two-hour reinstatement test in the previously cocaine-paired context during adulthood.

Results: Adolescent rats acquired lever pressing for cocaine infusions and displayed decreased responding by the last day of extinction training. Robust reinstatement of drug-seeking behavior in the previous drug-associated context was observed during adulthood. No differences in reinstatement behavior were observed between rats that were single or paired housed. Minimal responding on the inactive lever was observed in all phases of the experiment.

Conclusions: Drug-context associations formed during an adolescence time period precipitated drug-seeking behavior during adulthood, with no effect on housing conditions. Future studies will examine how drug-context associations formed during adolescence influence drug-seeking behavior within the adolescent time window.

Keywords: Self-Administration, Adolescent, Context-Induced Reinstatement

Disclosure: Nothing to disclose.

M226. Fully Automated System to Explore the Differential Effects of Psychedelic and Non-Psychedelic Serotonin 2 A (5-HT2A) Receptor Agonists on Behavioral Tolerance

Mario de la Fuente Revenga, Urjita Shah, Javier González-Maeso*

Virginia Commonwealth University, School of Medicine, Richmond, Virginia, United States

Background: Psychedelic drugs, such as LSD, psilocybin, mescaline or DOI induce potent cognitive, perceptual and mood changes in humans mostly via activation of the serotonin 5-HT2A receptor (5-HT2AR), which belongs to the G protein-coupled receptor (GPCR) family of neurotransmitter receptors. All drugs classified as serotonergic psychedelics are 5-HT2A agonists, however, not all 5-HT2A agonists are capable of inducing a psychedelic state in humans. Thus, we can phenotypically classify drugs targeting 5-HT2AR in two categories based on their ability to induce such altered state of consciousness: psychedelic and non-psychedelic 5-HT2AR agonists. In rodents, this classification is paralleled by the ability of psychedelic 5-HT2AR agonists to induce a distinct paroxysmal head movement known as head-twitch response (HTR). Although the quintessential effect of psychedelics in humans cannot be replicated in animals, HTR serves as a surrogate to explore the differential behavioral pharmacology of these drugs. Tolerance and cross-tolerance builds up after repeated exposure to psychedelics via desensitization of 5-HT2AR. In the present study we employ the HTR model to explore the differential action of psychedelic and non-psychedelic 5-HT2AR agonists on behavioral tolerance, and potential mechanisms behind 5-HT2AR desensitization.

Methods: We set up a custom fully-automated HTR detection system for mice. The system relies on a small neodymium magnet implanted on the dorsal surface of the skull, and a magnetometer that registers the movement of the mouse head. Additionally, we developed a script on MatLab for the automated detection of HTR events. All drugs described in the method section were administered intraperitoneally (i.p.). Experiments were conducted in accordance with NIH guidelines, and were approved by the corresponding committee.

Results: Firstly, we validated our system and the automated detection script by assessing the well-known 5-HT2AR-dependance of HTR in 5-HT2AR-knock-out (KO) mice and control littermates. The magnetometer registered a robust induction of HTR in control mice injected with DOI (0.5 mg/kg) that did not occur in 5-HT2AR-KO mice.

Beta-arrestin 2 (Barr2) activation is a mechanism commonly observed in the development of tolerance to GPCRs. Hence, we next aimed to study the effect of repeated administration (every 24 h for 5 days) of DOI (1 mg/kg) to Barr2-KO and control mice. Consistent with previous results, both genotypes showed comparable HTR counts during the first administration of DOI. The following doses of DOI reduced the total number of HTR per session, indicating the development of tolerance. The evolution of this tolerance was comparable between both genotypes indicating that such phenomenon is Barr2-independent. Our results are consistent with previous reports that demonstrate, in vitro in mammalian cell tissue culture, that the mechanism through which 5-HT2AR desensitization occurs is Barr2-independent.

The robust attenuation of HTR count after repeated administration of DOI prompted us to study how psychedelic and non-psychedelic 5-HT2AR agonists affect the development of tolerance. The 5-HT2AR agonists LSD (psychedelic) and lisuride (non-psychedelic) greatly differ in their subjective effects in human despite their structural similarity. Control mice were administered LSD (0.2 mg/kg) or lisuride (maleate, 0.4 mg/kg) every day for 4 days. As expected, LSD induced a marked increase of HTR count on day 1 that was attenuated in the consecutive days of treatment (days 2-4). On basal conditions (i.e., absence of drug) mice showed a low frequency of spontaneous HTR. Interestingly, on day 1, lisuride not only failed to induce HTR, but it significantly blocked the spontaneous occurrence of HTR. On the consecutive days of repeated administration of lisuride (days 2 - 4), a partial recovery of baseline HTR occurred.

Cross-tolerance between psychedelics is well documented, therefore, we next aimed to explore cross-tolerance between psychedelic and non-psychedelic 5-HT2AR agonists. Mice that received lisuride for 4 consecutive days were administered LSD (0.2 mg/kg) on day 5. Surprisingly, these mice showed a trend toward increase in HTR count compared to naïve mice treated with LSD.

In light of the opposite effects of lisuride and LSD on HTR induction and development of tolerance, we tested the agonist properties of both drugs in HEK293 cells stably expressing 5-HT2AR. We observed that both LSD and lisuride had comparable ability to induce $Ca2+$ mobilization; thus confirming their agonism on 5-HT2AR.

Conclusions: We set up and validated a system for the automated detection of HTR to investigate the behavioral pharmacology of the 5-HT2AR receptor in mouse models. More specifically, we determined, in vivo, that tolerance to 5-HT2AR psychedelic agonist DOI is Barr2-independent. We confirmed in vitro the 5-HT2AR agonist properties of the psychedelic drug LSD and its non-psychedelic analogue lisuride. Our results suggest that 5-HT2AR agonists that differ in their ability to induce psychedelic effects in humans also differ in their ability to produce behavioral tolerance to HTR in mice. Cross-tolerance between psychedelics is well established, yet our data suggests that cross-tolerance might not be transversal to all 5-HT2AR agonists. Further work is granted to delve into alternative pathways of 5-HT2AR desensitization and how they are differentially affected by 5-HT2AR agonists.

Keywords: Serotonin 5-HT2A Receptor, Hallucinogens, Tolerance, Behavioral Phenotyping, Animal Models

Disclosure: Nothing to disclose.

M227. Infant Biobehavioral Foundations of Adolescent Binge Drinking and Alcohol Intake: A Nonhuman Primate Model

J. Dee Higley, Elizabeth Wood, Maribeth Champoux, Stephen Suomi*

Brigham Young University, Provo, Utah, United States

Background: Early identification of biological markers that predict alcohol abuse disorders is a primary focus of NIAAA. One potential marker that has received a great deal of support is early temperament. Temperament is the genetically-mediated, biologically-based foundation of personality and future psychopathology. As such, it is stable across time and predictive of future risk for pathological behaviors. The Neonatal Behavioral Assessment Scale (NBAS) is a standardized series of tests used to test temperament and neurocognitive functioning in infants, measuring visual and auditory orienting, motor maturity, and emotionality. These testing scales were adapted for use in rhesus monkeys from measures used by researchers and pediatricians to test human neonates and infants early in life. Studies show its utility in detecting developmental abnormalities and that it is predictive of future normative and psychopathological development. Based on findings from these studies, we hypothesized that adolescent alcohol binging and relatively high alcohol intake could be predicted from an assessment of infant neurocognitive and temperamental traits using the NBAS.

Methods: Subjects (N=145) were 14-day-old, infant rhesus monkeys, assessed using the NBAS. Infants were reared in one of two conditions: Nursery-reared-removed from their mothers at birth and reared in a highly standardized neonatal nursery ($n = 82$) for the first 30 days of life. After which, they were allowed to interact with other peers each day. The other subjects were reared in a control condition with parents, other same-aged playmates and their mothers (Mother-Reared—$n = 63$), a condition that approximates the natural rhesus monkey condition. As adolescents (about 3.5 years later), subjects were allowed unfettered access to a sweetened-alcohol solution for 1-hour/day, 4 days/week, over 5-7 weeks. Subjects drank in one of two condtions: while housed alone ($n = 70$) or socially in their home cage ($n = 55$). They were neither food or water deprived during the alcohol intake phase of the study.

Results: Controlling for sex, rearing, and drinking conditions, analyses showed that alcohol intake was predicted by neonatal orienting ability ($\beta = -.24$; $p < .05$) and motor maturity ($\beta = -.58$; $p < .01$). When the infants were tested for alcohol intake three years later, the adolescents with the lowest orientation and motor maturity scores as infants consumed the most alcohol independent of sex, rearing, or drinking condition. Males, and Nursery-reared subjects drank more than females and Mother-Reared subjects, respectively.

Conclusions: These findings suggest that neonatal temperament (likely because of its biological underpinnings) provide the foundational basis for adolescent binge drinking and excessive alcohol intake. Our results show evidence that the NBAS and similar assessments may be used to understand risk and to potentially intervene and prevent adolescent binge drinking and excessive alcohol intake in at-risk individuals.

Keywords: Adolescent Alcohol, Early Identification of Risk, Temperament, Early Life Adversity

Disclosure: Nothing to disclose.

M228. Long-Term Consequences of Adolescent Cannabinoid Exposure: A Closer Look at Reward Behaviors and Circuitry

*Travis Todd, Michael Aaberg, Lucas Dwiel, Wilder Doucette, Jibran Khokhar**

University of Guelph, Guelph, Canada

Background: Adolescent cannabis use occurs commonly, affects neurodevelopment, and results in behavioral changes related to reward and motivation. These reward-related changes have been studied in humans in the context of "the gateway hypothesis" and the "amotivation syndrome," however the causal nature of these two associations remains unknown. Thus, we were interested in whether Δ9-tetrahydrocannabinol (THC) exposure during adolescence would influence reward related behaviors in adulthood, and the neural correlates of these changes.

Methods: We assessed the effects of adolescent THC (or vehicle) treatments (post-natal day 28-42; 6 mg/kg i.p.) on: (a) free-access 2-bottle choice alcohol (20% v/v) drinking; (b) context-based instrumental food reward acquisition, extinction, renewal and reinstatement; and (c) limited access sweet-fat food binge-like eating (n=5/group). In a subsequent study, we assessed the effects of adolescent THC (or vehicle) treatment on the acquisition and extinction of Pavlovian autoshaping (sign-tracking) behavior (n=16/group). We also performed local field potential recordings from regions of the brain reward circuit in the sign-tracking cohort (n=5/group) using custom built arrays targeting the nucleus accumbens, orbitofrontal cortex, and medial prefrontal cortex.

Results: Adolescent THC treatment significantly impaired the motivation to lever press for a food reward in the instrumental task; both THC treated groups showed decreased responding throughout the entire acquisition period. Extinction or renewal of lever pressing did not differ between groups. Lastly, THC-treated animals displayed decreased binge-like sweet-fat food consumption in a limited-access paradigm. In the sign-tracking study, adolescent THC treatment significantly increased sign-tracking compared to vehicle treatment. This study suggests the adolescent THC exposure may produce long-term changes in reward-related behaviors. A hyperconnectivity (increased coherence) phenotype was observed in the THC treated animals compared to the vehicle treated animals across both cortico-limbic (nucleus accumbens and orbitofrontal cortex) and cortico-cortico (orbitofrontal cortex and prelimbic cortex) nodes (Cohen's d=1.11).

Conclusions: These behavioral and neural circuit findings are consistent with those observed in patients and begin to uncover the causal underpinnings of the long-term consequences of adolescent THC exposure.

Keywords: Cannabis Use, Adolescents, Mesolimbic Reward Circuitry

Disclosure: Nothing to disclose.

M229. Long-Term Self-Maintained Treatment (Aerobic Exercise) Blocks Incubation of Cocaine and Nicotine Craving and Multi-Triggered Relapse

Marilyn Carroll, Ben Dougen, Lydia Fess, Jack Smethells, Natalie Zlebnik*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Addiction to stimulants such as nicotine and cocaine continues to be a repetitive and devastating problem for many, and it has serious morbidity and mortality consequences. After drug use stops there is an incubation of craving period for these drugs that accelerates over weeks to months, but treatments end after several weeks. Thus, relapse occurs after treatment when craving is accelerating. In males we have proposed a model of self-maintained treatment to block the incubation of cocaine craving over extended time periods after abstinence (Zlebnik & Carroll 2015), and recently we extended that study to examine sex differences in incubation of cocaine vs. nicotine craving. In the first study, after drug self-administration was established and allowed to stabilize for several weeks in female and male rats, drug access was terminated, and rats were moved to another environment, a plastic home cage with a running wheel attached. For half the groups, the animals can run in the wheels, and for the other half rats can enter the wheel, but

it is locked. In these studies, potential for relapse was examined by testing for incubation of craving over short intervals (3 or 7 days) vs.long (30 or 28 days), for cocaine or nicotine, respectively, and then returning rats to the operant self-administration chamber to be tested for relapse responding on the original drug self-administration equipment that stimuli associated with the drug and responses on the drug vs. inactive levers were counted, but there was no drug access. In a second study, a similar procedure was used, but rats received multiple stimuli in the operant chamber: such as: the self-administered drug, other drugs, cues, common drugs (caffeine, nicotine), yohimbine (stressor), and combinations.

Methods: To examine the effects of aerobic exercise on incubation of craving rats were allowed to self-administer cocaine (0.4 mg/kg) or nicotine (0.03 mg/kg) during 6 h sessions for 10 days. After a 10 -day extinction period, rats in the incubation study were removed to a different environment, a clear plastic rectangular cage that was different then the octagonal stainless-steel operant chamber they formerly occupied, and the clear plastic cage was attached to a running wheel. Half of the rats for each drug studied could run in the attached running wheel, and half could enter the attached wheel, but its turning action was locked. In each drug/treatment condition rats were allowed access to the wheel 6 h a day for 30 or 28 days for cocaine and nicotine, respectively. The daily food allotment and water were provided in the plastic cage during this time. At the end of the incubation study rats were reintroduced to the operant chamber and re-exposed to cocaine-paired cues to examine cocaine- or nicotine-seeking behavior under extinction conditions. In the multi-triggered relapse studies rats were allowed to self administer cocaine or nicotine for 10 days and were then placed into abstinence for 21 days and provided access to a locked or unlocked wheel. Rats were then returned to the operant chamber, and lever responses were recorded while they received priming conditions each separated by a few days, such as: the self-administered drug, other drugs, cues, common drugs (caffeine, nicotine), yohimbine (stressor), and combinations.

Results: In the incubation of craving study for cocaine, rats with access to a locked wheel during 30 days of withdrawal had greater cue-induced cocaine-seeking than rats that had 3 days of access to a locked running wheel. Cocaine seeking was elevated at 30 days vs. 3 days of withdrawal indicating incubation of drug-seeking (or craving) had occurred. Cocaine seeking was reduced in females and males in the 30-day groups that were exposed to the unlocked wheel (vs. locked), but not in the 3-day group. Thus, wheel running reduced incubation of cocaine craving in the 30-day groups compared to 3 days groups in both females and males. These results indicated that incubation of cocaine-seeking was suppressed by access to exercise for 30 days in females. Similar results were found in the nicotine 28-day nicotine condition for females, but males did not show an incubation of craving effect. This was consistent with results of the multi-triggered relapse study with cocaine and nicotine, access to an unlocked running wheel reduced extinction and reinstatement of drug-seeking, with greater reductions in females than males. In the locked wheel group, female rats showed greater reinstatement of cocaine and nicotine seeking than males. With the unlocked wheel, reinstatement was reduced in both males and females, and there were no sex differences.

Conclusions: Voluntary aerobic exercise (wheel-running) was an effective intervention to reduce incubation of craving for cocaine in female and male rats in the 30-day withdrawal groups. Similarly, voluntary aerobic exercise reduced incubation of nicotine craving in female rats in the 28 day vs. 7-day exposure group. However, with nicotine, incubation of craving was reduced only in the female group with 28-day access (vs. 7 day) to nicotine withdrawal. These findings are consistent with a recent report of reduced incubation of methamphetamine craving by voluntary choice of social interaction (Venniro et al. 2018). In a second study, multi-triggered relapse was also reduced by voluntary aerobic exercise during prolonged abstinence. These long term, voluntary, self-maintained treatments offer great promise for reducing incubated, accelerated craving and relapse that occurs weeks-months after treatments end.

Keywords: Incubation of Craving for Cocaine and Nicotine, Multi-Triggered Relapse, Prevention of Relapse by Voluntary Aerobic Exercise

Disclosure: Nothing to disclose.

M230. Nicotine Administration Modifies the Developmental Trajectory of Brain Networks in the Adolescent Rat

Robin Keeley, Pei-Jung Tsai, Tom Mayer, Hanbing Lu, Yihong Yang, Elliot Stein*

National Institute on Drug Abuse, Baltimore, Maryland, United States

Background: Smoking remains a pervasive health burden, with 20% of the world's population engaging in regular smoking. Approximately 88% of smokers begin smoking before the age of 18, during adolescence. Clinical data support that the earlier one starts to use any nicotine product, the more difficult it is to quit. Adolescence is an evolutionarily conserved developmental period characterized by distinct, non-linear transitions in brain circuitry and behavior. In preclinical models, adolescent nicotine exposure can have both short- and long-term consequences on brain function and behavior, although global consequences on brain network function have yet to be clearly identified. In human populations, using resting state functional connectivity (rsFC), various brain circuits change as a function of nicotine dependence, although it remains unclear whether these changes predisposed subjects to smoking or were the direct result of smoking itself. Preclinical models of nicotine exposure in adolescence offer a unique opportunity for insight into the direct, longitudinal consequences of nicotine administration. Given the pervasive burden of smoking on health and society at large, a better understanding of the development of nicotine addiction from adolescence through adulthood may inform treatment interventions.

Methods: We exposed adolescent (postnatal day (p33)) and adult (p68) rats to 6 continuous weeks of saline, low (1.2 mg/kg/d) or high dose (4.8 mg/kg/d) nicotine (N = 10-13/group). Nicotine was passively administered continuously using osmotic mini-pumps. Before nicotine administration and every 2 weeks after administration for 6 weeks, nicotine dependence was assessed using a precipitated withdrawal test, wherein 1.5 mg/kg s.c. of mecamylamine, a nicotinic receptor antagonist, was administered, and rats were observed for somatic signs of withdrawal in a distinct contextual chamber and compared to withdrawal signs following an injection of saline, administered in a second, distinct contextual chamber. Preference for the withdrawal-paired chamber was quantified as an aversion score. Immediately after preference testing, rats were lightly anesthetized using a combination of low dose isoflurane (0.25-0.75%) and dexmedetomidine (0.015 mg/kg/h). High-resolution anatomical images and BOLD functional MRI (fMRI) data were acquired using a Bruker 9.4 T/30 cm scanner. Resting BOLD data were acquired in three 15 min sequential sessions. Immediately after the final scanning session, rats were euthanized, and their brains were harvested and processed for autoradiography quantification of nicotine acetylcholine receptor (nAChR) binding.

Resting BOLD imaging analysis consisted of identifying developmentally regulated circuits in saline-exposed rats followed by determining the effects of nicotine on these developmentally

regulated circuits. We set aside one of the three resting scans for each saline treated rat for the former analysis and included all remaining resting scans for the latter analysis. A whole brain analysis was conducted including ~90 unilateral and bilateral regions of interest (ROIs), spanning across cortical and subcortical regions. Using randomization and bootstrapping methods, group correlation matrices were generated for each time point and age group, and all edges between the ROIs were tested for significant AGE (adolescent or adult) by TIME (0, 2, 4 or 6 weeks) interaction effects.

Results: As expected from published data using cytoarchitectonic and tracer methodologies, a subset (~30%) of all edges tested demonstrated statistically significant developmental changes ($p < 0.01$). The developmental trajectory of these edges, i.e., the directionality, magnitude, and rate of change in rsFC between ROIs over the observed period of 6 weeks, varied as a function of the implicated ROIs. For example, connectivity both within insular structures and between insular and subcortical structures (including striatum and thalamus) were stable by p61. Conversely, connectivity within frontal regions, including cingulate and orbital frontal cortex, and between frontal and subcortical regions (including hippocampus, striatum and thalamus) did not reach adult levels until p75. Initial analysis of nicotine exposure on the identified developing circuits demonstrates that nicotine can developmentally delay changes in connectivity, specifically targeting frontal cortical regions and their connections to subcortical areas. For example, connectivity between the hippocampus and medial prefrontal cortex showed significant effects of nicotine. These results are paralleled by significant interactions between AGE (adolescent or adult) and DOSE (saline, low and high nicotine) for nicotinic receptors from brains collected immediately after the last scanning period in the same cortical regions showing developmental effects of nicotine, including insula, cingulate and orbital frontal cortical regions ($p < 0.05$).

Conclusions: Results from this study highlight the developmental sensitivity of specific brain circuits and the differential effects of nicotine on these circuits, allowing us to define those connections and developmental stages most sensitive to nicotine to use them as specific targets for treatment strategies, ultimately influencing clinical investigations.

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Keywords: Adolescence, Nicotine, Rat models, Resting State fMRI

Disclosure: Nothing to disclose.

M231. Striatal Connectivity With Prelimbic and Orbitofrontal Cortex Correlates Strongly With Compulsive Self-Administration of Methamphetamine

Betty Jo Salmeron, Yuzheng Hu, Hong Gu, Irina Krasnova, Jean Lud Cadet, Elliot Stein, Yihong Yang*

National Institute on Drug Abuse, Baltimore, Maryland, United States

Background: The balance between a putative "go" circuit (striatum-orbitofrontal cortex (OFC)) and a putative "stop" circuit (striatum-dorsal anterior cingulate cortex (dACC)) correlates with the severity of human cocaine dependence, while each circuit alone only marginally correlates with severity. Individual differences in the relative strength of these circuits before exposure to drug may predispose to or protect from future compulsive use while changes subsequent to drug intake may also contribute to compulsive use. In a rat model of stimulant dependence (self-administration of methamphetamine despite foot shock), we used fMRI to examine striatal connectivity to OFC and prelimbic (PrL) cortex across the development of compulsive drug use.

Methods: Adult male Sprague-Dawley rats were trained to self-administer (SA) methamphetamine (METH) (n=18) or saline (SAL) (n=11) 9 h/day under an Fr-1 schedule with 20-second timeout. A 5-second light-tone cue was paired with the active lever but not inactive lever. After 20 days of SA, active lever presses were paired with foot shocks (FS) of increasing intensity for 5 days. Three days and 30 days after the end of the FS phase, rats underwent a 30-minute extinction session during which lever presses resulted in cue presentation in the absence of drug or shock. Resting-state BOLD scans were obtained at baseline, after the SA phase, FS phase and the 30-day abstinence extinction session. One-way ANOVAs were applied to lever press data across the SA and FS phases. Escalation during SA and decline during FS were computationally modeled. A Compulsivity Index (CI) was calculated by normalizing model estimated SA on the last day of FS to that on the last day of SA. K-means clustering of CI divided METH SA rats into shock sensitive (SS) and shock resistant (SR). Seed based whole brain connectivity was calculated with seeds in PrL and OFC and submitted to 3 ×4 linear mixed effects ANOVAs with GROUP (SR, SS, SAL) and SESSION (baseline, SA, FS, abstinence) as factors. Correlations of CI to striatal-PrL and striatal-OFC connectivity as well as the balance of these circuits at each time were calculated using striatal regions showing significantly different connectivity based on the ANOVA results.

Results: Rats quickly learned to SA METH but not SAL ($F(4.91,73.67) = 25.34$, $P < 0.00001$). All METH SA rats reduced SA in the face of FS ($F(2.63, 44.64) = 22.81$, $P < 0.00001$) but to greatly varying degrees. K-means clustering of the CI yielded 7 SR and 11 SS rats ($T(16) = 10.24$, $P < 0.00001$) who did not differ on amount of drug taken during the SA phase ($T(16) = 0.48$, $P = 0.64$). A significant GROUP x SESSION interaction was seen between the OFC seed and striatum encompassing nucleus accumbens and extending caudally and superiorly along the medial wall into the dorsal striatum. This putative "go" circuit did not differ at baseline but increased in strength after METH SA, was still elevated after FS but returned to baseline levels after 30 days abstinence. A significant GROUP x SESSION interaction was seen between the PrL seed and ventral striatum. This putative "stop" circuit weakened in all METH SA rats after SA but returned towards baseline after FS in SS rats while it weakened further in SR rats. It did not differ from SAL rats at baseline nor after 30 days of abstinence. The balance of "go" and "stop" circuits similarly increased after METH SA, but trended towards baseline after FS in SS rats, while it remained elevated in SR rats before returning to baseline in all METH SA rats after 30 days of abstinence. The balance between these circuits ("go" – "stop"), especially the change in this balance from the end of SA to the end of FS, correlated strongly with CI, but only in SR rats ($R= 0.96$, $P= 0.00078$), not SS rats ($R= -0.22$, NS). "Go" and "stop" circuits after FS individually correlated positively and negatively, respectively, with CI in SR rats, with "go" – "stop" correlating significantly stronger than "stop" alone but only marginally stronger than "go" alone. These circuits did not correlate with CI at baseline nor end of SA in either subgroup. Nor did the change from baseline to SA predict CI in either group. They did not correlate with lever presses nor drug infusions at the end of SA in either group.

Conclusions: We combined long access SA with SA in the face of FS punishment to capture the loss of control over drug use in the face of negative consequences that is the key feature of addiction. Only 7 of 18 rats with 20 days of long access SA went on to develop compulsive SA after FS was introduced. Unique changes in a putative "go" circuit (OFC-striatum) and a putative "stop" circuit (striatum-PrL) after experiencing FS punishment of SA identify both of these circuits as important for aberrant SA in the face of punishment. Stronger correlation to the difference of the circuits indicates that, even in this rat model, individual

differences in the contribution of drive to use and control over impulse are important in producing compulsive drug use. We found no evidence that circuit strength before exposure to SA in the face of FS identifies individuals vulnerable to developing compulsive SA. Human analogues of these circuits have already shown a strong correlation to severity of dependence and may serve as individualized treatment targets in stimulant addiction.

Keywords: Addiction Circuitry, Individual Differences, Compulsive Models of Drug Use, Resting State Functional Connectivity, Stimulant Dependence

Disclosure: Nothing to disclose.

M232. Fentanyl Vapor Self-Administration in Mice: A Novel Non-Invasive Pre-Clinical Opioid Addiction Model

Khaled Moussawi, Maria Ortiz, Brendan Tunstall, Antonello Bonci, George Koob, Leandro Vendruscolo*

National Institute on Drug Abuse Intramural Research Program/NIH, Catonsville, Maryland, United States

Background: Opioid addiction is a growing problem in the United States and deaths from opioid overdoses are rising exponentially, with fentanyl alone accounting for nearly half these deaths. Although mouse models have been critical for the investigation of opioid-related brain and behavior changes, models of opioid addiction are limited. Currently, intravenous (IV) drug self-administration is considered the "gold standard" model in the addiction field. However, maintaining catheter patency in mice, especially in prolonged training protocols and conditions of extended access to the drug is challenging. Here, we describe the development of a non-invasive fentanyl vapor self-administration model of opioid addiction in mice that bypasses the limitations of the IV self-administration model.

Methods: Mice are trained to self-administer fentanyl by nosepoking a hole in an air tight operant chamber. This activates a custom-built device that delivers vaporized fentanyl (dissolved in a mixture of vegetable glycerol/propylene glycol) to the chamber. Each chamber is equipped with an active and an inactive nosepoke (NP) hole. An active NP results in vapor delivery for 1.5 or 5 sec accompanied by a light stimulus for 60 sec, and initiation of a 60 sec timeout period during which NPs are counted but are inconsequential. A vacuum system connected to the chambers actively clears the vapor in less than 60 sec. Air flow is controlled with a flow meter set at 1 L/min. To further determine whether fentanyl vapor was pharmacologically relevant, mice were tested in the hot-plate test after exposure to 4 passive vapor deliveries (2 sec each) over 8 min for assessment of fentanyl-induced analgesia. We also determined fentanyl concentration in the blood in response to different fentanyl vapor concentrations.

Results: Mice readily learned to self-administer fentanyl vapor over 1-h sessions at 5 and 10 mg/ml and to discriminate between the active and inactive nosepoke holes. Mice self-titrated their fentanyl vapor intake to the dose of vaporized fentanyl, i.e., the number of fentanyl vapor deliveries was inversely related to the fentanyl dose. Further, mice escalated their fentanyl vapor intake over a period of 4 weeks. After self-administration, mice underwent extinction training over 2-3 weeks during which they were placed in the operant chamber in the absence of discrete cues or fentanyl vapor. Mice successfully extinguished their nosepoke response and showed robust reinstatement to drug seeking when presented with a cue previously associated with fentanyl vapor delivery. Mice that received passive fentanyl vapor exposure at 3, 10, and 30 mg/ml exhibited a dose-dependent increase in the latency to nociception. Blood fentanyl concentration was directly correlated with the concentration of delivered fentanyl vapor.

Conclusions: We developed and validated a non-invasive mouse model of opioid addiction. Given the availability of numerous behaviorally selected and transgenic mouse strains, and the myriad of imaging modalities and genetic tools available for mice, the present model has the potential to provide an unprecedented understanding of the neurobiology of opioid addiction.

Keywords: Mouse models, Opioid addiction, Fentanyl, Vapor

Disclosure: Nothing to disclose.

M233. Individual Differences in MDPV Self-Administration in Rats: Inappropriate and Shock-Punished Responding

Gregory Collins, Brenda Gannon, Michelle Doyle, Agnieszka Sulima, Kenner Rice*

University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

Background: Synthetic cathinones function as cocaine-like inhibitors or amphetamine-like substrates of monoamine transporters; however, a subset of these drugs (e.g., MDPV, α-PVP, and related analogs) are reported to function as significantly more effective reinforcers than cocaine or methamphetamine. In addition, we have also observed that a subset of rats (i.e., high-responders) develop unusually high levels of MDPV intake when they are allowed to self-administer MDPV (but not cocaine) under a fixed ratio (FR) 5 schedule of reinforcement during daily 90-min session. The goal of the current study was to directly compare responding for MDPV and cocaine under schedules of reinforcement that incorporated periods of signaled drug unavailability and intermittent foot-shock in order to determine if 1) MDPV engendered greater levels of inappropriate responding than cocaine; 2) MDPV-maintained responding was less sensitive to punishment than cocaine; and 3) MDPV high-responders engaged in more inappropriate responding and/or were less sensitive to punishment than MDPV low-responders, or rats that responded for cocaine.

Methods: Adult male Sprague Dawley rats (n=16 for MDPV, n=10 for cocaine) were trained to self-administer 0.032 mg/kg/inf MDPV, or 0.32 mg/kg/inf cocaine under a fixed ratio (FR) 1 schedule of reinforcement. After a 10-day acquisition period, dose substitution was used to generate full dose-response curves for each MDPV (0.001-0.1 mg/kg/inf) or cocaine (0.032-1 mg/kg/inf) under a multiple component, FR5 schedule of reinforcement in which drug was available during three 30-min blocks separated by 5-min periods of signaled unavailability (e.g., blackouts). Subsequently, all rats were transitioned to 90-min sessions in which either MDPV (0.032 mg/kg/inf) or cocaine (0.32 mg/kg/inf) was available for responding under an FR5, with approximately every other (2 of every 4) infusion delivered in conjunction with a 0.5-sec foot-shock (0.05-0.7 mA). Shock intensities were evaluated in ascending order, with each intensity evaluated for 3 consecutive sessions, and separated by at least 3 sessions (and until responding stabilized) in which responding for MDPV or cocaine was not paired with shock.

Results: Rats rapidly acquired responding for MDPV and cocaine. When evaluated under the multiple component FR5 schedule, a subset of rats (n=7) responding for MDPV exhibited high levels of inappropriate responding (i.e., responding during post-infusion timeouts and inter-component blackouts), whereas all other rats made few inappropriate responses regardless of whether they were responding for MDPV (n=9) or cocaine (n=10). MDPV high-responders were also less sensitive to the punishing effects of foot-shock, requiring shock intensities of ~0.5 mA to decrease drug intake to 50% of their un-shocked level

of intake, whereas MDPV low-responders and cocaine rats only required shock intensities of ~0.3 mA. There were no differences among the rats with regard to their behavioral responses to non-contingent foot-shock.

Conclusions: Previous studies have shown that rats provided extended access to cocaine can develop compulsive-like patterns of cocaine self-administration (e.g., increased levels of intake, and insensitivity to punishment). The current studies provide direct evidence that a subset of rats (i.e., high-responders) provided short access to MDPV, a synthetic cathinone and selective DAT/NET inhibitor, engage in similarly compulsive patterns of responding for MDPV, characterized by high levels of MDPV intake, responding during periods of signaled drug unavailability, and an insensitivity to shock-punished responding. Importantly, none of the MDPV low-responders, and none rats with an identical history of cocaine self-administration exhibited these compulsive-like behaviors. Together with anecdotal reports of compulsive use of "bath salts" in humans, these findings suggest that synthetic cathinones, such as MDPV, may be unique in their capacity to establish compulsive-like patterns of drug-taking.

Keywords: MDPV, Cocaine, Compulsive Models of Drug Use, Synthetic Psychoactive Cathinones

Disclosure: Nothing to disclose.

M234. The Effects of Acamprosate and CaCl2 on Prefrontal Cortical Function Depend on the History of Alcohol Exposure

*Patrick Melugin, Fei Wu, Grishma Pradhan, Aarron Phensy, Sven Kroener**

The University of Texas at Dallas, Richardson, Texas, United States

Background: Alcohol abuse leads to functional impairment of the prefrontal cortex (PFC), which weakens inhibitory control over excessive drinking, leading to increased alcohol consumption, forming a vicious cycle that contributes to alcohol addiction and dependence. Acamprosate is the leading medication approved for the maintenance of abstinence, shown to reduce craving in both animal models and human alcoholics. It has been hypothesized that acamprosate may reduce relapse by restoring balance of glutamatergic synaptic transmission in the PFC to facilitate inhibitory control over drug-seeking. We have previously shown that alcohol dependence induced by chronic-intermittent ethanol (CIE) exposure leads to increased N-methyl-D-aspartate receptor (NMDAR) function, which causes aberrant synaptic plasticity in the PFC and disruption of normal PFC function (Kroener et al., PLoS One, 2012). Treatment with acamprosate, or its active moiety calcium (CaCl2), prior to testing recovered the behavioral deficits in an attentional set-shifting task but did not significantly affect the synaptic dysfunction (Hu et al., ACER, 2015; Pradhan et al., Psychopharmacol., 2018). In order to better distinguish alcohol-induced effects on learning processes and goal-directed behavior from the pharmacological effects of high-level alcohol exposure (as they occur in CIE), we examined if mice that self-administer alcohol in brief daily training sessions show similar deficits in behavior and synaptic plasticity, and if so, whether these changes can be ameliorated by acamprosate or CaCl2.

Methods: C57BL/6 adult male mice were trained in an attentional set-shifting task that required them to switch from an egocentric response strategy to a cue-based (allocentric) response strategy to navigate a t-maze to obtain food rewards. Drug-naïve animals were trained on the initial response strategy before they learned to self-administer alcohol (or water) in daily 30-minute sessions. A separate cohort of animals underwent CIE in addition to operant self-administration. After several weeks of stable alcohol self-administration, mice (n = 9-11 per experimental group) were then treated twice-daily for 3 days with saline, acamprosate (Ca-AOTA, 200 mg/kg), calcium (CaCl2, 73.4 mg/kg), or a version of acamprosate in which calcium was replaced by sodium (Na-AOTA, 200 mg/kg). On the last day of treatment, animals were retested on the original (egocentric) response strategy to control for potential effects of alcohol treatment on long-term memory. On the next day, the effect of alcohol on cognitive flexibility was tested by requiring the mice to switch to a visual cue-based strategy to obtain the rewards. Finally, animals were sacrificed and acute slices of the medial PFC were prepared for whole cell patch-clamp recordings (n = 9-13 per group) to analyze changes in synaptic transmission at layer 5/6 pyramidal neurons. Data were analyzed using one- or two-way analyses of variance (ANOVA) as appropriate, followed by Bonferroni post hoc tests.

Results: Alcohol-exposed animals showed impairments in attentional set shifting, as well as an upregulation of the NMDA:AMPA ratio at PFC pyramidal neurons. Acamprosate (Ca-AOTA, but not Na-AOTA) and CaCl2 both ameliorated the behavioral deficits and recovered NMDA:AMPA ratios to levels similar to those seen in water-drinking controls. Mice that were exposed to high levels of alcohol via CIE in addition to operant alcohol self-administration showed the same alcohol-induced deficits in synaptic plasticity; however, under these conditions acamprosate or CaCl2 were ineffective in restoring NMDA:AMPA ratios. All effects reported here were significant at least at $p<0.05$, following correction for multiple comparisons.

Conclusions: These preclinical data suggest that even low levels of daily alcohol consumption alter synaptic function in the medial PFC and impair PFC-dependent cognitive flexibility. These results also indicate that the effect of acamprosate (or calcium) depends on the previous history of alcohol exposure. Acamprosate appears to be more effective at altering glutamatergic transmission in the PFC if mice drink under goal-directed conditions.

Keywords: Alcohol Seeking, Glutamate, Cognitive Impairments, Acamprosate, Prefrontal Cortex

Disclosure: Nothing to disclose.

M235. The Effects of Dopamine D3R Compounds on Oxycodone Self-Administration, Reinstatement and Antinociception in Female and Male Monkeys

Michael Nader, Kendall Woodlief, Jeremy Cornelissen, Jianjing Cao, Matthew Banks, Amy Newman*

Wake Forest School of Medicine, Winston-Salem, North Carolina, United States

Background: Opioid use disorder (OUD) has become a national problem, resulting in the current overdose epidemic. Although effective for treating pain, opioids have been shown to have high abuse liability. In addition, sex differences have been identified in opioid pharmacology, yet few preclinical studies have examined opioid self-administration in female subjects. Most drugs of abuse alter dopamine concentrations and recent studies indicate the dopamine D3 receptor (D3R) as a potential therapeutic target for OUD. The goal of the present study was to examine the effects of two novel and highly selective D3R compounds, the partial receptor agonist VK4-40 and the D3R-selective antagonist VK4-116 in monkey models of opioid abuse and analgesia.

Methods: Experiment 1: Oxycodone self-administration was studied in female (N=4) and male (N=3) cynomolgus monkeys. Monkeys were implanted with an indwelling intravenous catheter and self-administered oxycodone (0.001-0.56 mg/kg per injection) under a fixed-ratio (FR) schedule of reinforcement. After

determining an oxycodone dose-response curve in each monkey, the effects of VK4-116, VK4-40 (both at doses of 1.0-10 mg/kg) and the opioid receptor antagonist naltrexone (0.001-0.1 mg/kg), all administered intravenously 5-min prior to the session, were examined at an oxycodone dose at the peak of the dose-response curve and at a dose on the descending limb of the oxycodone dose-response curve. Following completion of this study, oxycodone self-administration was extinguished by substituting saline for oxycodone and the effects of each compound were studied alone and in combination with a dose of oxycodone that reinstated responding, administered intravenously 1-min prior to the start of the session. Finally, to confirm that the effects were due to an interaction between D3R and opioid effects, the highest dose of each compound was tested on food-maintained responding.

Experiment 2: Oxycodone-induced antinociception was studied in male rhesus monkeys (N=3) using a warm-water tail withdrawal procedure (see Cornelissen et al., J Pharmacol Exp Ther 365: 37-47, 2018). The subject's tail was shaved from 10-12 cm from the distal end weekly and immersed in a thermal container containing warm water. If the subject did not remove its tail by 20 s, the experimenter removed the animal's tail and a latency of 20 s was assigned. All latencies were recorded using a stopwatch. During each 15-min cycle, tail-withdrawal latencies were recorded from water warmed to 38°C, 50°C, and 54°C. In each successive cycle, the presentation of the warm-water stimulus was randomized. VK4-116 (10 mg/kg) and VK4-40 (1.0-3.2 mg/kg) and vehicle (250 mg/mL beta-cyclodextrin) were administered intravenously as a 60-min and 5-min pretreatment, respectively. Naltrexone (0.032 mg/kg) was administered intramuscularly (IM) as a 30-min pretreatment. Oxycodone (0.01-3.2 mg/kg, IM) was administered using a cumulative dosing procedure consisting of five to six 15-minute cycles composed of a 10-min drug pretreatment phase and a 5-min testing phase. 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: Experiment 1: Oxycodone self-administration was characterized as an inverted U-shaped function of dose in most monkeys. In general, in female monkeys the peak of the oxycodone dose-response curve was to the right (i.e., less potent) of the peak dose in male monkeys. When tested with the oxycodone dose that maintained peak rates, naltrexone and VK4-40, but not VK4-116, significantly ($p<0.05$) decreased responding. When tested with a dose of oxycodone on the descending limb, only naltrexone consistently increased response rates, shifting the oxycodone dose-response curve to the right. There were sex differences noted, such that VK4-40 was more effective in males compared to females. Two-way repeated measures ANOVA was significant for VK4-40 dose ($p=0.025$) and sex X dose interaction ($p=0.04$). Within each sex, dose was significant in males ($p=0.011$) but not females ($p=0.765$). After saline extinction, both naltrexone and VK4-40 significantly ($p<0.05$) attenuated the effects of 0.1 mg/kg oxycodone to reinstate responding. To confirm that the effects were not due to general rate suppression, the highest doses of naltrexone and VK4-40 did not significantly decrease food-maintained responding.

Experiment 2: Oxycodone produced dose-dependent antinociception at both noxious stimulus intensities. Acute pretreatment with the highest dose of VK4-116 (10 mg/kg) or VK4-40 (3.2 mg/kg) did not significantly alter the potency of oxycodone-induced antinociception. In contrast, naltrexone decreased the potency of oxycodone by approximately 10-fold.

Conclusions: The present findings show that the D3R partial agonist VK4-40, effectively decreased oxycodone self-administration and reinstatement, suggesting direct effects on the opioid reinforcement and on conditioned stimuli. Importantly, VK4-40 did not significantly attenuate oxycodone-induced antinociception, suggesting that D3R effects primarily influenced reinforcement. These studies suggest that co-administration of D3R compounds may attenuate the abuse liability of opioids without affecting their clinical utility in pain management.

Keywords: Opioid Addiction, Dopamine3 Receptors, Intravenous Drug Self-Administration, Antinociception, Nonhuman Primate

Disclosure: Nothing to disclose.

M236. Epigenetic Regulation of Cholinergic Neurons: Effects of Adolescent Alcohol Exposure

Fulton Crews, Ryan Vetreno, John P. Bohnsack, Subhash Pandey*

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States

Background: Binge drinking, and alcohol abuse are common during adolescence, and cause lasting pathology. Preclinical rodent studies find decreased basal forebrain cholinergic (i.e., ChAT+ and VAChT+) neurons that persist into adulthood (i.e., P56 – P220).

Methods: Wister rats were exposed to adolescent intermittent ethanol (AIE; 5.0 g/kg, i.g., 2-day on/2-day off from postnatal day [P]25 to P55) and assessed at P80 with or without exercise. Methylation of choline acetyltransferase was assessed by CHIP. Learning and reversal learning were assessed using the Morris Water Maze.

Results: AIE-induced a loss of cholinergic neuron markers (i.e., ChAT, TrkA, and p75NTR), reduced cholinergic neuron size, increased expression of the neuroimmune marker pNF-kappaB p65 following AIE exposure and continuing to P80. Rats allowed to exercise (wheel in cage) from P56 – P95 restored cholinergic neuron number. DNA methylation can silence gene expression. AIE caused a persistent increase in methylation of promoter regions on both the ChAT and TrkA gene, which was restored by wheel running. Exercise also restored the AIE-induced reversal learning deficits on the Morris water maze.

Conclusions: These data suggest AIE increases methylation of TrkA and ChAT, reducing expression of ChAT. Exercise restoration of loss of cholinergic neurons and reversal of DNA methylation suggest DNA methylation regulates cholinergic neuronal phenotype through gene silencing that is reversable.

Keywords: Acetylcholine Esterase Inhibtors, Muscarinic Receptors, Dementia, Adolescent Alcohol Use, Epigenetic Modification, Cognition

Disclosure: Nothing to disclose.

M237. Nicotine Self-Administration Modulates Choroid Plexus Function and Release of MicroRNAs Into the CSF

*Valeria Lallai, Amina Ahmed, James Fowler, Christie Fowler**

University of California, Irvine, Irvine, California, United States

Background: Circulating microvesicles in the cerebrospinal fluid (CSF) have been recently identified to contain a variety of signaling factors, such as proteins, enzymes, and RNA species. While microvesicles, or exosomes, have been implicated in a few pathological conditions, such as Alzheimer's disease and cancer, their importance in other aspects of physiological function is unknown. In the current studies, we sought to systematically

characterize whether nicotine acts directly on the choroid plexus to alter the release of miRNAs into the CSF.

Methods: Choroid plexus from the lateral, third and fourth ventricles were first examined for the expression of choline acetyltransferase (ChAT) and nicotinic acetylcholine receptor (nAChR) subunit mRNA expression. Next, rats underwent chronic intravenous nicotine or saline self-administration, and choroid plexus tissue and CSF were assessed for changes in miRNA expression. Since differences were found in miRNA expression, we then examined the expression of these circulating miRNAs both in vitro and in vivo.

Results: ChAT and nAChR subunit expression were found in the lateral, third and fourth ventricle choroid plexus sites, indicating that endogenous cholinergic signaling mechanisms are expressed in a site-specific manner. During intravenous nicotine self-administration, miRNAs were found to be differentially expressed and released from the choroid plexus. This was determined to be due to nicotine's direct actions on nAChRs, as administration of a nAChR antagonist prevented miRNA upregulation and release.

Conclusions: In conclusion, we provide evidence that nicotine acts directly on the choroid plexus to modulate the release miRNAs into the CSF. These data support the hypothesis that nicotine alters extracellular transfer of miRNAs, which could potentially lead to downstream changes in neuronal gene expression. In addition to nicotine dependence, findings from these studies may provide insight into normal physiological function and other pathological disease states.

Supported by the National Institute on Drug Abuse (NIH DA039658 to CDF)

Keywords: MicroRNA, Extracellular Vesicles, Exosomes, Nicotine

Disclosure: Nothing to disclose.

M238. PPARγ Agonism Modulates the Structural and Functional Landscape Induced by Chronic Cocaine Use

*Kelly Dineley, Andrea Dimet, Robert Fox, Sonja Stutz, Larry Denner, Kathryn Cunningham**

University of Texas Medical Branch, Galveston, Texas, United States

Background: Chronic cocaine use causes behavioral changes by altering brain structure and function. The rodent self-administration model parallels certain drug seeking behaviors seen in cocaine use disorder. One notable behavior is increased responsiveness to cocaine-paired cues in the cue reactivity task, a surrogate for self-reported cocaine craving in humans. This responsiveness is particularly observable following forced abstinence. Cocaine self-administering rats treated with a peroxisome proliferator-activated receptor-γ (PPARγ) agonist (pioglitazone) during forced abstinence exhibit significantly attenuated cocaine cue reactivity.

The mechanisms underlying pioglitazone-mediated attenuation of cocaine cue reactivity have yet to be elucidated. Since PPARγ is a transcription factor, one hypothesis is that the mechanism may involve induction of transcriptional targets. Previous work has demonstrated that many of the downstream targets of PPARγ are important to brain structural integrity. Several human studies have demonstrated widespread loss of white and gray matter in individuals with cocaine use disorder. We recently-published a study showing that pioglitazone decreased self-reported craving in subjects with cocaine use disorder simultaneous with improved white matter integrity (e.g., splenium and genu of the corpus callosum, posterior and anterior thalamic radiations). Using the rat self-administration model, we are focused on revealing the underlying structural plasticity that drives pioglitazone-mediated attenuation of cocaine cue reactivity.

Since PPARγ is involved in a complex with phosphorylated extracellular signal-regulated kinase (phospho-ERK), we explored the putative role of this complex in the mechanism. Phospho-ERK can act upon a signaling cascade which ultimately modulates transcription through cyclic-AMP response elements. Thus, we explored our transcriptomic results for enrichment of putative PPARγ and cyclic-AMP response elements (PPAREs and CREs) in addition to holistic analyses of the genes regulated by PPARγ agonism. We hypothesized that PPARγ- and ERK-mediated gene transcription attenuates cocaine cue reactivity through remodeling of the structural and functional landscape induced by repeated cocaine self-administration.

Methods: All rodent experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council) and with the approval of the Institutional Animal Care and Use Committee at UTMB. Brain tissue from rats that underwent a two-week self-administration cocaine (0.75 mg/kg/inf) paradigm followed by 30 days of forced abstinence and subsequent cue reactivity testing. Upon completion of the behavioral experiments, brains were harvested and used for next generation sequencing, immunohistochemistry, histological staining and immunoblot.

Results: RNA sequencing (RNA-seq) results were robust, identifying 12,036 genes in the hippocampus and 12,014 genes in the medial prefrontal cortex. Of these, 259 of the genes were significantly increased or decreased by PPARγ agonism in the hippocampus; in the prefrontal cortex, this number equaled 125. Roughly one-fifth of the genes identified in these brain regions contained PPAR-response elements (PPAREs), evidence that pioglitazone induced PPARγ-dependent gene transcription. Approximately 10% of the genes induced by pioglitazone contained CREs. However, this does not demonstrate enrichment for PPAREs compared to the total population of genes identified.

Further analysis using Ingenuity® Pathway Analysis revealed that genes regulated by PPARγ agonism were particularly involved in cell survival. In contrast to the overall gene population identified with RNA-seq, there was a statistically significant enrichment within cell survival pathways for genes containing PPAREs, suggesting that our hypothesized transcriptional mechanism specifically drives cell survival pathways in distinct brain regions.

Alongside our transcriptomic study, we tested for structural integrity using the Luxol Fast Blue stain and and other markers of structural integrity with immunohistochemistry. The Luxol Fast Blue stain results suggest that there is an interactive effect with cocaine and PPARγ agonism in the corpus callosum and in the dentate gyrus of the hippocampus.

Finally, immunoblotting experiments additionally support the hypothesis that structural and functional integrity are improved with PPARγ agonism by identifying alterations of aquaporin 4 and proteolipid protein 1 expression between cocaine self-administering rats treated with pioglitazone or untreated.

Conclusions: Our results support the hypothesis that pioglitazone induces both PPARγ- and ERK-mediated gene transcription to attenuate cocaine cue reactivity through remodeling of the structural and functional landscape induced by chronic cocaine use.

Keywords: Cocaine, ERK, Transcriptomics

Disclosure: Nothing to disclose.

M239. Serotonin 2 C Receptor (5-HT2CR) Genetic Variation Controls Cellular Function and Receptor Trafficking

Noelle Anastasio, Michelle Land, Lisa Elferink, F. Gerard Moeller, Kathryn Cunningham*

University of Texas Medical Branch at Galveston, Galveston, Texas, United States

Background: Serotonin neurotransmission through the 5-HT2CR within corticolimbic circuitry has been implicated in Parkinson's disease, depression, suicide, schizophrenia, and is a critical driver of cognitive and/or behavioral dimensions underlying relapse-related behaviors in cocaine use disorder. Single nucleotide polymorphisms (SNPs) of the human 5-HT2CR gene (HTR2C), located on the X chromosome, associate with behavioral phenotypes, psychiatric conditions, and response to psychiatric medications including atypical antipsychotics and antidepressants. A non-synonymous SNP of the human 5-HT2CR gene that converts a cysteine (Cys) to a serine (Ser) at amino acid codon 23 (Cys23Ser) appears to impact 5-HT2CR pharmacology at a cellular and systems level. The Cys23Ser SNP has been linked to changes in efficacy of psychiatric therapeutics and clinically to several psychiatric disorders and related behaviors, including impulsivity and cocaine cue reactivity, and thus may serve as a biomarker for cocaine use disorder-related behaviors. While the functional impact of this SNP is not well understood, overall the Ser23 variant could impact behavioral and pharmacological responses, possibly due to reduced function and a distinct subcellular localization profile. The Cys23Ser SNP may impact phenotypic behaviors and cellular function through alterations in the structural integrity of the 5-HT2CR protein, the efficiency of 5-HT2CR ligands and signal transduction mechanisms and/or receptor trafficking/recycling processes. Here, we tested the hypothesis that the Cys23Ser SNP fundamentally alters 5-HT2CR functional capacity via changes in receptor subcellular localization within the endocytic recycling pathway in vitro.

Methods: We engineered CHOp38 cells (CHO cells expressing synaptophysin/p38) to stably express the Cys23 allele or the Ser23 allele of the 5-HT2CR. We assessed intracellular calcium (Cai++) release to measure 5-HT2CR-mediated signaling in our two cellular lines. Western blotting and dual-labeled immunocytochemistry was used to detect localization of the 5-HT2CR with the plasma membrane and/or markers of the endocytic recycling pathway in cells expressing the Cys23 allele or Ser23 allele.

Results: Serotonin evoked concentration-related Cai++ release in the wildtype Cys23 (EC50=0.58 nM) and the Ser23 (EC50 2.29 nM) cells ($p<0.05$). The Ser23 variant demonstrated 43% lower maximum 5-HT-induced Cai++ release and a rightward shift in potency vs the Cys23 ($p<0.05$). Western blot and immunocytochemistry results show lower 5-HT2CR plasma membrane expression in the Ser23 vs the Cys23 cell lines ($p<0.05$); no differences in total protein expression between the Cys23 or Ser23 variant was detected. Subcellular localization studies show that both the Cys23 and Ser23 alleles can enter the recycling pathway essential for receptor resensitization. Interestingly, receptor distribution within this pathway is altered, with the Ser23 variant having decreased colocalization with an early endosomal marker ($p<0.05$).

Conclusions: The wildtype Ser23 variant exhibits a distinct pharmacological and subcellular localization profile vs. the Cys23 allele, which could impact aspects of receptor pharmacology in individuals expressing the Cys23Ser SNP.

Keywords: Serotonin 5-HT2C Receptor, SNP, g Protein Signaling, Receptor Internalization, Trafficking

Disclosure: Nothing to disclose.

M240. Neuronal-Specific Variants of LSD1 Modulates the Response to Psychostimulants

Maria Andres, Gianluca Merello, Verónica Noches, Marcela González, Montserrat Olivares-Costa*

Pontificia Universidad Católica de Chile, Santiago, Chile

Background: Lysine-specific demethylase 1 (LSD1) is an epigenetic modifier that regulates the expression of immediate-early genes (IEGs) in the brain. LSD1 splicing variants that include the micro-exon E8a, which encodes four amino acids, are expressed only in neurons (neuroLSD1). E8a inclusion starts early in brain development and its expression is highly regulated by neuronal activity. Mice null for neuroLSD1 show low anxiety behaviors and are unable to induce IEG in the brain in response to relevant stimuli, allowing to propose neuroLSD1 as an important player in molecular mechanisms that govern drugs of abuse-induced sensitization.

Methods: To test the hypothesis, we treated male and female adult wild-type (WT), heterozygous (HT) and null neuroLSD1 (KO) mice with acute and repeated doses of amphetamine (6 mg/kg ip) and assessed behavioral and molecular changes.

Results: neuroLSD1 HT and KO mice showed a similar significant increase in locomotor activity compared to WT mice, after an acute dose of amphetamine. However, they did not show a preference for the compartment associated with the drug in the conditioned place preference paradigm (CPP). Repeated amphetamine administration increased neuroLSD1/LSD1 ratio in several brain nuclei of WT mice, accompanied by a significant decrease of the IEG Nur77. As expected, no changes in Nur77 expression were observed in neuroLSD1 KO mice after an acute or repeated administration of amphetamine. All neuroLSD1 genotypes have similar content of dopamine, glutamate, and GABA in the striatum, hippocampus, and prefrontal cortex.

Conclusions: Our data show that neuroLSD1 is a crucial regulator of plastic changes induced by chronic psychostimulant administration and allow to suggest that neuroLSD1 as a potential target to treat drugs of abuse-induced compulsive behaviors.

Funded by Fondecyt Project N° 1150200 and PMI PUC 1566

Keywords: Epigenetics, Sensitization, Locomotor Activity, Amphetamine

Disclosure: Nothing to disclose.

M241. Using 3D Human Stem Cell-Derived Cerebral Organoids to Model the Impact of in Utero Drug Exposure on Early Neural Development

Kimberly Christian, Daniel Zhang, John Dani, Mariella De Biasi, Hongjun Song, Guo-li Ming*

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Early brain development relies on orchestrated interactions between intrinsic programs and cues from the local environment in utero. Perturbations in utero can lead to aberrant neural development in the fetus and long-term physiological and cognitive impairments that emerge at later developmental stages. Although it is widely recognized that prenatal exposure to drugs of abuse or alcohol can disrupt fetal development, more systematic investigations are needed to understand the etiopathology. In addition, there is a need for new translational models to evaluate the safety of therapeutic drugs that may be taken by women throughout pregnancy. A considerable challenge to these objectives has been the inability to access the developing human brain directly. To model human brain development

in vitro, we can generate human induced pluripotent stem cells (iPSCs) from adult somatic cells, which in turn can be differentiated into most human cell types in the body, including those found in the central nervous system. This cellular reprogramming strategy facilitates the investigation of neuronal development and neurological disorders using a renewable source of human cells. Building on this technology, we can model organogenesis by initializing the fate specification of iPSCs toward a target system or region, and then relying on self-organizational properties of differentiating cells to form 3D structures that recapitulate many features of developing biological systems. We have recently optimized technology and protocols to model brain development in the form of human iPSC-based 3D forebrain organoids. With this system, we can perform controlled experiments to model the consequences of prenatal exposure to perturbagens during brain development, using the most relevant human cell types.

Methods: For modeling the developing cerebral cortex using iPSC-based cell cultures, we use a miniaturized spinning bioreactor to provide structural support and enhanced nutrient and oxygen exchange. To reduce heterogeneity, we pre-pattern embryoid bodies to a forebrain cortical fate before transfer to the spinning bioreactor. These 3D cell cultures self-organize into organoids that acquire morphological, electrophysiological, and transcriptional features of the developing brain. We have begun to profile the impact of several drugs of abuse and alcohol, as well as therapeutic drugs, such as the antiretrovirals taken by pregnant women to prevent vertical transmission of HIV. Following chronic exposure to either drugs or alcohol in the cell culture medium, organoids are processed at several timepoints for RNA sequencing, morphological analysis, cell fate specification, neuronal proliferation and cell viability.

Results: Organoid cultures recapitulate many features of the developing human brain including the emergence of the proliferative ventricular, subventricular and outer subventricular zones that give rise to multiple brain regions. We are able to generate neuronal subtypes expressing markers for all six cortical layers, three subtypes of GABAergic neurons, as well as astrocytes that appear at later timepoints. Based on comparisons to published datasets characterizing human fetal brain development, these organoids can approximate the laminar organization and transcriptional dynamics of the developing cerebral cortex through the first two trimesters of pregnancy. Results from ongoing RNA sequencing experiments revealed differential gene expression following exposure to alcohol and drugs of abuse, which has generated a list of target genes for validation and further functional analyses.

Conclusions: Recently developed technology to generate 3D models of specific brain regions using human cells provides a new platform to model early human brain development. Using this approach, we can systematically evaluate how acute and chronic exposure to various drugs or environmental factors may alter the course of neuronal development, potentially leading to the disruption of neural circuit formation. This platform can be used not only for discovery-based studies of biological mechanisms underlying neural development under different conditions but also for diagnostic screens to evaluate new therapies.

Keywords: Brain Organoids, Neurodevelopmental Disorders, Substance Abuse, HIV Associated Neurocognitive Disorder

Disclosure: Nothing to disclose.

M242. Endogenous Neurosteroid (3α,5α)3-Hydroxypregnan-20-One (3α,5α-THP) Inhibition of Proinflammatory TLR4 Signaling in Cultured Macrophage and Neuronal Cells

*Irina Balan, Todd O'Buckley, Laure Aurelian, A. Leslie Morrow**

University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States

Background: Activation of toll-like receptor 4 (TLR4) signaling pathways plays a significant role in the pathogenesis of alcoholism, depression, traumatic brain injury, schizophrenia, multiple sclerosis, and Alzheimer's disease. The endogenous neurosteroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP, allopregnanolone) has protective activity in these conditions, but its mechanism of action is still poorly understood. Until recently TLR4 signaling was believed to be limited to glial cells in the brain. It is now known that neurons also express TLR4, but the mechanism of TLR4 activation and signaling as well as the role of 3α,5α-THP in the TLR4 signal regulation in neurons are still poorly understood. We recently demonstrated that 3α,5α-THP inhibits the innately activated TLR4 signal in the ventral tegmental area (VTA) of selectively bred alcohol-preferring P rats as well as LPS activation of Raw264.7 cells (Balan et al., under review). Here, we extend this work to cultured neuronal cells (Neuro 2 A) that innately express TLR4 receptors.

Methods: Mouse monocyte macrophage cells (RAW264.7) or mouse neuroblastoma cells (Neuro2a) that innately express TLR4 were obtained from American Type Culture Collection (Manassas, VA, USA). The cells were grown in Dulbecco's modified Eagle's medium (DMEM) (Gibco; Gaithersburg, MD, USA) supplemented with 10% fetal bovine serum (FBS, Gemini, West Sacramento, CA, USA), 1% penicillin/streptomycin 100 ×(Gibco) at 37°C in a 5% CO2 humidified atmosphere and refreshed with media lacking serum 16 h prior to experimentation.

Preparation of cell lysates, immunoblotting and co-immunoprecipitation were conducted as previously described. Total protein was determined by the bicinchoninic acid assay (BCA, Thermo Fisher Scientific, Waltham, MA, USA, Cat.# 23228 and Cat.# 1859078). The proteins (100 μg/lane) were separated by SDS–polyacrylamide gel electrophoresis, transferred to polyvinylidene fluoride membranes (PVDF, Bio-Rad, Cat.# 162-0177), blocked with 5% Blotting-Grade Blocker (Bio-Rad, Cat. # 1706404) or 5% BSA (for phosphorylated primary antibodies) and exposed to primary antibody overnight (4°C), followed by horseradish peroxidase-labeled secondary antibodies. Immunoreactive bands were visualized with the Plus-ECL kit reagents (Perkin Elmer, Waltham, MA, USA, Cat.# NEL105001EA) followed by exposure to high-performance chemiluminescence film (Hyperfilm ECL; Amersham). Quantitation was by densitometric scanning with a Bio-Rad GS-700 imaging densitometer. Each densitometric measurement was divided by the corresponding β-Actin densitometric measurement and the results are expressed as the mean β-Actin-adjusted densitometric units ± SEM.

Results: LPS activated the TLR4 pathway in RAW264.7 cells as evidenced by increased levels of pTAK1, TRAF6, NFkB p50, phospho-NFkB-p65, pCREB, HMGB1, and inflammatory mediators, including MCP-1 and TNFα. 3α,5α-THP (0.5–1.0 μM) substantially (~80%) inhibited these effects, indicating pronounced inhibition of TLR4 signaling. The mechanism of inhibition appears to involve blockade of TLR4/MD-2 protein binding, as measured by 3α,5α-THP (1 μM) and pregnenolone (1 μM) inhibition of TLR4/MD2 co-immunoprecipitation.

In neuronal N2a cells, LPS does not activate the TLR4 pathway, as evidenced by the failure to increase the levels of both phospho-NFkB-p65 and pCREB. However, transfection of these cells with GABA-A α2 subunit increased pCREB and its nuclear translocation, suggesting that GABA-A α2 protein activates the TLR4 signal in neurons. Moreover, the GABA-A α2-activated TLR4 signal in N2a cells involves the binding of TLR4 and GABA-A α2 as evidenced by co-immunoprecipitation of these proteins. 3α,5α-THP (1 μM) and pregnenolone (1 μM) inhibited the effects of GABA-A α2 transfection of Neuro2A cells on pCREB expression by 80-90%. Furthermore, 3α,5α-THP (55.9 ± 6.0% reduction, $p<0.01$) and pregnenolone (20.0 ± 2.9% reduction, $p<0.05$) inhibited the co-immunoprecipitation of TLR4 with GABA-A α2 subunit.

Conclusions: The data identify the ability of the endogenous neurosteroid 3α,5α-THP to inhibit pro-inflammatory signaling in macrophages and neuronal cells. In addition, we demonstrate binding of GABA-A α2 with TLR4 in neurons. The results suggest that inhibition of proinflammatory neuroimmune TLR4 signaling underlies protective effects of 3α,5α-THP in immune cells and brain, apparently involving blockade of protein-protein interactions that induce TLR4 signal activation. Future studies will address neurosteroid and TLR4 specificity to delineate the structural requirements for inhibition of pro-inflammatory signaling. These results may lead to new treatments for brain diseases that involve inflammation induced by TLR signaling.

Keywords: Allopregnanolone, Neurosteroids, Toll-Like receptors (TLRs)

Disclosure: Nothing to disclose.

M243. The Actin-Binding Protein Drebrin Mediates Opiate-Induced Behavioral and Structural Plasticity in the NAc

Abstract not included.

M244. Early Life Alcohol Exposure Primes Hypothalamic Microglia to Later-Life Hypersensitivity to Immune Stress: Possible Epigenetic Mechanism

Dipak Sarkar, Lucy Chastain, Tina Franklin, Omkaram Gangisetty, Miguel Cabrera, Pallavi Shrivastava, Shaima Jabbar*

Rutgers University, New Brunswick, New Jersey, United States

Background: Growing evidence has shown that developmental alcohol exposure induces central nervous system inflammation and microglia activation, which may contribute to long-term health conditions such as fetal alcohol spectrum disorders. These studies sought to investigate whether neonatal alcohol exposure during postnatal days (PND) 2-6 in rats (third trimester human equivalent) leads to long-term disruption of the neuroimmune response by microglia. We also sought to determine epigenetic factors by which developmental alcohol might program microglia to long-term disruption.

Methods: Neonatal rat pups (third trimester human equivalent) were fed by oral gavage a milk formula containing 11.34% ethanol (vol/vol), yielding a total daily ethanol dose of 2.5 g/kg (AF), or isocaloric control (PF), or they were left in the litter with the mother (AD) for 5 days (postnatal days 2-6). Two hours after the last feeding, some pups were sacrificed, and hypothalamus was dissected. Brains were collected and frozen at -80°C for later use for immunohistochemical staining of microglia or microglia were isolated from dissected mediobasal hypothalamus (MBH) for measurement of RNA, protein, DNA methylation, or for chromatin immunoprecipitation (ChIP). Rest of the pups were kept with the dam until PND 23 when they were then weaned and housed 2-3 animals/cage until they were utilized at PND 90. Adult animals were either sacrificed for basal measurements or were challenged with lipopolysaccharide (LPS) (100 µg/kg body weight) injected i. p., and sacrificed 2 h later. For measurement of stress hormones, tail blood was collected at baseline and trunk blood was collected 2 h after LPS. For immunohistochemical staining of microglia, brains were collected at baseline and post LPS and frozen at -80°C until use. In addition, microglia were isolated from dissected MBH for measurement of RNA, protein, DNA methylation, or ChIP at baseline and post LPS.

Results: Exposure to neonatal alcohol resulted in acute increases in activation and inflammatory gene expression in hypothalamic microglia including TNF-α and IL-6. Adults with neonatal alcohol pre-exposure (alcohol fed; AF) animals showed an exaggerated peripheral stress hormonal response to an immune challenge (lipopolysaccharides; LPS). In addition, there were significantly more microglia present in the hypothalamus of adult AF animals, and their hypothalamic microglia showed more Cd11b activation, TNF-α expression, and IL-6 expression in response to LPS. Interestingly, blocking microglia activation with minocycline treatment during PND 2-6 alcohol exposure ameliorated the hormonal and microglial hypersensitivity to LPS in AF adult animals. Investigation of possible epigenetic programming mechanisms by alcohol revealed neonatal alcohol decreased several repressive regulators of transcription in hypothalamic microglia, while concomitantly increasing histone H3 acetyl lysine 9 (H3K9ac) enrichment at TNF-α and IL-6 promoter regions. Importantly, adult hypothalamic microglia from AF animals showed enduring increases in H3K9ac enrichment of TNF-α and IL-6 promoters both at baseline and after LPS exposure.

Conclusions: These results suggest that neonatal alcohol activates microglia possibly by decreasing transcriptional repressors HDACs and H3K9ac, revealing a possible epigenetic mechanism for the adverse effects of alcohol on hypothalamic inflammation and neuroimmune activation. Furthermore, concomitant long-lasting epigenetic changes in HDACs and H3K9ac in adult hypothalamic microglia from animals pre-exposed to neonatal alcohol suggest a possible epigenetic mechanism for the long-term immune disruption due to hypothalamic microglial priming.

Keywords: Fetal Alcohol Syndrome, Neuroimmune Activation, Stress Reactivity, Epigenetic Modification, Hypothalamus

Disclosure: Nothing to disclose.

M245. Effects of Naltrexone on Large Scale Network Dynamics of the Executive Control and Salience Network in Methamphetamine Use Disorder

Milky Kohno, Holly McCready, Laura Dennis, Daniel Schwartz, Ethan Sawyer, William Hoffman, Philip Todd Korthuis*

Oregon Health and Science University, Portland, Oregon, United States

Background: Methamphetamine (MA) use disorder is a substantial public health problem and is associated with impulsivity and abnormalities in brain biochemistry and function (London et al., 2015). MA-induced impairments in behavioral impulsivity and associated brain function may facilitate unprotected sexual behavior, which may contribute to the two-fold increase in risk for HIV infection in MA users (Plankey, et al., 2007). Behavioral interventions are often aimed at strengthening executive control to limit behaviors that promote drug use, which in turn, reduce high-risk sexual behaviors. These treatments, however, depend on neural substrates of self-control and motivation, which may be compromised with MA exposure.

The reward/salience and executive networks are particularly vulnerable to drug exposure (Zilverstand et al., 2018). The executive control network is thought to promote cognitive control, while the salience network is sensitive to immediate salient stimuli. These networks and their interconnections play a critical role in integrating cognitive and motivational processes to produce adaptive behavior. Although abnormalities within executive control and salience networks may contribute to the maintenance of alcohol use disorder (Camchong et al., 2013), it is unclear how large-scale network correlations are affected in MA use disorder, and whether impairments in executive control and salience networks may impact sexual risk behavior. As regions within the executive control and salience networks are vulnerable

to the effects of MA, this study aimed to examine whether the engagement in risky sexual behaviors reflect abnormalities in network connectivity, and whether a pharmacological intervention of extended release naltrexone (XR-NTX) can restore a balance between large-scale networks to reduce MA use and risky sexual behavior.

Methods: Thirty-seven participants with MA use disorder underwent resting-state magnetic resonance imaging, followed by randomization to a double-blind, single injection of XR-NTX lasting 4 weeks (n=18) or placebo injection (n=19). Study measures were repeated 3 weeks following injection. Imaging was performed on a 3 T Siemens TIM Trio. An independent component analysis using FSL's Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) was conducted on baseline resting-state data. The number of components generated was not restricted, and 67 independent components were identified with a free estimation for the number of components. Dual regression was used to decompose the independent components into spatial maps to generate average time courses for each subject across both time points for each component. Network correlations for each subject was carried out with R studio. Two-way repeated measures ANOVA on correlation coefficients between executive control and salience networks, which were identified by cross correlating the spatial maps of our independent components with that of the resting-state template (Smith et al., 2009) were examined in SPSS 22. To examine how changes in network correlations affect changes in sexual risk taking, changes in the Fisher transformed Z statistic of the correlation between the executive control and salience networks and changes in the sex risk index from the Risk Assessment Battery (RAB) were tested.

Results: Of 37 participants, 28 were male, 9 were HIV-infected, mean age was 37.49 (SD 9.74) years, and mean education was 12.70 (SD 1.57) years. The two-way repeated measures analysis shows significant Group x Time interaction in correlations between executive control and salience networks ($p = 0.05$ with substance dependence severity (SDS) as a nuisance covariate; $p > 0.05$ with no covariates). The XR-NTX group show a reduction in network coupling compared to the Placebo group. When examining whether a change in network cohesion affect changes in the sex risk index, a Group by Time interaction shows a negative relationship for the XR-NTX group and a positive relationship for the Placebo group ($p=0.04$ with SDS as a nuisance covariate; $p=0.05$ with no covariates).

Conclusions: The results of this study extend previous findings of a reduction in MA use and striatolimbic connectivity with XR-NTX (Kohno et al., 2018) by showing that XR-NTX affects large-scale networks, specifically the coupling between salience and executive control networks. In addition, network decoupling is associated with less sexual risk taking. The reduction in sexual risk behavior may result from the ability of the executive control network to exert more influence towards adaptive behavior with less bias and interference of the salience network, which promotes immediate reward-driven behavior. This is inline with reports of MA users consistently showing enhanced sensitivity for potential reward and diminished cortical inhibition of reward-driven responses. This behavioral bias may stem from the imbalance of networks that promote goal-directed and reward-based impulsive behavior and extend to sexual risk taking, as studies show frontal cortical involvement in executive control and sensitivity of the striatum to cues associated with sexual behavior (Goldenberg et al., 2013; Demos et al., 2012). Although still preliminary, this study begins to identify the complex relationships between MA use, risky sexual behaviors and large-scale brain networks and clarify how XR-NTX affects neural markers that may promote adaptive behavior.

Keywords: Extended-Release Naltrexone, Large Scale Networks, Methamphetamine, Risky Decision-Making, fMRI Resting State

Disclosure: Nothing to disclose.

M246. Varenicline for the Treatment of Cocaine Use Disorder

Kyle Kampman, Mark Morales, Kevin Lynch*

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Varenicline is a medication approved for the treatment of Tobacco Use Disorder. It is a partial agonist at α2β4 nicotinic acetyl choline receptors and a full agonist at α7 nicotinic acetyl choline receptors. By its effects on cholinergic activity at α7 and α2β4 receptors, varenicline may reduce dopaminergic and glutamatergic activity in the midbrain and reduce symptoms of Cocaine Use Disorder. A preliminary trial of varenicline in human cocaine users suggested that varenicline treatment was associated with reductions in cocaine use. The current trial was intended to confirm these promising preliminary results.

Methods: This was a 12-week, double blind, placebo controlled parallel group clinical trial involving 156 DSM IV cocaine dependent subjects. Subjects received 2 mg of varenicline or identical placebo each day along with weekly individual cognitive behavioral relapse prevention psychotherapy. The primary outcome measure was cocaine use measured by thrice weekly urine drug screens. Additional outcome measures included cocaine craving measured by the Minnesota Cocaine Craving Scale (MCCS), cocaine withdrawal symptoms measured by the Cocaine Selective Severity Assessment (CSSA) and global improvement measured by the Clinical Global Impression Scale (CGI). End of study cocaine abstinence was analyzed using a Chi-square test. Urine drug screen results, CSSA, CGI improvement and MCCS scores were analyzed using generalized estimating equations (GEE) with treatment and study week as covariates.

Results: There was no significant difference in treatment retention between the two groups. Abstinence from cocaine as measured by urine drug screens during the last three weeks of the trial was not different between groups (8% in the varenicline treated subjects vs. 9% in placebo treated subjects, chi-square = .149, p=.70). GEE analysis of urine drug screen results showed no significant difference between groups (GEE chi-square(1)=0.03 p=0.91). There was no significant differences between the two groups in cocaine withdrawal symptom severity measured by the CSSA (GEE chi-square(1)=2.12, p=0.15). Complete results will be available at the meeting.

Conclusions: Varenicline plus cognitive behavioral therapy does not appear to be an effective treatment for Cocaine Use Disorder.

Keywords: Cocaine, Varenicline, Clinical Trial

Disclosure: Nothing to disclose.

M247. Adolescent and Current Binge Drinking Predict Changes in Attentional Bias to Alcohol Related Cues After Acute Dopamine Depletion in Male Social Drinkers

Monica Faulkner, Ambika Paulson, Lauryn Harvey, Donita Robinson, Charlotte Boettiger*

National Institute on Alcohol Abuse & Alcoholism, Bethesda, Maryland, United States

Background: The excess allocation of attention toward addiction-related stimuli has been widely reported across a variety of addictions, including alcohol use disorder (AUD). This

phenomenon is defined as attentional bias (AB) and is presumed to reflect reward-conditioning of stimuli, whereby repeated pairing of these stimuli with addiction-related reward comes to attribute motivational salience to these stimuli. Preclinical research has identified the role of dopamine and dopaminergic pathways in reactivity to addiction related reward cues. This reactivity appears to mirror AB in humans however there remain key unanswered questions regarding the neural bases of alcohol AB. These key dopamingergic pathways appear particularly vulnerable to specific patterns of alcohol use during development, such that binge drinking in adolescence has been shown to cause significant changes in adult neurobiology and cognitive function. Moreover, recent studies have found that adolescent binge drinking significantly predicts reward conditioning in adulthood. Taken together, both adolescent alcohol exposure and dopamine function may play a role in AB to alcohol related reward cues seen in adulthood.

Methods: To investigate the role of dopamine and adolescent alcohol exposure in adult alcohol AB, we acutely depleted dopamine by administering a dopamine precursor deficient amino acid beverage, using a double-blind, placebo-controlled, within-subject design in social drinkers with a history of adolescent binge alcohol drinking. We recruited 34 healthy male participants (ages 22-40 years; mean = 26.3) from the University of North Carolina, Chapel Hill (UNC) campus and surrounding communities. To include a broad spectrum of alcohol use, we recruited participants in two groups based on their self-reported alcohol drinking patterns: heavy, binge drinkers (HD; n=15) and moderate, social drinkers (MD; n=19). HD participants self-reported ≥14 alcoholic drinks/week and ≥12 binge episodes (≥5 drinks/2 h for males in the past 12 months. MD participants self-reported <14 alcoholic drinks/week, <10 lifetime binge episodes, and no binge episodes in the past 12 months. Participants completed two AB tasks, a spatial cuing task thought to reflect selective attention capture and a modified attentional blink task to measure extended attentional hold under both conditions. We hypothesized that acute dopamine depletion would reduce AB to alcohol cues and this reduction would be magnified in individuals with a history of binge drinking. Furthermore, we hypothesized that adolescent binge drinking would predict changes in AB after dopamine depletion. Using multiple linear regression models, we investigated the role of current and adolescent binge drinking frequency and changes in dopamine levels in AB to alcohol related stimuli.

Results: We found that frequency of binge drinking before age 18 significantly predicted the change in AB after dopamine depletion ($F(4,27) = 3.37$, $p=0.026$) as measured by the spatial cuing task. More frequent binge drinking prior to age 18 predicted a greater decline in AB to alcohol cues following acute dopamine depletion. This relationship was present in MD and HD, reaching statistical significance in the MD group ($F(4,14)=3.599$, $p=.046$), and trend level significance in the HD group ($F(4,12)=3.177$, $p=.077$). For the attentional blink task, the overall model did not reach significance ($F(4,28)= 2.477$, $p=0.071$), but several independent predictors did significantly predict the change in AB. Current binge drinking, and binge drinking frequency between the ages 18-21 years significantly predicted the change in AB to alcohol cues after dopamine depletion and appeared to be driven by the HD group, as when we repeated these analyses separately for each group, we found similar results in the HD group. Specifically, current binge drinking score significantly predicted the change in AB after DA depletion, reflecting a greater increase of AB to alcohol cues following dopamine depletion associated with heavier binge drinking behavior. In contrast, more frequent binge drinking between ages 18 and 21 predicted a greater decline in AB to alcohol cues following acute dopamine depletion.

Conclusions: Our finding that increased frequency of adolescent binge exposure predicts the change in the form of AB thought to reflect selective attention capture to alcohol cues after dopamine depletion supports the animal literaturesthat suggest the adolescent prefrontal cortex is particularly vulnerable to the damaging effects of alcohol and leads to changes in adult neural mechanisms of cognition in adulthood. Furthermore, the relationship between current binge drinking and AB on the attentional blink task may indeed reflect the continual insult of binge drinking to regions such as the OFC. Taken together, these findings emphasize the potential role of past and current binge drinking in changes to the neural mechanisms that maintain or hold AB to alcohol related stimuli

Keywords: Dopamine, Binge Drinking, Attention, Adolescent Binge Drinking

Disclosure: Nothing to disclose.

M248. Nicotine Abstinence Modulates Dynamic Functional Connectivity Across the Brain in Smokers

John Fedota, Thomas Ross, Tianwen Chen, Xiaoyu Ding, Michael McKenna, Allison Matous, Betty Jo Salmeron, Vinod Menon, Elliot Stein*

National Institute on Drug Abuse, Baltimore, Maryland, United States

Background: In tobacco smokers, the withdrawal syndrome precipitated by acute nicotine abstinence is a significant early hurdle to protracted cessation. Along with well characterized subjective and behavioral disruptions associated with acute abstinence, changes in brain network communication have been observed in smokers. Much prior evidence has characterized static functional connectivity, with an implicit assumption that the average correlation between network nodes over time is an accurate proxy of network communication. However, recent studies of time-varying connectivity suggest that changes in nodal or network communication vary over time. These dynamic measures provide greater temporal resolution and may offer more nuanced, mechanistic understandings of substance use disorder (SUD). Further, dynamic measures employing graph theoretical analyses can characterize communication across the entire brain, and thus may better characterize disruptions between large scale networks impacted by SUD. Two such dynamic, graph theoretical measures are temporal flexibility and spatial temporal diversity—the frequency and uniformity, respectively, of a brain region's interactions outside its own community over time. Previous work in healthy populations demonstrate that these metrics differ in nodes across the brain, with higher values in regions of the Salience Network, previously implicated in SUD. Additionally, temporal flexibility is reduced, and spatiotemporal diversity is increased as a function of chronic exposure to cocaine across the brain. The current study seeks to characterize state-related changes in the dynamic network communication across the entire brain as a function of nicotine state in tobacco smokers.

Methods: 8 minutes of resting-state BOLD data were collected from 36 smokers on two occasions—during baseline smoking and again following ~48 h of full, biochemically assessed nicotine abstinence—to characterize changes in network connectivity during withdrawal. Network dynamics were characterized across 240 nodes spread across the brain and grouped into 14 large scale brain networks. At the individual level, a 40 s sliding window was applied to characterize dynamic functional connectivity between nodes at 251 intervals. For each participant, optimal community structure across each interval was determined using the Louvian method as implemented in the Brain Connectivity Toolbox, and nodes within a given community grouped into an adjacency matrix. The temporal mean of the adjacency matrix served as a temporal co-occurrence matrix where each cell measures the

proportion of time two nodes shared a community over the course of data collection. From the temporal co-occurrence matrix, temporal flexibility was calculated as the ratio of a given node's interactions outside its community to total interactions over time, and spatiotemporal diversity was calculated as the uniformity of a given node's interactions outside its community over time. Results were averaged across the nodes in each of the 14 large scale networks. At a network level, the difference between each of these measures as a function of nicotine state was quantified via a repeated measures ANOVA.

Results: Participant abstinence was verified physiologically and subjectively. For each of the 14 large scale networks tested, both temporal flexibility and spatiotemporal diversity were reduced during nicotine abstinence.

Conclusions: Nicotine abstinence decreases measures of dynamic functional connectivity at multiple nodes across the brain. Together, the observed changes in dynamic flexibility may indicate a reduction in the incidence of communication among disparate communities (decreased temporal flexibility) and a loss of overall network structure (decreased spatiotemporal diversity). That is, during abstinence, a given node spends less time communicating outside of its community and these interactions are less widely distributed across other nodes. Importantly, the observed changes are not confined to nodes or networks more strongly associated with nicotinic receptor expression or abstinence related dysfunction, nor to nodes or networks that show high dynamic flexibility during satiety. Instead, it appears the dynamics of functional connectivity are disrupted on a whole-brain scale. This work builds on previous findings identifying specific circuits shown to be sensitive to nicotine state manipulations and reductions in state transitions among network configurations during abstinence. The functional significance of these large-scale changes and their amenability to therapeutic interventions remains to be characterized.

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Keywords: Tobacco Smoking, Abstinence, Resting-State Functional MRI, Dynamic Connectivity

Disclosure: Nothing to disclose.

M249. Nicotine Reduces Habenula Activity Among Abstinent Cigarette Smokers During Performance Feedback

Matthew Sutherland, Jessica Flannery, Michael Riedel, Angela Laird, Thomas Ross, Betty Jo Salmeron, Elliot Stein*

Florida International University, Miami, Florida, United States

Background: Most smokers attempting to quit will fail often due to nicotine withdrawal symptoms including negative affect, irritability (enhanced responsivity to negative outcomes), and anhedonia (reduced responsivity to positive outcomes) [1,2]. While such withdrawal symptoms are a product of dysregulated reward processing and the ventral striatum (VS), anterior cingulate cortex (ACC), and insula are regarded as constituents in the neurocircuitry of addiction [3,4], emerging preclinical evidence implicates the habenula (Hb) as a contributor to negative reinforcement mechanisms perpetuating smoking [5]. The Hb is a small and understudied epithalamic nucleus that integrates information from limbic forebrain regions to modulate midbrain structures involved in monoamine neurotransmission. Specifically, the Hb inhibits dopamine releasing neurons following the absence of expected rewards [6], possesses a high density of nicotinic acetylcholine receptors [7], and is linked with the aversive effects of nicotine withdrawal and high nicotine doses [7,8]. While the Hb's small size limits its assessment in human fMRI studies [9], we utilized a performance feedback task previously shown to differentially activate the Hb, VS, ACC, and insula [10]. Our aims were three-fold, to: (a) characterize brain activity associated with positive and negative performance feedback (task effect), (b) elucidate brain activity differences as a function of a chronic smoking history (group effect: smokers vs. nonsmokers), and (c) delineate activity modulations as a function of acute pharmacological administration (drug effect: nicotine and varenicline).

Methods: Overnight-abstinent smokers ($n = 17$) and nonsmokers ($n = 17$) participated in 6 fMRI sessions during a two-drug, placebo-controlled, double-blind, crossover study. All participants were assessed twice (PATCH factor: once each wearing a transdermal nicotine patch and a placebo patch) at three points during a varenicline administration regimen (PILL factor: pre-pill, varenicline pill, placebo pill). Participants completed questionnaires to quantify trait-levels of addiction severity (FTND) and state-levels of negative affect and social anhedonia. To probe Hb functioning, we employed a 'motion prediction task' [10] in which participants predicted which of two moving balls, starting from different locations and traveling at different speeds, would reach a finish line first after viewing a short sequence of the balls' motion. Task difficulty was dynamically adapted thereby maintaining error rates at ~35% so that participants remained uncertain about their performance until feedback presentation. Participant responses (correct vs. error) were followed by feedback that did or did not provide information about trial outcomes (informative vs. non-informative). Task effects were assessed in a dependent samples t-test (informative-correct vs. informative-error trials, $p_{corrected} < 0.001$), group effects were assessed in an independent samples t-test (smokers vs. nonsmokers, $p_{corrected} < 0.05$), and drug effects in an ANOVA (PILL by PATCH among smokers, $p_{corrected} < 0.05$).

Results: Regarding task effects, across all participants, we largely replicated a previous implementation of the task [10] and observed increased activity following negative feedback notably in the Hb, ACC, and bilateral anterior insula, and increased activity following positive feedback in the bilateral VS. Regarding group effects, smokers (vs. nonsmokers) showed lower responsivity to positive feedback in the bilateral VS, yet greater responsivity to negative feedback in the left insula. Notably, greater reductions in VS responsivity following positive feedback correlated with higher FTND scores among smokers ($r[16] = 0.60$, $p = 0.02$) and more self-reported negative affect across all participants (PANAS, $r[33] = 0.48$, $p = 0.004$). Regarding drug effects, we observed a PATCH main effect such that placebo (vs. nicotine) administration was linked with elevated Hb activity following positive feedback among smokers, but not nonsmokers. A repeated measures correlation assessment among smokers indicated that greater Hb activity following positive feedback was linked with greater self-reported social anhedonia ($r[74] = 0.28$, $p = 0.02$), this relation was not observed among nonsmokers. No significant clusters were observed when considering the PILL or PILL by PATCH effects.

Conclusions: These results support contemporary views that an extended smoking history is associated with lower responsivity to positive outcomes (anhedonia) and enhanced responsivity to negative outcomes (irritability). Critically, our results contribute to a growing literature demonstrating Hb involvement in positive and negative outcome processing and provide novel evidence that Hb activity in smokers can be modulated by nicotine.

Disclosure: The authors have no conflicts to declare and are supported by grants from NIDA (K01DA037819, R01DA041353), NICHD (U54MD012393, sub-project 5378), and by the NIDA Intramural Research Program.

Keywords: Nicotine Addiction, Functional MRI (fMRI), Habenula

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M250. Marijuana Use and Major Depressive Disorder are Additively Associated With Reduced Verbal Learning and Altered Cortical Thickness

Jodi Gilman, Milena Radoman, Susanne Hoeppner, Randi Schuster, A. Eden Evins*

Harvard Medical School, Boston, Massachusetts, United States

Background: Marijuana (MJ) use and major depressive disorder (MDD) have both been associated with deficits in verbal learning and memory as well as structural brain abnormalities. It is not known if MJ use by those with MDD confers additional impairment. The goal of this study was to examine the unique and combined effects of MDD and MJ use on verbal memory and brain structure in young adults.

Methods: Young adults aged 18-25 with current MJ use and lifetime MDD (MDD+MJ, n=24), current MJ use (at least weekly) and no lifetime MDD (MJ, n=46), MDD and no MJ use (MDD, n=23), and healthy controls without lifetime MDD or current MJ use (CON, n=48) completed the California Verbal Learning Test, Second Edition (CVLT-II), a measure of verbal learning and memory. A sub-sample of 82 participants (20 MJ, 18 MDD, 21 MDD+MJ, 23 CON) also underwent a structural magnetic resonance imaging (MRI) scan. Group differences in CVLT-II performance were assessed using two-way ANOVAs with MDD and MJ use as group factors. To assess cortical thickness and hippocampal volume, generalized linear mixed models (GLMMs) were conducted, controlling for hemisphere, age, and gender.

Results: Both MDD and MJ use were associated with fewer words recalled after short (free and cued) and long (free only) delays, and there was an additive effect of MDD and MJ use on recall. Lifetime MDD, but not MJ use, was associated with poorer initial learning during Trial 1, fewer words recalled across all learning trials, a higher rate of intrusion errors, fewer words recalled with cues after a long delay, and lower percent retention. There was also an additive effect of MDD and MJ use on reduced cortical thickness in the middle temporal gyrus. Current MJ use was associated with reduced cortical thickness in the medial orbitofrontal cortex and superior frontal gyrus, and reduced hippocampal volume.

Conclusions: These findings provide evidence of additive adverse effects of MDD and MJ use on learning and memory performance, with cortical thickness reductions in memory-related brain regions predominantly in current MJ users. Findings from this study suggest that the combined effect of MJ use and MDD may result in greater adverse effects on learning and memory, compared to MJ use or MDD alone. While further research is required to establish the clinical significance of these findings, MJ use among depressed patients may be contraindicated.

Keywords: Cannabis, Memory Encoding and Retrieval, Depression, Brain Volumes, Human Neuroimaging

Disclosure: Nothing to disclose.

M251. Influence of Alcohol and Acetaldehyde on Human Psychomotor Functions: Findings From the Alcohol Clamping in Healthy Young Population

Fumihiko Ueno, Hiroyuki Uchida, Sachiko Hara, Sachio Matsushita, Susumu Higuchi*

National Hospital Organization Kurihama Medical and Addiction Center, Yokosuka, Japan

Background: Alcohol sensitivity is closely associated with blood acetaldehyde concentrations (BAAC) as acetaldehyde causes a variety of discomforting symptoms. On the other hand, effects of alcohol and acetaldehyde on multiple domains of psychomotor functions have not been thoroughly investigated in a large sample, which was addressed in this study.

Methods: Healthy Japanese students aged 20-24 years without a diagnosis of alcohol dependence were included. Having semi-structured interview for diagnosis and ALDH2 genotyping, they were sorted to one of the three groups based on their ALDH2 genotypes: ALDH2*1/*1 (both active), ALDH2*1/*2 (hetero), and ALDH2*2/*2 (both inactive). Those with ALDH2*2/*2 were excluded from the study since they are extremely sensitive to alcohol. The remaining subjects underwent three neuropsychological tests: the continuous performance test (CPT) for sustained attention, the neuropsychological test (NPT) for reactivity, and the paced auditory serial addition test (PASAT) for working memory. These examinations were conducted at baseline and 60 and 180 minutes after alcohol administration was started. Scores of these tests were compared within subjects by using analysis of variance (ANOVA). Alcohol clamping technique was used to maintain 50 mg% of blood alcohol concentration (BAC) for 180 minutes through the intravenous infusion of diluted ethanol solution. BAAC was assessed 6 times in 240 minutes.

Results: 429 subjects participated in this study; of these, 5 were excluded (ALDH2*2/*2 [n=3], extremely low body weight [n=1], and difficult vascular access [n=1]). In the remaining 424 subjects, 160 (37.7%) were found to carry inactive ALDH2 (ALDH2*1/*2). Eighteen (4.2%) dropped out because of unpleasant feelings, and 406 completed. Targeted BAC was achieved in 15 minutes and maintained for 180 minutes within the 50±5 mg% range. While BAAC in the subjects with ALDH2*1/*1 was stable (mean±SD μg/ml, 0.033±0.005 at baseline; 0.080±0.061 at 60 minutes; and 0.041 ±0.030 at 180 minutes), it peaked at 60 minutes and then gradually declined in those with ALDH2*1/*2 (0.029±0.007; 2.426 ±0.087; 0.909±0.043). The ALDH2*1/*2 group showed worsening in the CPT at 60 minutes (correct detection, 38.36±2.81 vs. 36.29 ±4.80, p=0.001; omission error, 1.53±2.73 vs. 3.47±4.59, p=0.014) while there were no differences in the ALDH2*1/*1 group. No significant differences were found between the two groups at baseline and 180 minutes. The reaction time assessed with Task C in the NPT was improved at 60 minutes in the ALDH2*1/*1 group (0.34±0.07 at baseline vs. 0.38±0.11 at 60 minutes, p=0.001), but not in the ALDH2*1/*2 group whereas no significant differences were observed in the other two tasks in either group. With regard to the PASAT, both groups demonstrated significant improvements at 60 and 180 minutes.

Conclusions: Acetaldehyde seems to have negative impact on sustained attention, BAAC and reactivity may not influence reactivity nor working memory. Moreover, alcohol could improve working memory although a possibility of practice effects cannot be rejected. These findings warrant further investigations, especially neuroimaging studies, to identify the mechanisms underpinning intoxication and possibly beneficial effects of alcohol and acetaldehyde.

Keywords: Alcohol Sensitivity, Psychomotor Speed, Aldehyde

Disclosure: Nothing to disclose.

M252. Beware the Scorpion! Cocaine Patients With a Heightened Subcortical (Amygdala, Pallidum, Insula) Response to Negatively-Valenced Nogo-Stimuli Will Proceed to Better Drug Use Outcomes

Anna Rose Childress, Kanchana Jagannathan, Paul Regier, Jesse Suh, Stefanie Darnley, Matthew Taylor, Zachary Monge, Marina Goldman, Kimberly Young, Teresa Franklin, Reagan Wetherill, Daniel Langleben, Michael Gawrysiak, Charles O'Brien*

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States

Background: A defining feature of the addictions is an over-pursuit of reward, despite the recurrent negative consequences (e.g., loss of jobs, homes, relationships) and acute dangers (e.g., overdose) of this over-pursuit. Toward developing therapeutics for this vulnerability, we recently developed an imaging task to capture the brain's effort to "put on the brakes" when a danger signal pops up during button pressing to positive stimuli. Our "Spiders - NO, Puppies - GO!" Go-NoGo task instructs individuals to press a button quickly when positive pictures (e.g., baby animals) appear on the screen, while inhibiting the button press to negative (e.g., spider or scorpion) pictures. As the positive pictures are very frequent, and the negative pictures are very infrequent, some button presses (inhibitory failures) occur even during the negative pictures. We were especially interested in whether the pattern of brain responses in the task (e.g., a heightened subcortical response to the danger stimuli, and/or a heightened response in 'top-down' cortical regions) could predict real-world drug use outcomes – encouraging use of the task for screening candidate anti-relapse medications.

Methods: Our participants were a subgroup of cocaine-dependent patients from a larger study (n=39; African American males in their mid-40's) focused on brain predictors of relapse. Each individual received inpatient stabilization followed by BOLD fMRI session at 3 T, with probes that included our novel "Spiders - NO, Puppies - GO!" Affect Congruent Go-NoGo task. The task features pleasant pictures that encourage approach as Go stimuli (87.5% of trials), and dangerous images that discourage approach as NoGo stimuli (12.5% of trials). Pre-planned contrasts (SPM 12; thresholded 2<t<5 for examination) compared the brain response during trials in which inhibition was successful (STOPS) vs. trials in which inhibition failed (ERROR trials). Following imaging, the inpatients were discharged into 12 weeks of outpatient treatment, with twice weekly urine samples. For the current outcome-linked comparisons, we selected two phenotypic extremes, "POOR" outcome individuals (more than 90% urines cocaine positive/missing; n=15) and "GOOD" outcome individuals (30% or fewer urines cocaine positive/missing, n=8).

Results: Cocaine patients who would proceed to a "GOOD" outcome evidenced a robust activation of three interconnected subcortical structures (bilateral amygdala and pallidum; l. insula) during successful inhibition ('danger signal') trials (peak t value = 9.3, r. amygdala). Interestingly, this "GOOD" outcome subgroup did not show recruitment of "classical" cortical modulatory regions. In contrast, cocaine patients who would proceed to a "POOR" outcome showed weak activation of the amygdala during successful inhibition ('danger signal') trials, but robust activation of the left cortical mantle, including cingulate and superior frontal gyrus, as well as the dorsal striatum / l. putamen.

Conclusions: Intriguingly, for cocaine patients who proceed to "GOOD" outcome, successful inhibition was characterized by a subcortical signature – likely reflecting heightened processing of the danger signals (e.g., scorpions and spiders). Patients who would proceed to a "POOR" outcome showed a different pattern during their successful inhibition trials: a dramatic activation of cortical/striatal circuitry. Though this cortical/striatal activation was sufficient to support performance in the laboratory task (as task performance did not differ significantly between the two subgroups), the results suggest it may not be sufficient for dealing with the powerful pull of drug rewards. Recruitment of the subcortical 'danger' circuitry may be an important feature of successful inhibition in the real-world struggle for recovery, helping an individual to take potential future negative consequences into account. Restoring and supporting the subcortical response to (drug) 'danger' could be a potential target for pharmacotherapy in the addictions, complementing medications that focus primarily on blunting the response to rewards. Go-NoGo tasks with valenced stimuli may offer a useful screen for discovering these new agents, and for identifying the individuals in greatest need of this biological support.

Keywords: fMRI, Relapse Biomarkers, Cocaine, Amygdala, GoNoGo

Disclosure: Nothing to disclose.

M253. Adolescent-Onset Cannabis Use: Associations Between Impaired Verbal Learning and Hippocampal Subfield Volumes

Monica Luciana, Paul Collins*

University of Minnesota, Minneapolis, Minnesota, United States

Background: Adolescent-onset cannabis use (CU) is associated with impairments in attention, executive function, and verbal learning/memory. Of these processes, deficiencies in verbal learning have been robustly observed across laboratories, including our own. Yet the neural underpinnings in the context of CU remain relatively unexplored.

Methods: The present analysis examined associations among CU, verbal learning, and hippocampal subfield volumes in chronic daily adolescent-onset CUs (n=37, 19 male) as compared to non-using demographically-matched psychiatrically healthy controls (HC; n=37, 24 male) using baseline data from a longitudinal study. HC and CU participants were aged 18-19 (M=19.6 years), attending college, and from middle to upper-middle socio-economic backgrounds with high average IQs (M=115.3, SD=9.8). The groups were matched in age, gender, and IQ. Those in the CU sample reported cannabis use at least 3 times weekly with ages of CU onset ranging from 12 to 18; most met diagnostic criteria for DSM-IV cannabis dependence, and several had current or past alcohol abuse. They were otherwise free of psychopathology. Both groups completed a comprehensive neurocognitive battery, including the Rey Auditory Verbal Learning Test, and a T1-weighted MP-RAGE scan on a Siemens 3 T Tim Trio scanner. Group differences in cognitive function have been published and include deficits in RAVLT-based verbal learning and memory, motivated decision-making (Iowa Gambling Task), planning (CANTAB Stockings of Cambridge), and working memory (spatial delayed response task) in CUs (Becker et al., 2013, JCEN). We have followed both groups over time and demonstrated that across a two-year longitudinal interval, nearly all CUs continue to engage in regular and heavy cannabis use. Relative impairments in working memory, planning and verbal memory remain stable over time, suggesting that these are enduring vulnerabilities associated with continued CU during young adulthood. A later age of CU onset is associated with better verbal learning and memory (partial r-.43) over time, controlling for alcohol use (Becker et al., 2017, JCEN). For the present analysis, MRI data were analyzed using FreeSurfer v. 6.0 (http://surfer.nmr.mgh.harvard.edu), with hippocampal segmentation that calculated separate volumes for subregions including the presubicular region, parasubiculum, fimbria, and several Cornu Ammonis subfields (CA1, CA3, and

CA4). Total brain volume was included as a nuisance covariate in all statistical computations. Linear regressions were utilized to predict group status from hippocampal segmentations while controlling for total brain volume, age, and past-year alcohol use. Hippocampal segmentations were also correlated with RAVLT performance after controlling for relevant covariates.

Results: CUs did not vary from HCs in total hippocampal volumes. However, CUs showed smaller volumes in the left hemisphere's parasubiculum (partial r=-.231) and CA3 head (partial r= -.27). Volumes in these regions were not associated with self-reported levels of past-year alcohol use (partial r's = -.02 and -.07, respectively) or with ages of CU onset. In the sample as a whole, combining across groups, the volume of the CA3 head region in the left hemisphere was associated with RAVLT learning performance (partial r = -.37), with immediate recall (partial r=-.27) and delayed recall (partial r=-.30). Subsequent regression analyses indicated that group status (CU vs. HC) was independently predicted by these regional hippocampal volumes as well as RAVLT performance (total adjusted R2 = .57).

Conclusions: Associations between brain structure/function and behavior in the context of CU are an increasing area of interest given advances toward cannabis legalization and the potential for CU-induced psychopathology. The CA3 subregion of the hippocampus is richly connected with other regions and receives input from the entorhinal cortex. It is involved in episodic memory and other higher-level cognitive functions. Cannabis use is robustly associated with deficits in verbal learning and memory, which can have significant social, vocational and educational impacts. Expected associations of verbal learning and memory with selective left-hemisphere hippocampal subfield volumes (CA3, parasubiculum) were observed in this study and merit further scrutiny within etiological models of cannabis-induced cognitive impairments.

Keywords: Cannabis Use, Hippocampus, Neurocognition

Disclosure: Nothing to disclose.

M254. Risk-Taking Behavior During Social Rejection Depends on Levels of Shyness and Impulsivity

David Hsu, Anjali Sankar, Kristen Villalobos, Erin McRobert, Asha Job, Stephan Taylor*

Stony Brook University School of Medicine, Stony Brook, New York, United States

Background: Being socially rejected can increase risk-taking behavior, leading some individuals to alcohol/substance use or other harmful behaviors. Few studies have examined the effects of rejection on risk-taking behavior in a laboratory setting, and little is known about the individual differences that predict the magnitude of these effects. The present study measured risk-taking behavior during social rejection, acceptance, and a neutral condition in a sample of healthy adults. Changes in risk-taking behavior were examined as a function of clinically-relevant traits including shyness and impulsivity.

Methods: Participants (n = 52) were physically and mentally healthy young adults (30 women, 22 men, mean age ± s.d., 21.5 ± 2.2 years), as determined by a physical exam and the Structured Clinical Interview for DSM-IV. Exclusion criteria included any DSM-IV disorder, actively abusing substances including alcohol, and being in a romantic relationship (as determined by participants' self-report), since the task required immersion into an online dating scenario. Participants were informed that they would rate others with whom they would like to form a potential relationship, and so it is important that they are comfortable doing so, and not currently in a romantic relationship. Participants rated online dating profiles of those whom they liked the most. Several days later they performed the Social Feedback Task (SFT) in which they were given feedback on a personal computer that they were not liked (rejection trial) or liked (acceptance trial) by their chosen profiles. As in our previous studies, participants were informed that the feedback are not real, however, we will ask subjects to imagine that they are real. Neutral trials consisted of feedback indicating that a person they liked had not yet viewed their profile. Between trials, participants completed the Balloon Analogue Risk Task (BART), a computer-based task in which participants inflated a virtual balloon in order to win money. Each balloon had a different and unknown explosion point, when the participant would lose the amount accumulated for that balloon. Risk-taking behavior was calculated as the number of balloon pumps prior to cashing out. Trait measures included the Cheek and Buss (1981) Shyness scale, and the UPPS-P, which measures several dimensions of impulsive behavior including Urgency, Premeditation, Perseverance, Sensation Seeking, and Positive Urgency (Lynam et al., 2009). The behavioral data reported here were collected during positron emission tomography (PET) to measure endogenous opioid release using the selective mu-opioid receptor radiotracer [11 C]carfentanil.

Results: Shyness was highly correlated with rejection-induced changes in risk-taking behavior (risk-taking during rejection minus neutral) ($r = 0.45$, $P = 0.001$), but not acceptance-induced changes in risk-taking behavior ($r = -0.13$, $P = 0.35$). Negative Urgency (i.e., tendency to act rashly during negative emotions), was correlated with rejection-induced risk-taking behavior ($r = 0.27$, $P = 0.06$), whereas Sensation Seeking (i.e., tendency to seek out novel and thrilling experiences) was significantly correlated with acceptance-induced changes in risk-taking behavior ($r = 0.29$, $P = 0.04$). No other impulsivity measures were correlated with changes in risk-taking behavior. In an analysis of sex differences, men showed higher levels of Sensation Seeking ($t = 2.69$, $P = 0.009$) and Positive Urgency ($t = 2.73$, $P = 0.008$). No sex differences were found in other traits or in risk-taking behavior.

Conclusions: In a sample of healthy adults, Shyness and Negative Urgency were associated with rejection-induced increases in risk-taking behavior, whereas Sensation Seeking was associated with acceptance-induced increases in risk-taking behavior. These findings have direct clinical implications given that Shyness is known to be associated with increased rates of social anxiety and substance use disorders, and Negative Urgency and Sensation Seeking are known to be associated with bipolar, personality, and alcohol and substance use disorders. These disorders also have high rates of comorbidity, suggesting that future studies can use this laboratory model to study a common neural mechanism underlying risk-taking behavior in these disorders following rejection or acceptance. Notably, Sensation Seeking was higher in men, suggesting that this trait may more strongly impact risk-taking behavior in the presence of positive social stimuli in men compared to women.

Keywords: Social Reward, Social Anxiety Disorder, Impulsivity, Risky Decision-Making, Social Stimuli

Disclosure: Nothing to disclose.

M255. Methamphetamine Alters Functional Connectivity During Resting State in Healthy Volunteers

Kathryne Van Hedger, Jessica Weafer, Sarah Keedy, Harriet de Wit*

Western University, Brain and Mind Institute, London, Canada

Background: This study examined the effects of acute methamphetamine on the function of frontostriatal circuits in the human brain. Frontostriatal circuits are associated with heightened

responses to drug cues and decreased control over drug-seeking behavior in established drug users, but less is known about how drugs affect these circuits in healthy volunteers.

Methods: Healthy young adults (N = 22) completed two sessions in which they received methamphetamine (20 mg) or placebo, in counterbalanced order, one hour before an fMRI resting state scan. We conducted seed-based voxelwise functional connectivity analyses to compare connectivity after methamphetamine and placebo using three bilateral seed regions in the striatum: nucleus accumbens (NAcc), caudate, and putamen. During the sessions, subjects also reported on subjective states including euphoria and arousal, allowing us to examine changes in functional connectivity in relation to subjective drug effects.

Results: Relative to placebo, methamphetamine increased functional connectivity in two circuits: between NAcc and medial frontal brain regions (orbitofrontal cortex, middle frontal gyrus, and superior frontal gyrus), and between putamen and left inferior frontal gyrus). In contrast, it decreased functional connectivity between NAcc and subgenual anterior cingulate cortex. Interestingly, the increased connectivity between putamen and left inferior frontal gyrus was associated with less drug-induced euphoria and arousal.

Conclusions: These results provide preliminary information about how methamphetamine changes brain function in humans, in ways that might relate to future drug-seeking behavior.

Keywords: Resting State Functional Connectivity, Methamphetamine, Healthy Subjects

Disclosure: Nothing to disclose.

M256. Neural Correlates of Cannabis-Impaired Virtual Driving Using fMRI

Godfrey Pearlson, Shashwath Meda, Catherine Boyle, Diana King, Erwin Boer, Nic Ward, Michael Stevens*

Olin Research Center, Hartford, Connecticut, United States

Background: With the legalization/decriminalization of medical and recreational cannabis (CB) in much of the US, plus the increasing % of THC available in various products, the number of CB-intoxicated drivers is on the rise. Understanding the neuroscientific basis of and detecting CB-related driving impairment is complex and there are few well-controlled studies to inform policymakers. Key questions include what cognitive and behavioral aspects of simulated motor vehicle driving are impaired acutely by marijuana use, what is the time course of these impairments following acute doses of CB, what is their relationship if any to saliva and blood levels of THC and its major metabolites, and finally, how do they relate to concomitant brain activation patterns.

Methods: As part of a NIDA-funded study, (R01DA 038807) N=16 adult regular recreational CB users were dosed with vaporized CB, using with 0.5 g of NIDA-supplied 13.4%, 5.9% or 0% (placebo) herbal cannabis, using a paced inhalation protocol. Drug was administered on three separate days one week apart, at the same time of day using a randomized, crossover, double-blind design. Participants were assessed using a 30-minute long, three-task, functional MRI driving paradigm, at 0.5 h post-dose, and then variably with two further fMRI sessions at either 2.5, 4 or 5.5 h after dosing in a counter-balanced design. Scanning took place in a Siemens 3-T wide-bore Skyra scanner. The functional MRI driving tasks employed an MRI-compatible steering wheel gas and brake pedals (Current Designs Inc.) and custom-created driving software (RealTime Technologies Inc.). The tasks assessed three separate aspects of motor vehicle driving; operational (road tracking), tactical (car-following), and strategic (gap-acceptance). An infra-red eye tracker signal was integrated into data capture to assess what subjects were visually fixated on at each time point. Saliva and blood levels of THC and its major metabolites were harvested at regular intervals, and subjective measures of "high", driving impairment and willingness to drive a real vehicle also assessed repeatedly.

Results: Main effects maps across all 9 driving epochs (3 per day for each of 3 days) at the 3 CB doses showed significant activation in expected brain regions that differed markedly by task, with more pronounced frontal activation associated with the strategic task. Using functional connectivity analysis, an across driving-tasks, low-(N =20 component) independent component analysis, thresholded at $p<0.016$ was used to assess the 30-minutes post-dose drive for each of the 3 dose days. Comparing the placebo and high-dose days, there were significant connectivity decreases between the frontoparietal/cerebellar and DLPFC/temporal independent components as well as between the frontoparietal/cerebellar and orbitofrontal components. In addition, there was significantly increased connectivity between the frontoparietal/cerebellar and default mode network/hippocampal components. Cohen's d values for these changes were 0.96, 1.02 and -0.95 respectively

Conclusions: Cannabis-intoxicated driving is an increasing public health concern. We have been able to demonstrate a significant alteration in neural connectivity associated with a simulated driving task under conditions of CB intoxication. Independent components altered by the drug include the following regions: DLPFC (executive), hippocampus a CB-1 receptor-rich region involved in memory and spatial memory functions, the cerebellum another CB-1-rich region involved in motor coordination, the default mode network related to CB intoxication, and the OFC which has inhibitory connections to basal ganglia and is involved in valuation/reward, amongst other functions. We will present the relationship of the above fMRI findings to subjective and drug concentration measures at the time of the meeting.

Keywords: Cannabis, Simulated Driving, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

M257. Protective Factors Against Early Substance Use Among Youth With a Family History of Alcohol Use Disorder: The Role of Frontostriatal Resting-State Functional Connectivity

Meghan Martz, Lora Cope, Jillian Hardee, Robert Zucker, Mary Heitzeg*

University of Michigan, Ann Arbor, Michigan, United States

Background: Dual systems models of adolescent brain development posit that the earlier maturation of the subcortical reward system relative to the prefrontal cognitive control system contributes to elevated risk-taking behaviors, such as substance use (Casey et al., 2008; Steinberg, 2008). Resting state functional connectivity (RSFC) allows for the study of interactions between top-down and bottom-up brain circuitry by measuring spontaneous blood-oxygen-level-dependent (BOLD) signal with functional magnetic resonance imaging (fMRI). As such, RSFC has been used to examine risk markers for substance use problems among vulnerable populations, such as youth with a family history of substance use disorder (FH+; Cservenka et al., 2014). However, relatively little is known regarding the neural mechanisms underlying resilience among FH+ youth (i.e., those who exhibit low levels of substance use despite parental addiction; Heitzeg et al., 2008; Martz et al., 2018). No studies to-date have examined differences in frontostriatal RSFC between resilient and high-risk FH+ youth. To address this gap, the goal of the present study was to use seed-based RSFC analysis to identify neural indicators of within-group heterogeneity in substance use outcomes among FH+ youth.

Methods: Participants were FH+ youth (N=36; 36.1% female; M=14.96 years old at the scan date, SD=1.36) who participated in the Michigan Longitudinal Study, a prospective study of families enriched for parental alcohol use disorder. FH+ youth were categorized into resilient and high-risk groups based on the absence or presence of: (1) at least one occasion of alcohol, cigarette, marijuana, or other illegal drug use by the age of 14; and (2) use of at least two different types of substances (e.g., marijuana and alcohol) by the most recent substance use assessment (M=16.89 years old, SD=1.50). Resilient and high-risk groups did not differ significantly on sex, scan age, or age at most recent substance use assessment. Masks of the following four regions of interest (ROI) were created using Wake Forest University Pickatlas (Maldjian et al., 2003): left dorsolateral prefrontal cortex (DLPFC), right DLPFC, left nucleus accumbens (NAcc), and right NAcc. To create these ROI masks, a 6 mm diameter sphere was centered at the DLPFC coordinates (left DLPFC: -42, 34, 20; right DLPFC: 44, 36, 20), and a 5 mm diameter sphere was centered at the NAcc coordinates (left NAcc: -10, 13, -8; right NAcc: 10, 13, -8). The DLPFC and NAcc are key ROIs involved in executive control and salience networks, respectively (Sutherland et al., 2012; Weissman et al., 2015). Therefore, these regions were the focus of the present study.

Results: Type I error was controlled at α=.05 by establishing the statistical significance threshold at p<.005, uncorrected for multiple comparisons, with a 77 voxel extent, based on simulation results generated by AlphaSim in AFNI (Cox, 1996). Results from two-sample t-tests indicated greater connectivity between the left DLPFC seed and the left posterior cingulate cortex (k=1065, t=4.71, Z=4.10, peak MNI: -10, -40, 20), left hippocampus (k=177, t=3.87, Z=3.50, peak MNI: -34, -34, -10), and left middle temporal gyrus (k=137, t=3.60, Z=3.29, peak MNI: -54, 0, -22) in the resilient group versus high-risk group. There were no significant differences in right DLPFC RSFC between resilient and high-risk groups. Compared to the high-risk group, resilient youth showed greater connectivity between the left NAcc seed and right superior frontal gyrus (k=83, t=3.56, Z=3.26, peak MNI: 22, 12, 38) and left middle temporal gyrus (k=83, t=3.45, Z=3.17, peak MNI: -68, -44, -2). Greater connectivity in the resilient versus high-risk group was also found between the right NAcc seed and right inferior frontal gyrus (k=301, t=5.11, Z=4.37, peak MNI: 44, 26, 10) and middle temporal gyrus (k=99, t=3.84, Z=3.48, peak MNI: 68, -44, 6).

Conclusions: Findings from the present study suggest that frontostriatal connectivity may be a neural indicator of resilience against early substance use problems among FH+ youth. Resilient youth showed stronger synchrony between the seed ROIs and brain regions associated with inhibitory control and socio-emotional processing. Thus, RSFC is a potentially useful biomarker of resilience that may inform prevention efforts aimed at strengthening self-regulation among FH+ youth. The results of this study set the stage for a continued focus on risk group heterogeneity in order to better identify protective mechanisms against substance use problems in vulnerable populations.

Keywords: fMRI Functional Connectivity, Resting-State fMRI, Alcohol and Substance Use Disorders, Adolescence

Disclosure: Nothing to disclose.

M258. The HTR2C Cys23Ser Variant (rs6318) Moderates the Effect of Mirtazapine on Cocaine Attentional Bias and Functional Connectivity in Cocaine Use Disorder Subjects

Albert Arias, F. Gerard Moeller, Liangsuo Ma, Joel Steinberg, Kathryn Cunningham, Noelle C. Anastasio*

Virginia Commonwealth University, West Haven, Connecticut, United States

Background: A functional polymorphism in the HTR2C gene (rs6318, Cys23Ser, G → C) for the serotonin 5-HT2C receptor (5-HT2CR) has been associated with greater attentional bias in cocaine use disorder (CUD) participants assessed on a cocaine-word Stroop task as a measure of cue reactivity. We previously observed an increased strength in effective connectivity (EC) between the left (L) anterior cingulate cortex (ACC) and the right (R) hippocampus (HIPP) of CUD participants during performance of the cue reactivity task. Our preclinical studies have identified a role for a 5-HT2A receptor (5-HT2AR)-5-HT2CR interaction in the control of cocaine cue reactivity. Based on these findings, we tested the hypothesis that the non-selective 5-HT2A receptor antagonist mirtazapine would affect ACC → HIPP EC related to cocaine cue reactivity dependent upon the HTR2C genotype.

Methods: Participants met DSM-5 criteria for CUD (n=25; 96% African American, 4% European American, 20% female) and participated in two fMRI scans on separate days approximately one week apart. Prior to the scans, placebo (PLC) or 15 mg of mirtazapine was administered orally. The order of the PLC and mirtazapine scans was random across subjects. Participants completed the cocaine-word Stroop task in the scanner. During the task, cocaine words (CW) and neutral words (NW) were presented and participants were instructed to indicate the color of each word but neglect the meaning. Dynamic causal modeling (DCM) was used to analyze EC within the ACC → HIPP pathway of participants treated with PLC vs. mirtazapine stratified based upon HTR2C genotype. The EC is expressed as the modulatory effect of CW over the NW (EC during CW trials minus EC during NW trials). Subjects were genotyped for the HTR2C Cys23Ser (G → C) polymorphism and since HTR2C is on the X chromosome, male subjects express one copy. There were no heterozygous females, thus resultant comparison included G/GG and C/CC genotypes.

Results: Linear regression of scans on PLC sessions within the DCM framework revealed that greater L ACC to R HIPP EC was associated with greater cocaine attentional bias (posterior probability [PP] = 1]), replicating our prior work. Relative to PLC, mirtazapine decreased L ACC to R HIPP EC for G/GG subjects (from 0.0808 Hz to -0.1739 Hz) but not for C/CC subjects

(from -0.0808 Hz to 0.1739 Hz) on the cocaine-word Stroop task; the PP for the strength of connectivity for both comparisons was 1.

Conclusions: In subjects with the "wild type" HTR2C G/GG genotype, and presumably normal receptor function, mirtazapine reduced attentional bias to cocaine-related stimuli, an effect that appears to be in part mediated by reducing the connectivity from the L ACC to R HIPP. These data suggest that the efficacy of mirtazapine to affect ACC → HIPP EC related to cocaine cue reactivity is dependent upon genetic variation in the HTR2C gene. These findings are consistent with other studies implicating interactions between the 5-HT2AR and 5-HT2CR in regulation of cocaine cue reactivity and suggest a novel perspective to inform choice of treatment medication or identify those at increased risk for relapse to CUD.

Keywords: Cocaine, Functional MRI (fMRI), Cue Reactivity

Disclosure: Nothing to disclose.

M259. Intrinsic Network Coupling During an Alcohol Cue Task: Association With Alcohol-Induced Stimulation and Effects of Aripiprazole

Hollis Karoly, Raymond Anton, Konstantin Voronin, Joseph Schacht*

University of Colorado, Boulder, Boulder, Colorado, United States

Background: Recent evidence supports the intrinsic functional organization of the brain into dynamic networks that are anti-

correlated with one another during task performance (Fox et al., 2005). The three networks that have garnered the most attention in the context of addictive disorders are the executive control network (ECN), which is involved in attention and cognitive control, the salience network (SN), involved in attentional allocation and orientation to internal and external stimuli, and the default mode network (DMN), which is thought to underlie self-referential thought processes that are stimulus-independent (Sridharan et al., 2008). It has been hypothesized that the SN may act as a "switch" that influences the interactions between other large-scale brain networks, particularly ECN and DMN. Altered coupling of the SN with other networks may underlie cognitive deficits associated with addiction (Sutherland et al., 2012). The SN is anchored by the dorsal anterior cingulate cortex (dACC) and orbitofrontal/insular cortices, which are strongly connected to subcortical and limbic regions (Seeley et al., 2007). Notably, alcohol-related cues elicit activation of a similar network of dopaminergically-innervated, reward-related brain areas, including these salience network anchors. The partial dopamine agonist aripiprazole (APZ) has been reported to affect static alcohol-cue-elicited activation (Myrick et al., 2010), but its effects on cue-elicited network dynamics have not been evaluated. Thus, the present study examined the effects of APZ on coupling between SN, DMN and ECN during an alcohol cue task.

Methods: Ninety-nine non-treatment-seeking AUD subjects (81 with usable imaging data; mean age=27, 25% female, mean drinks/drinking day) were randomized to receive aripiprazole (titrated to 15 mg) or placebo over eight days. Subjects completed an fMRI alcohol cue reactivity task after 7 days of medication. On day 8, subjects completed a "bar lab" session, during which they were given a priming drink, targeted to produce a breath alcohol concentration (BAC) of 30 mg% (adjusted for gender, age, and weight). The Biphasic Alcohol Effects Scale (BAES) was used to assess self-reported alcohol-induced stimulation 10, 20 and 30 minutes after the priming drink.

Group ICA (FSL MELODIC) was used to decompose the data from this task into independent spatial and temporal components (ICs). Intrinsic connectivity networks of interest (SN, DMN, right ECN [RECN] and left ECN [LECN]) were identified from the ICs generated by MELODIC by cross-correlation with canonical network templates (Smith et al., 2009). To assess between-network coupling, correlation coefficients between component time courses derived from these 4 networks were calculated. Specifically, correlations between LECN:SN, RECN:SN and DMN:SN were calculated, as described in Lerman et al. (2014). Differences in these correlations between the APZ and placebo group were examined. Associations between network coupling and self-reported stimulation after the priming drink in the bar lab were also tested.

Results: There was no effect of medication on network coupling for any of these network pairs. However, across all subjects, stimulation measured 10 minutes after the priming drink was significantly positively correlated with connectivity between each of the three network pairs (rs=.22-.29). Controlling for breath alcohol level and self-reported baseline drinking, the specific relationship between LECN:SN coupling and stimulation was significantly stronger in the placebo group than the APZ group [$F(1,75) = 4.65$, $p = .034$].

Conclusions: Hyperconnectivity between SN and ECN during an alcohol cue reactivity task was associated with alcohol-induced stimulation following a priming drink. APZ, a dopamine partial agonist, thought to regulate cortical and striatal dopamine tone, reversed this association. Notably, LECN:SN coupling was only related to the stimulation measurement most proximal to administration of the priming drink, suggesting that interactions between these networks are most salient for immediate alcohol-induced stimulation. Taken together, these findings suggest that the failure of the SN to disengage from ECN during alcohol cue reactivity could contribute to heightened alcohol-induced stimulation which has been associated with AUD risk. Intrinsic network connectivity during alcohol cue reactivity may also merit additional attention as an influence on subjective response to alcohol and as a potential biomarker of pharmacotherapy efficacy.

Funding: K99/R00 AA021419 (Schacht); K05 AA017435 (Anton); P50 AA010761 (Becker).

Keywords: Alcohol and Substance Use Disorders, Task-Based Functional Connectivity, Salience Network

Disclosure: Nothing to disclose.

M260. Interaction of Cannabinoid Receptor Genes and Stress on Neural Responsivity to Reward Cues

Francesca Filbey, Derek Beaton, Shikha Prashad*

The University of Texas at Dallas, Dallas, Texas, United States

Background: The endocannabinoid (eCB) system influences motivation for natural rewards and modulates the rewarding effects of addictive substances [1–4]. Studies have shown that dysregulation of eCB signaling occurs as a result of THC exposure [6,7]. Prior work has revealed differences in fMRI BOLD response to cannabis-related cues in long-term, heavy cannabis users, suggesting an alteration in response to reward cues compared to non-using controls [8]. This response has also been shown to be modulated by individual factors such as genetic predisoposition (e.g., cannabinoid receptor genes; CB1) [5]. However, it is currently unknown how these known genetic factrs may interact with environmental factors to modulate this neural response to cues. The aim of this study was to examine the interaction between genetics (CNR1, FAAH) and environmental stress markers (early trauma, perceived stress) in cue-responsivity in heavy, long-term cannabis users and non-using controls.

Methods: Using a pharmacogenetic approach of eCB signaling, we examined the relationship between single nucleotide polymorphisms (SNPs) in cannabinoid receptor genes (i.e., CNR1 and FAAH) on the BOLD response to reward cues in 56 cannabis users (MJ; mean (SD) age = 29.7 (8.1) years) and 72 non-using controls (CON; mean (SD) age = 30.5 (10.4) years). We used partial least squares (PLS), a multivariate technique that reveals the common information between two data sets [9] and expresses that information as latent variables (LVs). The two data sets used here were: 1) BOLD response during a cannabis cue-exposure task and 2) combined genetic and behavioral data (group: cannabis users vs. non-using controls, genetic: CNR1, FAAH, and stress: early life trauma (Early life Trauma Inventory, ETI), current perceived stress (Perceived Stress Scale, PSS).

Results: We found two latent variables that explained the majority of the variance (59.8%). The first latent variable (LV1) explained 34.1% of the variance. Group, CNR1, and both stress measures (i.e., ETI and PSS) significantly contributed to LV1. CON and CNR1 TT (major homozygote) contributed to the negative side of LV1, while MJ, CNR1 CC+CT (presence of minor allele), PSS, and ETI contributed to the positive side of LV1. The second latent variable (LV2) explained 25.7% of the variance. Group and PSS significantly contributed to LV2 where as FAAH had a moderate contribution (boot strap ratio $\approx \pm 2.78$). Thus, CON and PSS contributed to the positive side of LV2 with a lesser contribution by FAAH CC (major homozygote), while MJ, and to a lesser extent FAAH AA+AC (presence of minor allele), contributed to the negative side of LV2.

Conclusions: We found that eCB genes, exogenous cannabinoids, and stress have a differential effect on reward responsivity. Specifically, CNR1, early life stress, and current perceived stress were associated with reward responsivity in long-term, heavy

cannabis users, while FAAH and current perceived stress were associated with reward response in non-using controls. These associations were also related to distinct neural responses to cannabis-related cue compared to a natural reward cue. Understanding the contributions of genetics and stress to eCB disruptions in neural mechanisms underlying addiction vulnerability may contribute towards targeted interventions.

Keywords: Cannabis Use Disorder, Endocannabinoid System, Early Life Stress, Chronic Stress, Functional MRI (fMRI)

Disclosure: Nothing to disclose.

M261. Reductions in Brain Glucose Metabolism and the Associated Cortical Atrophy in Healthy Alcoholics are Consistent With Neuropathology

Dardo Tomasi, Corinde Wiers, Ehsan Shokri Kojori, Amna Zehra, Veronica Ramirez, Clara Freeman, Jamie Burns, Christopher Liu, Peter Manza, Sunny Kim, Gene-Jack Wang, Nora Volkow*

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, United States

Background: Excessive alcohol consumption is associated with cortical atrophy and reduced brain glucose metabolism but the relation between these two measures has not been investigated. Here we test the hypothesis that in alcoholics lower cerebral metabolic rate of glucose (MRGlu) reflect alcohol-induced neurotoxicity due to oxidative stress or neuroinflammation.

Methods: Twenty healthy controls (HC) and 19 treatment-naïve alcohol use disorder (AUD) participants with no medical history of co-morbidities and tested within one week of last alcohol use underwent FDG-PET to map MRGlu and MRI to assess cortical thickness (CT). CANTAB was used to assess delay aversion, set-shifting processing, psychomotor speed, pattern recognition, reaction time, spatial planning, working memory capacity, response inhibition, and spatial working memory. A FreeSurfer pipeline was used to compute the pial and white matter surfaces, segment the anatomical MRI scans into cortical and subcortical gray matter ROIs, and estimate the average CT within the ROIs. FSL tools were used for realignment and spatial normalization of MRGlu maps corrected for partial volume effects with a voxel-wise approach. The MRGlu values were averaged within ROIs. ANCOVA with two groups (HC and AUD) and CT as a covariate of interest was used to assess group and interactions effects on MRGlu. For ROI analyses, corrections for multiple comparisons were based on Bonferroni or FDR, and for voxelwise analyses on a familywise error (FWE) rate. Causal mediation analysis was used to test if the effect of excessive alcohol use on CT was mediated by its decreases in MRGlu or whether the decreases in MRGlu were mediated by the changes in CT.

Results: Cognitive performance did not differ significantly between AUD and HC for any of the domains assessed with CANTAB. CT was significantly lower for AUD in frontal regions, supramarginal, entorhinal, and fusiform gyri ($p < 0.004$, FDR-corrected). Compared to HC, AUD subjects showed lower cortical MRGlu in primary and association auditory, language, motor, premotor, and parietal attention regions ($p<7E-04$, Bonferroni-corrected). Within the cerebellar cortex MRGlu did not differ between groups, therefore the cerebellum was used as a control region to normalize MRGlu (referred to as rMRGlu), reducing the variability across subjects for subsequent analyses. The averages of CT and rMRGlu showed significant correlation across AUD participants ($R=0.6$; $p=0.006$). Increases in CT were associated with increases in rMRGlu in visual areas, inferior frontal gyri, inferior frontal operculum, precuneus, middle cingulum and superior temporal pole ($p<0.05$, FWE-corrected). Increased total lifetime alcohol (TLA) was associated with significant decreases in CT and rMRGlu ($F>8.3$; $p<0.007$, FDR-corrected). The direct effects of TLA and abstinence on rMRGlu were significant ($p<0.01$) but those on CT were not. The causal mediation effects of CT on rMRGlu, or vice versa, were not significant.

Conclusions: We show that AUD participants without cognitive deficits had reduced CT and lower MRGlu in frontal, parietal and temporal regions compared to HC. Alcohol use history and AUD severity explained 25% of the variance in CT and cortical MRGlu but without MRGlu-mediation effects on CT or CT-mediation effects on MRGlu, which suggests that a common factor(s) contribute to lower CT and lower MRGlu in AUD. Findings suggest that AUD-hypometabolism reflects cortical thinning, but also reduced glucose utilization by the atrophied neuronal tissue, which is consistent with neurotoxicity from excessive alcohol consumption in otherwise healthy alcoholics. In contrast, the AUD's lack of impairments in cognitive performance highlights the limited sensitivity of traditional neurocognitive tests for detecting alcohol-related neuropathology.

Keywords: F-18 PET Imaging, Alcohol Use Disorders, Cortical Thickness, Brain Glucose Metabolism

Disclosure: Nothing to disclose.

M262. Hippocampal Neurochemistry, fMRI Response, and Memory Dysfunction in Emerging Adult Marijuana Users

Alecia Dager, Malgorzata Marjanska, Graeme Mason, Madelynn Tice, John Ragland, Marisa Silveri, Gregory Book, Chelsea Meagher, Keith Hawkins, Michal Assaf, Michael Stevens, Godfrey Pearlson*

Yale University, Hartford, Connecticut, United States

Background: Marijuana (MJ) use rates are highest among emerging adults ages 18-22, and have been escalating over the past decade, in parallel with increasing legalization and medicalization in the United States. Given ongoing neurodevelopment during this age range, emerging adults may be especially vulnerable to MJ-related cognitive dysfunction. Memory decrements are one of the most consistently observed cognitive deficits associated with MJ use, yet the neural substrates of MJ-related memory dysfunction are poorly understood. The hippocampus, a primary memory region, is dense in cannabinoid receptors and may be particularly susceptible to MJ effects. Some work has characterized altered functional magnetic resonance imaging (fMRI) response associated with MJ use in young people, yet it is unclear which aspects of memory function are most impacted. Moreover, the neurochemical underpinnings remain unknown. To this end, we ascertained both hippocampal neurochemistry and fMRI response during an encoding and recognition task in emerging adult MJ users and controls. We predicted that MJ users would demonstrate poorer memory performance and altered relationships between neurochemical markers and fMRI response.

Methods: Participants were 12 (5 females) current heavy MJ users and 12 (6 females) controls, ages 18-22. The California Verbal Learning Test (CVLT) assessed out-of-scanner verbal list learning. Magnetic resonance spectroscopy was collected in left hippocampus to yield N-acetylaspartate (scaled to total creatine, NAA/tCr), a marker of neuronal integrity. During fMRI, participants performed the Relational and Item-Specific Encoding (RISE) task (Ragland et al., 2012), which ascertains encoding and recognition of object pairs, and was designed to disentangle neural systems involved in relational vs. item encoding, as well as recognition of single items and recognition of associated object pairs. Region of interest analyses obtained fMRI response in right and left hippocampus during encoding, item recognition, and associative

recognition of object pairs. Groups were compared on memory performance, hippocampal fMRI response, and NAA/tCr using independent samples t-tests. Regression analyses determined relationships between NAA/tCr and left hippocampal fMRI response, and whether MJ use moderated these relationships.

Results: MJ users performed more poorly than controls on CVLT free recall on Trial 1 (t=2.4, p=0.31) and on List B (t=2.3, p=.033). On the RISE task, MJ users performed worse than controls during associative recognition (t=3.2, p=.004), but not during item recognition. During item recognition, MJ users showed significantly less fMRI response than controls in both left (t=2.6, p=.016) and right (t=2.7, p=.015) hippocampus. There were no group differences in hippocampal fMRI response during encoding or associative recognition, or in NAA/tCr, and no relationships between NAA/tCr and hippocampal fMRI response during encoding. During item recognition, NAA/tCr was positively related to fMRI response in left hippocampus (t=2.1, p=.049), although there were no group differences in this relationship. During associative recognition, group moderated the relationship between NAA/tCr and fMRI response in left hippocampus (t=2.7, p=.014); here, MJ users demonstrated a negative relationship (t=-2.5, p=.034) whereas controls demonstrated no relationship.

Conclusions: In summary, emerging adult heavy MJ users showed reduced hippocampal fMRI response during item recognition, as well as poorer memory performance, corroborating previous evidence. Moreover, MJ users also demonstrated altered relationships between hippocampal neurochemistry and memory-related fMRI response, which could partly underlie memory performance deficits in MJ users. Ongoing data collection will further characterize these relationships, providing critical insight into memory dysfunction in MJ users. This work has important implications as marijuana use increases with legalization and medicalization.

Keywords: Marijuana, Cannabis, Functional MRI (fMRI), MR Spectroscopy, Memory

Disclosure: Nothing to disclose.

M263. Acute Alcohol Exposure Alters Circulating Endocannabinoid Levels in Humans

*Matthew Sloan, Caroline Grant, Resat Cinar, Bethany Stangl, Timothy Klepp, Honoree Brewton, Nancy Diazgranados, George Kunos, Vijay Ramchandani**

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, United States

Background: The endocannabinoid system has been implicated in alcohol use and related phenotypes in both animal and human models. It has been shown to modulate response to alcohol and other drugs of abuse as well as display persistent adaptations to chronic use. Variation in endocannabinoid system genes has been found to contribute to individual differences in response and adaptations to both acute and chronic exposure to alcohol. In particular, functional polymorphisms in genes encoding the cannabinoid receptor 1 (CNR1), and the fatty acid amide hydrolase (FAAH), which breaks down the endocannabinoid anandamide, are associated with alcohol use disorders. However, it remains unclear how acute alcohol administration alters endocannabinoid signaling in humans. In the current analysis, we examined the effects of acute alcohol administration on circulating anandamide levels in healthy non-alcohol-dependent individuals.

Methods: Data for this analysis were obtained from two studies. Study One enrolled forty-eight healthy volunteers that received, in randomized order, alcohol infusions to achieve and maintain a steady-state ("clamped") exposure of 50 mg% or saline. Study Two enrolled twenty-five healthy volunteers that underwent an intravenous alcohol self-administration procedure to achieve their preferred alcohol level. In both studies, the alcohol infusion profiles were individually computed based on a physiologically-based pharmacokinetic model to provide precision and consistency of exposure across subjects. Blood samples were collected at baseline and following infusion in both studies and plasma was assayed for anandamide levels by LC-MS.

Results: In Study One, a general linear model showed a significant reduction in anandamide following IV alcohol compared to placebo (p=0.021). Percent body-fat showed a significant interaction with decrease in anandamide (p=0.002). In Study Two, a paired t-test revealed a significant reduction in anandamide levels post infusion compared to baseline (p<0.001). Examination of exposure-response relationships indicated a trend for a significant negative association between the breath alcohol concentration (BrAC) achieved and the change in AEA levels across subjects. (r= -0.43, p=0.065). Exploratory analysis of the effect of FAAH C385A genotype indicated similar decreases in CC homozygotes and A-allele carriers in both studies.

Conclusions: These results indicate that alcohol decreases circulating anandamide levels in humans, with no influence of FAAH genotype on this change. Our findings also suggest an exposure-response relationship between alcohol intake and anandamide reduction, such that individuals who consume alcohol to higher BrAC have greater reductions in anandamide levels. Future investigations will examine the potential underlying biobehavioral mechanisms of this alcohol-induced change in anandamide levels on response measures of alcohol motivation and reward.

Keywords: Anandamide, Alcohol Exposure, FAAH

Disclosure: Nothing to disclose.

M264. DBS-Like Optogenetic Stimulation of Accumbens Dopamine D2 Receptor-Containing Neurons Attenuates Cocaine Reinstatement

Sarah Swinford-Jackson, Phillip Huffman, Melissa Knouse, Arthur Thomas, Chris Pierce*

University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States

Background: Previous work indicated that deep brain stimulation (DBS) of the nucleus accumbens (NAc) shell attenuated reinstatement of cocaine-seeking in rats. However, the potential differential impact of DBS on specific populations of neurons to drive the suppression of cocaine-seeking is unknown. Medium spiny neurons in the NAc are differentiated by the expression of dopamine D1 receptors (D1DRs) or dopamine D2 receptors (D2DRs), activation of which promotes or inhibits cocaine-seeking behavior, respectively. We tested the hypothesis that DBS-like optogenetic stimulation of D1DR-containing neurons in the NAc shell would potentiate cocaine-primed reinstatement, whereas DBS-like optogenetic stimulation of D2DR-containing neurons in the NAc shell would attenuate cocaine-primed reinstatement.

Methods: We used recently-developed transgenic rat lines that express Cre recombinase selectively in D1DR-containing or D2DR-containing neurons in combination with a Cre-dependent adeno-associated viral vector expressing channelrhodopsin or yellow fluorescent protein (eYFP) to deliver high frequency optogenetic stimulation selectively to each population of neurons in the NAc shell. Male and female rats self-administered cocaine (0.254 mg/infusion) in 21 daily self-administration sessions, after which lever pressing was extinguished (<20% responses for cocaine). Cocaine

seeking was reinstated by delivery of cocaine (10 mg/kg, i.p.) immediately prior to 1-hour reinstatement sessions, throughout which intra-accumbens DBS-like 473 nm light stimulation (130 Hz) or no stimulation (sham) was administered in a within-subects counterbalanced design.

Results: High frequency, DBS-like optogenetic stimulation of D2DR-containing neurons attenuated reinstatement of cocaine seeking, whereas DBS-like optogenetic stimulation of D1DR-containing neurons did not alter cocaine-primed reinstatement. In rats which only expressed eYFP, intra-accumbens DBS-like optogenetic stimulation did not alter cocaine reinstatement relative to sham stimulation, indicating that the effect of DBS-like stimulation to attenuate cocaine reinstatement is mediated specifically by channelrhodopsin rather than as a consequence of prolonged light delivery.

Conclusions: Collectively, these results suggest that DBS of the NAc attenuates cocaine-primed reinstatement through the selective manipulation of D2DR-containing neurons.

Keywords: cocaine seeking, optogenetics, deep brain stimulation, Nucleus Accumbens Shell, dopamine receptor type 2-expressing striatal medium spiny neuron

Disclosure: Nothing to disclose.

M265. Cannabinoid-Opioid Interactions: Weeding Out the Rewarding Effects of Delta-9-Tetrahydrocannabinol by Mu-Opioid Receptor Antagonism

Joao De Aquino, Rajiv Radhakrishnan, Ashley Schnakenberg, Christina Luddy, Deepak D'Souza, Mohini Ranganathan*

Yale University, New Haven, Connecticut, United States

Background: The rapidly changing legal landscape surrounding the use of cannabis, the burden of the opioid epidemic, and the notion that cannabis may reduce the opioid burden highlight the need to understand the interactive effects of cannabinoids and opioids. This could also inform the common practice of co-occurring cannabis and opioid use. Converging preclinical data indicates that direct and indirect interplay between the cannabinoid and opioid systems may explain some of the effects of cannabinoids, such as their rewarding effects and their possible attenuation of opioid-withdrawal syndrome. In particular, numerous animal studies suggest that opioid mu-receptor (MOR) antagonists may reduce the rewarding properties of cannabinoid 1 receptor (CB-1R) agonists. Further, CB1-R knockout mice show attenuated opioid withdrawal. However, the pharmacological interactions between cannabinoids and opioids in humans have not been completely characterized.

This pilot human laboratory study aims to evaluate the effects of the MOR antagonist naloxone, on the rewarding, behavioral and cognitive effects of the CB1-R agonist, delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, in healthy humans. Further, the potential of naloxone for precipitating cannabis withdrawal syndrome was investigated. We hypothesized naloxone will attenuate the rewarding effects of THC and will precipitate cannabis withdrawal symptoms among cannabis users.

Methods: In this 4-test day study, separated by at least 72 h, participants received active or placebo THC and active or placebo naloxone (2 ×2 design), in a double blind, randomized, counterbalanced order.

Six healthy human subjects with either > 4 occasions per week of cannabis use or who met diagnosis for cannabis use disorder within 30 days prior to the study were screened carefully for any other medical or psychiatric illnesses. Subjects with opioid use disorder were excluded. Subjects were administered THC or placebo IV infusion (dose equivalent to 1.75 mg in a 70-kg adult: 0.025 mg/kg administered over 20 minutes). IV Naloxone was administered in a dosing paradigm to prolong its brief effects for ~60 minutes to coincide with most of the effects of THC (2 mg IV bolus, followed by 18 mcg/kg over 1 h, and additional 1 mg IV bolus). Rewarding, cannabis withdrawal, perceptual altering, and psychotomimetic effects were assessed before and repeatedly measured at several points after each drug administration. Cognitive testing was performed once per test day.

Results: As expected, THC produced rewarding effects, transient perceptual alterations, psychotomimetic effects and cognitive impairments. Naloxone did not produce any effects when administered alone, nor it did precipitate cannabis withdrawal syndrome in cannabis users. However, naloxone did reduce the acute THC-induced rewarding effects with an effect size of d=0.41 but not other THC-induced behavioral or cognitive effects.

Conclusions: In otherwise healthy regular cannabis users, MOR antagonism may reduce the rewarding effects of THC, the principal active constituent of cannabis and a CB-1R agonist. These data are consistent with recent findings indicating that the co-administration of cannabinoids and opioids may produce synergistic rewarding effects, thus increasing abuse liability. Future studies should investigate the therapeutic potential of naloxone in cannabis use disorder, and the safety profile of CB1-R antagonists for reducing opioid-induced rewarding effects and abuse liability.

Keywords: Cannabinoids, Opioids, Abuse Liability

Disclosure: Nothing to disclose.

M266. Efficacy of Residential Substance Abuse Treatment With and Without Medication Assisted Treatment (MAT) in a 4 Year Longitudinal Cohort Study Among 1163 US Veterans

Kevin Li, Lynn E. DeLisi*

VA Boston Healthcare System/Harvard Medical School, Brockton, Massachusetts, United States

Background: In the United States, the prevalence of opioid addiction, often secondary to non-medical use of prescribed opiates, has skyrocketed to epidemic rates. In 2011, conservative estimated societal costs of opiate abuse in the United States exceeded 14 billion dollars. Military veterans are particularly vulnerable to this addiction, given their tremendous risk for physical injury during active service, leading to chronic pain and consequently increased rates of prescribed opiates. When these prescriptions expire and doctors are no longer willing to prescribe these dangerous drugs, individuals often turn to illicitly obtained heroin. Most recently the synthetic opiate, fentanyl, which is 50 times more potent than heroin, has been increasingly seen mixed with heroin, leading to fatal overdoses. Opioid related mortality has been increasing at an alarming rate. More than 50% of drug-related overdoses in the United States involve opiates. Medication assisted treatment (MAT) – such as buprenorphine, methadone, and oral and injectable naltrexone - has been shown to reduce cravings and improve outcomes. However, the evidence for prolonged residential substance abuse treatment is controversial. In 2011, a 10-year long Danish study showed that abstinence rates did not differ between patients with and without residential treatment. However, several studies completed on patients in the emergent adult age group (18-25 years old) in the United States have shown that residential treatment improved several outcomes, including increased self-reported abstinence at 12-month follow-up, attitudes toward 12-step programs, and number of relapses. To date, there have been no investigations into the

efficacy of residential treatment in the veteran population. This is the first study investigating not only the efficacy of residential substance abuse treatment, but also the effects of combining MAT with residential treatment.

Methods: Retrospective chart review was conducted for 1163 United States veterans who had been admitted between 2014-2017 to the Veterans Affairs (VA) Boston Healthcare System for inpatient treatment for a primary ICD9 304 or ICD10 F19.20 diagnosis of opioid dependence. Patients were placed into 4 cohorts: 1) detox admission only 2) detox admission and MAT 3) detox admission and residential 4) detox admission, residential, and MAT. Furthermore, residential treatment was stratified into subacute (defined as less than 3 months) and chronic (defined as more than 3 months). Follow up was conducted for 1-year post-index admission. Primary outcome measured is number of relapses. Secondary outcomes include days until first relapse, length of relapses, number of overdoses, and number of re-admissions for opiate use.

Results: Data from records for the patients included from the study are currently being extracted from the VA national system of electronic medical records and evaluated by physicians trained in the methodology. All extracted data will be analyzed using standard programs in SPSS. These analyses are ongoing and will be presented for the first time as novel unpublished data.

Conclusions: This data will allow conclusions about whether the emphasis by the VA on MAT for all patients with an opiate addiction reduces number of presentations for detox, the number of overdoses, and effects on abstinence. Additionally, this investigation will allow us to conclude the effectiveness of residential substance abuse treatment programs within the veteran population.

Keywords: Opioid addiction, Medication Assisted Treatment, Substance Use Disorder, Opioid Agonist Treatment, Opioid abuse

Disclosure: Nothing to disclose.

M267. Elimination of 11-Nor-9-Carboxy-THC During Thirty Days of Abstinence Among Adolescents Who Use Cannabis Regularly

Randi Schuster, Kevin Potter, Tiana Raphel, David Schoenfeld, Maya Hareli, Jodi Gilman, Adrian Alvarez, Alexandra Medeiros, A. Eden Evins*

Harvard Medical School/Massachusetts General Hospital, Boston, Massachusetts, United States

Background: Adolescent cannabis use is likely to become more prevalent in the era of legalization. Limited research exists on the rate of elimination of Δ9-tetrahydrocannabinol (THC) metabolites in adolescents.

Methods: Urine cannabinoid concentrations were determined over 30 days of abstinence in 64 non-treatment seeking adolescents, aged 15 to 25 years, who reported cannabis use at least weekly and within two days of the baseline visit. Urine specimens were collected at non-abstinent baseline and after 2, 3, 8, 15, 21 and, 28 days of abstinence. Concentration of creatinine-adjusted 11-nor-9-carboxy-THC (THCCOOH) in urine was quantified using liquid chromatography–mass spectrometry (LC-MS) at each timepoint. A mixed effects pharmacokinetics model was fit to the data, with correlated random effects for CN-THCCOOH level at estimated time of last cannabis use and elimination rate. Sex, body mass index (BMI), years of cannabis use, and frequency of past month cannabis were modeled as candidate predictors of CN-THCCOOH concentration at estimated time of last use and elimination rate.

Results: At estimated time of last cannabis exposure, the average CN-THCCOOH level was 125 ng/mL (SD = 110 ng/mL; range: 17 – 890 ng/mL). The average window of urinary CN-THCCOOH detection was 12 days (95% CI: 10 – 15 days), with a range of 3 to 80 days, based on subject-level estimates from the model (limit of quantitation (LOQ) = 5 ng/mL). The average half-life of CN-THCCOOH was 2.9 days (SD = 4.2 days). The rate of elimination was not significantly associated with the starting CN-THCCOOH level, frequency of past month cannabis use, or any other candidate predictor evaluated. CN-THCCOOH concentration at estimated time of last cannabis use was associated with frequency of past month cannabis use, with heavier users having higher starting urine CN-THCCOOH concentrations ($\beta = 0.61$, $p < 0.0001$). Sex, BMI, and years of cannabis use did not predict starting CN-THCCOOH levels. Nested four-fold cross-validation indicated good reliability and predictive validity for the results; 95% prediction intervals captured on average 91.8% of the holdout test sample, with an average R2 of 0.41.

Conclusions: To our knowledge, this is the largest study of THCCOOH elimination and the first to be reported in adolescents. Findings suggest that a pharmacokinetics model can be used to robustly estimate the rate of elimination of cannabis metabolites during one month of abstinence among adolescents. A 3-day half-life and 12-day window of detection together with high variability in starting THCCOOH concentrations and eliminations rates is consistent with findings from the adult literature and suggests that the presence of detectable cannabinoid metabolites does not necessarily indicate recent use in adolescents who use cannabis weekly or more frequently. Frequency of cannabis use predicted baseline THCCOOH levels, but no predictors evaluated were significantly associated with elimination rate. Factors not measured in the current study (e.g., genetics) may explain the substantial inter-individual variability observed. Future studies are needed to examine whether variability in cannabinoid elimination rate is associated with withdrawal, susceptibility for addiction, and resolution of residual neurocognitive impairment.

Keywords: Cannabis, Adolescence, THC

Disclosure: Nothing to disclose.

M268. Development of Novel Orexin Receptor 1 Antagonists for Opioid Dependence

Alexander Smith, Maya Williams, Paul Kenny*

Icahn School of Medicine at Mount Sinai, New York, New York, United States

Background: Each day, over 115 people die of opioid overdose in the USA, and this has been declared a public health emergency. In the past 5 years, the sharpest rise in overdose deaths was due to synthetic opioids, which have surpassed heroin-related deaths since 2015. Furthermore, in 2016, while 1% of people over age 18 reported abusing heroin in the previous 12 months, 11% reported abusing prescription painkillers. Approximately 80% of heroin addicts first began abusing prescription opioids for nonmedical reasons, and oxycodone is one of the most commonly abused prescription opiates. Despite the large unmet clinical need for pharmacotherapeutics for treatment of opiate addiction, very few studies have used rodent models of oxycodone self-administration. Thus, we established intravenous oxycodone self-administration procedures for both rats and mice. We went on to examine the effects of a novel selective antagonist of the orexin receptor 1 (OX1R) on self-administration and reinstatement behavior. Finally, ongoing studies are examining c-Fos expression following early withdrawal, late withdrawal, and cue-induced reinstatement and the role for OX1R in these responses.

Methods: First, male Sprague-Dawley rats were implanted with chronic indwelling catheters and were trained to lever press to self-administer oxycodone (0.003–0.240 mg/kg/infusion) and a conditioning stimulus (light cue). Once stable intake was established at the highest dose tested (28 sessions), we examined the effects of a novel orexin receptor 1 antagonist on oxycodone self-administration under fixed ratio 1 (FR1) and FR5 schedules of reinforcement. Rats were then subjected to extinction training for 10 sessions, and the effect of OX1R antagonism was tested on cue-induced reinstatement. 90 minutes following the final cue-induced reinstatement test, rats were transcardially perfused, and immunohistochemistry and fluorescence microscopy were used to examine c-Fos immunoreactivity. In a second experiment, male C57Bl/6 J mice were trained to self-administer oxycodone (0.01-0.6 mg/kg per infusion) and a conditioned stimulus. Following 14 days of self-administration, mice underwent 7 extinction sessions prior to cue-induced reinstatement, and subsequent transcardial perfusion. Brains were divided into two hemispheres. One hemisphere was sliced into 40 µm sections and stained for c-Fos via traditional immunohistochemistry. The second hemisphere was left intact, stained for c-Fos, and lipid-cleared via the iDISCO+ clearing protocol. Intact brains were then imaged on a light-sheet microscope, and the ClearMap python package was used for automated cell detection and counting, and for mapping coordinates of detected cells onto the Allen Brain Atlas.

Results: We have established that both rats and mice reliably self-administer oxycodone, and that there is an inverted U dose-response relationship, as hypothesized. Furthermore, we show that OX1R antagonism reduces intake of oxycodone during FR5, but not FR1 schedules of reinforcement. Both species showed an extinction burst on the first day of withdrawal, followed by normal extinction of responding, and significant reinstatement of drug seeking following cue re-exposure. Importantly, OX1R antagonism significantly reduced cue-induced reinstatement. Both rats and mice showed considerable c-Fos immunoreactivity within areas often associated with motivated drug seeking and cue-induced reinstatement, including the prelimbic cortex, the nucleus accumbens core, and the lateral hypothalamus. While still preliminary, iDISCO+ and ClearMap analysis of whole-brain c-Fos staining has proven to be a powerful tool for conducting efficient high throughput analysis of immediate early gene expression.

Conclusions: These data establish a model of oxycodone self-administration in rats and mice. Furthermore, we show here that the orexin system, which has previously been implicated in motivated seeking of cocaine, nicotine, and heroin, is implicated in both oxycodone intake as well as cue-induced reinstatement. Furthermore, we have begun to characterize immediate early gene expression profiles within intact mouse brains for high-throughput analysis.

Keywords: Opiate Addiction, Opiate Epidemic, Drug Relapse, c-Fos, orexin Receptor Antagonist

Disclosure: Nothing to disclose.

M269. Preclinical Assessment of Abuse-Related Behavioral Effects of Novel NMDA Receptor Modulators With Rapid Antidepressant Effects: (S)-Ketamine and Rapastinel

Katherine Nicholson, Joseph Moskal, Pradeep Banerjee, Jeffrey Burgdorf, Keith Shelton*

Virginia Commonwealth University, Richmond, Virginia, United States

Background: Racemic (R,S)-ketamine produces a rapid and long-lasting antidepressant response in treatment resistant patients with major depressive disorder (MDD). However, the production of psychotomimetic effects and a well-known propensity for abuse have limited its therapeutic use. The (S)-isomer of ketamine is being investigated for treatment resistant depression and may have an improved side-effect profile relative to the racemate. Similarly, rapastinel (formerly GLYX-13), a novel NMDA receptor positive modulator, is in development for use in treating MDD. Both compounds have been shown to be effective in preclinical and clinical studies of depression. The goal of this study was to determine their reinforcing effects in an intravenous (IV) self-administration procedure and their (R,S)-ketamine-like subjective effects in a drug discrimination procedure.

Methods: This research was conducted following NIH Guidelines for the Care and Use of Laboratory Animals (8th Edition) and the research and environmental enrichment protocols were approved by the Virginia Commonwealth University Institutional Animal Care and Use Committee.

For the drug discrimination study, 7 male Sprague-Dawley rats were trained to discriminate 5.6 mg/kg (R,S)-ketamine, administered intraperitoneally (IP), from saline in standard two-lever operant chambers during daily (Mon-Fri) 15-min sessions. Correct responding was reinforced with food pellet delivery under a fixed ratio (FR) 10 schedule. Generalization tests with subcutaneously (SC) administered saline or doses of (R,S)-ketamine (0.3 – 5.6 mg/kg), (S)-ketamine (0.3 – 10 mg/kg) or rapastinel (100 and 170 mg/kg) were conducted twice weekly. For the self-administration study, two groups of 4 adult, male Rhesus monkeys (Macaca mulatta) were surgically implanted with chronic IV catheters. Monkeys were trained to respond for 56 or 100 µg/kg/infusion (R,S)-ketamine under a FR 30 schedule during daily (7 days/week) 1-hour experimental sessions. Saline or different doses of (R,S)-ketamine (10 to 170 µg/kg/inf), (S)-ketamine (3 to 100 µg/kg/inf) or rapastinel (0.01 to 10 mg/kg/inf) were substituted for the training solution over four consecutive sessions. Any test solution which maintained responding significantly above saline levels was also tested using an across-session progressive ratio (PR) procedure in which the ratio requirement for each infusion was increased by 30 during consecutive behavioral sessions until infusion numbers reached saline levels.

Results: In the discrimination procedure, (R,S)-ketamine and the (S)-isomer of ketamine dose-dependently generalized from the training dose with one or more doses producing full substitution (> 80% (R,S)-ketamine-lever responding). (S)-ketamine was approximately 1.9-fold more potent than (R,S)-ketamine for substitution but was equipotent in suppressing rates of responding. Conversely, rapastinel did not substitute for (R,S)-ketamine-lever responding at any dose nor did it disrupt behavior. In the self-administration study, one or more doses of (R,S)-ketamine and (S)-ketamine maintained levels of responding significantly above saline levels. In the PR procedure both (R,S)-ketamine and (S)-ketamine maintained self-administration behavior across sessions with PR values greater than 200 to 300 responses/inf. In contrast, rapastinel failed to maintain self-administration significantly above saline levels at any of the doses tested. (R,S)- and (S)-ketamine doses that served as positive reinforcers of behavior also maintained responding throughout the session whereas those ketamine doses that failed or only weakly supported self-administration showed saline-like patterns of extinction behavior. Rapastinel solution availability was consistently associated with initial sampling followed by extinction of responding similar to the behavior seen with saline availability.

Conclusions: The data show that (S)-ketamine, including doses that commonly produce anti-depressant-like effects in rats, share discriminative stimulus effects with (R,S)-ketamine. In contrast, rapastinel failed to substitute for (R,S)-ketamine across a wide range of doses including doses at least 10-fold greater than those producing antidepressant-like effects in rats. In the self-administration assay, (S)-ketamine served as a positive reinforcer of behavior under FR conditions with peak intake levels and break points under the PR conditions comparable to (R,S)-ketamine.

Conversely, rapastinel, over a very wide range of doses, did not function as a positive reinforcer. Based on these outcomes we would predict that (S)-ketamine may share a risk for abuse liability and other adverse behavioral effects (dissociation) similar to (R,S)-ketamine. Conversely, rapastinel appears to lack abuse liability when compared to (R,S)-ketamine or (S)-ketamine.

Keywords: Drug Discrimination, Self-Administration, Esketamine, Rapastinel, Abuse Liability

Disclosure: Allergan Sales LLC, Grant

M270. ITI-333 for the Treatment of Pain and Psychiatric Co-Morbidities Accompanying a Broad Spectrum of Substance Use Disorders: Pharmacologic and Safety Profile

Robert Davis, Gretchen Synder, Peng Li, Wei Yao, Stephanie Cruz, Lei Zhang, Joseph Hendrick, Kimberly Vanover, Sharon Mates*

Intra-Cellular Therapies, Inc., San Diego, California, United States

Background: New medications are needed to treat opioid use disorder (OUD) by easing the somatic symptoms of drug withdrawal and effectively mitigating the dysphoria and psychiatric comorbidities (e.g., mood and anxiety disorders) that drive opioid use/abuse. A series of novel compounds has been discovered that bind 5-HT2A, D1 and mu opiate receptors. This series is exemplified by ITI-333, which possesses low nanomolar affinity for 5-HT2A, D1 and mu opiate receptors with Ki values of 8.3 nM, 50 nM and 11 nM, respectively. Here, we update the pharmacologic and safety profile of ITI-333 in animal models of analgesia and opioid withdrawal.

Methods: The pharmacological profile of ITI-333 was explored using in vitro receptor binding and cell-based functional assays for 5-HT2A, D1, D2, and mu opiate receptors (MOP). Analgesic effects were tested in the mouse tail flick assay of acute pain and the formalin test for inflammatory pain. Naloxone-induced opioid withdrawal in oxycodone-dependent mice was used to assay for effects on opioid withdrawal symptoms. Abuse liability was studied in tests of intravenous self-administration and physical tolerance/dependence after chronic dosing to rats. Gastointestinal (GI) and pulmonary side effects were examined in rats.

Results: ITI-333 binds with high affinity to 5-HT2A, D1 and MOP receptors, with negligible binding to other opioid receptors. Data from cell-based and in vivo assays, demonstrate that ITI-333 functions as a biased MOP receptor ligand with partial agonist activity, acting as an antagonist to block effects of high doses of morphine in both analgesia and motor activity models while acting alone to provide potent analgesia in models of acute and inflammatory pain. In cell-based assays using human recombinant MOP receptors expressed in CHO cells, ITI-333 alone induces cAMP accumulation (agonism) while blocking the effects of a full MOP agonist, DAMGO (antagonism). Further, ITI-333 displays biased agonism at MOP receptors, acting as an antagonist on beta-arrestin pathways that mediate opioid side effects. In mice, ITI-333, alone (0.01-1 mg/kg, SC, 10 mice/group), produces naloxone-sensitive analgesia in the tail flick (TF) assay, while attenuating morphine-induced analgesia in TF (0.1-1 mg/kg, SC, 10 mice/group). ITI-333 blocks hyperactivity induced by morphine (32 mg/kg, SC, 6 mice/group) without significant effects on spontaneous locomotor activity. In drug abuse liability assays, ITI-333 (0.3, 1, and 3 mg/kg, SC) dose-dependently suppresses the somatic and behavioral signs of opioid withdrawal precipitated by naloxone injection in oxycodone-dependent mice (i.e., oxycodone given for 8 days at increasing daily doses of 9-33 mg/kg b.i.d., 10 mice/group). Chronic (28-day q.d. treatment) of ITI-333 (0.3 or 3 mg/kg, SC) does not result in tolerance or physical dependence in rats; acute doses of ITI-333 (0.3 or 3 mg/kg, SC, 8 rats/group) do not induce GI or pulmonary side effects and reverse GI effects of morphine in this model. Finally, ITI-333 (0.003-0.01 mg/kg, IV, 8/group) is not self-administered by heroin-maintained rats.

Conclusions: The pharmacological profile of ITI-333 uniquely combines potent 5-HT2A antagonism, D1 antagonism and MOP partial agonism. This profile is predicted to translate into utility for safely treating pain, drug dependence and psychiatric co-morbidities (e.g. depression, anxiety) accompanying a broad spectrum of substance use disorders.

Keywords: Opiates, Analgesia, Opioid Dependence, Pharmacotherapy, Animal Model, Withdrawal

Disclosure: Intra-Cellular Therapies, Inc., Employee

M271. The G-Protein Biased Mu Opioid Receptor Ligand SR17108 Produces Less Tolerance and Dependence Relative to Morphine

Travis Grim, Cullen Schmid, Fani Pantouli, Nicole Kennedy, Nina McFague, Michael Cameron, Thomas Bannister, Laura Bohn*

Scripps Research, Jupiter, Florida, United States

Background: The opioid crisis is a continuing public health concern, with over 42,000 deaths attributed to opioid overdose in the United States in 2016. While clinically indispensable for their unrivaled analgesic properties, mu opioid receptor (MOR) agonists carry unwanted side effects, notably respiratory depression, abuse liability, tolerance, and dependence. Repeated use and abuse of MOR agonists may necessitate increasing doses (i.e. tolerance), thus enhancing the risk of overdose. Chronic intake may also result in dependence, a state in which cessation of opioid administration results in withdrawal signs such as diarrhea, agitation, hyperalgesia, and general discomfort. The withdrawal syndrome can be alleviated by further administration of MOR agonists, which in turn may exacerbate tolerance and/or dependence. An idealized MOR agonist would preserve the analgesic properties of MOR activation while avoiding the side effects which lead to ongoing and/or escalating dosing.

The MOR is a seven transmembrane G-protein coupled receptor (GPCR) which signals not only through G-proteins, but via alternative pathways, notably β arrestin 2 (BARR2). Arrestins are so named because they "arrest" further signaling at the receptor following their recruitment, resulting in downregulation and internalization. Previous work utilizing mice with genetically deleted BARR2 demonstrated enhanced morphine potency, less tolerance, and less dependence relative to their wild type litter mates. These results suggest that a hypothetical ligand of the MOR which signaled preferentially via G-proteins while minimizing BARR2 recruitment would be of great utility. One way to achieve this separation in potency to recruit downstream effectors is via a concept known as functional selectivity, or ligand bias. Recently, our lab has synthesized and screened a library of novel MOR agonists, searching for compounds with divergent signaling profiles in G-protein and BARR2 recruitment assays. When selected MOR agonists with the highest bias for G-protein signaling were tested for acute effects in mice, they preserved G-protein-mediated antinociception while displaying reduced potency to elicit respiratory depression. The MOR agonist with the great bias factor (approximately 80-fold selective for G-protein signaling versus BARR2 recruitment), SR17018, was selected for study under chronic dosing conditions versus morphine.

Methods: Male C57BL6 mice were implanted with either minipumps containing morphine or dosed twice daily via gavage with SR17018 to achieve chronic dosing conditions. Pharmacokinetic studies were utilized to confirm effective drug delivery, and cumulative dosing of either morphine or SR17018 was utilized to

assess loss of potency in hot plate and tail flick assays, i.e. tolerance after chronic treatment. In a subset of mice, dependence was assessed via observation at selected time points following morphine minipump explant or cessation of oral dosing with SR17018. The number of paw flutters, wet dog shakes, jumps, incidences of mastication and diarrhea were recorded and consolidated into a global withdrawal score.

Results: Mice treated with morphine displayed robust tolerance and dependence, while SR17018 mice exhibited relatively less in both cases. Pharmacokinetic studies confirmed effective drug delivery for both drugs in their respective chronic dosing conditions. Following the switch from chronic morphine to twice daily dosing with SR17018, antinociceptive efficacy for both SR17018 and morphine was restored while withdrawal signs were suppressed.

Conclusions: The results presented here suggest biased MOR agonists may represent a step closer towards the aforementioned "idealized" opioid, one which can provide pain relief without deleterious side effects. With reduced tolerance, dependence, and respiratory depression, SR17018 demonstrates proof of concept for biased MOR agonists, and could result in new analgesic therapies which avoid complications associated with conventional MOR agonists.

Keywords: Opioid Abuse, Opioid Dependence, Opioid Tolerance

Disclosure: Nothing to disclose.

M272. Preclinical Evidence in Support of Repurposing Everolimus for the Treatment of Cocaine-Craving

*Alvin Chiu, Eleanora Shulman, Anne Fabella, Kalysta Holder, Brooke Barger, Mathangi Sankaran, Tod Kippin, Karen Szumlinski**

University of California, Santa Barbara, Santa Barbara, California, United States

Background: Drug-craving is a cardinal feature of addiction that is elicited by re-exposure to drug-associated cues/contexts. Insidiously, the intensity of cue-elicited drug-craving not only incubates during protracted withdrawal but becomes resistant to extinction. We have theorized that these phenomena contribute majorly to the chronic, relapsing, nature of addiction by driving perseverative cue super-reactivity in drug-abstinent individuals. As such, understanding the neurobiological underpinnings of perseverative drug-cue super-reactivity during protracted abstinence will inform not only our basic understanding of drug-related learning/memory but importantly, the more rationale design & timing of anti-craving therapies. To this end, we have identified increased PI3K/Akt/mTOR signaling within the ventromedial prefrontal cortex (vmPFC) as critical for perseverative drug-craving during cocaine abstinence in rodent models of addiction. PI3K/Akt/mTOR signaling is one of the major intracellular transducer pathways targeted for immunosuppression and in cancer therapy. As such, there exist a number of FDA-approved, orally bioavailable, medications that inhibit this signaling pathway. One such medication - Everolimus (formerly RAD 001; a.k.a., Zortress, Certican, Afinitor, Votubia, Evertor) - has been FDA-approved for nearly 10 years for treating advanced kidney cancer and, since that time, has been repurposed as an immunosuppressant for organ transplant and for treating a number of inoperable tumors.

Methods: Based on the results of our neuropharmacological studies, we tested the hypothesis that acute, oral, pretreatment with Everolimus (1 mg/kg), would block the incubation of cue-elicited cocaine-seeking in rats. To test this hypothesis, rats were trained to self-administer intravenous cocaine (0.25 mg/0.1 ml/infusion) under operant-conditioning procedures during which each cocaine infusion was paired with a 20-sec tone-light stimulus (Day 1: 6 h-session; Days 2-10: 2 h-session). On withdrawal day 3 (WD3), a subset of rats were gavage-infused with 1% DMSO vehicle (VEH) and then subjected to a 30-min test for cue-elicited cocaine-seeking to provide a baseline for determination of Everolimus' effects upon incubated responding during protracted withdrawal. On WD30-46, other subsets of rats were infused with either VEH or 1.0 mg/kg Everolimus prior to a comparable test of cocaine-seeking. To examine for carry-over effects, rats were tested the next day in the absence of any further treatment. To examine for potential effects of Everolimus upon the consolidation of extinction learning, VEH-infused rats were then infused with 1.0 mg/kg Everolimus immediately following the 2nd cue test session and were tested for cocaine-seeking on a 3rd test, conducted the next day.

Results: Relative to VEH-infused rats tested on WD3, VEH-infused rats tested during protracted withdrawal exhibited greater cue-elicited responding, while Everolimus-infused rats exhibited a level of responding comparable to that of the WD3 controls. When tested the next day, a nearly identical pattern of group differences was observed. However, Everolimus treatment post-testing did not impact the incubated level of responding exhibited on a subsequent test, conducted the next day.

Conclusions: These data provide novel, exciting, evidence that acute oral Everolimus pretreatment blocks the expression of incubated cocaine-seeking in a rat model of cocaine-craving and does so in a manner that persists for at least 24 h. The capacity of Everolimus to reduce cue-elicited responding does not appear to reflect an effect of the inhibitor upon the consolidation of extinction learning as post-treatment was ineffective. As this pattern of Everolimus findings are similar to those observed upon intra-vmPFC infusion of PI3K inhibitors, we hypothesize that interrupting PI3K/Akt/mTOR signaling within vmPFC may be the mechanism of action through which systemic Everolimus exerts its anti-craving effects. While requiring further study, the present findings nevertheless provide initial preclinical evidence in favor of repurposing the FDA-approved drug Everolimus for interrupting cocaine-craving during protracted withdrawal.

Keywords: Incubation of Drug Craving, mTOR, Cocaine, PI3K

Disclosure: Nothing to disclose.

M273. Rapastinel, a Nonopioid Pharmacotherapy for Opioid Dependence?

Cynthia Kuhn, Nidesh Lamichhane, Christopher Armstrong, Julia Ferrante, David Walker, Ashwin Patkar*

Duke University Medical Center, Durham, North Carolina, United States

Background: An increasing number of opioid overdose deaths have resulted from the rising availability of both prescription and nonprescription opioids. The current pharmacotherapies (methadone and buprenorphine) maintain the opioid-dependent state and require long-term taper to attain drug-free abstinence. This therapeutic approach may be particularly problematic for the rising population of opioid-dependent adolescents. Few clinical trials have investigated efficacy of these treatments in adolescents, and prolonged pharmacotherapy could extend their period of opioid dependence for as long as or longer than their period of active opioid self-administration. Research in animal models suggests that the NMDA receptor is involved in the maintenance of opioid dependence and that its blockade might reverse opioid-induced neuroadaptation that contributes to dependence. By regulating the NMDA receptor, it may be possible to accelerate

reversal of opioid dependence (Glass, 2011). Ketamine, an NMDA antagonist, has potential as a treatment, but is restricted due to severe side effects. Rapastinel, a novel antidepressant, acts as an allosteric modulator of the glycine site of the NMDA receptor complex. Rapastinel has not been shown to produce any negative side effects during treatment in animal models (Moskal et al., 2016) or in human clinical trials for depression. The purpose of this study was to determine if rapastinel could accelerate the loss of opioid withdrawal symptoms in adolescents and adults without sedating or dissociative side effects associated with ketamine treatment.

Methods: Male and female adolescent and adult rats (PN 28-30 and PN 70-72) from Charles River Laboratories were experimental subjects. They were treated with a 5-day, increasing dose morphine regimen (5 mg/kg bid, increasing 5 mg/kg/day to 25 mg/kg). In Study 1, animals received a 25 mg/kg morphine dose on day 6 followed 1 h later by a naloxone challenge (1 mg/kg) and withdrawal behaviors were quantified as described by Gellert and Holtzman (1978). Animals were returned to the home cage, and a second naloxone challenge given 21 days later (day 27 of the study). In Study 2, male and female adolescent rats received the same morphine treatment, but on day 6 they received naloxone only (1 mg/kg) and withdrawal signs were assessed as in Study 1. Then animals received saline, ketamine (1 mg/kg) or rapastinel (5 mg/kg) twice daily for 2 days. On day 9, animals received a second naloxone challenge (1 mg/kg) without a previous morphine treatment. Aggregate scores from day 9 were subtracted from those on day 6 to produce a difference score reflecting the extent to which withdrawal signs had decreased from the end of morphine treatment to the end of brief pharmacotherapy. Study 3 compared the ability of rapastinel to accelerate the loss of opioid withdrawal signs in adult and adolescent rats. Treatment results were analyzed by sequential 3-way (age x sex x treatment) and 1-way (treatment) ANOVA using NCSS followed by post-hoc Fishers LSD multiple comparison test to compare differences between groups. All experiments were approved by the Duke University IACUC and conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Results: The results of Study 1 ($N = 10$-15/morphine group, 6-10/saline group) indicated that naloxone elicited a robust withdrawal response on Day 6 ($p < 0.0001$ for effect of treatment by ANOVA) but there was no effect of sex or age. The response to the second naloxone challenge on Day 27 was smaller but statistically significant ($p < 0.003$ for effect of treatment) with significant effect of sex ($p < 0.04$) and interaction of sex x age ($p < 0.0009$). Female adults exhibited slightly higher withdrawal scores than male adults, while male and female adolescents had comparable withdrawal scores. In Study 2 ($N = 12$ for ketamine, 14 for rapastinel, 24 for saline), no sex differences were observed so results were collapsed by sex. Rapastinel but not ketamine caused an enhanced loss of opioid withdrawal signs between day 6 and day 9 in adolescent males and females. Finally, Study 3 ($N = 14$-16 for adolescent groups, 5-6 for adults) showed rapastinel was effective ($p < 0.002$ for effect of treatment) but no age or sex differences were observed.

Conclusions: These studies show that opioid withdrawal signs are comparable early during withdrawal in adolescent and adult males and females. Females showed comparable withdrawal scores on Day 6 and Day 9 but slightly exaggerated scores on Day 27 relative to males, suggesting that they may show slightly slower loss of opioid dependence, but these effects were modest. Rapastinel significantly enhanced recovery from opioid dependence in both adolescent and adult rats, while ketamine was only marginally effective. This result could simply reflect a protracted effect of the previous rapastinel injections (as has been observed for depressive-like behaviors), or it could represent an actual accelerated reversal of opioid dependence. Future studies will investigate these two possibilities, as well as ability of rapastinel to blunt relapse during prolonged withdrawal using morphine conditioned place preference. Regardless of mechanism, these effects of rapastinel could prove clinically useful during early phases of recovery from opioid dependence. Supported by Duke Institute for Brain Sciences, Department of Pharmacology and Cancer Biology funds

Keywords: Opioid Dependence, Pharmacotherapy, Animal Model, Withdrawal

Disclosure: Nothing to disclose.

M274. Reduced PTPRD Activities via Heterozygous Knockout or an Illudalic Acid Analog Inhibit Ptprd Phosphatase and Reduce Cocaine and Morphine Reward

George Uhl, Maria Martinez, Paul Paik, Agnieszka Sulima, Guo-hua Bi, Malliga Iyer, Elliot Gardner, Kenner Rice, Zheng-Xiong Xi*

VA, UNM, Biomedical Research Institute of New Mexico, NIDA IRP (guest worker), Albuquerque, New Mexico, United States

Background: PTPRD (receptor type protein tyrosine phosphatase D) is a neuronal cell adhesion molecule and synaptic specifier that has been implicated in addiction vulnerability (including opiates), stimulant reward and ability to quit smoking by human GWAS (genome wide association) and mouse cocaine-conditioned place preference data. Features of PTPRD's neurobiology (including its expression in dopamine and other neurons implicated in addiction and its ability to alter phosphorylation of addiction-associated molecules including Cdk5) enhance prior probabilities that modulating PTPRD activities might reduce reward from addictive substances and aid quitting. However, there have been no reports of effects of reduced expression on cocaine self-administration or on reward from opiates. There have been no reports of PTPRD targeting by any small molecule. There is no data about behavioral effects of any PTPRD ligand.

Methods: A 13 step synthesis provided 7-butoxy illudalic acid analog 7-BIA. Heterozygous PTPRD knockouts and wildtype littermate mice of both genders, bred from heterozygote x heterozygotes crosses, underwent conditioned place preference with four pairings with morphine (10 mg/kg) or were catheterized and lever pressed for 1 mg/kg cocaine infusions under fixed-ratio 1 (FR1) or progressive ratio schedules (2, 4, 6, 9, 12,15, 20, 25, 32, 40, 50, 62, 77 presses/infusion) with vehicle or 7-BIA pretreatments. In vitro phosphatase assays used recombinant human PTPRD and PTPRS phosphatase fusion proteins expressed in E Coli and OD405nM spectrophotometric assessment of p-nitrophenyl phosphate dephosphorylation to p-nitrophenolate. Receptor binding and uptake assays for 77 brain sites of action of known drugs were performed by EUROFINS and Dr Aaron Janowsky. Ip 6 - 60 mg/kg 7-BIA doses ascended acutely and then were repeated for two weeks. Locomotor activity, mnemonic (Morris water maze) and somatosensation (pain) were tested. Gross and histopathologic evaluations were performed by veterinarian/veterinary pathologists.

Results: There are: a) robust effects of heterozygous PTPRD knockout on cocaine self-administration.; b) substantial effect of heterozygous knockout on morphine-conditioned place preference (initial data); c) inhibition of recombinant PTPRD phosphatases by 7-BIA, with > 10 fold greater potency than at PTPRS; d) lack of toxicity when 7-BIA is administered to mice acutely or with repeated dosing, e) reduced cocaine- and morphine (initial data)-conditioned place preference when 7-BIA is administered prior to conditioning sessions in wildtype, but not in heterozygous PTPRD knockouts, e) reductions in well-established cocaine self-administration when 7-BIA is administered prior to a session (in

wildtype, not PTPRD heterozygous knockouts). There was no evidence for gross pathological, histopathological or behavioral toxicity from 7-BIA administration or for effects only in one gender. There was no evidence for significant off-target 7-BIA effects in EUROFINS or NIDA/Janowsky screens.

Conclusions: These results support: a) PTPRD as a target for novel medications to combat opiate and stimulant use disorders and b) 7-BIA as a novel lead compound PTPRD phosphatase inhibitor for new antiaddiction therapeutics.

Keywords: Cell Adhesion Molecule, Opiate Addiction, Cocaine Addiction, GWAS LOCI, Drug Discovery/Development

Disclosure: Nothing to disclose.

M275. Adolescent Nicotine Exposure Alters Cognitive Flexibility and Immune Mediators in the PFC of Adult Mice

Vinay Parikh, Evelynn Harrington, Zoe Steinberg, Joseph Meissler, Toby Eisenstein*

Temple University, Philadelphia, Pennsylvania, United States

Background: Vulnerability to nicotine addiction is known to significantly increase in individuals who begin smoking during adolescence; however, the underlying mechanism for this phenomenon remains poorly understood. Dysfunction in the prefrontal cortex (PFC)-dependent cognitive processes is hypothesized to contribute to impairments in behavioral control and inability to consistently abstain from drugs in addicts. In the current study, we examined the consequences of nicotine experience given to adolescent mice on the ability to adaptively make and maintain a behavioral shift (described as cognitive flexibility) to probe PFC function during adulthood. Because the immune system is critically involved in the developmental programming of PFC, and nicotine exerts immunosuppressive effects, we also assessed the levels of immune mediators in the PFC.

Methods: Adolescent C57BL/6 J mice (PND33-35) of either sex were implanted with mini-osmotic pumps for subcutaneous delivery of either saline or nicotine (low dose: 3 mg/kg/day; high dose: 12 mg/kg/day) for 2 weeks. After chronic saline/nicotine administration, a 2-week washout period was given following which behavioral testing in adult mice commenced. Animals were trained and tested in an operant task that required the animals to switch from using a spatial response-driven strategy to a visual cue-based strategy to achieve rewards. After the behavioral testing, brains were removed to measure immune mediators using the Proteome Profiler (R&D Systems) array.

Results: Mice exposed to nicotine during adolescence required more trials to reach strategy set-shifting criterion ($F(2,29)=5.49$, $p=0.01$). When examining specific error types, adolescent nicotine-exposed mice committed more perseverative errors as compared to saline-treated mice (both doses: $p<0.05$) indicating that the former adhered to using the previously engaged strategy despite a new rule was implemented. Examination of maintenance errors revealed no significant difference between adolescent nicotine exposed and saline control animals ($F(2,29=0.32$, $p=0.73$). Although the behavioral performance remained similar between the animals exposed to low and high dose of nicotine, we observed a sex x dose interaction for trials to criterion ($F(2,29)=6.72$, $p=0.005$). Surprisingly, lower nicotine dose impaired performance in adult female mice while higher nicotine dose was more detrimental to adult male mice (both $p<0.05$). It is possible that this dissociation might be linked to sex-specific differences in nicotine pharmacokinetics in adolescent mice. Analysis of immune mediators based on the results of the array revealed significant reduction of complement component C5a, s-ICAM and IFN-γ in the PFC of adolescent nicotine-exposed mice (all $p<0.03$).

Conclusions: Our data suggests that nicotine exposure during adolescence, regardless of dose, disrupts cognitive flexibility in mice during adulthood. These cognitive deficits are mainly associated with a disruption in the animals' ability to disengage from a previously acquired behavioral strategy. Earlier literature implicated the involvement of PFC in adapting to new strategies with changes in environmental demands. Thus, it is possible that adolescent nicotine exposure might exert long-term detrimental effects on executive processes by disrupting immune function that interferes with the developmental maturation and refinement of the PFC.

Keywords: Adolescence, Nicotine Addiction, Cognition, PFC, Immune System

Disclosure: Nothing to disclose.

M276. Long-Lasting Effects of the Pseudo-Irreversible Mu Opioid Receptor Antagonist Methocinnamox on Remifentanil Versus Food Choice in Rhesus Monkeys

David Maguire, Lisa Gerak, James Woods, Stephen Husbands, Alex Disney, Charles France*

University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

Background: Opioid abuse remains a serious public health challenge, despite the availability of medications that are effective in some patients (naltrexone, buprenorphine, and methadone). Methocinnamox (MCAM) is a pseudo-irreversible mu opioid receptor antagonist that suppresses heroin self-administration in rhesus monkeys for several days following a single administration, demonstrating the potential for MCAM for treating opioid abuse. However, the selectivity of MCAM for decreasing drug versus non-drug (e.g., food) reinforced behavior has not been well characterized. This study compared effects of MCAM with those of naltrexone on responding under a food versus drug (opioid) choice procedure. Under choice procedures, subjects can choose between multiple alternatives, and the primary measure of reinforcing effects is based on allocation of behavior among the alternatives rather than overall response output (i.e., response rate), which can be influenced by many factors not directly related to reinforcing effectiveness. Thus, this choice procedure is more selective for changes in reinforcing effectiveness as compared to single-response procedures. Naltrexone was chosen as a comparator because it is the only opioid antagonist approved to treat opioid abuse.

Methods: Three male rhesus monkeys served as subjects. Responding on one lever delivered a 300-mg sucrose pellet and responding on the other lever delivered an i.v. infusion of remifentanil; the unit dose of remifentanil (0.000032-0.001 mg/kg/infusion) increased across blocks within the session. Naltrexone (0.01-0.32 mg/kg) or MCAM (0.32-3.2 mg/kg) was administered i.v. 15 min (naltrexone) or 24 h (MCAM) prior to a test session.

Results: Remifentanil dose-dependently increased choice of remifentanil over food and dose-effect curves were stable across days. Naltrexone and MCAM decreased choice of remifentanil and increased choice of food, shifting the remifentanil dose-effect curve rightward and downward. In some cases, following MCAM administration, the remifentanil dose-effect curve was flattened with monkeys choosing food exclusively. Effects of naltrexone were transient, lasting less than one day. On the other hand, effects of MCAM lasted several days, with the largest dose tested (3.2 mg/kg) decreasing remifentanil choice (and increasing food choice) for more than one week.

Conclusions: MCAM decreased choice of drug and increased choice for food for several days following a single administration. The total number of choice trials completed was not significantly altered by any treatment, indicating that effects were the result of reallocation of behavior rather than a generalized suppression of behavior. The selective attenuation of opioid-maintained behavior coupled with a long duration of action indicates that this novel drug could be superior to currently available treatments for opioid abuse. This work was supported by the National Institutes of Health [Grant R01DA005018] and the Welch Foundation [Grant AQ-0039].

Keywords: Opioid Abuse, Opioid Antagonist Treatment, Choice Procedure, Remifentanil, Preclinical

Disclosure: Nothing to disclose.

M277. Ethanol Acts on KCNK13 Potassium Channels to Activate Ventral Tegmental Area Neurons: A Novel Target for Alcohol on Reward Neurons

*Chang You, Antonia Savarese, Bertha Vandegrift, Donghong He, Tara Teppen, Subhash Pandey, Amy Lasek, Mark Brodie**

University of Illinois at Chicago, Chicago, Illinois, United States

Background: The ventral tegmental area (VTA) provides dopamine inputs to various brain regions including components of the central reward/reinforcement system. As a brain area involved in incentive and behavioral motivation, it has a major role in neurobiological theories of drug and alcohol addiction. While it is known that alcohol activates dopaminergic (DA) VTA neurons, the precise target of alcohol that mediates excitation of VTA neurons has been elusive. Two-pore potassium channels mediate "leak" current that controls membrane potential and firing rate of neurons and other excitable cells. Quinine and quinidine block both two-pore channel conductance and ethanol excitation of VTA neurons, suggesting to us that some two-pore channels could mediate ethanol excitation.

Methods: In initial experiments, isoflurane mimicked ethanol, in that it excited VTA neurons. We therefore focused on the THIK sub-type of two-pore potassium channels, KCNK12 or KCNK13, because these are inhibited by volatile anesthetics, which would result in neuronal excitation. Subjects were male C57BL/6 J mice and Fisher 344 or Sprague-Dawley rats. RNA interference (RNAi) knockdown of Kcnk12 or Kcnk13 was performed, and, using in vitro extracellular recordings, we assessed the response of VTA neurons to ethanol (40-120 mM). In addition, real-time PCR and immunohistochemistry were used to examine expression of these channels in the VTA. Most importantly, binge-like drinking was examined in the drinking in the dark test in mice after shRNA-mediated knockdown of Kcnk12 or Kcnk13 in the VTA.

Results: Ethanol-induced excitation of VTA neurons was reduced by siRNA targeting Kcnk13 but not Kcnk12. Expression of Kcnk13, but not Kcnk12, in the VTA was increased by acute ethanol exposure. Knockdown of Kcnk13 using shRNA resulted in a significant reduction in ethanol-induced excitation of VTA neurons. For example, 40 mM ethanol produced 11.0 ± 2.2 % increase in firing rate in mouse VTA neurons, whereas 40 mM ethanol increased firing rate by only 4.9 ± 0.8% in VTA neurons from mice in which KCNK13 was reduced. In the drinking in the dark experiments, shRNA-mediated knockdown of Kcnk13, but not Kcnk12, in the VTA significantly increased alcohol intake. For example, on day 3, the control mice consumed 2.9 ± 0.4 g/kg ethanol, whereas the mice in which KCNK13 was knocked down consumed 3.9 ± 0.25 g/kg ethanol.

Conclusions: Together, these results show that the action of alcohol on KCNK13 is a factor in ethanol-induced excitation of VTA neurons, and lowered levels of KCNK13 can increase intake during binge drinking. KCNK13 is a novel alcohol-sensitive molecule. Reduced levels of KCNK13 may constitute a risk factor for increased binge drinking, and, ultimately, KCNK13 may be an important target for development of a pharmacotherapy for alcoholism treatment. (Supported by NIAAA grant P50AA022538 (SCP, AWL and MSB), R01AA05846 (MSB), U01 AA020912 (AWL), and VA Senior Research Career Scientist Award to SCP)

Keywords: THIK1, Ethanol, Binge Drinking, Ventral Tegmental Area (VTA), Mesolimbic Reward Circuitry

Disclosure: Nothing to disclose.

M278. Prior Cocaine Self-Administration Alters the Strength of Reward Size and Movement Direction Encoding in Distinct DMS Neuron Populations in Rats

Lauren Mueller, Andrew Wikenheiser, Melissa Sharpe, David Dietz, Thomas Stalnaker, Geoffrey Schoenbaum*

National Institues of Health, National Institue of Drug Abuse, The State University of New York at Buffalo, Baltimore, Maryland, United States

Background: When the rules that govern our actions change, it is useful to learn about the new situation in a way the preserves old learning, building a library of associations that can be deployed as needed to match the current context. One way to achieve this is to compartmentalize learning about different contexts into distinct "states," each containing information relevant to a particular scenario. Cholinergic interneurons (CINs) in the dorsomedial striatum (DMS) use inputs from the orbitofrontal cortex to represent such task state information, and such CIN state representations may influence behavior by affecting the activity of other prominent DMS populations, such as medium spiny neurons (MSNs) and fast-spiking interneurons (FSIs).

Methods: Here, we assessed how prior cocaine self-administration affected neural representations in these cell groups of the DMS in rats. Single-unit activity was recorded from DMS in male rats that had self-administered either sucrose (n=4) or cocaine (n=5) for several weeks prior to recording. Units were recorded during performance of a simple odor discrimination task in which odors predicted large or small rewards reversibly across 2 blocks of trials or "states."

Results: We found that cocaine-experienced rats were slower to adjust responding following a state change as compared to sucrose-experienced controls. This behavioral change was accompanied by differences in the encoding of task-related variables in DMS neuron subtypes. The proportion of MSNs that prospectively encoded the size of upcoming outcomes was decreased relative to sucrose-experienced rats, but the fraction of neurons that encoded responses did not differ. In contrast, a greater proportion of CINs encoded responses in the cocaine-experienced group, but there were no differences in the proportion of CINs encoding outcome size between groups. In FSIs, the encoding of both outcome size and response direction was similar between groups.

Conclusions: These data demonstrate a cell-type specific double dissociation in the encoding of task-related information in DMS neurons caused by prior cocaine experience. These results are consistent with a role for DMS cell populations in the regulation of behavioral flexibility and suggest that alterations in task encoding may contribute to the poor decision-making that is observed in individuals following exposure to drugs of abuse.

Keywords: Decision Making, Cocaine Self-Administration, Electrophysiology

Disclosure: Nothing to disclose.

M279. A History of Cocaine Alters Prelimbic to Accumbens Neural Activity During Learning and Impairs Subsequent Behavioral Flexibility

Abstract not included.

M280. Cortical-Brainstem Projections Gate Compulsive Alcohol Drinking

Cody Siciliano, Xinhong Chen, Habiba Noamany, Joyce Wang, Daniel Leible, Yi Ning Leow, Eyal Kimchi, Caitlin Vander Weele, Kay Tye*

Massachusetts Institute of Technology, Vassar Street, Massachusetts, United States

Background: Over 80% of the adult population in the United States has used alcohol; however, only a relatively small subset of users, about 6%, will develop an alcohol use disorder. Compulsive alcohol use is a cardinal symptom of alcohol abuse disorders and is typically defined in rodent models as continued drug use in the face of negative consequences. Previous research has highlighted the role of the medial prefrontal cortex (mPFC) in encoding motivational value and decision making, and alcohol-induced plasticity in mPFC has been implicated in the development of compulsive drinking behaviors. However, we have little understanding of how neurons in mPFC are encoding alcohol-related stimuli in real-time, and what downstream circuits are involved. We identified cells in the mPFC that project to the dorsal periaqueductal gray area (dPAG), which encode the valence of unconditioned stimuli. Here, we sought to dissect the role of this projection-defined subpopulation within mPFC in compulsive (i.e. punishment-resistant) alcohol drinking.

Methods: Using a dual virus approach in male wildtype C57BL/6 J mice we selectively expressed the genetically encoded calcium indicator GCaMP6m in mPFC cells projecting to dPAG (mPFC-dPAG). By implanting a lens into the mPFC and attaching a miniature head-mounted microscope we were then able to record calcium dynamics, a proxy for action potential activity, with single-cell resolution over days. We developed a novel Pavlovian conditioning task where animals were given access to alcohol, or alcohol adulterated with the bitter tastant quinine, designed to examine individual differences in compulsive drinking. Following training, a cue predicting the delivery of alcohol (15% v/v) to a port was presented over three repeated daily sessions, to assess individual differences in baseline alcohol consumption. Over days, ascending concentration of quinine (0.25-1.0 mM) were then added to the alcohol to test for differences in compulsive alcohol drinking. Animals were then allowed to drink in a modified two-bottle choice procedure daily for two weeks, used to model binge alcohol consumption. Following binge alcohol consumption, animals were retested in the Pavlovian conditioning task, first for alcohol and then for alcohol adulterated with quinine. For optogenetic experiments, halorhodopsin or channelrhodopsin-2 was expressed in mPFC-dPAG projectors using the same dual virus strategy described above, and fibers were implanted bi-laterally above the mPFC. Control animals received the same surgery and implants but were injected with a virus carrying only a fluorophore.

Results: Prior to binge exposure, animals uniformly decreased alcohol intake as quinine was added to the solution. Following binge alcohol drinking, we found wide individual differences in alcohol consumption, and the ability of quinine to decrease consumption, where a subset of animals showed a persistent compulsive phenotype defined by high alcohol intake and insensitivity to punishment. We found that mPFC-PAG projectors decreased their activity during alcohol consumption; surprisingly, and the magnitude of this decrease during each animals' initial alcohol experience was correlated with the development of a compulsive phenotype more than three weeks after the initial session.

To test if this inhibitory signaling during initial alcohol use was a biomarker or a behavioral driver, we used a closed-loop optogenetic approach to photoinhibit mPFC-dPAG neurons during licking for alcohol with quinine, mirroring the endogenous inhibitions observed during drinking. Inhibition conferred a compulsive phenotype, even in animals with minimal prior alcohol exposure. Conversely, closed-loop optogenetic activation of mPFC-dPAG neurons paired with licking for unadulterated alcohol decreased consumption, demonstrating that activation of this pathway is sufficient to recapitulate some of the effects of quinine on alcohol intake.

Conclusions: Here, we introduce a novel alcohol abuse model where wide individual variations in the development of compulsive alcohol drinking are induced by a relatively short binge alcohol exposure. We show that mPFC-dPAG projectors are involved in encoding of alcohol related stimuli, whereby inhibitory responses during initial alcohol use strongly predicts a compulsive drinking phenotype several weeks later. Importantly, temporally specific optogenetic inhibition was sufficient to drive compulsive-like alcohol consumption. Together, our results support a model where inhibition or activation of the mPFC-dPAG circuit attributes positive or negative valence to unconditioned stimuli, respectively. Binge drinking reduces the sensitivity of this cortical-brainstem pathway to punishment in the context of alcohol drinking, thereby driving compulsive drinking in a subset of animals.

Keywords: Compulsive Models of Drug Use, in Vivo Calcium Imaging, Pavlovian Conditioning, Alcohol and Substance Use Disorders, Medial Prefrontal Cortex

Disclosure: Nothing to disclose.

M281. Neural and Hormonal Factors Underlying Poor Inhibitory Control in Heavy Drinking Women

Jessica Weafer, Harriet de Wit*

University of Chicago, Chicago, Illinois, United States

Background: Alcohol abuse has been traditionally considered a male-oriented problem and as a consequence research on risk factors specific to women has been minimal. However, the sex gap in alcohol abuse is closing rapidly, and findings from both animal and human studies suggest that females are actually more vulnerable to substance use than males. As such, it is important to understand the biological basis of sex differences in risk factors to develop sex-specific prevention and treatment efforts. Here we examined neurobiological factors underlying poor inhibitory control, a risk factor that we and others have shown is more strongly linked to heavy drinking in women than in men. Specifically, we tested the degree to which sex hormones influence neural correlates of inhibition.

Methods: Female and male heavy drinkers, matched on demographic and alcohol consumption measures, performed the stop signal task to assess inhibitory control while undergoing fMRI. Women were tested once in the early follicular phase of their menstrual cycle (when estradiol levels are low) and once in the late follicular phase (when estradiol levels peak), and men were tested twice at similar intervals. Blood samples were taken to assess serum levels of estradiol at both sessions.

Results: Data collection is currently ongoing, and to date 18 women and 8 men have completed the study. Preliminary

analyses confirmed low levels of estradiol in the early follicular phase (mean = 48.1 pg/ml), and high levels in the late follicular phase (mean = 201.9 pg/ml). Women showed less brain engagement during response inhibition in the early compared to the late follicular phase in right frontal regions, including the right inferior frontal gyrus, middle frontal gyrus, and supplementary motor area. In line with this, correlational analyses showed that estradiol was positively associated with brain activation during inhibition. Further, women had less brain activation compared to men when tested in the early follicular phase, but no sex differences were observed when women were tested in the late follicular phase.

Conclusions: These data suggest that the inhibitory impairments observed in heavy-drinking women are influenced by fluctuating levels of estradiol. Further, they suggest that inhibitory deficits may be exacerbated in the early follicular phase of the menstrual cycle, possibly contributing to increased difficulty controlling alcohol consumption during this time. Identification of such vulnerable periods for problematic alcohol consumption could have important implications for prevention and treatment of alcohol use disorders in women.

Keywords: Sex Differences, Addiction, Inhibitory Control

Disclosure: Nothing to disclose.

M282. Escalation of Aggressive Arousal by Alcohol: Dissociation of Motivation and Fighting Performance by CRF Pathways

*Herbert Covington III, Emily Newman, Michael Leonard, Klaus Miczek**

Tufts University, Medford, Massachusetts, United States

Background: How alcohol persistently escalates the motivation to commit intense aggressive acts in some individuals remains undetermined. Neuropeptides, like corticotrophin releasing factor (CRF), are initial mediators of emotional responses; and their function in specific brain areas adapts, particularly in the extended-amygdala, like the bed nucleus of the stria terminalis (BNST), in response to repeated alcohol administrations. Here, anticipatory arousal, followed by the initiation of aggressive acts, were experimentally examined in WT and CRF-Cre C57BL/6 J mice, with or without alcohol exposures.

Methods: Male "resident" mice were trained to respond on a fixed interval ten-minute (FI10) schedule with aggression serving as a reward. Accelerating patterns of responding established by the FI schedule allow for direct, stable and quantifiable measurements of the motivation to fight, prior to performance measures of aggressive behavior. Specifically, after the completion of an FI10 schedule, an intruder was presented to each resident, and aggressive acts were quantified. The general role of CRF receptor 1 was examined on both, motivation and fighting performance, in WT mice, with or without a history of oral alcohol administrations (N=20/group). Next, optical control of CRF-specific pathways from BNST-VTA (n=8) or BNST-NAc (n=8) were examined in CRF-Cre mice during FI responding and fighting performance. For CRF-R1 antagonism data, two-way repeated measures ANOVA were used to detect significant differences in FI rates of responding or the number of attack behaviors between alcohol and non-alcohol treated mice. Dunnet's tests were used to compare doses of the CRF-R1 antagonist within and between alcohol treatment groups. FI rates of responding and fighting performance were compared across different stimulation parameters (i.e., 2, 10, 20 Hz) in groups of mice receiving AAV9-DIO-ChR2 into the VTA, or NAc, during later optical control over the BNST in CRH-Cre mice, using one-way repeated measures ANOVA, and Dunnet's post-hoc analyses for each group. All mice were cared for according to the NIH guide for the Care and Use of Laboratory Animals and procedures were approved by the Institutional Animal Care and Use Committee of Tufts University.

Results: Tolerance and sensitization, with regards to the motivation to fight, are reliably observed with repeated oral (gavage) administrations of alcohol. Interestingly, low doses of the selective CRF-R1 antagonist CP 376395 blocks the expression of alcohol-induced sensitization of aggressive motivation ($p<0.05$), but without significantly influencing fighting performance. CRF-mediated control of anticipatory arousal appears to be pathway-specific, in that BNST-VTA and BNST-NAc CRF tone differentially regulates the motivation to fight and fighting performance.

Conclusions: Here, we conform that EtOH alters the regulation of sympathetic responses, which exacerbate "hot" acts of aggression. The specific escalation of aggressive arousal is dependent on CRF, perhaps through direct and indirect modulation of mesocorticolimbic DA. Differentiating the neural circuits mediating the urge to fight vs. those responsible for the performance can be achieved using fixed-interval schedules of reinforcement.

Keywords: Aggression, CRF, Dopamine, Motivation, Reinforcement

Disclosure: Nothing to disclose.

M283. Comorbid Mild Traumatic Brain Injury and PTSD Chronically Increase Behavioral Dysfunction and Substance Abuse Risk in Veterans and Mice

Abigail Schindler, Erin Cooper, Britahny Baskin, James Meabon, Mayumi Yagi, Rebecca Hendrickson, Kati Pagulayan, Ge Lee, Paul Phillips, Elaine Peskind, David Cook*

VA Puget Sound Health Care System and University of Washington, Seattle, Washington, United States

Background: Repetitive mild traumatic brain injury (mTBI/concussion) and post-traumatic stress disorder (PTSD) have been called the "signature injuries" of military personnel serving in the Iraq and Afghanistan wars, and are major sources of morbidity among Veteran patients enrolled in the VA health care system but diagnoses and treatment options are limited. Blast exposure is a primary source of mTBI (75% of all TBIs reported by Veterans) and gives rise to a multi-factorial behavioral and pathophysiological syndrome that is highly comorbid with PTSD. Moreover, many symptom outcomes are associated with increased risk for maladaptive behaviors such as substance abuse. Indeed, we have previously reported increased PTSD, risk-taking behaviors and irritability symptoms by blast-mTBI Veterans, as well as an increase in risky drinking. Translational research efforts using rodent models can provide much needed insight into underlying mechanisms by which blast exposure produces dysfunction and are needed in order to facilitate the search for therapeutic approaches that can reduce and/or prevent adverse/maladaptive outcomes such as substance abuse in persons with blast-related mTBI and/or PTSD.

Methods: The current study integrated behavioral, neurochemical, physiological, and neuropathology approaches in mice to better understand underlying mechanisms that mediate mTBI/PTSD maladaptive outcomes, with a specific focus on substance abuse risk. To create a blast overpressure, we used a well-established pneumatic shock tube that accurately models battlefield-relevant open-field blast forces generated by detonation of high explosives. Male C57Bl/6 mice were exposed to either 1x sham, 3x sham, 1x blast, or 3x blast treatments (one exposure per day). An extended behavioral and physiological battery of tests were conducted at baseline and chronically (1-4 months)

following blast or sham exposure (blood and fecal samples were collected at each timepoint, and brains were collected a time of sacrifice). The battery consisted of behaviors related to adverse Veteran-reported blast outcomes (physical impairments (e.g. motor, vision, and hearing), hyperarousal/vigilance, avoidance, aggression, cognitive difficulties, depression, and anxiety). Blood was processed using flow cytommetry and fecal samples were used for microbiome analysis. Brains were processed by Neuroscience Associates for microglia (IBA1), astrocytes (GFAP) and dopamine/norepinephrine synthesis (tyrosine hydroxylase). In a separate set of mice, we examined ethanol self-administration using the intermittent two-bottle choice paradigm and ethanol sedation using loss of righting reflex. Finally, we used a pavlovian conditioned approach (PCA) procedure to investigate the attribution of incentive-motivational value to food reward cues. Phasic dopamine release in the nucleus accumbens core (NAcc) was measured via fast scan cyclic voltammetry at a carbon fiber microelectrode.

Results: Blast exposure chronically (>4 months post-blast) increased a variety of maladaptive outcomes related to either/both mTBI and PTSD (e.g. decreased heart rate variability ($p < 0.05$), sensory-motor impairments ($p < 0.0001$), aversion to blast-related environments ($p < 0.01$), novelty seeking ($p < 0.05$), anxiety ($p < 0.01$), dysphoria ($p < 0.01$), and aggression ($p < 0.001$)). Furthermore, reward learning during PCA was shifted towards sign-tracking behavior following blast exposure ($p < 0.01$), supporting a potential for increased substance abuse risk in mTBI/PTSD. Indeed, blast exposed mice demonstrated an increase in ethanol consumption ($p < 0.01$) and preference ($p < 0.05$). Surprisingly, blast exposed mice had an increased sensitivity to the sedative properties of ethanol ($p < 0.0001$) but did not differ in blood ethanol metabolism or ethanol tolerance. In accordance with these behavioral outcomes, blast chronically increased evoked phasic dopamine release in the NAcc ($p < 0.0001$).

Conclusions: Taken together these findings in mice demonstrate that blast exposure is sufficient to give rise to a constellation of adverse neuropathologic and behavioral outcomes that are accompanied with increased substance abuse risk. These results strengthen the translational relevance of this animal model of blast-related mTBI by recapitulating important psychological/behavioral co-morbidities common among Veterans with blast-related mTBI that can now be wedded more effectively with the attending neuropathology. Of particular importance to the findings of increased alcohol use and risky behaviors in blast exposed mice, our findings implicate the mesolimbic dopamine system, which plays a key role in motivation, reward processing, and decision making. Therefore, such changes may mediate aspects of the complex behavioral dysfunction reported in blast-exposed Veterans and provide potential new therapeutic targets and treatment strategies.

Keywords: TBI, Combat PTSD, Substance Abuse, Neuroinflammation

Disclosure: Nothing to disclose.

M284. Serotonergic Modulation of Compulsive Ethanol Drinking Behavior

Catherine Marcinkiewcz, Dipa Pati, Jeffrey Diberto, Cayce Dorrier, Eric Delpire, Thomas Kash*

University of Iowa Carver College of Medicine, Iowa City, Iowa, United States

Background: Serotonin (5-hydroxytryptamine; 5-HT) orchestrates emotional responses to stress through a variety of pre- and postsynaptic receptors distributed across functionally diverse neuronal networks in the central nervous system. Efferent projections from the dorsal raphe to the bed nucleus of the stria terminalis (BNST) are generally thought to enhance anxiety and aversive learning by activating 5-HT2C receptor (5-HT2CR) signaling (Ravinder et al., 2012; Marcinkiewcz et al., 2015; Marcinkiewcz et al., 2016; Pelrine et al., 2016), although an opposing role for 5-HT at 5-HT1ARs has recently been suggested (Garcia-Garcia et al., 2017). Furthermore, the precise contribution of pre- and postsynaptic 5-HT1ARs to these behavioral outcomes is still unclear.

Methods: In the present study, we sought to delineate a role for postsynaptic 5-HT1ARs in the BNST in aversive behaviors using a transgenic mouse line containing a conditional knockout of the 5-HT1AR. Site-specific infusion of an adeno-associated viral vector (AAV-cre-GFP) into the BNST selectively ablated 5-HT1ARs from postsynaptic neurons in order to assess their contribution to anxiety and fear-related behavior. We assess behavior on the elevated plus maze, open field, novelty suppressed feeding test, light dark test, and cued and contextual fear recall. Both males and females were tested to tease out sex-specific effects. We also looked at cfos expression in the BNST after contextual fear recall and intrinsic and stimulus evoked excitability in the BNST using whole cell patch clamp electrophysiology.

Results: We found that postsynaptic deletion of 5-HT1ARs in the BNST did not significantly alter anxiety-like behavior under high or low stress conditions in either sex but heightened both cued and contextual fear recall in male mice only. Deletion of 5-HT1ARs in the BNST also enhanced cfos expression after intrinsic basal excitability of BNST neurons after contextual recall in fear conditioned male mice, but not in unconditioned mice or female mice.

Conclusions: These results suggest that postsynaptic 5-HT1AR signaling can buffer against aversive memory in a sex-specific manner without affecting anxiety-like behavior. Ongoing studies using whole-mount fos immunolabeling (iDISCO) will elucidate how 5-HT1AR signaling in the BNST shapes global brain networks recruited during contextual fear recall. Together, these studies will reveal important insights into serotonergic modulation of aversive memory, which may lead to new therapeutic targets for psychiatric disorders like PTSD.

Keywords: Serotonin 1a Receptor, Bed Nucleus of the Stria Terminalis, Contextual Fear, Anxiety, Serotonin

Disclosure: Nothing to disclose.