ABSTRACTS COLLECTION

ACNP 60th Annual Meeting: Panels, Mini-Panels and Study Groups

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PANEL

1. Compulsivity: New Advances in Trans-Diagnostic Models and Treatments

1.2 Trans-Diagnostic Perspectives on Compulsivity: Latent Phenotypes, Impact of the Pandemic, and Functional Brain Dysconnectivity

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Background: Compulsivity is highly relevant to a range of prevalent psychiatric disorders, as well as in understanding the normal range of human behaviors. In order to advance beyond categorical psychiatric models (focusing exclusively on overt symptoms) it is necessary to identify latent ‘brain relevant’ phenotypes of compulsivity that exist along a dimension (or set of dimensions), are measurable in a continuous fashion in the general population, and exist in more extreme forms in people with diagnosed mental disorders. However, studies examining true trans-diagnostic compulsivity phenotypes are lacking, due to reliance on disorder specific outcome measures and examination of disorders in isolation.

Methods: In addition to presenting findings from case-control studies of compulsivity (binge-eating disorder, obsessive-compulsive disorder, and problematic usage of the internet), the presentation will showcase:

1. A large scale validation of a new self-report trans-diagnostic compulsivity instrument, and examination of compulsivity's role in the impact of COVID-19 pandemic. Participants were recruited from the general UK population, and completed self-report questionnaires and cognitive tasks online. Individuals completed a novel compulsivity instrument, and provided other contextual demographic and mental health measures. Canonical correlation analyses (CCA) were applied using a robust train-test cross-validation pipeline to quantify multivariate associations between compulsivity and pandemic impact, controlling for confounders (Family Wise Error, FWE, $p < 0.05$).
2. An evaluation of the link between trans-diagnostic compulsivity and resting state brain connectivity. A longitudinal study of representative young adults was conducted using an online platform (including the validated compulsivity

instrument outlined above). Relationships between compulsivity (quantified using the tool validated in ‘1’) and resting state functional connectivity were quantified using graph theory analysis (Brain Connectivity Toolbox), Bonferroni-corrected $p < 0.05$.

Results: 1) 370,000 individuals took part, with relatively high levels of inclusivity (e.g. 14.3% from minority ethnic groups). CCA showed that trans-diagnostic compulsivity statistically accounted for impact of the pandemic, with the relationship being strongest for health concerns (mean $r = 0.32$, $p < 0.0001$) followed by disrupted lifestyle (mean $r = 0.24$, $p < 0.0001$) (FWE $p < 0.05$).

2) Network-based statistics analysis ($n = 117$ individuals, demographically representative of the full cohort) revealed a subnetwork of 15 edges across 15 regions, significantly negatively associated with compulsivity (FWE $p < 0.05$). The connections primarily linked the right inferior frontal brain region (right pars opercularis) to bilateral lateral occipital regions (9 out of 15 connections/edges), and the right lateral occipital region to the right parietal (supramarginal) region (4 edges). Two other edges connect the right pars opercularis to the left precentral and left superior frontal gyri.

Conclusions: Compulsivity can be fruitfully measured trans-diagnostically, statistically explains impact of stressors (as exemplified by self-reported impact of the pandemic) and is related to functional brain dysconnectivity. The findings extend upon previous literature that examined disorder-specific measures of compulsivity in case-control designs, suggesting that compulsivity may constitute a vulnerability marker for a range of symptoms.

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1.3 Pharmacotherapy Treatment of Compulsivity

Jon Grant

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Background: Compulsivity is an important component in a range of conditions, including the Obsessive-Compulsive and Related Disorders trichotillomania (hair pulling disorder) and Obsessive-Compulsive Disorder (OCD) itself. This presentation will highlight the use of pharmacotherapy targeting compulsivity, developed from preclinical and clinical work using translational modeling.

ClinicalTrials.gov Identifier: NCT03348930

Methods: This presentation will showcase two recent studies:

1) Response inhibition, a measure of top-down executive control and one domain of compulsivity, in body-focused repetitive behavior disorders, and its neurochemical modulation. In this study, there were three components. First, patients with trichotillomania ($n = 27$) were compared to matched controls ($n = 196$) on the stop-signal task using a case-control design in laboratory controlled conditions. Second, stop-signal performance between trichotillomania patients ($n = 95$) and controls ($n = 263$) was examined using meta-analysis. Finally, the effects of 5-day treatment with the glutamate modulator (SXC-2023) on response inhibition was examined ($n = 24$), in a double-blind, placebo-controlled, cross-over design.

2) An examination of tolcapone in a double-blind, placebo-controlled cross-over study in OCD. Tolcapone, a catechol-O-methyl-transferase (COMT) inhibitor, enhances dopamine signaling in the cortex. In the frontal cortex, optimal dopamine modulation of prefrontal cortical networks appears to be necessary for a variety of cognitive functions, including executive control and inhibition. Importantly, dysfunction of these cognitive domains has been implicated in OCD. This was a fully counter-balanced, double-blind, placebo-controlled cross-over design in which 28 participants received EITHER tolcapone 100mg twice daily for two weeks, followed by one-week washout, followed by placebo twice daily for two weeks; OR placebo twice daily for two-weeks, followed by one-week washout, followed by tolcapone 100mg twice daily for two weeks. The order of treatment was randomized.

Results: In the laboratory study, stop-signal reaction times were significantly impaired in trichotillomania compared to controls (trichotillomania mean 261.2msec [SD 124.5], controls 183.1msec [65.0]; $F = 26.0401$, $p < 0.0001$; Hedges' $g = 1.05$). In the meta-analysis, stop-signal reaction times were impaired in trichotillomania (Hedges' $g = 0.91$, $z = 3.415$, $p < 0.001$). In the clinical trial, stop-signal reaction times improved significantly following glutamate modulation (SXC-2023 at the higher dose) ($t = +3.142$, $p = 0.009$), but not placebo ($t = -1.074$, $p = 0.292$).

In the tolcapone study, when taking tolcapone, participants experienced a mean decrease in their total YBOCS scores of -4.24 ($SD = 6.20$), which differed significantly from the change observed under placebo treatment of -1.10 ($SD = 4.71$) ($t = 2.194$, $df = 19$, $p = 0.0409$). The mean percentage decreases in the total YBOCS scores for the entire sample over the corresponding two-week periods were 16.4% for tolcapone and 3.6% for placebo.

Conclusions: These findings indicate impairments in top-down inhibitory and executive control in compulsive disorders, as exemplified for trichotillomania and OCD, may be ameliorated by pharmacotherapies. Thus, they shed light on neurochemical processes implicated in top-down cortical control in compulsive conditions. The work indicates that novel glutamatergic and dopaminergic modulators may be capable of improving cortically-mediated inhibitory control and thereby aspects of symptomatology across compulsive disorders.

Disclosures: Otsuka: Grant (Self)

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1.4 Attentional Capture by Reward Cues Predicts Compulsive Behaviours

Lucy Albertella

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Background: An emerging body of literature shows attentional capture by reward cues as a promising transdiagnostic risk marker for transdiagnostic compulsivity, with cross-sectional findings

showing a clear relationship with compulsivity-related problems across diagnostic boundaries. Its potential further lies in its links to decades of evidence from animal incentive salience learning models, offering novel mechanistic insights into the drivers of compulsivity. However, to bridge this link with incentive salience models of risk, research needs to move beyond cross-sectional findings to show that attentional capture by reward cues predicts risk. This presentation will discuss recent findings from work aimed at answering this question specifically, that is, does attentional capture by reward cues predict the development of compulsivity-related problems over time?

Methods: 580 participants completed one to three online assessments across a 9-month period (during the COVID-19 pandemic), including the cognitive assessment. Assessments included measures of problematic addiction-related and obsessive-compulsive behaviours, as well as a measure of attentional capture by reward cues. Multiple imputation was carried out for missing data at timepoints two and three. Generalised Estimating Equations examined whether attentional capture by reward cues (at Timepoint 1) predicted increases in obsessive compulsive behaviours and/or addictive behaviours over time. Analyses adjusted for the time-varying influence of psychological distress.

Results: Attentional capture by reward cues at Timepoint 1 predicted increases in obsessive compulsive behaviours over time ($p = 0.024$) and showed trend-level ($p < 0.060$) associations with two addiction-related behaviours over time.

Conclusions: The current findings highlight the potential of attentional capture by reward cues as a risk marker for compulsivity across different problematic behaviours, with the pattern of findings suggest that contextual influences may influence the expression of this risk.

Disclosure: Nothing to disclose.

PANEL

2. Therapeutic Mechanisms of Psychedelic Drugs in Psychiatric Disorders

2.3 Psilocybin Produces Aberrant Prediction Error Processing of Tactile Mismatch Responses Associated With Altered Self-Experience: An ERP-fMRI Study

Franz Vollenweider

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Background: The psychedelic-induced dissolution of self-boundaries obtained through subjective psychometric ratings has been proposed to contribute to lasting beneficial outcomes in healthy subjects and depressed patients. However, the neuronal correlates and neurocognitive processes underlying the multi-layered alterations of self-experience in psychedelic states are largely unknown.

Methods: The integration of bodily states and sensory inputs with prior beliefs has been linked to the generation of bodily self-consciousness. The ability to detect surprising tactile stimuli is essential for the survival of an organism and for the formation of mental body representations. We therefore investigated the effect of psilocybin (Psi), known to induce alterations in self-experience, on tactile mismatch responses by combining pharmacological manipulations with simultaneous EEG-fMRI recording in healthy subjects ($n = 20$).

Results: Psi-induced subjective alterations in self- and body-perception including experiences of "unity" and "disembodiment"

as indexed by standardized psychometric means (5D-ASC Scale). Psi reduced activity in response to tactile surprising stimuli in frontal regions, the visual cortex, and the cerebellum. Furthermore, Psi reduced tactile mismatch negativity EEG responses at frontal electrodes, correlated with alterations of body- and self-experience.

Conclusions: This study provides first evidence that Psi alters the integration of tactile sensory inputs through aberrant prediction error PE processing and highlights the importance of the 5-HT_{2A} system in tactile deviancy processing as well as in the integration of bodily and self-related stimuli. These findings may have important implications for the treatment of psychiatric disorders such as depression characterized by increased self- and body-characterized by increased self- and body-focus (e.g., rumination and diffuse bodily symptoms).

Disclosure: Nothing to disclose.

MINI PANEL

3. Breaking the Box of Psychiatric Research

3.1 High Fidelity Prediction of Psychiatric Cases With Artificial Intelligence

Nina de Lacy

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Background: Psychiatric illness is a leading global burden of disease and the costliest health condition in the US. While psychiatric disorders disproportionately affect the productive years of adulthood, their origins lie in youth. Incidence increases exponentially from 10 to 20 years old (yr) with 50% of lifetime psychiatric illness diagnosed by 14yr and 75% by 24yr. By 25yr, ~20% of the population is affected. In this crucial 10-24yr peri-adolescent period, psychiatric illness is the main cause of years lost to disability and death. However, we currently possess no ability to predict at the individual level which youth will develop mental illness. Leading challenges include the sheer number of risk factors associated with the development of the major mental illnesses and how to determine which types of risk factors are germane to prediction.

Methods: We hypothesized that artificial intelligence could successfully predict individual psychiatric cases with high fidelity. Our study submitted 160 risk factors (110 bio-psycho-social risk factors and 50 brain connectivity measures derived from resting-state fMRI) and specified which factors predicted cases of anxiety, attention deficit, depression, disruptive behaviors and PTSD in a naturalistic, transdiagnostic sample of 1120 youth. For each mental illness target we constructed predictive models using deep learning with artificial neural networks, tree-based learning with the XGBoost algorithm and a linear ElasticNet baseline. A novel evolutionary algorithm architecture optimized model selection with automated hyperparameter tuning and feature selection.

Results: We successfully predicted individual youth cases of anxiety, attention deficit, depression, disruptive behaviors and PTSD with 85–96% accuracy. Our study determined that optimized deep learning with artificial neural networks outperformed other methods. For each of the major mental illnesses in the study, we determined that shared and specific risk factors were present and found that psycho-social risk factors were the most important type of risk factor in making accurate predictions.

Conclusions: This study demonstrates that methods from artificial intelligence can successfully predict individual psychiatric

cases with very high fidelity across illness categories in the crucial peri-adolescent period. We believe this is the first time this has been accomplished. Our study demonstrates that evolutionary algorithms are powerful methods to achieve efficient model optimization and moreover provide automated feature selection while retaining interpretability in deep learning. From a translational perspective, our results also suggest that a relatively small amount of information need be collected in the community or clinic to provide accurate individual predictions of mental illness risk for youth, opening a potentially valuable and practical opportunity for early detection, intervention and prevention.

Disclosure: Nothing to disclose.

3.2 The Non-Random Edges of Neurobiological Networks and Their Implication for Computational and Statistical Analyses

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Background: The discovery of "preferential attachment" in natural networks by Barabasi led to a transformative questioning about conventional modeling of clinical and biomolecular network data using parametric statistics that rely on the assumption of randomness. While non-parametric statistics are applicable, we and others have developed more accurate analytical methods that leverage preferential attachment.

Methods: We illustrate why the statistical assumptions of randomness had to be cast aside in favor of preferential attachment assumptions. We will demonstrate how complex multiscale networks can be deconvoluted by recursively applying information theoretic distance (ITS) metrics (effect size) with scale-free analytics conducted on empirical networks to estimate the statistical significance. The results implicate explicitly how distinct single nucleotide polymorphisms associated to disease risks (e.g., Alzheimer, schizophrenia) and located on different chromosomes far from protein coding regions can coordinate to alter the translation of common coding regions. The ITS is described the statistical section.

Results: We previously predicted accurately antagonistic genetic interactions for a subset of prioritized SNP pairs in independent studies of Alzheimer's disease (entropy $P = 0.046$), which was confirmed prospectively in a genetic study (NPJ genomic medicine. 2016 Apr 27;1(1):1-2.). The massive studied network of Biomolecular relationships comprised 1092 intergenic SNPs, 1266 intragenic SNPs, 6301 associated mRNAs by eQTL, and 467 diseases.

The massive network was deconvoluted to obtain SNP-SNP association due to downstream convergent of their associated mRNA functions using conventional statistics assuming randomness as well as new scale-free statistics. The effect sizes and statistical significance of the two statistical methods were compared. A hex binning plot shows substantial excess predictions from conventional statistics: ~ 30-40%. Approximately 20,000,000 core hours of high-throughput computations were conducted on the Beagle Cray XE6 Supercomputer of the Computation Institute at the Argonne National Laboratory.

Conclusions: Scale-free statistics models that assume preferential attachment can deconvolute complex networks of biomolecular associations with substantially more true positive and less false positive results than conventional statistics based on random associations. However, the empirical resampling requires new models not available in conventional statistical packages and require expensive computing and storage.

Disclosure: Nothing to disclose.

3.3 Multi-Modal Approaches to Breaking the Box of Psychiatric Research

Amir Kalali

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Background: Psychiatric research is boxed in by many constraints. These include limits of understanding in basic science, the basis of our diagnostic criteria and methodological issues in clinical trials including subjective outcome measures and reaching the right patient populations

Methods: This talk will address multiple approaches to tackle these shortcomings all the way from diagnostic, to outcome measures to ensuring wider and equitable access to clinical trials utilizing decentralized methodologies

Results: The presentation will summarize initiatives (such as the DTRA) and studies aimed at improving the success of clinical trials in psychiatry.

Conclusions: New approaches to diagnosis, outcome measures and clinical trial methodology are beginning to show the path forward to more successful drug development

Disclosure: Nothing to disclose.

PANEL

4. Impact of Sex Differences in Immunity on the Brain, Behavior and Psychiatric Disorders Across the Lifespan

4.1 Immune Origins of Sex Differences in Brain and Behavior

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Background: Brain sex differences are established during a perinatal (rodent) or prenatal (primate) sensitive period during which male androgens drive masculinization of neural endpoints ranging from cell number to patterns of connectivity. Mechanistic studies reveal surprising roles for the innate immune cells of the brain, microglia and mast cells. In the developing medial amygdala of males, microglia engulf and phagocytose newborn astrocytic precursors, permanently reducing the number of mature astrocytes compared to females. The consequences of reduced astrocyte density are not manifest until adolescence when increased neuronal activation in males induces higher rates of rough-and-tumble play. In parallel, a population of mast cells in the preoptic area was previously found to be greater in neonatal males and directs microglia production of prostaglandins, which in turn promotes synaptogenesis associated with adult male sexual behavior. These observations prompted us to explore a 2-hit model of genetic vulnerability combined with early life inflammation on adolescent social behavior and a distinct population of brain mast cells as an additional potential site of dysregulation, with sex as a major variable.

Methods: Sprague-Dawley wild-type and SD-Nrxn1tm1sage KO rats were assessed for social preference (3-chamber choice test), open field activity and playfulness with an age matched partner during adolescence. Inflammation was induced by injection of the viral mimetic Poly I:C (5mg/Kg BW i.p.) on postnatal days 8 and 10. Separate animals were injected with the proliferative markers EdU or BrdU and mast cells were assessed by a combination of flow cytometry gated for CD45⁺/FcER1a⁺ and triple fluorescent immunohistochemistry (BrdU, avidin and serotonin). Images were captured on a W1 Nikon microscope and quantified using Imaris.

Results: There were no main effects of sex or genotype on % time spent in the social chamber but SD-Nrxn1tm1sage Heterozygous males treated with Poly I:C showed significantly reduced time in the chamber containing an age matched conspecific (trmmt X sex X genotype interaction: $F(1,51) = 4.122$, $p = 0.0476$; $\eta^2(p) = 0.074$; $n = 6-8/\text{group}$). There was no effect of Poly I:C treatment on open field behavior but SD-Nrxn1tm1sage Het males moved more than WT males ($F(1,46) = 4.200$, $p = 0.0461$; $\eta^2(p) = 0.084$). Lastly, collectively juvenile male rats played more frequently than females, as expected ($F(1,41) = 14.80$, $p = 0.0004$, $\eta^2(p) = 0.2652$) but playfulness was significantly reduced in SD-Nrxn1tm1sage Het males compared to WT males after postnatal inflammation ($F(1,41) = 4.576$, $p = 0.0383$, $\eta^2(p) = 0.100$, $n = 7/\text{group}$). We further discovered a dense population of mast cells dorsal to the hippocampus that are actively proliferating (~10-20%), with division rates 10X-greater than in the skin ($p = 0.01$; $n = 3$ males, 4 females) but less than bone marrow ($p = 0.003$). There were no sex differences in proliferation or number of mast cells which declines with age. Similar results were seen by immunohistochemical stain of sections from 8 males and 6 females at 4, 6, 7, and 11 days old.

Conclusions: Innate immune cells of the brain are essential contributors to the establishment of sex differences in brain and behavior. The role of the immune cells differs by region and endpoint but can be disrupted by externally induced inflammation against a vulnerable genetic background, particularly in males.

Disclosure: Nothing to disclose.

4.2 Sex-Specific Blood-Brain Barrier Alterations and Vascular Biomarkers Underlie Chronic Stress Responses in Mice and Human Depression

Caroline Menard

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Background: Prevalence, symptoms, and treatment of depression all point toward major sex differences. Social stress-induced neurovascular pathology is associated with depressive symptoms and passage of circulating proinflammatory mediators into the male nucleus accumbens (NAc) however it remains unknown if it contributes to this sexual dimorphism. Here we investigated if stress-induced loss of blood-brain barrier (BBB) integrity is occurring in a sex- and region-specific manner and if it could inform on depression diagnosis.

Methods: The impact of chronic social defeat stress, a mouse model of depression, was evaluated for BBB-related gene expression, morphology, and function using qPCR, immunofluorescence, and confocal microscopy on male and female C57Bl/6 (8-12 weeks, $n = 10-20/\text{group/sex}$). Chronic stress is a prominent contributor to mood disorder prevalence and suicide attempts in victims of bullying. BBB integrity was also assessed on post-mortem human brain samples (Douglas-Bell-Canada brain bank, $N = 10-20/\text{group/sex}$). Next, cell-specific transcriptomic analysis was performed in a separate cohort of mice ($n = 6-15/\text{group/sex}$) allowing identification of key pathways and novel genes underlying stress vulnerability vs resilience. In parallel, viral-mediated manipulations were performed to confirm a causal role of altered BBB integrity in the development of anxiety- and depression-like behaviors in females ($n = 8-10/\text{virus/group}$). Finally, sex-specific vascular biomarkers of stress responses were investigated in mice ($n = 5-12/\text{group/sex}$) and tested in human samples from depressed individuals (Signature biobank, $N = 11-26/\text{group/sex}$).

Results: After chronic social stress exposure, gene expression is unchanged in the NAc of stress-susceptible females but altered in the prefrontal cortex (PFC) ($F = 6.455$, $p = 0.0042$), a brain region

regulating decision making and social behaviors, when compared to unstressed controls and resilient mice. Loss of BBB integrity was confirmed in the postmortem PFC samples of depressed women when compared to matched controls (t -test = 2.914, p = 0.0068). Viral-mediated BBB disruption in the female PFC induced anxiety (F = 6.476, p = 0.0161), anhedonia (F = 31.27, p < 0.0001), and social avoidance towards females (t -test = 2.783, p = 0.0123). Transcriptomic analysis of PFC endothelial cells revealed increased expression of genes and pathways associated with inflammation in susceptible mice but not in resilient animals. Therefore, stress-induced BBB leakiness in the female brain was confirmed along with high release of proinflammatory vascular biomarkers, such as soluble E-selectin, in the mouse blood (F = 5.003, p = 0.0131). Translational value of this sex-specific biomarker was confirmed on blood samples obtained from depressed women (t -test = 2.016, p = 0.0494).

Conclusions: Our results provide the first characterization and functional interrogation, in a sex-, region-, and cell-specific manner, of the role played by the BBB in chronic stress responses in mice. We also identified sex-specific circulating vascular biomarkers in depressed patients that could help better diagnose and inform novel treatment strategies for mood disorders.

Disclosure: Nothing to disclose.

4.3 Prenatal Immune Programming of Sex Differences in Cellular Aging and Memory Circuitry Function

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Background: There is growing evidence for a fetal antecedence to cellular aging and adult memory impairments, potentially through the disruption of stress-immune pathways, with significant sex-dependent outcomes. Using an unprecedented prenatal cohort, followed since 1959, we prospectively assessed sex differences in the impact of maternal prenatal immune dysregulation on adult offspring telomere length (TL), an important cellular marker of biological aging, and memory circuitry function 50+ years later.

Methods: 212 adults (ages 45–55; 106F:106M) recruited from the New England Family Study (NEFS) underwent a blood draw, clinical assessments, and structural and functional MRI (s/fMRI). NEFS is a unique prenatal cohort that has been followed for >50 years. Their mothers were followed through pregnancy and maternal cytokine levels were measured from sera drawn at the beginning of 3rd trimester. In the adult offspring, leukocyte TL was measured by extracting genomic DNA from buffy coats using the QIAmp 96-spin blood protocol. Face-Name Associative Memory (FNAME) and 6-Trial Buschke Selective Reminding Test (SRT) were used to assess associative and verbal memory, respectively. Automatic brain masking of sMRI scans was conducted using Multi Atlas Brain Segmentation. Segmentation of sMRI scans was executed using FreeSurfer and label maps of memory circuitry regional brain volumes were manually corrected. A verbal encoding task was administered during fMRI and β weights were extracted from memory circuitry regions using SPM8. Finally, reproductive history and serology were used to determine menopausal staging following STRAW-10 criteria. Generalized estimating equation models were run by sex and menopausal staging groups to assess associations between prenatal maternal cytokines, TL, and memory outcomes.

Results: In women, shorter TL was associated with poor memory performance (SRT: β = 0.19, p FDR = 0.03), and in postmenopause, was further related to smaller volume in the right hippocampus (β = 111.92, p FDR = 0.04). Examining the impact of maternal immune dysregulation, we found that elevated prenatal

exposure to proinflammatory cytokine IL6 was associated with both shorter TL (β = -0.72, p = 0.03) and poor memory performance (FNAME: β = -0.80, p FDR = 0.01) in early midlife, specifically in postmenopausal women. Higher prenatal exposure to TNF α was also related to poor memory in postmenopausal women (FNAME: β = -0.74, p FDR = 0.02). In men, elevated prenatal IL6 exposure was negatively associated with task-evoked BOLD activity in the left ventrolateral prefrontal cortex (β = -0.47, p FDR = 0.02) and hippocampus (β = -0.17, p FDR = 0.05). Further, shorter TL tended to be associated with smaller volumes in the parahippocampus (β = 127.86, p FDR = 0.08) and anterior cingulate cortex (β = 271.64, p FDR = 0.08) in men.

Conclusions: Overall, results demonstrated that longer TL is associated with better memory function and larger volume in memory circuitry regions in early midlife. Further, maternal immune dysregulation during pregnancy negatively impacts both offspring telomere biology and memory circuitry aging in a sex-dependent manner. Importantly, in women, negative effects were revealed postmenopause, suggesting that reproductive aging, beyond chronological aging, may exacerbate the impact of prenatal immune exposure on cellular and brain aging.

Disclosure: Nothing to disclose.

4.4 Sex, Heat, and Mood: Immune Mechanisms of Hyperthermic Treatment for Depression

Simmie Foster

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Background: Major Depressive Disorder (MDD) exhibits a significant sex difference, with females being twice as likely to experience depression. Part of this difference may be explained by pathological inflammation, as depression is associated with increased inflammation and females often have higher rates of autoinflammatory disease. Consistently, anti-inflammatory therapies have shown some promise in alleviating depressive symptoms. Elevating body temperature (hyperthermia) is a proposed treatment for MDD that may have anti-inflammatory properties, but these mechanisms are poorly defined. Furthermore, the influence of gonadal hormones on the immune response during heat exposure is not understood. Here we conducted preliminary studies investigating the impact of hyperthermia on immune pathways in murine macrophages and in individuals with MDD receiving an 8-week course of hyperthermic yoga for depression.

Methods: Immortalized macrophages derived from murine bone marrow were heat shocked (39–42 °C for up to one hour) or left at 37 °C and stimulated with inflammatory inducers (lipopolysaccharides +/- ATP). Heat-shocked macrophages were also exposed to gonadal hormones (17 β -estradiol and progesterone) for 30 minutes prior to inflammatory stimulation. Cell lysates and supernatants were analyzed for production of IL-1 β and other inflammatory mediators. In preliminary studies aimed at extending our findings to human subjects, we performed RNA-seq on peripheral blood monocytes (PBMC) isolated from depressed individuals (IDS-CR > 24) in a previously completed longitudinal study (8 weeks) of hyperthermic yoga for depression. 66 samples (time=0 and 8 weeks from n = 9 active treatment and n = 26 waitlist controls; 91% female) were analyzed. Differential gene expression (DGE) and weighted gene co-expression network analysis (WGCNA) were performed, followed by functional annotation using DAVID.

Results: In vitro heat shock of murine macrophages produced a significant and rapid (within 15 minutes) inhibition of IL-1 β protein to undetectable levels (n > 3 biological replicates, p < 0.0001),

correlated with inhibition of caspase 1 cleavage and decrease in membrane permeability. Gonadal hormones trended toward potentiating the inhibition of IL-1 β mRNA by heat. From the RNA-seq on human PBMC, testing for a total of 12,289 genes, significant differential gene expression analysis (FDR < 0.1, absolute log2FC (FC < -1, FC > 1)) of the active hyperthermic treatment vs waitlist controls revealed 11 genes, including 5 genes involved in downregulation of inflammatory responses. These genes included inhibitors of IL-8, a chemokine that has been associated with MDD in females. WGCNA produced 12 modules, 4 of which were significantly correlated ($p < 0.05$, absolute corr > 0.3) with the IDS-CR scores.

Conclusions: We have found that in vitro heat shock rapidly inhibits the inflammasome and consequently IL-1 β , an inflammatory mediator implicated in MDD and sensitive to gonadal hormones. Furthermore, successful hyperthermic treatment of individuals with MDD induces a distinct gene expression profile that includes negative regulators of inflammation. Our results indicate hyperthermia inhibits potentially harmful inflammation at a molecular level and may inform future studies refining this treatment for MDD.

Disclosure: Nothing to disclose.

STUDY GROUP

5. Translational Drug Development for Pediatric CNS Disorders

William Potter*, Meg Grabb, Gahan Pandina, Shafali Jeste, Adriana Di Martino, Raquel Gur, Christoph Hornik, Valentina Mantua, Perdita Taylor-Zapata, Daniel Umbricht

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Study Group Summary: While various psychiatric and neurologic CNS disorders develop in childhood, pharmacotherapeutic development for pediatric CNS disorders lags far behind that devoted to adult disorders. Increasingly, developmental CNS disorders have become the focus of collaborative consortia to understand their etiologies and trajectories such as those focused on fragile X syndrome and autism spectrum disorder, as well as clinical high risk for schizophrenia. The goal of such research is to identify therapeutic interventions earlier in development. This study group will address where we are, and what we need, to most effectively translate scientific studies of neurodevelopmental disorders into exploration of pharmacotherapies. It will include considerations which have risen to the forefront of approaches to treatment development for CNS disorders whereby drug trials will depend on biomarkers to select patients who may have manifested only some or none of the clinical symptoms which characterize the syndrome in question. Primary and secondary prevention treatments are the ultimate goal.

To make this approach possible in pediatric populations requires both an investment in pediatric clinical pharmacology for agents which may have no clinical application in adult populations as well as the deployment of biomarker “drug development tools” which are validated and feasible for the relevant context of use in translational pediatric drug development.

The question of how to move quickly into pediatric drug development and what will be required in the absence of previous regulatory approval for use in adults will be addressed from both a clinical pharmacology and regulatory perspective. The potential and limitations, especially with regard to studies in young children, of the needed translational biomarkers of brain

biochemistry and function will be addressed comparing EEG vs fMRI. Heterogeneity of disorders, such as ASD, will be discussed and whether existing measures are sensitive enough to capture specificity of symptoms in a drug development program or whether they should be more domain specific. The integration of traditional fluid based clinical pharmacological PK/PD studies with evolving brain measures will be discussed as well as the multiple types of regulatory questions that arise when moving into pediatric populations, including relevance or not of animal models.

The study group will include perspectives from multiple stakeholders: William Potter (Independent Consultant); Meg Grabb (Program Officer, NIMH); Shafali Jeste (Associate Professor in Psychiatry, Pediatrics and Neurology, UCLA); Perdita Taylor-Zapata (program lead for the NICHD's Best Pharmaceuticals for Children Act/BPCA Clinical Program); Gahan Pandina (Director, Clinical Leader: Janssen Research and Development); Adriana Di Martino (Research Director, Autism Center, Child Mind Institute); Raquel Gur (Professor of Psychiatry Neurology and Radiology at the University of Pennsylvania); Christoph Hornik (Associate Professor of Pediatrics, Duke University); Valentina Mantua (Medical Officer at FDA); Daniel Umbricht (Associate, McArthur and Associates GmbH), who will address key aspects such as industry/academic experiences in pediatric trials, opportunities and limits of building CNS biomarkers into pediatric trials, BPCA and NIH's resources and incentives for pursuing pediatric indications, and regulatory perspectives.

Disclosures: Merck: Stock/Equity (Self)

Karuna, Eliem, Neurocrine Biosciences, Regenacy, Boston Pharmaceuticals: Consultant (Self)

Otsuka: Advisory Board (Self),

Praxis Bioresearch: Employee (Self).

PANEL

6. Kynurenic Acid and Mental Health: Translational Perspectives of a Gliotransmitter That Regulates Sleep, Arousal, Oxidation and Cognition

6.2 Modulation of Kynurenic Acid Production by N-Acetylcysteine Prevents Cognitive Impairment Induced by Lead Exposure During Lactation

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Background: Lead (Pb) is a well-known environmental pollutant that can induce a wide range of physiological and biochemical dysfunctions in humans and rodents. Pb intoxication during early life induces cognitive impairments; however, the mechanisms involved have not been well elucidated. Recently, we showed that mice exposed to Pb during the lactation period exhibited elevated brain kynurenic acid (KYNA) levels and cognitive impairment. KYNA has been characterized as an antagonist of NMDA and α -7 nicotinic receptors hence, its brain fluctuations have been related to cognitive performance impairments. Recent evidence showed that N-acetylcysteine (NAC) inhibits kynurenine aminotransferase II activity (main enzyme for KYNA production), decreases brain KYNA levels and improves cognitive performance in mice. This study was carried out to investigate whether NAC can ameliorate Pb-induced cognitive impairment through a reduction of brain KYNA levels.

Methods: The dams were divided in four groups: Control, Pb, NAC and Pb+NAC, and received tap water (Control and NAC groups) or 500 ppm of lead acetate (Pb and Pb+NAC groups) in

drinking water ad libitum, from 0 to 23 postnatal day (PND). NAC and Pb+NAC groups received NAC (350 mg/day) in the chow from 0 to 23 PND. Upon termination of the treatments, the offspring received normal rodent chow and tap water until evaluation. The learning and memory performance were evaluated at 60 PND using buried food location test (BFLT) and novel object recognition (NOR) test. After cognitive evaluation, lipid peroxidation, GSH levels, cellular function, kynurenic acid (KYNA) levels and kynurenine aminotransferase II (KAT II) activity were evaluated in the whole brain.

Results: In the training phase of BFLT, the experimental groups showed the same learning pattern as the control group. However, when long-term memory was evaluated, both parameters the travelled distance and the time spent to reach the target were higher in the Pb group than the control group ($p < 0.01$). However, the co-administration of NAC with Pb ameliorated the memory impairment induced by Pb ($p < 0.01$). The NOR test showed that the control group explored the new object for a longer period of time compared to the familiar one, while Pb group could not discriminate between the novel and the familiar object. This alteration induced by Pb was prevented by the co-administration of NAC. Pb group showed altered cellular redox environment and cellular dysfunction compared to the control group ($p < 0.05$). The co-administration of Pb with NAC reduces lipid peroxidation ($p < 0.01$), increases GSH levels ($p < 0.01$) and restores the cellular function ($p < 0.05$) compared to Pb group. KYNA levels are increased in Pb group compared to the control group ($p < 0.01$), however; in the Pb+NAC group KYNA levels remained similar to those of the control group. Moreover, NAC and Pb+NAC groups showed a decrease on KAT II activity compared to the control group ($p < 0.05$). Finally, a positive correlation between travelled distance and KYNA levels was observed ($n = 21$, $p = 0.02$) in the BFLT.

Conclusions: These results showed that an elevation in brain KYNA levels is associated with the cognitive impairment induced by Pb exposure during early life and indicate that NAC could be tested in several contexts where KYNA levels are associated with cognitive performance alterations, as NAC reduces KYNA levels through modulation of the cellular redox environment and direct inhibition of KAT II.

Disclosure: Nothing to disclose.

6.4 Kynurenic Acid Reduces, While Kat Inhibition Enhances, the Firing of Aged Primate Dorsolateral Prefrontal Cortical Neurons Needed for Working Memory: A Therapeutic Strategy to Protect From Inflammation

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Background: Kynurenic acid signaling is increased by COVID19 infection. Kynurenic acid (KYNA) blocks both NMDAR at the glycine site and nicotinic α -7 receptors (Nic-a7R), and is generated under conditions of inflammation by kynurenine aminotransferase (KAT). The recurrent excitatory microcircuits in deep layer III of primate dorsolateral prefrontal cortex (dlPFC) are particularly dependent on NMDAR/Nic-a7R neurotransmission to generate the persistent neuronal firing needed for working memory. Thus, these circuits may be particularly vulnerable to KYNA synthesis under inflammatory conditions, impairing working memory and other dlPFC cognitive abilities.

Methods: Aged rhesus monkeys have naturally-occurring neuroinflammation and reduced dlPFC neuronal firing and thus were used in these experiments ($n = 2$ male and female). In vitro experiments labeled dlPFC with antibodies detecting KYNA; in vivo experiments tested the effects of iontophoresing KYNA

vs. the KAT inhibitor, PF-04859989, onto dlPFC neurons in aged monkeys performing an oculomotor delayed response (ODR) test of spatial working memory, focusing on "Delay cells" with spatially-tuned persistent firing across the delay epoch. Drug effects on neuronal firing and local field potentials (LFPs) were analyzed by ANOVA. Actions at the glycine site on the NMDAR were tested with the agonist, d-serine; actions at Nic-a7R were tested with the agonists PHA543613 (PHA) or galantamine.

Results: KYNA labeling was seen in aged monkey dlPFC, consistent with neuroinflammation. Iontophoresis of KYNA produced a dose-related reduction in dlPFC Delay cell firing, reducing firing for the neurons' preferred direction (2-way ANOVA-R, $p = 0.0001$) and reducing gamma band LFPs ($p = 0.0003$). In contrast, iontophoresis of a KAT inhibitor enhanced Delay cell firing ($p = 0.01$). The enhancing effects of the KAT inhibitor were reversed by application of KYNA ($p = 0.01$). KYNA's effects were blocked by the glycine site agonist, d-serine ($p < 0.0001$), or the Nic-a7 agonists, PHA ($p = 0.016$) or galantamine ($p = 0.012$), consistent with NMDAR/Nic-a7R actions.

Conclusions: Either exogenously applied or endogenously-generated KYNA reduces the firing of dlPFC Delay cells via blockade of the NMDAR/Nic-a7R actions needed for working memory. Thus, the generation of KYNA under inflammatory conditions may impair cognition via KYNA blockade of NMDAR/Nic-a7R in dlPFC. Inhibition of KAT to reduce KYNA synthesis may be helpful in treating the cognitive symptoms of inflammatory disorders such as COVID19.

Disclosure: Shire/Takeda: Royalties (Self).

STUDY GROUP

7. Brains Before Brawn: Using Brain-Based, Outcome-Relevant, Endophenotypes in Phase 2 Medication Development for Psychiatric Disorders – to Improve Our Success in Larger Phase 3 Clinical Trials

Anna Rose Childress*, Tanya Ramey, Diego Pizzagalli, Maria Oquendo, Joseph Schacht, Kathleen Brady, Hamed Ekhtiari, F. Gerard Moeller, Patricio O'Donnell, George Koob, Nora Volkow

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Study Group Summary: Despite elegant preclinical neuroscience on the brain circuits important in psychiatric disorders, including the addictions, many patients do not respond fully to existing medications (e.g., antidepressants) and an FDA-approved medication is entirely lacking for several drug classes (e.g., stimulants, cannabis). Though candidate psychiatric medications usually have stated brain targets, most Phase 2 clinical medication trials have not been informed by brain measures – either by confirmation of receptor occupancy (by PET) at the study dose and/or by confirmation of action on the intended brain systems (by functional MRI). Getting brain information for a brain-directed intervention in Phase 2 – before moving to the 'brawn' (larger size and expense) of Phase 3 trials – may seem like an obvious need, but it is still relatively rare. Brain information may be critical for understanding why a medication 'failed' – e.g., did the medication even reach the intended brain target, at the tested dose? Equally important – the brain information may be helpful in understanding why the medication 'succeeded' for some patients but not others, a heterogeneity familiar in most clinical trials of psychiatric medications. Brain information can provide rational guidance for the 'next step' in developing a medication, and in selecting the responsive clinical population.

The NIMH has formally (2018) encouraged the use of hypothesis-driven, brain-based endophenotypes in Phase 2a studies, to determine whether the candidate medication engages the target circuitry, before moving the medication to (much more expensive) Phase 3 trials. Positive results from this "FAST-FAIL" approach recently demonstrated that a kappa opioid antagonist may indeed target reward circuitry dysfunction in patients with anhedonia (Pizzagalli, et al. 2020; Krystal, et al. 2020). Encouragingly, there are ongoing medication-development efforts with brain-based, outcome-relevant, endophenotypes at NIMH, NIAAA and NIDA. The proposed Study Group panelists will highlight efforts with brain endophenotypes for anhedonia (Dr. Diego Pizzagalli) and suicidality (Dr. Maria Oquendo), and for reward, stress and inhibitory circuitry dysfunction in alcohol and substance use disorders (Drs. Joseph Schacht, Kathleen Brady, Hamed Ekhtiari, and Gerard Moeller). Dr. O'Donnell (Takeda) will comment on the utility of endophenotypes from the perspective of the pharmaceutical industry. Finally, Drs. Nora Volkow (NIDA) and George Koob (NIAAA) will offer their own and their Institutes' perspective on the promise of endophenotyping for medication development, noting the in-common circuitry dysfunctions across discussed disorders. These "cut-across" shared brain endophenotypes have encouraging implications for medication development: e.g., an agent normalizing function in reward, inhibitory and stress circuitry could have broad clinical impact across the mood and substance use disorders, including their common co-occurrence. FDA has approved several medications in non-psychiatric disorders based on highly-specific (genetic, metabolic or other) endophenotypes, but this has not yet happened for psychiatric medications. Our field is ready, and in great need.

Disclosure: Nothing to disclose.

PANEL

8. Augmenting Vs. Switching Antidepressant for Treatment Resistant Depression in Older Adults: Results From the Optimum Study

8.1 Augmentation Vs. Switch Approaches for Treatment-Resistant Depression in Older Adults: Methods and Main Results From the Optimum Study

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Background: The OPTIMUM trial was a pragmatic trial conducted in the community, using measurement-based care support from the OPTIMUM team to guide patients through treatment. Understanding the benefits vs. risk of these medication strategies is crucial for this population, which has high morbidity from depression but also significant risks from pharmacotherapy. The "Optimizing antidepressants for TRD in older adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized 744 depressed individuals aged 60+ with TRD.

Methods: The "Optimizing antidepressants for TRD in older adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized 744 depressed individuals aged 60+ with TRD. It is the largest-ever pragmatic clinical trial of TRD in older adults, with a similar design as the STAR*D and VAST-D studies that were conducted in younger adults.

Participants were randomized into one of three arms: augmentation with aripiprazole, augmentation with bupropion, or switch to

bupropion. Those who did not remit were then randomized into a second step with two arms: augmentation with lithium and switch to nortriptyline. Participants were measured at the beginning and end of these 10-week steps with a measure of remission (based on Montgomery Asberg Depression Rating Scale), and were measured throughout the steps for safety, including falls.

Results: The study found that augmentation with aripiprazole and augmentation with bupropion had similar effectiveness (remission rates of 29% per arm) and were more effective than switch to bupropion (remission rate of 19%). In contrast, all three of these strategies were roughly equal in their risks such as falls and serious adverse events (the rates of SAEs were 7.9% in the augmentation with aripiprazole vs 7.7 % in the augmentation with bupropion vs 10.5% in the switching arm). In the second step of the trial, lithium augmentation and a switch to nortriptyline were roughly equivalent in both effectiveness (remission rates of 22% in each arm) and with the similar tolerability and SAEs of 9.8% in the augmentation with lithium and 9.2% in the switching to nortriptyline arm.

Conclusions: Augmentation strategies may be a safe and efficacious option in this difficult to treat population. At the conclusion of the presentation, we will explain the study implication for future care of older adults with TRD using OPTIMUM treatment algorithm.

Disclosure: Fluvoxamine for COVID19: Patent (Self).

8.2 Pragmatism, Stakeholders, and Planning for Impactful Dissemination: Lessons Learned From the Optimum Trial

Jordan Karp

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Background: About 14% of older Americans are prescribed an antidepressant, but this broad use is not associated with a decrease in the burden of geriatric depression. Indeed, treatment resistance is the norm, not the exception in older depressed adults, as most fail to remit with standard antidepressant pharmacotherapy, and persistent depression decreases older adults' quality of life more than any other illness. Effective use of antidepressants for TRD in real-world settings would address a leading cause of disability, excess mortality, and cognitive decline. While it is established that antidepressants are more efficacious than placebo, patients with TRD treated with active antidepressants should experience at least the improvement associated with the use of a placebo. However, some published data suggest that patients whose depression is treated under usual care (nonstudy) conditions are actually less likely to respond to antidepressant treatment or to experience remission of their depressive symptoms than depressed patients who receive a placebo in an RCT. Testing algorithmic, measurement-based antidepressant pharmacotherapy of TRD in real-world settings is needed to guide personalized and safe prescribing and advance clinical science beyond tightly controlled efficacy studies which may not translate to routine clinical care.

To address this, Dr. Karp will describe: 1) the characteristics of the patient sample from the multi-site OPTIMUM trial; 2) balancing the Pragmatic-Explanatory Continuum when planning impactful pragmatic research; 3) the significance of engaging stakeholders in a pragmatic clinical trial, from inception to dissemination; and 4) some challenges and solutions to conducting a successful pragmatic clinical trial.

Methods: In Step 1, participants were randomized to one of three strategies: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion. Treatment effectiveness was assessed using the Montgomery Asberg Depression Rating Scale (MADRS) after ten weeks of treatment. Those who did not

remit proceeded to Step 2 where they were randomized to either lithium augmentation of an index antidepressant or switch to nortriptyline.

Results: Step 1 involved 621 participants, of which 212 were randomized to augmentation with aripiprazole, 206 to augmentation with bupropion, and 203 to a switch to bupropion. Step 2 involved 251 participants of which 127 were randomized to augmentation to augmentation with lithium and 124 to a switch to nortriptyline.

Challenges which were successfully overcome in this pragmatic trial include sustaining engagement with primary care partners, minority recruitment, safe management of alcohol and occult benzodiazepine use and co-prescribed medications, adverse event reporting in a pragmatic design without a placebo condition in medically compromised older adults, and planning for impactful dissemination.

Conclusions: OPTIMUM is the largest stakeholder-informed study of pharmacotherapy for late-life TRD. It is a model for balancing pragmatic and explanatory approaches for a successful clinical trial. Listening to a variety of stakeholder voices during every six-month advisory board meetings makes OPTIMUM highly relevant and patient-centered.

Disclosures: NightWare: Consultant (Self)

Otsuka: Honoraria (Self),

Aifred Health: Stock/Equity (Self).

8.3 Improvements in Psychological Wellbeing With Augmentation Vs. Switch Approaches for Treatment-Resistant Depression in Older Adults: The Optimum Study

Helen Lavretsky

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Background: The "Optimizing antidepressants for TRD in older adults" (OPTIMUM) study, funded by the Patient-Centered Outcomes Research Institute, is a 5-center collaboration that randomized 744 depressed individuals aged 60+ with TRD, the largest ever pharmacological study of late-life depression.

A key goal of this pragmatic trial was measuring outcomes of interest to patients, and in our stakeholder advisory phase prior to starting the trial, patients told us that psychological wellbeing was of most interest to them. This construct is closely tied to physical and psychological functioning and can be measured by self-report.

OPTIMUM is one of the first studies to measure antidepressant effects on psychological wellbeing. This presentation will show changes in psychological wellbeing during acute treatment.

Methods: Participants were randomized into one of three arms: augmentation with aripiprazole, augmentation with bupropion, or switch to bupropion. Participants were measured at the beginning and end of this 10-week step with the NIH Toolbox Psychological Wellbeing battery. Two wellbeing scales were measured: positive affect (34 items), and general life satisfaction (16 items).

Results: The study found that augmentation with aripiprazole and augmentation with bupropion had similar effectiveness (remission rates of 34% per arm) and were more effective than switch to bupropion (remission rate of 24%). In contrast, all three of these strategies were roughly equal in their risks such as falls and serious adverse events (the rates of SAEs were 7.9% in the augmentation with aripiprazole vs 7.7 % in the augmentation with bupropion vs 10.5% in the switching arm). In the second step of the trial, lithium augmentation and a switch to nortriptyline were roughly equivalent in both effectiveness (remission rates of 22% in each arm) and with the similar tolerability and SAEs of 9.8% in the augmentation with lithium and 9.2% in the switching to nortriptyline arm.

Conclusions: For the general life satisfaction subscale, participants randomized to either of the two augmentation arms (aripiprazole or bupropion) showed an increase, while those randomized to switch (to bupropion) did not.

For positive affect, participants randomized to either of the two augmentation arms (aripiprazole or bupropion) showed an increase, while those randomized to switch (to bupropion) showed a smaller increase.

Disclosure: Nothing to disclose.

8.4 A Nightmare: Providers' Experiences Treating Older Adults With Treatment-Resistant Depression

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Background: Treatment-resistant depression (TRD) in older adults is common, and its care is challenging. The perspectives of primary care providers (PCPs) and psychiatrists treating older adults with TRD provides insights into the unique challenges and potential solutions for managing TRD.

Methods: We performed a qualitative descriptive study using telephone semi-structured interviews with 50 care providers in the five participating sites of the PCORI-sponsored OPTIMUM RCT (Los Angeles, New York City, Pittsburgh, St. Louis, and Toronto): 24 PCP's, 22 Psychiatrists, and 4 Depression Care Managers.

We elicited provider perspectives on treatment options for older adults, including treatment within the primary care setting and referral to psychiatry, and we sought suggestions for improvement.

Results: We identified three themes: (1) existing psychiatric services are inadequate to meet the needs of older patients with TRD, mainly because of lack of access; (2) PCP's often attempt to treat older patients with TRD, despite low confidence in their ability to do so; and (3) to better meet the needs of older patients with TRD, providers recommend collaborative treatment models involving PCP's, psychiatrists, and psychotherapists,-- potentially more now feasible to implement due to improved access through telemedicine; and improved treatment algorithms, based on the results of the OPTIMUM RCT, to help PCP's manage older patients with TRD.

Conclusions: Results of these qualitative interviews should inform:

(1) the dissemination of findings from psychiatric intervention science (dealing with comparative effectiveness, safety, and real-world personalization of treatment) to providers, policy-makers, and other stakeholders in the mental health delivery system; and

(2) structural changes to clinical practice that may increase the implementation of evidence-informed treatment strategies to improve long-term outcomes in older adults with TRD

Disclosure: Nothing to disclose.

MINI PANEL

9. Recent Advances in Transdiagnostic Neural Monitoring and Modulation With Electroencephalography During Childhood

9.1 Neural Network Modeling of Trigeminal Nerve Stimulation in ADHD

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Background: External trigeminal nerve stimulation (TNS) is a non-invasive method of brain modulation that recently received FDA device clearance for the treatment of children with ADHD, ages 7-12 years old. In the pivotal trial of TNS, subjects randomized to active TNS exhibited significantly greater improvements in ADHD symptoms ($p < .005$) relative to sham and 52% of participants showed clinically meaningful improvement compared to 14% in the sham group ($p = .003$). Within the same trial, electroencephalography (EEG) recorded at baseline and after 4-weeks of TNS treatment revealed significant treatment group effects in the right frontal (F4) and frontal midline (Fz) channels. Subsequent analyses indicate that treatment-related change in F4 theta power ($AUC = .81$, $p = .03$) was significantly predictive of TNS treatment response, suggesting this is a biomarker, and potentially part of the neural mechanism mediating treatment response. In the current presentation, we examine post-treatment resting state functional connectivity and clinical correlates to more fully characterize the neural network underlying TNS treatment related improvements in ADHD.

Methods: 62 children aged 8-12 years, with KSADS-diagnosed ADHD were randomly assigned to four weeks of nightly active or sham TNS treatment. Primary outcomes were clinician rated ADHD Rating Scale (ADHD-RS) and Clinical Global Impression (CGI) scales. Secondary outcomes included baseline cognitive measures, weekly ratings of behavioral executive functions (BRIEF), and electroencephalography (EEG) measures at baseline and post-treatment. To estimate resting state functional connectivity, the following procedures were used: 1. EEG data are decomposed using independent components analyses, 2. Dipole density was calculated for 76 regions of interest (ROIs), 3. Information flow between ROIs based on contribution of each dipole source, 4. Between-group, pixelwise t-tests were performed for each connection between ROIs, 5. Run permutation test to perform cluster-level correction to control for multiple comparisons.

Results: After 4-weeks of TNS treatment, the active group exhibited significantly decreased functional connectivity along the midline, particularly between mid- and right-frontal (i.e., right superior frontal gyrus, anterior cingulate) connections with parietal (i.e., precuneus, right/left superior parietal) and occipital (i.e., calcarine, right/left superior occipital) nodes. In addition, the right frontal to superior parietal connection was significantly negatively correlated with right frontal (F4) EEG theta power ($r = -.51$, $p = .004$) and trended toward significance with ADHD inattentive symptoms ($r = .28$, $p = .14$), indicating that lower connectivity is associated with higher F4 theta power and lower inattention symptoms. The right frontal to left cuneus connection was correlated with BRIEF Initiate ($r = .41$, $p = .03$) and Working Memory ($r = .35$, $p = .07$) scores, indicating lower connectivity is associated with better executive functioning. These data suggest that right frontal (F4) EEG power modulation is a biomarker for putative changes in fronto-parietal (FP) network connectivity, both of which are associated with improved executive function and reduced ADHD symptoms.

Conclusions: The neural mechanism underlying TNS treatment effects in ADHD is activation of the fronto-parietal network resulting in increased EEG power in the mid- and right- frontal electrodes and subsequent improvement in executive functions and ADHD behaviors.

Disclosure: Nothing to disclose.

9.2 Brain-Behavioral Intervention for Anxiety in Preschoolers: Evidence for Error-Monitoring Specificity

Kate Fitzgerald

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Background: Accumulating evidence indicates that the error-related negativity (ERN) – an index of error monitoring that is

modulated by anxious psychopathology – may be susceptible to tailored interventions. Here, we examined how cognitive training modulates cognitive control indexed by behavioral tasks and brain markers of error monitoring, inhibitory control and attention allocation among clinically anxious preschoolers.

Methods: Games tapping response inhibition, working memory and selective attention were taught to 4-to-6-year-old children over 4 days with game difficulty titrated over this period. Before and after training, the Spence Preschool Anxiety Scale (PAS), behavioral tests of cognitive control and several event-related potentials (ERPs) were collected. ERPs included the error-related negativity (ERN), error positivity (Pe), N2, and P3 during a child-friendly Go/No-Go task. The ERN indexes unconscious error monitoring, the Pe indexes attention allocation to errors; the N2 taps response inhibition, and the P3 indexes attention allocation to oddball stimuli (e.g., errors).

Results: Thirty-one children provided pre- and post- intervention anxiety and behavioral data, and 22 had usable ERP data. Paired t-tests revealed decreased anxiety ($t(30) = 3.08$, $p = .006$) and improved performance on the Dinky Toys ($t(27) = 2.14$, $p < .05$) and Head Toes Knees Shoulders behavioral tasks ($t(30) = 3.75$, $p < .001$). Electrode Site $\times$ Trial Type $\times$ Time (Pre vs. Post) analyses of variance (ANOVAs) showed robust effects of Trial Type for the ERN ($F = 131.55$, $p < .001$), Pe ($F = 23.11$, $p < .001$), and P3 ($F = 38.14$, $p < .001$), but no effect for the N2 ($F = 0.33$, $p = .57$). Across all ERPs, only the ERN was significantly increased from pre- to post-intervention, 3-way interaction: $F(2, 42) = 6.91$, $p = .007$; all other ps $> .05$.

Conclusions: Findings suggest that play-based cognitive training increases brain-behavioral capacity for cognitive control and may reduce anxiety. Several well-known neurophysiologic indices of cognitive control were successfully elicited in the young children studied, but only early error monitoring (ERN) processes were impacted by cognitive control training. These data highlight the utility of the ERN as being sensitive to training and represents a promising intervention target for future work.

Disclosure: Nothing to disclose.

9.3 Quantitative EEG Markers of Suicide Implicit Association Test in Hospitalized Adolescents

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Background: Implicit Association Test (IAT) has been used in cognitive neuroscience to measure implicit biases toward different concepts. In suicide research it has been shown that positive implicit associations between self and death/suicide was associated with approximately six-fold increase in the odds of making a suicide attempt at 6-month follow-up. Yet a little known about the neural correlates of implicit cognitive processes associated with suicidality and to our knowledge no previous study has investigated quantitative EEG correlates of Suicide-Implicit Association Test (S-IAT). Therefore, in this study we aimed to investigate qEEG markers of S-IAT in inpatient adolescents with suicidal ideations and behaviors as compared to healthy controls.

Methods: Thirty adolescents between ages 13-18 admitted to the Mayo Clinic child and adolescent psychiatry unit with suicidal ideations and suicidal behaviors (screened by Columbia-Suicide Severity Rating Scale (C-SSRS)) and thirty adolescents with no prior psychiatric diagnoses were recruited. All participants underwent diagnostic assessments and EEG recordings. Primary outcomes were the associations between the behavioral outcomes of S-IAT (d-score) and event-related potentials elicited during S-IAT, and the group differences between healthy controls and patients.

Hierarchical GLMs (ANCOVA) with spatio-temporal clustering were used to identify significant event-related potentials associated with S-IAT and assess group differences.

Results: Behavioral results (d-score) showed that the patient group had stronger implicit associations between "death" and "self" as compared to the healthy group (ANCOVA, $p = .007$, $F = 7.87$) when controlled with age, gender and the IAT order. Within the patient group the intensity of suicidal ideations in the past 2 weeks (based on C-SSRS) was higher in those who had stronger implicit associations between "death" and "self" ($p = .043$). ERP analysis showed that there was a significant correlation between d-scores and N100 component over the left occipito-parietal cortex, in a way that incongruent trials yielded larger visual N100 components (p -corrected $< .05$ for the cluster). Significant group differences (p -corrected $< .05$ for the cluster) were present for later ERP components (> 600 ms, LPP) over this region (occipito-parietal cortex), but d-scores did not correlate with the ERP activity at these later latencies. Other significant group differences (all with p -corrected $< .05$ for the cluster) were found over the centro-parietal areas (also N100) and left dorsolateral prefrontal cortex (P200).

Conclusions: Our results suggest that N100 may be a marker of attentional resources allocated to the discrimination of the stimulus that is congruent or incongruent to one's associations between death and self. Group differences over centro-parietal areas and prefrontal cortex may be explained by other factors such as emotional salience (N100), selective attention (frontal P200), and semantic processing (LPP) independent of the behavioral effect of S-IAT.

Disclosure: Nothing to disclose.

PANEL

10. Hormonal Influences on Indices of Mental Health Across the Life Span

10.1 Regulation of Sex-Specific Cocaine Induced Behaviors and Transcription by Thyroid Hormone Signaling

Deena Walker

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Background: Sex differences in reward-associated behaviors are necessary for the perpetuation of many species. Such behaviors emerge during the adolescent period, a developmental window associated with increased vulnerability to psychiatric disorders, including substance use disorder, in humans. Previously, we have shown that adolescent social isolation disrupts sex-specific reward- and stress-related behaviors and the transcriptional response to cocaine in the medial amygdala. These data were the first to implicate the medial amygdala as a key brain region for the regulation of the sex-specific response to cocaine.

Methods: Through integration of gene co-expression analysis of RNA-seq data from males and females exposed to acute (1 dose 7.5mg/kg; Male Saline $N = 7$; Male Cocaine $N = 7$; Female Saline $N = 6$; Female Cocaine $N = 8$) and chronic cocaine (10 doses 7.5mg/kg; Male Saline $N = 8$; Male Cocaine $N = 7$; Female Saline $N = 7$; Female Cocaine $N = 8$) we identified the thyroid hormone binding protein, crystalline mu (Crym), as a sex-specific upstream regulator of the transcriptional alterations induced by cocaine.

Results: Using viral mediated gene transfer to overexpress Crym in the adult medial amygdala, we disrupted cocaine conditioned place preference in a sex specific manner.

Overexpression of Crym in males increased preference for cocaine (7.5mg/kg) when compared to GFP control males (GFPM ($N = 24$) vs CrymM ($N = 10$) $p = 0.05^*$). While overexpression of Crym in females had no significant effects on cocaine preference (GFP-F ($N = 25$) vs Crym-F ($N = 8$) $p = 0.776$) it did result in a bimodal distribution of preference for cocaine in which females either formed a preference or aversion to cocaine. Importantly, the behavioral effects of Crym overexpression were reflected in the transcriptional profile induced by Crym overexpression in males and females. RNA-sequencing revealed that Crym overexpression altered expression of more genes in males (295) than females (181) and induced sex-specific expression in 523 genes. Importantly, these sex differences in expression were not observed in GFP males vs. females (295 genes total). These gene expression changes closely mirrored the transcriptional profiles of males and females injected with cocaine.

Conclusions: These data suggest that disruption of thyroid hormone signaling, through the overexpression of a thyroid hormone binding protein, within the medial amygdala influences sex-specific behaviors through transcriptional changes. Currently, we are expanding on these studies by investigating the epigenetic mechanisms by which thyroid hormone signaling might program the sex-specific response to stress and cocaine in the medial amygdala.

Disclosure: Nothing to disclose.

10.2 Early Life Adversity Induces Sex-Specific Changes in Motivated Behavior

Debra Bangasser

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Background: Early life experiences can alter risk/resilience for disorders linked to changes in motivated behavior. Early stress that is not overwhelming can have an "inoculating" effect that promotes later resilience. Our lab uses the limited bedding and nesting (LBN) model of mild early life adversity. We found that this model reduces impulsivity and morphine self-administration in male but not female rats, suggestive of an "inoculation" effect against addiction-related behaviors in males. LBN also increases plasma estradiol (E2) in male rats. Here we extend this work to link endocrine changes to relevant motivated behaviors and explore the genetic and epigenetic alterations that can contribute to stress inoculation.

Methods: In LBN, pups from postnatal day 2–9 and their dams were exposed to a low resource environment and compared to rats raised in standard housing. E2 mediates male reproductive behaviors, so we predicted LBN males, who have more E2, would have facilitated reproductive behaviors. To test this, adult LBN and control males were paired with a novel receptive female for three 30 min sessions separated by 1 week and behaviors were assessed. The medial preoptic area (mPOA) mediates reproductive behaviors, so we examined LBN-induced transcriptional changes in this region using RNAseq. To extend our understanding of mechanisms that promote stress-inoculation of addiction-related behavior, we measured histone post-translational modifications in the nucleus accumbens (NAc) using a HPLC-MS mass-spectrometry.

Results: In the reproductive behavior test, the latency to engage behaviors decreased across session as both groups learned to be more effective at mounts ($p = .012$) and intromissions ($p = .004$). However, LBN males performed better than controls in session 2: they were quicker to mount ($p = .044$) and ejaculate ($p = .023$). This suggests they learn these behaviors more quickly. In the mPOA, LBN induced 176 and 212 differentially

expressed genes in males and females, respectively, with only 15 common genes across sex. Pathway analysis identified changes in phosphatidylinositol and VEGF signaling that may drive the behavior changes in males. Crucially, several genes in these pathways are regulated by E2. Ongoing studies are linking previous transcriptomic results to alterations in histone marks in the NAc to better understand mechanisms of stress inoculation against addiction-related behavior. LBN altered 1 histone mark in females vs. 3 in males, including H4K12ac, which is found in active promoters and regulated by estrogen receptor- α . Thus, reduced addiction-related behavior in LBN males may be driven, at least in part, by higher E2 levels.

Conclusions: We found LBN facilitates the acquisition of male reproductive behaviors. Animals raised in environments with limited resources are likely remain in such environments, which can reduce life expectancy. Thus, it may be adaptive for LBN males to learn to pass on genes more quickly to the next generation. Mechanistically these behavioral changes are linked to alterations in signaling pathways in the mPOA and may be driven by increased E2. LBN also induces epigenetic changes in the NAc that can promote resilience to addiction-related behavior. There are motivational aspects to reproduction, so this combination of findings may indicate that LBN increases motivation for natural rewards while decreasing motivation for morphine in males. Studies are currently underway to test this idea. Crucially, LBN is an important model for understanding mechanisms underlying stress resilience.

Disclosure: Nothing to disclose.

10.3 Sex Differences in Effects of Modulation of the G-Protein Coupled Estradiol Receptor 1 on Motivation for Cocaine in Adult Rats

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Background: There are sex differences in the response to psychomotor stimulants. Females exhibit a greater response to cocaine or amphetamines than males, due at least in part to the presence of the gonadal hormone estradiol (E2). Extensive research has demonstrated that E2 also enhances the rewarding properties of drugs of abuse and some natural rewards in females. The dorsolateral striatum is implicated in mediating drug-seeking behaviors and this brain region contains E2 receptors α , β , and G-protein coupled estradiol receptor 1 (GPER1). The effects of modulation of GPER1 in the dorsolateral striatum (DLS) on drug-seeking behaviors was investigated.

Methods: Experiments examined the effects of pharmacological treatments into the DLS that activated or inhibited GPER1 on conditioned place preference (CPP) and cocaine self-administration in gonad-intact male and female rats. Animals received intra-DLS stylets containing 10% G1 (GPER1 agonist) in cholesterol, G15 (GPER1 antagonist) in cholesterol or cholesterol alone (control). In experiment one, animals were tested for CPP after compartments were paired with cocaine (5 or 10 mg/kg, ip) or saline. In experiment two, animals underwent testing on a progressive ratio (PR) schedule of self-administration to determine their motivation to attain cocaine (0.4 mg/kg/inf). Halfway through PR testing, a GPER1 agonist was administered intra-DLS. The effects of intra-GPER1 activation on drug-induced reinstatement after extinction was also determined.

Results: In experiment one, we found that in males only, GPER1 activation in DLS attenuated CPP for 10 mg/kg cocaine ($F(1,15) = 7.429$; $p = 0.016$, $n_2p = 0.33$), while inhibition of GPER1, via G15, enhanced preference at a 5 mg/kg cocaine dose ($F(1,15) = 8.194$;

$p = 0.0119$, $n_2p = 0.353$). G1 treatment had no effect on CPP for cocaine in female rats. In experiment two, intra-DLS treatment enhanced PR responding for cocaine in females, but there was no effect in males (main effect of sex ($F(1,47) = 6.973$; $p = 0.0112$; $n_2p = 0.129$). Additionally, there was no effect of prior G1 treatment on extinction of cocaine-taking in females, however, intra-DLS treatment with G1 resulted in greater drug-induced reinstatement of responding (10 mg/kg cocaine, i.p.) ($p < 0.04$). There were no effects of intra-DLS GPER1 activation on cocaine-induced reinstatement of responding for cocaine in males.

Conclusions: In males, GPER1 activation attenuated acquisition of CPP for cocaine. Conversely, in females, GPER1 activation enhanced motivation for cocaine. In summary, the results of this study support a novel role of GPER1 in males vs. females and provides a future target for preclinical research, as well as clinical research, targeted at selective estradiol receptor modulators.

Disclosure: Nothing to disclose.

10.4 Depression During the Perimenopause: Clinical, Endocrine and Cellular Characteristics, Accompaniments and Possible Antecedents

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Background: Epidemiologic studies have documented an increased risk of depression in women during the perimenopause compared with the premenopause. However, it remains unclear if there are changes in reproductive function or stress axis responsivity that increase the risk of or accompany perimenopausal depression (PMD).

Methods: Study 1: Eighty-eight asymptomatic, premenopausal, healthy women, no current Axis 1 illness (SCID), age 40-55 years, medication free, were monitored longitudinally during the early follicular phase (or randomly if amenorrheic) for an average of 5.9 years (range of 1.3 – 12 years) until 6-12 months after their last menstrual period (LMP). Outcome measures included blood hormone measures, structured diagnostic interviews (SCID), and symptom ratings (daily, weekly, at clinic visit). Study 2: Dex/CRH tests and 24-hour UFC measures were performed in 20 women with PMD and 20 women who were also perimenopausal but without current or past depression (control women). Main outcome measures were plasma levels of cortisol and ACTH and 24-hour urinary free cortisol. Results were analyzed with mixed models GEE and Wilcoxon ranked sum tests. Finally, recently published whole transcriptome sequencing in cell-lines from women with PMD and controls identified several differentially expressed genes (CXCL10, CYP7B1), the products of which could be relevant for the risk of PMD or its comorbidities (e.g., heart disease). Measures of CXCL10 protein and neurosteroid levels metabolized by CYP7B1 from Study 1 will be presented.

Results: Study 1: We prospectively identified twenty-nine episodes of major or minor (subsyndromal) depression that occurred in twenty-two women; Twenty episodes occurred in the 24 months surrounding the LMP. In 19 of 22 women, episodes only occurred after plasma FSH levels rose (i.e., > 14 IU/L). Only four women with PMD had a past major depression (i.e., 18 of 22 women had 1st onset depression in perimenopause). Preliminary results show that the patterns of secretion of plasma estradiol and FSH over time significantly differ between women who develop PMD and those who remained asymptomatic (estradiol - time by depression: $p = 0.0235$ (linear),

time2 by depression: $p = 0.0299$ (quadratic); FSH - time by depression: $p = 0.0240$ (linear), time2 by depression: $p = 0.0323$

(quadratic)). Significant differences in hormone secretion in PMD occurred in the early stages of the perimenopause. Study 2: No diagnosis-related differences were present in either baseline or stimulated ACTH and cortisol secretion (AUCs of cortisol ($p = 0.935$) and ACTH ($p = 0.871$) after CRH administration, or in baseline measures of 24-hour UFCs ($p = 0.957$).

Conclusions: Episodes of PMD cluster during the late menopause transition, and the majority of episodes are preceded by evidence of reproductive aging (i.e., elevated FSH plasma levels). In addition to the link between changes in reproductive stage and depression that we observed, we show that a common accompaniment of non-reproductive depression, an abnormal HPA axis, is not present in PMD, and we identify genetic variants that might help explain comorbidities accompanying PMD.

Disclosure: Nothing to disclose.

PANEL

11. Lateral Septum: From Ontogeny to Functions in Motivated Behaviors

11.1 Diversity and Embryonic Origin of Septal Neurons: Analysis of Developmental Trajectories

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Background: The septum is ventral forebrain structure responsible for the regulation of emotional states including anxiety, fear and depression. The septum contains an extremely diverse array of short- and long-range projecting GABAergic neurons distributed across its two histological subdivisions, the medial and lateral septal nuclei. It is currently unclear how septal neuronal diversity and the wiring of its circuits are specified during development. We used a combination of single-cell RNA-seq, histology and genetics to study the developmental trajectories by which embryonic septal progenitors give rise to different types of neurons, and how these transition through subsequent maturation steps towards their mature function. Our results provide novel insights into the assembly of the complex circuitry underlying the regulation of internal states carried out by the septum.

Methods: Wild-type animals for single cell sequencing and validation experiments were purchased as timed-pregnant females or as entire litters at the following developmental time points: embryonic days (E)11, 14 and 17; and postnatal days (P)3, 10, and 30. 2-3 biological replicates composed of septa from entire litters for embryonic timepoints and individual septa for postnatal ages. All results reported include animals of both sexes, balanced equally wherever possible; the sex of embryos and P3 animals was not determined.

Quantification of RNAscope puncta was performed using an automated data processing pipeline in MatLab, guided by the SpotsInNucleiBot (<https://hms-idac.github.io/MatBots>). Values are presented as the density of puncta for each mRNA analyzed normalized to the density of puncta for the corresponding cell type marker.

Results: We used SPRING, a tool that generates a force ordered k-nearest-neighbor graph where each cell is represented as a node extending edges to the 'k' other nodes within the dataset with most similar gene expression profiles. We produced SPRING plots of E11 and E14 timepoints that correspond to the peak MS and LS neurogenesis periods respectively. Expression of the genes *Nes* (nestin), *Ascl1* (achaete-scute family bHLH transcription factor 1), and *Dcx* (doublecortin), were used as cell type markers for radial glia, intermediate progenitors, and newborn neurons,

respectively. We compared the gene expression profiles of each of the three main cell types present along the neurogenic sequence (radial glia, intermediate progenitors, and newborn neurons) across the three embryonic stages, and found numerous genes that were differentially expressed. Using single molecule fluorescent in situ hybridization we show that in RG *Hmga2* was significantly enriched in E11 septum ($p = 0.0010$), while the gene *Ccnd2* was significantly enriched in E14 intermediate progenitors ($p = 0.0295$). Together, our data provides a framework for characterizing dynamic gene expression as progenitors transition from generating MS neurons to LS neurons.

Conclusions: Using genetic fate mapping and single cell trajectories we describe the spatial and temporal molecular codes for the production of diverse groups of neurons within the septal nucleus. Our data provides identifies the developmental origin and key genetic pathways involved in the production of specific subtypes of neurons in the septal nucleus.

Disclosure: Nothing to disclose.

11.4 Deconstructing Hippocampal-Dorsolateral Septum Projection Logic Underlying Contextual Calibration of Feeding and Social Behavior

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Background: The execution of adaptive motivated behaviors relies on faithful relay of mnemonic information about our external world, social and spatial experiences or "contexts" with subcortical circuits.

We and others have begun to edify the role of the dorsolateral septum (DLS) as a conduit between the hippocampus and subcortical circuits that mediate a range of motivated behaviors. The DLS is comprised of numerous subtypes of inhibitory neurons (INs) with somatostatin INs (SST) being the predominant class. Dorsal and ventral hippocampal projections relaying spatial and social or goal related information, respectively, terminate in non-overlapping DLS domains. We previously showed using in vivo behaving calcium imaging and optogenetics that SST INs are functionally heterogeneous and that a subset of SST INs calibrate motion when mice need to attend to contextual cues to guide their behavior. Thus, different SST subpopulations in the DLS are likely to integrate distinct cortical and hippocampal inputs and recruit diverse downstream subcortical circuits to mediate motivated behaviors. However, the identities, anatomical and functional logic of these SST subpopulations are poorly defined. Bridging this knowledge gap may illuminate circuit-based closed loop approaches to rectify aberrant or exaggerated context-evoked social and feeding behaviors that characterize social and eating disorders.

Methods: We performed single cell RNA sequencing (DROP-seq) in the DLS to generate a molecular blueprint of SST heterogeneity. We characterized distribution of different SST subpopulations in the DLS by triple fluorescence in situ hybridization. We used anterograde and retrograde monosynaptic viral tracing to map input and output architecture of the prodynorphin (Pdyn) expressing subpopulation of DLS INs. We performed electrophysiological recordings of Pdyn subpopulation of SST INs in DLS. We used optogenetics to functionally interrogate the contribution of Pdyn INs in motivated behaviors. We are performing in vivo optical imaging to characterize the properties of these neurons during context calibration of motivated behaviors.

Results: We have identified several potential subtypes of DLS SST INs characterized by enrichment of different neuropeptides

such as prodynorphin (Pdyn), proenkephalin (Penk), neurotensin (Nts) etc. Systematic analysis of these putative SST subtypes by triple fluorescence in situ hybridization (FISH) using RNAscope identified a Pdyn expressing DLS SST IN subpopulation that is exclusively localized to the dorsal region of the DLS where dorsal hippocampal projections terminate. Viral based mapping of input-output architecture of Pdyn INs identified the dorsal hippocampus as the primary input onto these neurons and the lateral hypothalamus as the major target. Functional optogenetic interrogation revealed a role for Pdyn DLS INs as mediators of contextual calibration of feeding and social behaviors.

Conclusions: Our studies begin to deconstruct Hippocampal-Lateral septal projection logic governing contextual calibration of motivated behaviors. Together with prior published work on the DLS, our unpublished data (showcased here) illuminates how a distinct SST subtype of inhibitory neurons, Pdyn INs relays dorsal hippocampal outputs to the lateral hypothalamus to provide contextual calibration of feeding and social behaviors.

Disclosure: Nothing to disclose.

STUDY GROUP

12. Ethical Issues Regarding Race and Ethnic Data in Clinical Research

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Study Group Summary: This work group considers the ethical use and appropriate interpretation of clinical research findings obtained from racial and ethnic minorities, as mandated by NIMH. This topic is proposed on behalf of the ACNP Ethics Committee as an issue of great importance to our field. The NIMH racial and ethnic minority recruitment policy, proposed in 2005 and revised in 2016, requires all clinical trials regardless of size and other studies enrolling 150 subjects or more to include data from racial and ethnic minorities, otherwise specified as Black, Indigenous, and People of Color (BIPOC), in the main study analyses. Principal Investigators (PIs) are required to establish recruitment goals and milestones that are monitored throughout the study. The policy actually defines “clinical research”, “clinical trials”, and the responsibilities of the PI and Recruitment Milestone Reporting (RMR) staff to include adequate proportions of such minorities in conducting the study. Left unclear, however, is the appropriate use and interpretation of this data in the literature.

This panel will address several topics related to the ethics of the diversity recruitment requirement. Do the findings contribute to health disparities research or perpetuate racist ideas? Are investigators adequately educated to know that race is a social concept and not a biological division? Do biological researchers understand the social determinants of health? Are clinicians aware of the misdiagnosis of schizophrenia in BIPOC with affective and other disorders? What is the impact of race-specified laboratory values on the health of minority persons? Is it ethical to withhold race specified data in study results? What is the responsibility of editors to request and evaluate such stratified findings? How can structural medicine guide research methodologies for the ethical interpretation of race/ethnicity specific data? How can clinical and biological investigators be educated that race is a social construct? How can grant reviewers consider this aspect of a study?

Disclosure: Nothing to disclose.

PANEL

13. Cannabis and Psychosis: Clinical Features, Risk for Relapse and Potential Mechanism

13.1 Behavioral, Cognitive, and Psychophysiological Comparison of Hospitalized Cases of First Episode Psychosis With vs. Without Cannabis Exposure

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Background: Converging lines of evidence suggest that exposure to cannabis increase the risk of several psychosis outcomes. A small proportion of persons using cannabis develop a first episode of psychosis (FEP) in the context of exposure to cannabis – Cannabis Induced Psychotic Disorder (CIPD). However, whether this syndrome differs from FEP unrelated to psychosis in its clinical profile, course and response to treatment is not clear.

Methods: In a prospective study funded by NIDA, hospitalized cases of new onset CIPD were compared to individuals who were hospitalized for FEP psychosis unrelated to cannabis. Cases of CIPD included sporadic ones and those associated with the ritual use of cannabis during certain annually occurring festivals in India. Exposure to cannabis was confirmed by urine toxicology. Demographic information, personal and family history of mental illness and drug use, psychosis, depression, mania, cognition, and psychophysiological (EEG) indices of information processing were assessed 1) at admission, 2) mid-hospitalization, 3) around discharge, and when feasible 4) within 6 months post-discharge.

Results: In this prospective study, 65 hospitalized cases of CIPD with confirmation of cannabis exposure have been studied and compared to hospitalized FEP unrelated to cannabis ($n = 50$) at the Central Institute of Psychiatry, Ranchi, India. Preliminary results suggest that cases of CIPD despite meeting the same threshold for hospitalization, have a distinct phenomenological presentation including 1) lower PANSS positive, negative and disorganization symptoms, 2) equivalent depression (Calgary) and mania (YMRS) symptoms, and 3) comparable performance on cognitive test performance (Cogstate Battery). Furthermore, CIPD and FEP unrelated to cannabis have band-specific widespread differences in neural connectivity and activation that lead to distinct electrophysiological fingerprints. Both groups showed overall similar magnitude of improvement in symptoms suggesting that they respond similarly to treatment with antipsychotic medications in the short-term and inpatient hospitalization. Within 6 months of the index hospitalization, 10 CIPD subjects were re-hospitalized for a relapse of psychosis that followed the resumption of cannabis use – this was confirmed with urine toxicology, self-report, and family-report. Lastly, examining longitudinal changes in EEG, CIPD patients have significantly higher widespread theta function compared to FEP unrelated to cannabis.

Conclusions: Compared to FEP without cannabis exposure, CIPD have less severe positive, negative, and disorganization symptoms, but there is no significant difference in mood symptoms or cognitive deficits. The two groups differ on a number of electrophysiological indices of information processing (specifically theta band power and connectivity), suggesting distinct biological differences. Lastly, resumption of cannabis use seems to contribute to a risk of relapse in CIPD. If these results are confirmed in a larger sample, it would suggest that CIPD has a distinct profile. Longitudinal studies are warranted to understand the course, expression, biology and prognosis of CIPD.

Disclosure: Nothing to disclose.

13.2 Cannabis Use and Risk of Relapse in Patients in Remission After Their First Psychotic Episode: Data From the OPTiMiSE Study

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Background: Up to 80% of the patients in their first psychotic episode respond to antipsychotics, and are considered to have a relatively good prognosis. This analysis examined the effect of cannabis use on risk for relapse in patients in remission following a first psychotic episode.

Methods: Analyses were performed on data from a large European first psychotic episode study (OPTiMiSE) on 446 patients. After 10 weeks of antipsychotic treatment, 282 (63%) achieved remission; 133/282 later completed a one-year follow-up. We assessed whether self-reported cannabis use at, and/or after remission had an effect on risk for relapse, and if this risk was independent from compliance with antipsychotics. Lag models investigated the temporal relationships between cannabis use, compliance with antipsychotics, social functioning and symptomatic worsening/relapse.

Results: Cox survival analyses adjusted for potential confounders found that, compared to non-users, cannabis use increased risk for relapse, hazard ratio = 3.19 (SE = .35), $P < .001$. Even patients who were compliant with their medications were at increased risk for relapse if they used cannabis (HR = 2.7, $p = .006$). Patients who continued to use cannabis had worsening of their social functioning ($t = 3.3$, $df = 347.9$, $p = .000$). Lag models showed that continued cannabis use preceded worsening of positive symptoms and of social functioning, but not vice versa.

Conclusions: In patients in remission from the first psychotic episode, cannabis use is associated with increased risk for relapse and worsening of social functioning, regardless of compliance with antipsychotics. Patients in remission after their first psychotic episode should be encouraged not to use cannabis.

Disclosure: Nothing to disclose.

13.3 Molecular Imaging Studies in Psychosis Patients Using Cannabis

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Background: Cannabis is the most widely used illicit drug (legal in some countries), particularly by adolescents and youth, making it a growing public health concern. In the US, approximately 51.8% of young adults aged 18-24 reported life-time cannabis use, with 34.8% reporting past year cannabis use. Schizophrenia (SCZ) is a debilitating mental disorder affecting about 1% of the world population, starting in early adulthood. Early cannabis use increases the risk of developing SCZ by almost twofold in vulnerable individuals making cannabis a strong risk factor for SCZ, acting through an unknown molecular mechanism.

Methods: Positron Emission Tomography (PET) studies were carried out in the High Resolution Research Tomograph (HRRT), with ^{11}C -(+)-PHNO and ^{11}C -FLB457 radioligands respectively. MAO-B was quantified in the HRRT with ^{11}C -SL25.1188 and kinetic modelling with full arterial input function.

Results: Here, using PET molecular imaging, we present, complimentary studies showing significant effects of cannabis use on brain dopamine function, both in striatum and cortical regions. In addition, we show novel unpublished data investigating the effects of cannabis use on Monoamine Oxidase B (MAO-B), a key dopamine metabolism enzyme in patients with psychosis

($n = 14$ vs $n = 17$ healthy controls). Preliminary data reveals a ~24.0 % reduction in MAO-B in patients with psychosis compared to controls in the associative striatum ($F(1,26) = 4.22$, $p = 0.050$). Interestingly, individuals with a positive urine drug screen for cannabis had ~19.5% reduced MAO-B compared to those without cannabis use, suggesting a potential reduction of MAO-B with cannabis use.

Conclusions: In summary, our data suggests significant effects of cannabis use on brain dopamine function and preliminary data in MAO-B reduction by cannabis use. This discovery, if confirmed in well powered studies, may help explain the exacerbated psychotic experiences in SCZ patients when using cannabis, earlier disease onset and relapse.

Disclosure: Nothing to disclose.

13.4 Shared Genetic Influences Underlying Cannabis Use Disorder, Psychosis-Like Experiences, and Schizophrenia

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Background: Recent genome-wide association studies (GWAS) have found modest but significant genetic correlations between schizophrenia (SCZ) and cannabis ever-use, and between SCZ and cannabis use disorder (CUD). Furthermore, we recently found that genetic liability to CUD was significantly associated with SCZ even when accounting for cannabis ever-use, ever-smoked tobacco regularly, and nicotine dependence as simultaneous predictors in a genomic structural equation model. These robust genetic correlations may partly explain the frequent co-occurrence of problematic cannabis use, psychosis, and schizophrenia. No study has yet examined the specific genetic loci and biological pathways associated with both CUD and SCZ liability. Furthermore, it is unclear the extent to which genetic risk for CUD and SCZ is associated with psychosis-like experiences in adolescents.

Methods: First, we applied ASSET, a cross-disorder method, to identify genome-wide significant loci that are pleiotropic for CUD ($N = 357,806$) and SCZ ($N = 161,405$). We also examined bivariate and local genetic correlations between CUD and SCZ after conditioning on tobacco smoking ($N = 632,802$), as smoking is correlated with both cannabis use and SCZ. Finally, we investigated whether polygenic risk scores derived using the CUD and SCZ GWAS are independently associated with psychosis-like experiences in a sample of 4,487 cannabis-naïve adolescents.

Results: We found 121 independent genome-wide significant ($p < 5e-8$) loci pleiotropic for CUD and SCZ (i.e., genetic variants exerting an effect on both CUD and SCZ). A chromosome 8 locus that contains the genes EPHX2 and CHRNA2 showed a particularly strong signal for both CUD and SCZ (lead SNP rs11783093 meta-analysis $p = 8.1e-19$; SCZ GWAS $p = 7.6e-12$; CUD GWAS $p = 2.7e-9$), suggesting that this may be a point of shared genetic vulnerability. Using a local genetic correlations approach, we identified one region (chr10: 79952997-81190573) that showed significant partial genetic correlation between CUD and SCZ after conditioning on tobacco smoking (partial $rg = 0.54$, $p = 0.003$). When both the CUD and SCZ PRS were included in a linear regression model simultaneously, only the CUD PRS was significantly associated with the total score of psychosis-like experiences weighted by level of distress ($\beta = 0.50$, $SE = 0.14$, $p = 4.2e-4$). However, both the CUD and SCZ PRS were significantly associated when jointly included in a logistic regression model that predicted a binary outcome of whether an individual reported any significantly distressing PLEs (CUD PRS $\beta = 0.14$, $SE = 0.04$, $p = 0.002$; SCZ PRS $\beta = 0.13$, $SE = 0.04$, $p = 0.005$).

Conclusions: Genetic liability for CUD is uniquely, positively correlated with SCZ risk, even after accounting for the genetic component of tobacco use. While both polygenic liability for SCZ and polygenic liability for CUD are associated with a binary measure of whether individuals in a population-based sample of cannabis-naïve adolescents have ever experienced a significantly distressing psychosis-like experience, only polygenic liability for CUD is significantly associated with a weighted score of all psychosis-like experiences (not just the significantly distressing ones). This suggests that, while genetic liability for both SCZ and CUD may underlie the most distressing psychosis-like experiences, genetic liability for CUD is correlated with a wider range of psychosis-like experiences.

Disclosure: Nothing to disclose.

PANEL

14. New Directions in Eating Disorders Research - Microstructure and Functional Response at the Intersection of Emotion Regulation and Reward Circuitry

14.1 White Matter Microstructure in Adolescents With Anorexia Nervosa: A Neurite Orientation Dispersion and Density Imaging Study

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Background: Behavioral and functional neuroimaging studies in those with anorexia nervosa (AN) provide evidence of abnormalities in reward processing and habitual decision-making, yet the microstructure of white matter dendrites and axons in the underlying circuits is not well understood. To investigate this, we employed neurite orientation dispersion and density imaging (NODDI) to estimate axon density, myelination, and angular variation of neurites in habitual decision-making circuits and reward circuits in 34 adolescents with AN and 30 controls. We also conducted whole-brain exploratory analyses across fiber tracts and gray matter regions.

Methods: We enrolled 34 adolescent females ages 12-19 with restricting-type anorexia nervosa who had recently completed an inpatient, residential, partial hospitalization, or intensive outpatient program and were partially or fully weight-restored. We also enrolled 30 age- and gender-matched controls. From a 3T scanner, we obtained data from a multi-shell, 99-direction diffusion-weighted sequence ($b = 3000\text{s/mm}^2$, $b = 1500\text{s/mm}^2$, and seven minimal diffusion-weighted scans). Preprocessing included correction for motion and eddy current distortions. T1-weighted images were registered to the aligned DWI using an affine transformation. NODDI parameters were calculated per voxel using the Quantitative Imaging Toolkit. Individualized gray matter (GM) ROIs were created based on Freesurfer Desikan-Killiany atlas and average neurite density index (NDI) was computed for each ROI. Individual white matter (WM) fiber tracts were estimated based on the IIT human brain atlas (<https://www.nitrc.org/projects/iit/>) and average NDI as well as orientation dispersion index (ODI) for all fiber-tracts were extracted. Two-sample, two-sided t-tests were used to reveal GM areas and WM fiber-tracts with significant differences between the groups. Significance was set at FDR corrected $q > .05$.

Results: Whole-brain analyses revealed lower neurite density in AN in bilateral inferior cerebellar peduncle, posterior arcuate

fasciculus, vertical occipital fasciculus, and the middle longitudinal fasciculus (FDR corrected $q > .05$). There was also reduced gray matter neurite density in the AN group in the bilateral rostral middle frontal cortex and the caudal anterior cingulate gyrus (FDR corrected $q > .05$). There were no significant regions showing higher neurite density in any white or gray matter regions in AN. There were no significant differences in white matter fiber orientation dispersion between groups.

Conclusions: We utilized NODDI to probe white matter microstructure in adolescents with AN, providing more specificity than previously-applied fractional anisotropy and diffusivity methods. Whole-brain analyses did not reveal differences in neurite density or orientation dispersion between AN and controls in habit and reward circuits. However, reduced neurite density was evident in pathways connecting limbic and cortical regions, which may be linked to aberrant processing of somatosensory information. Further, there was evidence of reduced neurite density in cerebellar tracts and in the visual system; the latter connecting dorsal and ventral visual streams, which may be linked to impaired global-local visuospatial integration found in AN. The neurite density microstructural findings could be accounted for by reduced packing density or myelination rather than aberrant fiber angular distribution, and point to either malnutrition effects or neurodevelopmental abnormalities.

Disclosure: NOCD, LLC: Consultant (Self)

14.2 Emotion Neurocircuitry in Bulimic-Spectrum Eating Disorders

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Background: Impaired regulation of intense and volatile emotion has been strongly implicated in the development and persistence of binge eating and purging. In addition, severe emotion dysregulation predicts poorer treatment outcome in bulimic-spectrum disorders. However, the neural mechanisms of this effect are unknown, and interactions within and between emotion-related neural networks remain poorly characterized in this population. In a pilot sample of patients with binge-eating and/or purging ($n = 19$), we previously found that the relative influence of an emotion regulation subnetwork on an emotion reactivity subnetwork predicted changes in symptoms and therapeutic skills use over the course of treatment. However, this resting-state internetwork influence in patients did not differ from controls. Here, we examined whether connectivity in emotion circuitry at rest and during an emotion-regulation task could identify clinically meaningful subgroups in a combined sample of 59 women with and without bulimia nervosa (BN).

Methods: Women with BN and healthy controls (HC) who were group-matched to the BN sample on age, body mass index, and full-scale IQ completed resting-state fMRI scans ($n = 28$ per group) and an fMRI task (29 BN, 30 HC) that required downregulation of negative emotion and upregulation of positive emotion. Group Iterative Multiple Model Estimation (GIMME) was used to characterize directed functional connectivity paths within an emotion network at rest and during emotion regulation. Individuals were clustered using community detection on estimates of neural connectivity, and exploratory analyses compared the women in resulting connectivity-based subgroups.

Results: Two subgroups based on resting-state emotion network connectivity were identified. Subgroup A had three times as many specific paths as Subgroup B, mostly connecting insular cortex with lateral prefrontal regions and amygdala. Connectivity-based subgroup predicted diagnostic group (Chi Square = 4.67,

$p = 0.031$, Cramer's $V = 0.289$), such that the subgroup characterized by fewer connections (Subgroup B), contained most (71.4%) of the participants with BN, and Subgroup A contained 57.1% of healthy controls. Exploratory analyses indicated that women with BN in Subgroup B had a longer duration of binge-eating than those in Subgroup A (Wilcoxon $W = 36.5$, $p = 0.028$; 95%CI [-7.00, -1.81e-05]). Parallel analysis of the emotion regulation task-based data is in progress and will be presented. Initial results from ratings of emotion intensity after each trial of the task indicate that women with BN were less successful than HC in down-regulating negative affect in the scanner (Wilcoxon $W = 276$, $p = 0.016$; 95%CI [-0.60, -0.08]).

Conclusions: Quantifying emotion circuit connectivity even at rest, may help to identify distinct subgroups of patients with bulimic-spectrum disorders. These functional connections could also serve as mechanistic targets for new interventions.

Disclosure: Nothing to disclose.

14.3 One-Shot Social Interactions in Anorexia Nervosa and Bulimia Nervosa

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Background: Both anorexia nervosa (AN) and bulimia nervosa (BN) are eating disorders that are more common in women, include problems with low self-esteem and interpersonal relationships, and typically begin in adolescence or early adulthood. However, they differ in the specific patterns of disordered eating that define the diseases. Anorexia nervosa is characterized primarily by restriction of food intake whereas bulimia nervosa is defined by binge-eating in conjunction with compensatory behaviors. Social stressors as well as changes in social environments have been closely related to both the development and maintenance of AN and BN.

Methods: Here, we utilized a well-established neuroeconomic game, the ultimatum game, to compare one-shot social interactions and responses to norm changes in healthy comparison (HC) as well as AN and BN cohorts. Twenty-four women with AN, twenty-four women with BN and twenty-five HC women played sixty rounds of the ultimatum game in an MRI, with the normative mean of offers shifting twice. With a model assuming people update their prediction about the norm at each new social interaction (based on the Rescorla-Wagner rule), we estimated each subject's predictions during the game.

Results: We found that, compared to the HC cohort, both the AN and BN cohorts had higher rejection rates to offers that are better than expected (i.e., offers with a positive prediction error [PE]), AN (mean [SD], 9.73% [19.8%]) > HC (1.80% [4.1%]), $t(47) = 1.957$, $p = 0.056$; BN (8.23% [13.6%]) > HC, $t(47) = 2.263$, $p = 0.028$, while no group difference was found in rejection rate for negative PE. In healthy players, a region in medial orbitofrontal cortex has been shown to track PE, responding more for higher positive PEs. Our study replicated these findings for the HC cohort (positive PE (0.55 [2.17]) > negative PE (-0.43 [1.16]), $p = 0.004$), but neither the AN nor BN cohorts modulated this region in response to positive PE. Specifically, when the receiving offers with positive PE, AN and BN cohorts had significantly attenuated activations in this region relative to the HC cohort, AN ((-0.58 [1.23]) < HC (0.55 [2.17]), $p = 0.022$); BN (-0.54 [1.22]) < HC, $p = 0.029$).

Conclusions: These results suggest positive social signals are diminished in both AN and BN. We hypothesize that this factor that may contribute to their difficulty in responding to social stressors.

Disclosure: Nothing to disclose.

14.4 Traumatic Childhood Experiences in Eating Disorders Selectively Reduce Response to Unexpected Reward Receipt, but Not Omission

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Background: Eating disorders (EDs) are severe psychiatric disorders and frequently comorbid with depressive, anxiety and trauma related disorders. Comorbid PTSD in patients with EDs ranges from 9 to 24% (Rijkers et al., 2019). A frequently applied measure for traumatic experiences is the Adverse Childhood Events (ACEs) questionnaire that found a dose-dependent effect between experienced traumatic events and severity of ED symptoms (Guillaume et al., 2016). The neurobiology that mediates the association between eating disorder symptoms and trauma is not known. The goal of this study was to investigate the association between brain reward system response, trauma experience and eating disorder behaviors.

Methods: We recruited 148 women, with anorexia nervosa (AN $n = 38$, age = 25.3 ± 6.5 years, body mass index, BMI = 16.3 ± 1.2 kg/m²), other specified feeding and EDs with food restriction (OSFEDr $n = 7$, age = 26.8 ± 4.9 years, BMI = 20.1 ± 7 kg/m²), bulimia nervosa (BN $n = 32$, age = 24.5 ± 3.9 years, BMI = 23.9 ± 8.9 kg/m²), OSFED or full threshold binge ED (BED $n = 11$, age = 30.5 ± 7.7 years, BMI = 33.6 ± 9.9 kg/m²), and healthy controls (HC $n = 60$, age = 27.3 ± 4.9 years, BMI = 21.5 ± 1.5 kg/m²). All participants underwent careful screening and completed self-assessments including the ACEs questionnaire. Functional brain imaging tested brain response during a classical conditioning paradigm that included violations of learned associations between conditioned visual and unconditioned taste stimuli. Pearson correlation analysis investigated brain-behavior associations and MANOVA group contrasts (data normalized, results multiple comparison corrected).

Results: In the ED group, ACEs score significantly correlated with body dissatisfaction ($r = .317$, $p = .003$, CI95% = .126 to .484). In EDs, but not HC, ACEs scores correlated negatively before and after controlling for the effects of body mass index (BMI), with regional brain response for unexpected stimulus receipt in bilateral anterior insula ($R:r = -.332$, $p = .005$, CI95% = -.544 to CI95% = -.099; $L:r = -.322$, $p = .007$, CI95% = -.530 to -.105), bilateral ventral striatum ($R:r = -.296$, $p = .014$, CI95% = -.535 to CI95% = -.021; $L:r = -.317$, $p = .008$, CI95% = -.520 to -.057), anterior cingulate cortex ($R:r = -.254$, $p = .035$, CI95% = -.461 to CI95% = -.014; $L:r = -.258$, $p = .032$, CI95% = -.465 to -.018), and amygdala ($R:r = -.292$, $p = .015$, CI95% = -.499 to CI95% = -.075; $L:r = -.306$, $p = .010$, CI95% = -.496 to -.099). ACEs scores did not correlate significantly with unexpected stimulus omission response in either group. A group by condition analysis for AN, BN and HC was significant for unexpected stimulus receipt when including ACEs score as covariate, in bilateral ventral striatum ($R: F = 6.792$, $p = .002$, partial $\eta^2 = .098$, power = .914; $L: F = 6.360$, $p = .002$, partial $\eta^2 = .092$, power = .894), anterior cingulate cortex ($R: F = 4.905$, $p = .009$, partial $\eta^2 = .073$, power = .797; $L: F = 5.131$, $p = .007$, partial $\eta^2 = .076$, power = .816), amygdala ($R: F = 4.228$, $p = .017$, partial $\eta^2 = .063$, power = .732; $L: F = 6.878$, $p = .001$, partial $\eta^2 = .099$, power = .917). Post hoc analysis confirmed that higher ACEs score was associated with lower brain response in AN and BN, independent from BMI.

Conclusions: This study has several important results. First, previously experienced trauma is directly related to body dissatisfaction across EDs. Second, traumatic childhood experiences selectively reduce brain response to unexpected reward receipt, but not omission. This imbalance may provide a

mechanism for how trauma creates negative bias as positive experiences are not processed adequately.

Disclosure: Nothing to disclose.

STUDY GROUP

15. Critical Issues in Advancing Psychedelic Medicine: Hype and Hope

Scott Thompson*, Jennifer Mitchell, Javier Gonzalez-Maeso, Natalie Gukasyan, Benjamin Kelmendi, Lindsay Cameron

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Study Group Summary: The use of psychedelic compounds for treating psychiatric disorders is one of the most exciting developments in neuropsychopharmacology. From depression to PTSD to substance use disorders, the first careful clinical trials of drugs like psilocybin and MDMA have revealed efficacy that meets or exceeds current therapeutics. Massive investments are being made in psychedelic medicine. Yet significant challenges remain to bring this class of compounds to patients. Efforts to speed translation are hampered by lack of understanding of mechanisms underlying their therapeutic effects.

Our study group, composed of active front line scientists in this burgeoning field, will lead an informed discussion around some of the issues facing the field from a preclinical and clinical perspective. We will encourage an active dialog with the audience throughout the session and, given the considerable attention in the scientific and lay press, we anticipate vigorous participation. Clinical questions to be discussed include 1) the role of the placebo effect, 2) study design and blinding, 3) choosing self-reporting instruments, 4) the role of the subjective response, and 5) equity of access to psychedelic therapy. Preclinical questions to be discussed include 1) serotonin receptor pharmacology, 2) molecular pharmacology of therapeutic compounds, 3) best models for preclinical studies, and 4) behavioral assays in female animals. Common to both clinical and preclinical topics will be a focus on neurobiological mechanisms underlying the therapeutic effects of these compounds.

Our study section is composed of a diverse range of investigators at all career stages and is balanced between women and men and between preclinical and clinical interests:

Scott Thompson, PhD. Professor and Chair, University of Maryland School of Medicine. Senior author of 2021 study in *PNAS* demonstrating anti-anhedonic actions of psilocybin in mice and suggesting that the therapeutic actions of psychedelic compounds may be independent of their ability to alter consciousness.

Jennifer Mitchell, PhD. Associate Professor, University of California San Francisco. First author of a 2021 study in *Nature Medicine* demonstrating that MDMA-assisted therapy is highly efficacious and safe in individuals with severe PTSD.

Javier Gonzalez-Maeso, PhD. Professor, Virginia Commonwealth University. Senior author of a study on the receptor pharmacology of psychedelic compounds and their actions on epigenetic and synaptic processes.

Natalie Gukasyan, MD. Assistant Professor, Johns Hopkins University. Practicing psychiatrist. Author of a 2021 study discussing the role of the placebo effect and set and setting in psychedelic therapy. Currently leading a clinical trial of psilocybin-assisted treatment for anorexia nervosa.

Benjamin Kelmendi, MD. Assistant Professor, Yale University. Basic and clinical studies of neuropsychiatric disorders. Practicing psychiatrist. Leading clinical trials of ketamine and psilocybin in major depression and obsessive-compulsive disorder.

Lindsay Cameron, PhD student/postdoc, University of California Davis. First author of a 2020 study on the identification and actions of a novel non-hallucinogenic psychedelic compound in preclinical models published in *Nature*.

Disclosure: Intellectual Property: Patent (Self)

PANEL

16. Epigenetics of Neurodevelopmental Disorders

16.1 Targeting Histone Modifying Enzymes for Autism Treatment in Mouse Models

Zhen Yan

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Background: Genetic studies have revealed that aberrations in histone modifiers and chromatin remodelers are the most prominent risk factors in autism and other neurodevelopmental disorders. Targeting epigenetic enzymes for the alleviation of autism-associated symptoms provides a promising therapeutic avenue.

Methods: Mutant mice with the deficiency of highly penetrating autism gene *Shank3* or *Cul3* were used to examine the epigenetic mechanism-based treatment strategies for autistic phenotypes. Combined electrophysiological, biochemical, genomic, epigenomic, and behavioral assays were employed.

Results: We found that histone lysine 4 dimethylation (H3K4me2), a histone mark linked to gene activation, is significantly decreased in the prefrontal cortex (PFC) of autistic human patients and mutant mice with *Shank3* or *Cul3* deficiency. A brief treatment of the autism models with highly potent and selective inhibitors of the H3K4me2 demethylase LSD1 (KDM1A) leads to the robust rescue of core symptoms of autism, including social deficits and repetitive behaviors. Concomitantly, LSD1 inhibition restores NMDA receptor function in PFC and AMPA receptor function in striatum of *Shank3*-deficient mice. Genome-wide RNAseq and ChIPseq reveal that treatment of *Shank3*-deficient mice with the LSD1 inhibitor restores the expression and H3K4me2 occupancy of downregulated genes enriched in synaptic signaling and developmental processes. The immediate early gene tightly linked to neuronal plasticity, *Egr1*, is on the top list of rescued genes. The diminished transcription of *Egr1* is recapitulated in PFC of autistic human patients. Overexpression of *Egr1* in PFC of *Shank3*-deficient mice ameliorates social preference deficits.

Conclusions: These results have for the first time revealed an important role of H3K4me2 abnormality in ASD pathophysiology, and the therapeutic potential of targeting H3K4me2 demethylase LSD1 or the downstream molecule *Egr1* for ASD.

Disclosure: Nothing to disclose.

16.2 Role of H3.3K27me1 and H3.3K27me2 in Conferring Susceptibility to Stress Across the Lifespan

Angélica Torres-Berrio

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Background: A life history of stress is the strongest risk factor for several psychiatric disorders. Early life stress (ELS) in particular is known to "scar" the brain, leading to increased susceptibility to developing depression later in life. These effects are linked to persistent transcriptional alterations in brain regions involved in mood regulation and cognitive control (e.g. prefrontal cortex, PFC, and nucleus accumbens, NAc). Here, we characterized the long-lasting changes to histone modifications induced by ELS in the

mouse PFC and NAc and assessed their role in mediating life-long behavioral and transcriptional alterations.

Methods: We exposed male and female mice to ELS by combining maternal separation and reduced bedding or to Standard (Std) conditions from postnatal day (PND) 10 to PND 17. PFC and NAc tissue was collected at PND21, PND35 and PND60 ($n=5$, pooled tissue from 2 mice; per group, sex and age) and processed for histone profiling via mass spectrometry. In parallel, an independent cohort of ELS exposed mice was subjected to subthreshold social defeat (SSD) in adulthood. Social interaction and cognitive flexibility were assessed as readouts for stress susceptibility ($n=8$; per group). We profiled the genome-wide enrichment of the most abundant histone modifications using CUT and RUN.

Results: ELS alters the methylation (me) dynamics of lysine (K) 27 of the histone variant H3.3—the predominant form of H3 present in the adult brain. We observed increased abundance of H3.3K27me1 and decreased abundance of H3.3K27me2 in the adult PFC and NAc of ELS exposed mice. H3.3K27me1 is primarily enriched in gene bodies and proximal promoters, suggesting a crucial role in determining stress-induced transcription. In contrast, H3.3K27me2 is weakly deposited in intergenic regions. Our behavioral results confirmed that mice with previous story of ELS exhibit high social avoidance following adult exposure to SSD. Remarkably, while ELS impairs cognitive flexibility in females regardless of adult SSD exposure, only ELS, in combination with SSD, affects cognitive flexibility in males.

Conclusions: Our results suggest that H3.3K27me1 and H3.3K27me2 are important epigenetic “scars” that mediate life-long susceptibility to stress in the PFC and NAc. Indeed, H3.3K27me1 and H3.3K27me2 alterations persist into adulthood, long after ELS has ceased. Using viral tools, we are now manipulating H3.3K27me1 and H3.3K27me2 dynamics to assess their impact on ELS-induced behavioral alterations. Further bioinformatic analysis will reveal the functional role of genes where H3.3K27me1 and H3.3K27me2 are deposited.

Disclosure: Nothing to disclose.

16.3 Histone Deacetylases in Adults With Autism Spectrum Disorder: A PET-MRI Study

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Background: Genetic studies, genome-wide acetylome analyses, and environmental risk factors strongly implicate histone deacetylases (HDACs) in autism spectrum disorder (ASD) etiology and pathophysiology. HDACs, epigenetic enzymes that reduce acetylation levels, are known to alter mRNA levels of neuronal and synaptic genes. Preclinical models have demonstrated that altered HDAC levels and altered acetylation underlie social deficits in ASD models, and that symptom amelioration is seen as a response to postnatal administration of HDAC inhibitor drugs. Despite the evidence that HDACs are implicated in disease etiology and pathophysiology and may represent a therapeutic target in ASD, HDACs have so far not been investigated in vivo in individuals with ASD.

Methods: Individuals with ASD (5 males, 2 females, mean age = 26.1 ± 6.9 years) and age- and sex-matched controls (CON) (5 males, 2 females, mean age = 26 ± 5.2 years) underwent a simultaneous PET-MRI scan with [11C]Martinostat, which binds HDAC 1, 2 and 3. Individuals with ASD met DSM-5 diagnosis of ASD, corroborated by Autism Diagnostic Observation Schedule, second edition (ADOS-2) and Autism Diagnostic Interview-Revised

(ADI-R). PET data were collected from 60 to 90 minutes post radiotracer injection. Behavioral assessments were conducted to assess language, social and restrictive/repetitive behaviors, and included the Peabody Picture Vocabulary Test, the Aberrant Behavior Checklist, Social Responsiveness Scale, and Repetitive Behavior Scale. Whole brain voxelwise analyses were conducted to compare [11C]Martinostat uptake between ASD and CON groups and correlate behavioral scores with [11C]Martinostat uptake in ASD.

Results: Compared to neurotypical controls, individuals with ASD exhibited regional alterations in HDAC levels. Adults with ASD had higher HDAC levels in the bilateral visual cortex and lower HDAC levels in several regions including bilateral anterior and middle cingulate cortices, right Heschl's gyrus, right middle temporal gyrus, right globus pallidus, and right amygdala ($Z > 2.3$, p cluster < 0.05). Significant associations were observed between regional HDAC levels and behavioral scores, particularly social skills.

Conclusions: In adults with ASD, in vivo imaging reveals altered regional levels of HDACs, including in brain regions associated with socio-emotional processing and previously implicated in ASD such as cingulate cortex and amygdala. This demonstrates that in adulthood HDAC expression is altered in ASD compared to age- and sex-matched controls.

Disclosure: Nothing to disclose.

16.4 Imaging of Epigenetic Mechanisms in Brain Health and Disease: A Roadmap for Neurodevelopmental Studies

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Background: Polygenetic risk for brain disease, regardless of diagnostic category, has disease specificity but provides limited information about manifest disease at the individual patient level. Environmental factors, which can have greater sensitivity, provide insights into individual risk, but have limited disease specificity. Epigenetic regulatory mechanisms may integrate polygenetic and environmental risks but are difficult to measure in the brain due to an inability to sample at a single time point, much less as a function of neurodevelopment, maintenance and neurodegeneration. Molecular imaging has the potential to provide insights into epigenetic regulation across lifespan and as a function of disease to connect genetic predisposition to disease manifestation and importantly to help understand the relevance of animal models of human brain disease mechanisms. The first human neuroepigenetic imaging agent, [11C]Martinostat, measures the density of class-I histone deacetylases (HDACs), which have a profound ability to regulate cell phenotypes, and downstream behavior and disease, has been used to explore human brain ageing, sex differences and brain disease (e.g. schizophrenia, bipolar disorder, and Alzheimer's disease). Given the critical involvement of class-I HDACs in fetal neurodevelopment, [11C]Martinostat imaging has the potential to elucidate epigenetic dysregulation that may contribute to neurodevelopmental disorders. This presentation will integrate previous studies with [11C]Martinostat and provide preliminary data related to its use in neurodevelopment in the non-human primate fetal brain.

Methods: [11C]Martinostat and simultaneous PET-MRI scanning in humans ($n=76$) was used to characterize the relationships between [11C]Martinostat distribution volume, regional uptake and variables including age, sex and disease. Ex vivo tissue from non-human primate (NHP) fetal brain was analyzed by RNA sequencing and immunohistochemistry for comparison to preliminary imaging data from in vivo pregnant NHP fetal brain.

Results: HDAC regional density, measured by [11C]Martinostat uptake, increases with age in periventricular white matter (PVM)

and is negatively correlated with age-associated alterations in PVM microstructure. Relative HDAC expression was lower in the DLPFC of patients with schizophrenia compared with controls, and HDAC expression positively correlated with cognitive performance scores across groups. Lower [11C]Martinostat uptake was found in the right amygdala of individuals with bipolar disorder. HDAC density in the NHP fetal brain increases with gestational age and preliminary studies indicate the feasibility of [11C]Martinostat imaging in brain development.

Conclusions: Epigenetic imaging holds the potential to measure gene regulatory mechanisms over life and as a function of disease in the human brain. HDAC imaging with [11C]Martinostat is one of many potential imaging concepts that can be applied to connect genetic and environmental disease risk. With further development and innovation, neuroepigenetic imaging may help explain disease conversion encoded as early as in the fetal brain.

Disclosures: Eikonizo Therapeutics: Stock/Equity (Self)

Psy Therapeutics, Fuzionaire Diagnostics, Delix Therapeutics, Sensorium Therapeutics: Advisory Board (Self)

Sanofi-Aventis, Abata Therapeutics, FogPharma: Consultant (Self)

Expesicor, Atai Life Sciences: Grant (Self).

PANEL

17. Clinical Trials Addressing Comorbidity

17.1 Doxazosin in the Treatment of Co-Occurring Alcohol Use Disorder and Posttraumatic Stress Disorder Among Veterans: A Randomized Clinical Trial

Sudie Back

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Background: Posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD) are among the most prevalent mental health concerns in the U.S., particularly among military Veterans. Co-occurring PTSD/AUD is associated with poorer treatment outcomes and numerous deleterious health outcomes such as medical problems and impairment in family, social, and vocational functioning. Research on pharmacological treatments for co-occurring PTSD/AUD has been limited and no efficacious medications have yet to be identified. Preclinical and clinical studies of doxazosin, an alpha-1 noradrenergic antagonist, among individuals with AUD or PTSD show reductions in alcohol use and PTSD severity. Doxazosin has not been fully evaluated, however, among individuals with co-occurring PTSD and AUD.

Methods: This 12-week, double-blind, placebo-controlled randomized trial evaluated the efficacy of doxazosin (16 mg/day, immediate release formulation) among 144 Veterans with current PTSD and AUD. Doxazosin was initiated at 1 mg/day and titrated up to 16 mg/day over 5 weeks. Placebo capsules were packaged in color-matched, opaque, identically sized capsules. All participants were receiving behavioral services from the local VA or affiliated community-based outpatient clinics. A subsample of participants who completed the study also completed functional magnetic resonance imaging (fMRI) scans at pre-treatment to examine reactivity to personalized alcohol, trauma, and neutral cues.

Results: Participants (84.7% male, mean age 45.9 years, 55.6% non-White, 67.4% Army) reported consuming alcohol on 51.0% of days, with 37.8% being heavy drinking days. Clinician Administered PTSD Scale (CAPS-5) and PTSD Checklist (PCL-5) scores at baseline were 33.3 and 47.1, respectively. Retention was good

(75.7%) and doxazosin was well tolerated. There were significant overall reductions (main effects of time, $p < .0001$) in percent days drinking (43%) percent days heavy drinking (71%), CAPS-5 (22%) and PCL-5 scores (31%) with no differences between medication groups. Findings from the neuroimaging component revealed that stronger connectivity between the right amygdala and regions of the prefrontal cortex at baseline was associated with more pronounced decreases in PTSD symptoms and alcohol related outcomes during treatment ($B_s = 14.84-174.86$; $p_s = 0.01-0.10$), but this effect was not moderated by medication group.

Conclusions: Support for the safety and tolerability of doxazosin was observed. However, the current findings do not support the use of doxazosin to treat co-occurring PTSD/AUD. Future work will examine pre-treatment moderators of response (i.e., blood pressure, alcohol withdrawal symptom, family history density of AUD) to elucidate possible selective efficacy for doxazosin and these findings will be included in the presentation. The neuroimaging findings, although preliminary, may inform future treatment development for this challenging comorbidity.

Disclosure: Nothing to disclose.

17.3 Efficacy of Combination Therapy With Varenicline and Nicotine Patch for Smoking Cessation in Heavy Drinkers: A Randomized Controlled Trial

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Background: Smokers with concurrent heavy alcohol drinking and alcohol use disorder (AUD) fare poorly in tobacco cessation using standard of care treatment (patch + counseling) than light and non-drinkers. Pharmacotherapies that reduce both smoking and drinking behaviors may be important to boost clinical outcomes for this subpopulation. Varenicline tartrate is an approved smoking cessation medication and may be a good candidate in combination therapy with nicotine patch in heavy drinking/AUD smokers.

Methods: We conducted a double-blind, placebo-controlled randomized clinical trial in 122 heavy-drinking smokers to evaluate the efficacy of varenicline (vs. placebo) plus nicotine patch for smoking cessation. Medication started one week before the target quit date at 0.5mg once daily for 3 days, 0.5mg twice daily for 4 days, and 1mg twice daily on the quit date and the ensuing 12 weeks of treatment. Nicotine patch started on quit day and continued daily at dosing levels recommended by the manufacturer for 10 weeks. Brief cognitive-behavioral counseling focus on smoking (alcohol drinking was not a focus of therapy) and included a 45-minute session prior to the quit date and a 15-minute booster session on the quit date.

Results: Participants (mean 44.0 years, 45% female, 54% non-White) reported 11.6 cigarettes/day with 25.2 years smoking duration with 24.7 alcoholic drinks/week, 33% heavy drinking days, and 56% with past year AUD. Retention was high as 109 participants (89%) completed treatment. For the primary outcome, cigarette abstinence during weeks 9-12, varenicline was superior to placebo (44% vs 28% placebo; OR = 2.2, 95% CI = 1.01-4.80, $p < 0.05$) as well as for continuous abstinence across treatment in survival analysis (26% vs 13%, respectively; Hazard Ratio = 0.61, 95%CI = 0.40-0.96, $p < 0.05$). There was a 50% reduction in alcoholic drinks consumed per week time and percent heavy drinking days (time, $p_s < .05$) with no differences between the groups. The combination of varenicline and patch was well-tolerated, but sleeping difficulties were more common with varenicline (51% vs. 25% placebo, $p < 0.01$).

Conclusions: The addition of varenicline to nicotine patch treatment significantly improved smoking outcomes vs. patch

alone, supporting the use of combination pharmacotherapy in smokers with co-occurring heavy alcohol use. Heavy-drinking smokers also showed sharp reductions in drinking behavior regardless of pharmacotherapy approach, and showed very high rates of retention. The results may help reduce the historic disparity in smoking cessation, and the adverse health consequences and premature death associated with chronic smoking and heavy drinking.

Disclosure: Nothing to disclose.

17.4 Efficacy of Combining Varenicline and Naltrexone for Smoking Cessation and Drinking Reduction: A Randomized Controlled Trial

Lara Ray

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Background: Pharmacological treatments that can concomitantly address cigarette smoking and heavy drinking stand to improve healthcare delivery for these highly prevalent co-occurring conditions. This superiority trial tested the combination of varenicline plus naltrexone versus varenicline alone for smoking cessation and drinking reduction among heavy drinking smokers. To elucidate neural mechanisms of medication effects, exploratory analyses examined medication effects on neural responses to alcohol cues in a subset of participants.

Methods: This was a phase 2, randomized, double-blind, clinical trial. Participants ($n = 165$) were daily smokers who drank heavily and received either (a) varenicline tartrate 1 mg twice daily plus naltrexone 50 mg once daily, or (b) varenicline tartrate 1 mg twice daily plus matched placebo pills for 12-weeks. Primary outcomes were (a) 7-day point prevalence of nicotine abstinence bioverified by breath carbon monoxide (CO) reading of ≤ 5 ppm at the 26-week follow-up, and (b) drinks per drinking day during the 12-week treatment phase. A subset of participants completed an fMRI alcohol cue-reactivity task and rated their in-scanner alcohol craving and were compared to a placebo medication group (culled from a parallel trial). Whole-brain analyses examined the effect of medication on alcohol cue-elicited neural response.

Results: Smoking abstinence at week 26 was significantly higher in the varenicline plus placebo condition than the varenicline plus naltrexone condition ($n = 37$ [45.1%] versus $n = 22$ [26.5%]; $\chi^2[1] = 6.22$, $p = .015$). For drinks per drinking day, there was a trend towards a main effect of medication [$\beta = 0.86$, $SE = 0.44$, $t(1,250) = 1.94$, $p = .054$], favoring the combination of varenicline plus naltrexone over varenicline alone across the 12-week treatment phase. For the fMRI analyses, Varenicline plus naltrexone attenuated alcohol cue-elicited activation in mesolimbic regions relative to varenicline alone and to placebo ($Z > 2.3$, $p < 0.05$). The combination varenicline and naltrexone group also endorsed lower in-scanner alcohol craving relative to varenicline alone group ($p = 0.04$).

Conclusions: These findings suggest that smoking cessation and drinking reduction can be concomitantly targeted with pharmacotherapy and that while varenicline alone may be sufficient as a smoking cessation aid in heavy drinking smokers, the combination of varenicline plus naltrexone may confer benefits with regards to drinking outcomes, particularly during the 12-week period of active medication treatment. The neuroimaging analyses provide a preliminary proof-of-mechanism for this combination pharmacotherapy and suggests that naltrexone may be driving the reductions in cue-elicited alcohol craving in the brain.

Disclosure: Nothing to disclose.

STUDY GROUP

19. Are LAI Antipsychotics Really Better Than Orals?

Mark Weiser*, Rene Kahn, Mark Weiser, Jari Tiihonen, John Kane, Wolfgang Fleischhacker, Michael Davidson, Diana Perkins, Iris Sommer, Stephen Marder, William Carpenter

Sheba Medical Center, Ramat Gan, Israel

Study Group Summary: Despite years of studies, the assumption that long acting injectable antipsychotics (LAI) are more effective than (their) oral equivalents in preventing relapse, hospitalization and suicide in schizophrenia, has not been unequivocally demonstrated. Mirror image trials and retrospective registry data support the superiority of LAIs, but the results of randomized prospective trials comparing the two formulations are ambiguous. A common explanation for the discrepant results between the results of these trial designs is that mirror image and retrospective analyses include treatment compliant and non-compliant patients, while prospective trials tend to exclude potentially non-compliant patients, hence obscuring the advantage of LAIs. However, that explanation may not hold up to scrutiny, as will be discussed here.

Drs. Weiser and Tiihonen will present unpublished data from retrospective longitudinal analysis supporting the advantage of depot formulation and Dr. Kane will present data from randomized controlled trials with similar results.

Dr. Fleischhacker will present unpublished results of a prospective, pragmatic randomized trial of 536 patients with schizophrenia, in which oral and depot formulations of aripiprazole and paliperidone were compared to each other, all cause discontinuation being the primary outcome. Dr. Davidson will present data on pros and cons of long-term maintenance treatment with antipsychotics.

Dr. Perkins will present her clinical experience with LAIs, as a proponent of the Health Belief Model used as a conceptual framework for understanding personal health decision making for persons with psychotic disorders.

Dr. Sommer will present details on long acting medication for male and female patients and propose recommendations for dosing and time of injections for pre and post menopausal females.

Dr. Marder will present studies indicating advantages for LAI's for recent onset patients.

Dr. Carpenter will discuss the issue from the perspective of patients, doctors and family members, and will present a critique of the reasons and implications of the conflicting results of clinical trials on this topic.

Disclosure: Nothing to disclose.

PANEL

20. An Answer May Be at Hand: Orexin/Hypocretin Antagonists for Treatment of Opioid Use Disorder

20.2 The Dual Orexin/Hypocretin Receptor Antagonist Suvorexant Reduces Addiction-Like Behaviors in an Animal Model of Fentanyl Addiction

Jennifer Fragale

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Background: The orexin (hypocretin) system is critical for motivated seeking of all drugs of abuse, including opioids. In 2019, the National Institute on Drug Abuse (NIDA) identified the orexin system as a high-priority target mechanism for novel

pharmacological therapies to treat opioid use disorder (OUD). Suvorexant (Belsomra™) is a dual orexin receptor 1/orexin receptor 2 (OxR1/OxR2) antagonist that is FDA-approved for the treatment of insomnia, and thus has the potential to be readily repurposed for the treatment of OUD. However, studies have yet to test the therapeutic potential of suvorexant with respect to reducing opioid addiction-related behaviors in preclinical models.

Methods: Experiment 1. Adult male Long Evans rats ($n = 19$) were implanted with jugular vein catheters and trained to self-administer fentanyl on an FR-1 schedule. Following self-administration training, animals' economic demand for fentanyl was assessed on a behavioral economics (BE) procedure. After achieving stability, rats were given suvorexant (0, 10 mg/kg or 30 mg/kg, ip) 30 min prior to BE testing using a within-subjects design.

Experiment 2. Next, the efficacy of suvorexant on several addiction-relevant behaviors including fentanyl demand, punished responding, and cue-induced reinstatement was tested in rats with a history of intermittent access (IntA) to fentanyl, a preclinical model of drug addiction that has been shown to increase addiction-related behaviors and is orexin-dependent. Rats ($n = 8$) from Experiment 1 were given IntA (6 hr sessions with 5 min access to fentanyl every 30 mins) for 14 days. Following IntA training, the efficacy of suvorexant (0, 10 mg/kg or 30 mg/kg; ip) was tested on the addiction-relevant behaviors mentioned above.

Experiment 3. Suvorexant is used to treat insomnia and increase sleep when administered prior to the onset of the inactive period. Therefore, the effect of suvorexant (0 and 30 mg/kg; ip) on general locomotor reactivity was tested in a novel environment and low-effort (FR-1) responding for sucrose in rats with a history of fentanyl self-administration.

Results: Experiment 1. In rats with limited drug experience, suvorexant decreased motivation for fentanyl on a BE task (rm-ANOVA with Holm-Sidak's post hoc 0 v. 30, $p = 0.003$). This effect was greatest in rats with the highest motivation for fentanyl (rm-ANOVA with Holm-Sidak's test, 0 v. 30, $p = 0.035$).

Experiment 2. Suvorexant was even more effective at decreasing motivation for fentanyl following IntA self-administration, when motivation for drug was highest (paired samples t-test, 10 mg/kg, $p = 0.026$; 30 mg/kg, $p = 0.027$). Suvorexant also attenuated punished responding for fentanyl (paired samples t-test, 0 v. 30, $p = 0.005$) and reduced cued reinstatement (rm-ANOVA with Holm-Sidak's test 0 v. 10, $p = 0.01$; 0 v. 30, $p = 0.005$) in IntA rats.

Experiment 3. Suvorexant did not affect general locomotor activity (independent samples t-test, $p = 0.281$) or sucrose self-administration (paired samples t-test, $p = 0.108$), indicating that as used here suvorexant can reduce drug seeking with limited sedative or off-target effects.

Conclusions: Together, these results highlight the therapeutic potential of suvorexant, particularly in individuals with severe OUD.

Disclosure: Nothing to disclose.

20.4 Dual Orexin-Receptor Antagonist Effects on Sleep, Opioid Withdrawal, and Craving in Persons With Opioid Use Disorder

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Background: There is an urgent need to develop novel pharmacotherapeutic approaches to improve opioid use disorder (OUD) treatment outcomes. Insomnia is a major recalcitrant problem for persons in OUD recovery. There is strong evidence from preclinical studies that orexin receptor antagonists can improve sleep, opioid withdrawal, and drug seeking outcomes, yet there are no published studies on orexin antagonists in humans with OUD. This randomized-controlled trial compared two doses of suvorexant (SUVO; 20mg and

40mg) to placebo in persons undergoing a buprenorphine taper. The primary aims examined whether SUVO versus placebo improved total sleep time (TST) and/or showed potential for abuse; the secondary aim examined whether SUVO versus placebo improved opioid withdrawal outcomes; exploratory aims examined opioid craving and the degree to which SUVO dose impacted outcomes to inform subsequent trials.

Methods: Individuals with OUD who were seeking supervised withdrawal were recruited for a 10-night residential study (clinical trials registration: NCT03789214). The study ran from June, 2019 to May 2021 but was suspended between March and October of 2020 due to COVID-19. All participants were initially inducted and maintained on 8-16mg buprenorphine for three days, then randomized to either placebo, 20mg, or 40mg SUVO before starting a 4-day buprenorphine taper and 4-day post-taper period. Each night participants wore a 3-lead electroencephalography (EEG) device to monitor sleep, and completed daily ratings of abuse potential (e.g., 0-100 visual analogue scale [VAS] of feeling "High" after taking medication), opioid withdrawal (Subjective Opioid Withdrawal Scale; SOWS), and 0-100 VAS "Craving". Chi-square analysis was utilized to assess differences in treatment attrition, intent-to-treat analyses were performed using independent-samples t-tests for differences between SUVO (collapsed across dose) and placebo during the taper and post-taper period, and one-way ANOVAs were used to assess differences between all three medication groups.

Results: Participants ($N = 38$) were 86.8% male, 52.6% white, and had a mean (SD) age of 41.5 (11.3). Participant attrition was not significantly different between placebo (33.3%), 20mg ($n = 35.7\%$), and 40mg ($n = 25.0\%$) groups. During the buprenorphine taper, participants on SUVO versus placebo displayed a mean (SE) improvement of 91.2 (36.5) minutes in TST ($t(36) = -2.50$, $p = .017$, $d = .86$), no difference in VAS High ($t(36) = .26$, $p = .795$, $d = .09$), a marginal reduction of 2.3 (2.4) in mean (SE) SOWS ($t(36) = 1.00$, $p = .325$, $d = .35$), and a mean (SE) reduction of 16.7 (8.1) in VAS craving ($t(36) = 2.07$, $p = .046$, $d = .70$). During the post-taper period, participants on SUVO versus placebo displayed marginal mean (SE) improvement of 57.6 (30.3) minutes in TST ($t(31) = -1.90$, $p = .067$, $d = .74$), no difference in VAS High ($t(32) = -.93$, $p = .36$, $d = .38$), a mean (SE) reduction of 4.5 (2.1) in SOWS ($t(32) = 2.17$, $p = .038$, $d = .76$), and a marginal mean (SE) reduction of 14.6 (9.3) in VAS craving ($t(32) = 1.57$, $p = .13$, $d = .54$). ANOVAs revealed no differences between the 20mg and 40mg doses of SUVO.

Conclusions: This preliminary, dose-finding study demonstrated initial efficacy for SUVO in improving sleep duration, decreasing craving during opioid tapering, and improving post-taper withdrawal severity, with no evidence for abuse risk in persons with OUD. Given the lack of differences between 20mg and 40mg SUVO doses, future RCTs are needed to examine the FDA-approved dose of 20mg SUVO to confirm its efficacy in treating sleep disturbances, opioid withdrawal, and craving in persons with OUD.

Disclosure: National Institute on Drug Abuse, National Heart, Lung, and Blood Institute, Ashley Addiction Treatment: Grant (Self).

PANEL

21. Prediction of Response to Evidence-Based Treatment for Major Depression: Whither the Holy Grail for Clinical Practice? New Evidence and New Controversies

21.2 Multimodal Imaging Biomarkers of Response, Relapse and Resistance in Major Depression

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Background: The evolution of treatment resistant depression (TRD) remains a major clinical challenge with no clear biomarkers to predict patients at increased risk after initial failed response to a first-line antidepressant treatment. These patients often face a protracted trial-and-error treatment course with decreasing response rates as the number of med trials increases. Extending past studies demonstrating distinct resting state fMRI patterns that predict differential remission and failure to SSRI and CBT in treatment naïve MDD patients (1), imaging patterns predictive of treatment response and failure to antidepressant medication (ADM) at different stages of illness were examined to identify brain states that might inform the evolution of TRD.

Methods: Structural and resting state functional MRI scans were acquired in 304 currently depressed patients (95M/129W) from 3 independent clinical trial cohorts (1-3) on a single scanner (Siemens 3T Tim-Trio) using an identical imaging protocol. MDD patients were grouped by past-Tx exposure (184 Tx-naïve, 56 past ADM, 29 past ADM + ECT, 35 controls). Total hippocampal volumes (corrected for total intracranial volume) were measured using Freesurfer. Functional connectivity (FC) was measured using bilateral hippocampus (HC) seeds. The stages of MDD were defined by the number of past treatments. One-way ANCOVA with age, gender as covariates, was performed to examine group differences ($p < 0.05$ for volume, corrected $\alpha < 0.05$ for FC). Post hoc analyses considered chronicity and response status within and across groups (uncorrected $p < .001$).

Results: All patient groups showed smaller right hippocampus volumes compared to healthy controls

without differences among the groups ($F = 2.86$, $p = .037$). In contrast, differential patterns of HC-FC were found across the groups despite similar HC atrophy. HC-right subcallosal cingulate (SCC) connectivity was increased in the two cohorts with past treatments but normal in treatment naïve patients ($F = 6.22$, $p < .001$). In contrast, HC-posterior cingulate (PCC) connectivity was increased exclusively in the patients with multiple past treatment failures including ECT ($F = 7.43$, $p < .001$).

Conclusions: These results demonstrated a mismatch between functional and structural abnormalities in the hippocampus as a function of the number of past treatments. The pattern suggests progressive change in key limbic nodes within known resting state functional networks as treatment resistance evolves, providing putative new biomarkers for identifying patients at risk for this illness course at presentation of new depressive episodes.

References:

1. Dunlop. Am J Psychiatry, 2017. 174: 533-45
2. McGrath. JAMA Psychiatry, 2013. 70: 821-9
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Disclosure: Abbott Labs: Patent, Consultant (Self).

PANEL

22. Innovative Approaches to Measuring Reward-Punishment Conflict

22.1 Sex Differences in Dopaminergic Modulation of Punishment-Based Risky Decision Making

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Background: Psychiatric diseases characterized by elevated risk taking are differentially represented in males and females. Progress towards understanding the relationship between psychiatric disorders and risk taking is constrained, however, by our limited knowledge regarding sex differences in risk taking. As a

first step toward addressing this gap, we have shown that females are more risk averse than males in a rat model of punishment-based risk taking. These sex differences likely arise from differential recruitment of neural substrates that govern such cognitive processes, such as the basolateral amygdala (BLA). Not only is the BLA necessary for biasing choice away from risky options, it is also sexually dimorphic in both structure and function. Intriguingly, D2 dopamine receptor (D2R) expression in the BLA is greater in females than males. This is notable because risk taking is exquisitely sensitive to D2R modulation in a sex-dependent manner. We therefore hypothesized that sex differences in risk taking may be a product of differential sensitivity of D2Rs in the BLA.

Methods: In Experiment 1, male ($n = 8$) and female ($n = 7$) rats were implanted with bilateral cannulae targeting the BLA and trained in a risky decision-making task in which rats chose between a small, "safe" food reward and a large, "risky" food reward accompanied by varying probabilities of mild footshock. Rats then received intra-BLA microinfusions of the D2R agonist quinpirole (0.0, 1.0, 10.0 μ g) and tested in the task. We used a randomized within-subjects design such that each rat received each dose of quinpirole. Procedures in Experiment 2 (males, $n = 8$; females, $n = 6$) were identical to those in Experiment 1 except that the D2R antagonist eticlopride (0.0, 0.1 and 1.0 μ g) was microinfused into the BLA. Dependent variables were percent choice of the large, risky reward (risk taking) and win-stay and lose-shift behavior. A three-factor repeated measures ANOVA was used to analyze the effects of quinpirole and eticlopride on risk taking. A two-factor repeated measures ANOVA was used to analyze changes in win-stay and lose-shift behavior as a result of D2R manipulations.

Results: In Experiment 1, analyses revealed a significant interaction between sex and dose on the effects of quinpirole on risk taking. Although there was no effect of quinpirole on risk taking in males, both the low and high dose decreased risk taking in females. This increase in risk aversion in females was accompanied by a decrease in win-stay behavior and an increase in lose-shift behavior, indicating that activation of D2Rs in the BLA decreased sensitivity to rewarding outcomes and increased sensitivity to aversive outcomes, respectively. In contrast to quinpirole, eticlopride did not impact risk taking in either sex.

Conclusions: These data reveal that D2R activation in the BLA promotes risk averse behavior through an enhancement in sensitivity to outcomes associated with punishment. Importantly, however, this mechanism appears to be dependent on sex, as D2R activation decreased risk taking only in females. Consequently, these findings suggest that differences in D2R sensitivity may account for greater risk aversion in females. Previous work has shown that estradiol not only regulates female risk taking, but also modulates BLA activity. Future experiments will therefore determine whether differences in D2R sensitivity related to risk taking are due to estradiol's modulatory influence on BLA function.

Disclosure: Nothing to disclose.

22.2 Investigating the Impact of Delayed Vs Immediate Punishment on Economic Decision-Making

Nicholas Simon

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Background: Optimal decision-making requires assessment of the positive and negative outcomes elicited by all available options. Importantly, negative consequences are not always immediate, often occurring long after a decision has been made. Despite the prevalence of delayed consequences in "real-world"

decision-making, basic research investigating the mechanisms of cost/benefit conflict has almost exclusively utilized consequences that immediately follow a decision. To this end, we developed the Delayed Punishment Decision-making Task (DPDT) to compare the impact of immediate vs delayed punishment on reward seeking. This presentation describes a series of experiments revealing the behavioral and neural factors regulating sensitivity to delayed punishment.

Methods: Male and female Long-Evans rats were trained in DPDT, which measures choice between 1 vs 3 pellets with the large reward accompanied by a mild shock. As the task progresses, delay between the decision and shock is enhanced across the session (0, 4, 8, 12, 16s). We compared decision-making across sexes, assessed the effects of cues bridging the gap between action and outcome on decision-making, and compared sensitivity to delayed punishment with delayed reward. Finally, we tested DPDT following inactivation of lateral orbitofrontal cortex (OFC) or basolateral amygdala (BLA), brain regions implicated in decision-making during reward/punishment conflict as well as reward delay discounting.

Results: DPDT revealed that rats underestimate, or “discount”, the negative value of delayed punishment. This was reflected as initial avoidance of the punished reward, followed by a shift in preference toward the punished reward with increasing punishment delay ($n = 20$; $F(5,40)=2.53$, $p = .044$). Males were more likely to choose rewards associated with delayed punishment than females ($n = 10$ /group; $F(2.327,41.879)=3.090$, $p = 0.049$), and adding a cue bridging the gap between the decision and punishment reduced discounting ($n = 20$; $F(1,17)=16.012$, $p = 0.001$). Critically, preference for delayed punishment was not correlated with preference for delayed rewards ($n = 17$; $r = -0.049$, $p = 0.852$). Bilateral inactivation of OFC reduced choice of rewards associated with delayed but not immediate punishment ($n = 10$; $F(5,40)=2.53$, $p = .044$). Reversing the order of delays resulted in a comparable discounting curve, suggesting that OFC's effects were not caused by inability to adapt to changes in task contingencies ($n = 8$; $F(5,30)=2.58$, $p = .047$). Inactivation of BLA did not affect sensitivity to delayed punishment ($n = 9$; $F(5,35)=1.29$, $p = .252$).

Conclusions: These experiments demonstrated that rats reliably underestimate the value of delayed negative consequences, and identified OFC, but not BLA, as a neural substrate underlying delayed punishment discounting. This represents the first step toward understanding how the brain processes delayed punishment invoked by reward seeking, which is critical for treating suboptimal cost/benefit decision-making in psychiatric disorders.

Disclosure: Nothing to disclose.

22.3 Translation of Anxiety Into Actions by Prefrontal Cortex Neurons

Bitá Moghaddam

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Background: Learning that routine goal-directed actions are associated with a risk of punishment is critical for development and expression of anxiety. To model this scenario, we have been designing and characterizing rodent behavior tasks where actions taken toward obtaining a reward are probabilistically punished with a mild shock. Our recently published work (Jacobs et al, J. Neurosci 2020; Park et al, eLife 2017) have shown that performance in these paradigms is sensitive to diazepam indicating relevance of this behavioral model to anxiety. Using electrophysiological recording after task learning we are observing

a bottom up relationship between ventral tegmental area (VTA) dopamine and prefrontal cortex (PFC) neurons that encodes the risk of punishment selectively during action execution. Here, we will present these data in addition to addressing questions on whether VTA and PFC neurons adapt to learning of punishment risk in correlation with behavior, and how diazepam or psilocybin influence these neural responses.

Methods: Behavioral paradigm and statistical analyses of data is as described in Jacobs et al, J. Neurosci 2020 and Park et al, eLife 2017. Multiwire electrodes were used to record from neurons in VTA and PFC. In addition, fiber photometry was used to measure population neural activity in VTA and PFC because this method allowed us to quantify PFC and VTA neural response to the shock itself. This was critical in order to distinguish adaptive neural responses to receiving versus expecting an aversive experience. Behavioral training and recording data included both male and female rats with sufficient power ($n > 10$ for each sex) to determine sex differences in results.

Results: We find that behavior of male and female animals, as measured by trial completion and action latency changes after 1-2 sessions exposure to punishment risk ($P < 0.01$). This form of learning is accompanied by a downward shift in phasic neural activity in PFC and upward shift in VTA, primarily during the peri-action period ($p < 0.005$). Response to the shock, however, did not change during learning with shock eliciting similar and robust activation of neural activity in PFC and VTA in both sexes. Diazepam or psilocybin did not change the phasic neural response of PFC or VTA to the shock indicating that pain or sensory perception of the aversive event is not responsible for its anti-anxiety effects. These drugs, however, significantly, and selectively, attenuated the peri-action phasic response of VTA neurons and correlative activity of VTA-PFC. Pre-stimulus activation of VTA neurons has been linked to preparatory attention and outcome anticipation. Reduction of this response may lead to attentional disengagement from harm probability and provide a mechanism for anti-anxiety properties of diazepam and possibly psilocybin.

Conclusions: Our findings provide a novel approach for modeling learned anxiety in laboratory animals. Using this approach, we found that anxiolytic treatment enhances VTA encoding of action selection and restores coactivity between VTA and PFC thus identifying a network mechanism for anxiolytic properties of these drugs.

Disclosure: Nothing to disclose.

22.4 Decision-Making Under Motivational Conflict

Gavan McNally

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Background: Foraging animals balance the need to seek food and energy against the conflicting needs to avoid injury and predation. This competition is fundamental to survival, but it rarely has a stable, correct solution. Appropriate solutions vary across spatial (danger proximity) and time (diurnal, seasonal) scales as well as internal states (hunger, thirst). Finding these solutions requires decision-making processes to rapidly match sensory information about the world to stored knowledge about reward or danger and support adaptive behaviour. Much is known about the brain correlates of reward - danger interactions, but the fundamental structure, dynamics, and mechanisms of decision-making during conflict are poorly understood. Here we addressed these issues by combining microstructural analysis of behavior with computational modelling of decision-making and fibre photometry of calcium transients.

Methods: Thirsty mice were trained in a linear track to approach a goal to obtain liquid sucrose. Then, conflict in the

form of footshock was introduced at the goal. We studied the microstructure of behaviour under this conflict, used Bayesian inference to estimate key decision variables, and used fibre photometry to relate paraventricular thalamus (PVT) and ventral hippocampal calcium transients to these decision variables.

Results: Behavior during motivational conflict was bistable and frequently interrupted by ventral hippocampal initiated pauses, well described by positively skewed, log-normal distributions with means proportional to their standard deviations and trade-off between the decision speed and outcome. During these pauses, modelling showed that evidence accumulated in favor of one outcome (e.g., reward) or another (e.g., danger) and once this evidence passed a threshold, mice approached or avoided until the next pause. The rate of evidence accumulation varied dynamically across space, so that approach but not avoid decisions were sensitive to the proximity of danger and PVT was central to this evidence accumulation. There were also strategic adjustments in response caution across space. Most caution was exercised closest to the goal. Together, these dynamic changes in decision-making generated a unique, bistable, behavioural phenotype whereby mice oscillated between the relative safety of the start box and the relative danger of the goal.

Conclusions: Decisions about whether to approach or avoid a reward source whilst under the threat of danger and predation must be made quickly and accurately. Sequential sampling is a highly efficient, domain-general solution to the problem of fast, accurate decision-making that uses a common mechanism to explain both decision outcome and decision time. We show that decision-making during motivational conflict in mice has the hallmarks of a sequential sampling mechanism that is shared by human (e.g., bistable perception, visual hallucinations, word versus non-word recognition) and non-human primate (e.g., motion perception) decision making, with PVT and ventral hippocampus serving complementary roles in this decision-making.

Disclosure: Nothing to disclose.

PANEL

23. Examination of Underlying Vulnerability and Long-Term Impacts of COVID-19 on Brain Health

23.3 Lasting Neurological Consequences of COVID-19 Infection: MRI Findings in Prenatally Exposed Infants and Self-Reported Mood and Cognitive Findings in Adults

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Background: The majority of what is known about neurological aspects of COVID-19 has been derived from data aggregated from clinical tertiary care centers, involving the most severely infected cases. For the >150M people worldwide infected with more mild forms of COVID-19, there is little or no information that addresses prevalence of lasting emotional and neurocognitive effects. Knowledge about ongoing symptoms following recovery from acute illness is needed to inform treatments for so called "long-haulers". Another important area for research is the potential impact of maternal prenatal infection on fetal brain development. While vertical transmission rates are low, maternal response to disease and to treatment may alter the intrauterine environment in ways that are relevant to fetal growth.¹ Here we investigate the prevalence of mood and cognitive complaints in a wide range of patients that have recovered from COVID-19, and we compare

neural functional network development in infants born to mothers that were or were not infected with COVID-19 during pregnancy.

Methods: The Novel Coronavirus Illness Patient Report (NCIPR) survey (DR2 ID: 24224) was used to obtain a proximal record of illness. 2,212 adults ages 18-98 provided electronic informed consent and completed the NCIPR on-line Feb-April 2021. After implementing data validation, 2,158 NCIPR surveys were retained for further analyses. We examined (i) establish frequency and type of lasting complaints, (ii) to evaluate the effect of sociodemographic determinants on lasting symptoms, and (iii) to test the impact of illness severity on neural and non-neural lasting symptoms. A separate study was conducted to address the impact of maternal prenatal COVID-19 infection on infant brain MRI outcomes. Data collection for the infant MRI study are ongoing with analyses to be completed in the future.

Results: 70.6% of COVID-19 infected individuals report any form of lasting symptom after recovery from primary infection and 44% report that changes in general health persist 10 weeks or longer. The most frequent lasting complaints reported are fatigue (38.76%), change in taste (23.42%), change in smell (19.70%), and mood symptoms (19.38%), all of which are neurological in nature. Anxiety was the most frequently reported mood symptom (57.5%) in those that endorsed lasting mood impacts. Short-term memory (29.15%) and attention (24.04%) were the most common reported lasting cognitive complaints in the 26% of the full sample that endorsed presence of any form of lasting cognitive or memory problem. Hierarchical linear regression results suggest there are deterministic patterns in who is most likely to manifest lasting symptoms after recovery from COVID-19. Specifically, minority identity, lower education, and illness severity are associated with more lingering symptoms following COVID-19 infection ($p < 0.0001$). Infant brain MRI studies continue to be collected and will be analyzed prior to presentation of these results.

Conclusions: Our data provide clear evidence that secondary lasting neurological effects are a consequence of COVID-19, and confirm that lasting neural symptoms accompany even mild forms of illness. Data also call attention to specific areas that patients identify as most problematic, specifically anxiety and executive function. Data also show that differences in lasting symptoms relate to sociodemographic factors and illness severity, which are critical to understand as knowledge about cause can inform development of therapeutic interventions and prevention in the future.

Disclosure: Nothing to disclose.

STUDY GROUP

24. Challenges and Opportunities for Translational Research and Clinical Strategies Within the LGBTQIA2S+ Community

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Study Group Summary: Research regarding the mental health of the Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual, 2 Spirit (LGBTQIA2S+) community has been historically biased by individual and structural homophobia, biphobia, and transphobia, resulting in findings that does not represent the best quality science. For example, bias research can occur when researchers conceptualize human experience in strictly heterosexual terms. Furthermore, much of this research does not serve the best

interests or priorities of LGBTQIA2S+ communities given that such research does not meet their needs. Significant mental health disparities are seen in the LGBTQIA2S+ community and a great need for quality mental health research and treatments in are needed specifically targeting these populations. In this panel, we will address this timely issue by describing current approaches toward understanding research and health disparities, and mechanisms toward clinical treatment strategies. Dr. Roepke, an expert on such research disparities, will highlight how preconceptions and bias in the literature have resulted in missed opportunities for advancing understanding of mental health within LGBTQIA2S+ people. This study group will also present up-to-date research on mental health disparities facing the LGBTQIA2S+ community and targeted treatment strategies, as well as provide guidance from health care professionals. Importantly, research will be presented from both preclinical (Dr. Anacker - an expert on preclinical studies on hormone treatment), and clinical perspectives (Dr. Ehrensaft - an expert researcher on clinical transgender affirmation in youth), with the aim of providing common language and research priorities from a translational perspective. The impact of historical and present day ciscentrism and structural transphobia in transgender mental health research will be covered from both clinical research (Dr. Edmiston) and translational research (Dr. Guthman) perspectives, with suggestions for future directions to improve the quality of this field. Finally, we will address current this research strategies drive best practices for treatment of mental health issues in this community (Dr. Eshel - a researcher and expert in treatment development research). This study group will provide an opportunity to dispel myths regarding the LGBTQIA2S+ community as well as inform the ACNP community of best practices to work with this community in an equitable manner. This study group will provide a launching point to tie preclinical and clinical research leading to treatment strategies for adversities faced within the LGBTQIA2S+ community.

This Study Group has numerous forms of diversity. Every member is part of the LGBTQIA2S+ community, with representation from the Gay, Bisexual, and Transgender communities. The study group includes multiple gender identities and expressions and includes women discussants. Moreover, there is a wide range of professional levels represented, with Professors, Associate Professors, Assistant Professors, and Post-Doctoral Scholars. Further, a range of interaction with the College is also represented; only the Chair is a Fellow, while some have attended meetings, and others have never attended.

Disclosure: Nothing to disclose.

PANEL

25. The Developmental Origins of Mental Health: Mechanistic Insights From Longitudinal Studies in Humans and Model Organisms

25.1 Fetal Origins of Epigenetic Aging

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Background: There is compelling evidence that the quality of the prenatal environment predicts individual differences in mental health across the lifespan; with increasing examples of sex-specific effects. Our previous work demonstrates that heightened maternal prenatal anxiety doubles the risk for a probable mental disorder, effects that emerge in early childhood and persist through adolescence. We currently lack a biomarker of exposure

to prenatal adversity that could inform our understanding of such individual differences.

Methods: Longitudinal cohorts provided 1,113 DNA methylomes used to describe pediatric epigenetic aging from distinct developmental periods spanning birth to 10 years of age. Participants were drawn from cohorts from the Netherlands (BIBO: $N=165$, 47% Female) and Singapore (GUSTO: $N=340$, 49% Female), which also provided data on maternal prenatal anxiety (Spielberger State/Trait Anxiety Inventory). Measures of epigenetic age acceleration were calculated using the PedBE clock and benchmarked against an established multi-tissue epigenetic predictor.

Results: Generalized estimating equations revealed that maternal prenatal anxiety predicted PedBE epigenetic age acceleration in both cohorts with effects restricted to males (BIBO: $\text{Est}=0.042$, $p=1.58\text{E-}04$; GUSTO: $\text{Est}=0.004$, $p=4.19\text{E-}04$) and not females (BIBO: $\text{Est}=-0.001$, $p=0.908$; $\text{Est}=0.002$, $p=0.206$). These results were independent of obstetric, socioeconomic, and genetic risk factors, and specific to prenatal anxiety. In turn, an epigenetic biomarker of glucocorticoid exposure associated with pediatric epigenetic age acceleration in a sex-specific manner, implicating hypothalamic pituitary adrenal axis activity in pediatric epigenetic aging (Males BIBO: $r=-0.28$, $p=0.01$; GUSTO: $r=-0.28$, $p<0.01$; Females BIBO: $r=-0.14$, $p=0.24$; GUSTO: $r=-0.08$, $p=0.41$).

Conclusions: Our results point to the fetal origins of epigenetic aging, revealing an increased sensitivity in males, and highlight the PedBE clock as a new tool to probe the biological embedding of prenatal adversity. These findings have clear implications for programs of early intervention, which target maternal prenatal mental health as a mechanism to improve child outcomes.

Disclosure: Nothing to disclose.

25.2 Early Life Stress Effects on Prefrontal Cortical Plasticity and Reward-Seeking Behavior

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Background: Depression is a fundamentally episodic form of mental illness, yet the neurobiological mechanisms underlying the induction and remission of depressive episodes over time are not well understood. Early life stress is among the most established risk factors for depression, but it is unclear how early life stress influences depression susceptibility in adulthood, especially at the level of neural circuits.

Methods: In both male and female mice, we used two-photon microscopy, calcium imaging, and novel optogenetic tools to investigate how early life stress influences prefrontal cortical synaptic remodeling and transitions between depression-like behavioral states in a two-hit chronic stress model and after antidepressant-dose ketamine treatment.

Results: The induction of depression-related behavior is associated with clustered, branch-specific elimination of post-synaptic dendritic spines on prefrontal projection neurons ($P=0.004$, Wilcoxon), mediated in part by a mineralocorticoid receptor-, transcription-dependent signaling process. Early life stress modulates stress susceptibility and reward-seeking behavior in adulthood through effects on dendritic spine remodeling. Antidepressant-dose ketamine reverses stress effects on prefrontal synapses by selectively rescuing eliminated spines ($P=0.001$, Wilcoxon) and restoring coordinated activity in multicellular ensembles that predict motivated escape behavior ($t=4.34$, $P<2\text{e-}5$). Using two novel behavioral paradigms for quantifying effortful reward-seeking behavior and cognitive flexibility ($N=9\text{--}12$ mice/group), we show that these ensembles play a critical role in encoding reward-predictive environmental cues and

feedback monitoring. Using behavioral interventions and optogenetic tools to bidirectionally modulate the survival of newly formed spines, we show that ketamine-induced synapse formation is required for the long-term maintenance of selected antidepressant behavioral effects ($P = 0.002$, Wilcoxon), but not for their induction.

Conclusions: These results define a previously unappreciated, causal role for prefrontal synaptogenesis in sustaining antidepressant effects on selected depression-related behaviors and suggest new avenues for optimizing interventions aimed at enhancing and maintaining remission after ketamine treatment. They also define a circuit-level mechanism by which early life stress influences stress susceptibility in adulthood.

Disclosure: Delix Therapeutics: Advisory Board (Self).

25.3 Effects of Early Life Adversity on Cortico-Limbic Serotonin Receptors in a Nonhuman Primate Model: Role in Adolescence Anxiety and Drug Use

Mar Sanchez

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Background: Early life stress (ELS) is linked to anxiety and substance use disorders, although the neurodevelopmental mechanisms are still poorly understood. We have been studying the long-term effects of ELS on the development of stress, emotion and reward neurocircuits, and how these neurobiological alterations underlie impaired stress and emotional regulation and increased risk for psychostimulant abuse during adolescence using a highly translational nonhuman primate ELS model. Here we focused on the alterations in cortico-limbic systems that regulate stress, emotion and reward/dopamine regions; in particular, prefrontal connectivity with amygdala and nucleus accumbens and levels of serotonin (5HT) receptors in these regions.

Methods: We will present recent findings from 25 adolescent macaques (11 Control -6 females, 5 males-, 14 ELS -6 Females, 8 Males-), where we examined their anxiety levels using measures of baseline acoustic startle amplitude used as a translational biomarker of anxiety across humans and animal models. Due to its role in emotional/stress regulation, prefrontal serotonin (5HT) 1A and 2A receptor binding potential (BP) was also examined using PET imaging during adolescence.

Results: ELS animals, particularly females, showed elevated levels of anxiety during adolescence, measured as higher acoustic startle responses than in Controls. We found alterations in prefrontal functional connectivity with amygdala and nucleus accumbens, and lower levels of serotonin (5HT) 1A and 2A receptor binding potential in these regions (using PET imaging). More importantly, lower levels of 5HT receptors in cortico-limbic regions was associated with increased anxiety and cocaine intake; as an example, there was a significant negative correlation between prefrontal 5HT_{1A} receptor BP and baseline startle amplitude ($r = -0.481$, $p = 0.0173$), such that reduced BP was predictive of increased baseline startle amplitude, consistent with human studies on anxiety and depression. Additional interesting relationships are being examined between alterations in prefrontal 5HT receptors and psychostimulant intake.

Conclusions: Our findings suggest ELS-related developmental alterations in cortico-limbic 5HT receptors that link increased risk for anxiety and psychostimulant abuse during adolescence and that can serve as potential targets for personalized treatment.

Disclosure: Nothing to disclose.

25.4 Gene Network by Early Environment Interactions: Role on Neuropsychiatric and Cardiometabolic Comorbidities

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Background: Cardiometabolic and psychopathological conditions share a developmental neurobiological origin, which may explain the high rates of co-morbidity in adulthood. The quality of the early life environment is a major determinant of the risk for adult chronic disease with evidence for both endangering effects of adversity and a protective influence of optimal conditions. Despite the strengths of these associations, individuals vary considerably in their sensitivity to both adverse as well as optimal environmental conditions, reflecting individual differences in "biological sensitivity to context". This study aimed to define the biological basis for such individual differences in environmental responsiveness.

Methods: RNA sequencing of ventral hippocampal dentate gyrus (vDG) in C57BL6/J male mice was used to identify transcripts commonly regulated in response to two different contexts: environmental enrichment or chronic social defeat stress to define "environmentally responsive" (EnResp) genes. Six hundred eighty-eight single nucleotide polymorphisms (SNPs) in the human orthologs of EnResp genes were used to compute a polygenic score (EnResp-ePGS). We examined whether variation in the vDG-specific EnResp-ePGS moderated the association between the environment and psychopathology in human cohorts at different ages (males and females, from children to adults in studies varying from 122 to 65,555 participants). As early adversity appears to influence cardiometabolic and psychopathological health outcomes through imbalance in inflammatory processes, we also investigated if the EnResp-ePGS predicted the temporal pattern of salivary cytokines (IL-6, IL-1 β , and IL-8) secretion in children. These data were analyzed using linear or logistic regression in R.

Results: 18 genes were differentially expressed in the same direction in response to both environmental enrichment and chronic social defeat compared to control. These differentially expressed genes were deemed environmentally responsive irrespective of the valence of the environmental condition. We then examined whether variation in the vDG-specific EnResp-ePGS calculated from these genes moderated the association between the environmental score (ranging from more adverse to more supportive) and anxiety and depression phenotypes in human cohorts. In the Canadian MAVAN cohort, the EnResp-ePGS significantly moderated the relationship between the environmental score and Anxiety Problems at 5 years old ($\beta = 0.29$; $\beta SE = 0.13$; $p < 0.05$). Simple slopes analysis revealed that among individuals with a high, but not a low EnResp-ePGS, Anxiety Problems increased as environmental adversity increased (β high = -0.38 ; $\beta SE = 0.10$; $p < 0.001$). These same associations with mood and anxiety disorders were replicated in independent cohorts of children, adolescents and adults. The ePGS was also positively associated with the stable high (OR = 1.66 [1.12-2.66], $p = .019$), and low to average (OR = 1.62 [1.12-2.54], $p = .018$) cytokine profiles.

Conclusions: The molecular underpinnings responsible for environmental responsiveness in mice predict a greater propensity to develop psychopathological symptoms in humans in a context dependent manner. Genetic environmental responsiveness was also associated with temporal pro-inflammatory cytokines profiles, suggesting a potential of targeting individuals at greater risk for poorer physical health.

Disclosure: Nothing to disclose.

MINI PANEL

26. Using Novel Dyadic Data to Elucidate Brain-Behavior Mechanisms of Maternal and Child Risk Factors for Affective Psychopathology**26.1 Mother-Infant Affective Concordance is Associated With EEG Correlates of Anxiety Risk in the First Two Years of Life****Koraly Perez-Edgar***Penn State University, University Park, Pennsylvania, United States*

Background: Caregiver-infant interactions are a central scaffold for cognitive, social, and emotional development. In typical development, attunement between caregiver and child may act as a conduit for the intergenerational transmission of traits and behaviors. In the case of anxiety, parental anxiety is associated with an elevated risk for child anxiety and is also a predictor of poor treatment response in the child. Distinct parenting behaviors marked by over-protectiveness and intrusiveness can potentiate risk, mediated by the extent to which children observe and internalize parental behaviors, which may be captured by parent-child affective concordance. We investigated mother-infant behavioral affective concordance at 8 mos and infant resting EEG longitudinally to examine relations with delta-beta coupling and alpha asymmetry over time. Delta-beta coupling captures the coordinated activity between subcortical and cortical brain systems involved in emotion regulation. Over-coupling is linked to a rigid behavioral phenotype and increased anxiety risk. Alpha asymmetry captures underlying motivations to withdraw (increased right asymmetry) and approach (increased left asymmetry) and is also associated with anxiety (right asymmetry). We predicted that mother-infant affective concordance would be positive, reflecting general attunement in the mother-infant relationship. We predicted that weaker concordance in mother-infant affect would be related to heightened delta-beta coupling and to greater right frontal alpha asymmetry.

Methods: Families were drawn from a multisite longitudinal study examining infant temperament and attention in a diverse community sample. Mother-infant dyads engaged in a 5-min interaction at 8 mos and were coded by observers trained to reliability. Affect for mother and infant was coded independently, and then synchronized for concordance. EEG measures were derived from 4 minutes of rest recorded at 8, 12, 18, and 24mos. Asymmetry was derived from relative alpha band power in frontal EEG sites, with delta-beta coupling derived from time series modeling at central EEG sites.

Results: Average affective concordance was significant and positive across the sample ($B = 0.42$, $p = .001$). Concurrent analyses indicated that mother-infant affective concordance was weaker for infants with heightened delta-beta coupling at central sites ($B = -1.04$, $p = .041$) and for infants with right asymmetry. Mother-infant dyads characterized by increases in affective concordance across the interaction had infants with increasing trajectories of delta-beta coupling from 8-18 mos. Region of significance analyses indicated that mother-infant affective concordance that became weaker and decoupled predicted a linear decrease in frontal alpha asymmetry, suggesting a developmental shift towards right asymmetry. Dyads with increases in affective concordance had a developmental shift towards left asymmetry.

Conclusions: Individual differences in mother-child interactions may influence broad patterns of neural development. These patterns, in turn, may lay the developmental foundation for early psychopathology risk and later emergence of anxiety-specific

symptoms. Final analyses will investigate affective concordance associations with maternal anxiety and child internalizing symptoms at 24mos.

Disclosure: Nothing to disclose.

26.2 Positive Affective Synchrony is Time Linked With Neural Synchrony in Mother-Child Dyads**Judith Morgan***University of Pittsburgh, Pittsburgh, Pennsylvania, United States*

Background: Mother-child positive affective behavior, characterized by shared positive emotion, affectionate touch, and harmonious play, serves to foster learning and exploration and to buffer against stress. Indeed, empirical research and theoretical models suggest that, during the first years of life, in which self-regulation occurs via external means, mother-child synchronization of positive affective behavior may facilitate regulation of homeostatic systems (e.g., heart rate, hormone expression). However, less research has evaluated whether mother-child synchronization of positive affective behavior is related to synchronization of neural systems, particularly those implicated in the regulation of affect and social processes. Early neurodevelopment of regulatory regions is important, as their altered functioning has been implicated in multiple psychiatric disorders. In the current study, we evaluated whether mother-child moment-to-moment matching of positive affect was associated with synchronized brain activity in frontal and parietal regulatory regions.

Methods: Participants were 44 mother-child dyads (59% girls) enrolled in an ongoing study. Children were on average 24.82 months old (range = 10- to 42-months-old). All mothers and children had no history of psychiatric illness. Mothers' and children's brain activity were assessed simultaneously using near-infrared spectroscopy (NIRS) while engaging in dyadic play with an age-appropriate toy. Independent coders trained to a high level of reliability observed the interaction and coded the presence of mother positive affect and child positive affect in 5-second increments separately. For each dyad, epochs were grouped to characterize periods in which (1) mothers and children matched on high levels of positive affect (2) matched on low/no positive affect or (3) showed a mismatch in positive affect (e.g., mother or child showed high positive affect, other dyad member showed low positive affect).

Results: Permutation tests revealed that greater positive affective synchrony (mother and child showed similarly high levels of positive affect) was related to greater neural synchrony in medial frontal, lateral frontal, and inferior parietal regions ($q_s < .01$). Post-hoc tests confirmed that synchrony of high levels of positive affect was associated with stronger neural synchrony in these regions of interest relative to synchrony of low/no levels of positive affect ($q_s < .01$). Future analyses will examine synchrony in dyads with maternal depression.

Conclusions: Mother-child dyadic interactions during early childhood that are characterized by high levels of affective state matching (e.g., shared smiling, coordinated vocalizations) appear to also be associated with synchronized brain activity in regions implicated in social cognition, bonding, and affectionate touch. Findings suggest that positive, synchronous mother-child interactions may serve to foster greater neural responding in frontoparietal regions, with implications for adaptive self-regulation and interpersonal bonds. Thus, targeting such dyadic interactions might be an avenue for the prevention of forms of childhood

psychopathology characterized by impaired social and affective regulation.

Disclosure: Nothing to disclose.

26.3 Intergenerational Effects of Maternal Depression on Brain Structure, Function and Child Psychopathology

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Background: Maternal depression is a robust intergenerational risk factor—contributing a 2-4-fold greater risk for psychiatric disorders among offspring and also increasing risk for deficits in cognitive control processes. Unknown is whether maternal depression has intergenerational effects on the structure and function of control circuits in mothers and their school-age offspring, contributing to the emergence or escalation of childhood psychopathology. We thus took a dyadic approach to understanding the effects of maternal depression on the structure and function of these circuits, as well as the impact on child internalizing and externalizing symptoms.

Methods: Multimodal MRI data were acquired from 40 mother-child dyads enrolled in an ongoing study. Children were mean=7.51 (SD = 1.02) years old and mothers were mean=31.35 (SD = 6.22) years old. Mothers self-reported on their lifetime and current depression symptoms (Mini-KID and the Center for Epidemiological Studies Depression Scale [CES-D]) and their child's symptoms (Child Behavior Checklist). Structural data were processed using Freesurfer; RSfMRI networks were processed with the DECAN pipeline and components isolated using FSL Melodic Independent Component Analysis (ICA) before components were extracted and examined within dyads and in relation to psychopathology, controlling for age, sex, race, and ethnicity.

Results: Maternal depression (lifetime) associated with thinner left inferior frontal gyrus (IFG) in both the mothers ($b = -.66$, $t = -2.14$, $p = .04$, $n = 36$) and children ($b = -1.08$, $t = -3.85$, $p < .001$, $n = 40$). Thickness of IFG in the mothers marginally predicted thickness in their children ($t = 1.77$, $p = .08$), and thickness in children mediated the relationship between maternal depression and child externalizing symptoms ($p = .02$, $n = 33$). Resting state fMRI analyses revealed that current maternal depression associated positively with frontal-DMN connectivity in mothers ($t = 3.69$, $p = .001$; i.e., weaker anti-correlation). Further, frontal-DMN connectivity in mothers predicted frontal-DMN connectivity in children ($t = 3.35$, $p = .003$) and associated positively with their internalizing symptoms anxiety ($t = 3.38$, $p = .003$) and Obsessions/Compulsions [$t = 4.66$, $p = .000$].

Conclusions: Maternal depression is associated with both structural and functional alterations in control circuits in both mothers and their children, with similar patterns for mothers and children in some cases. This intergenerational effect of maternal depression on brain structure-function in offspring may contribute to both externalizing and internalizing symptoms. These findings point to the importance of studying mother-child dyads to identify the effects of maternal depression on child outcomes, a meaningful advance from child-only studies of brain structure/function. These findings also set the stage for future research aimed at targeting control circuits for the prevention of child psychopathology. Data collection is ongoing and subsequent analyses in a larger sample will relate dyadic structure-function to both lifetime and current maternal depression, controlling for additional variables (e.g., poverty, trauma) that are often associated with brain, maternal depression, and child psychopathology.

Disclosure: Nothing to disclose.

MINI PANEL

27. Effects of Race-Related Stressors on Neurophysiology in Black Adults: Putative Neurobiological Pathways for Race-Related Health Disparities

27.1 Associations of Racial Discrimination With Brain Structure and Function in Trauma-Exposed Black American Women

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Background: Racism-related stressors such as racial discrimination are thought to increase risk for adverse brain health outcomes in Black Americans, but little is known about the direct effects of these stressors on the brain. The objective of this study was to examine associations of RD with brain (white matter) structure and function in a sample of trauma-exposed Black American women.

Methods: One hundred sixteen Black American women aged 18-62 years were recruited as part of the Grady Trauma Project, a long-standing study of trauma and posttraumatic stress disorder (PTSD) in inner-city Atlanta, Georgia. Participants completed assessments of racial discrimination, trauma exposure, and PTSD and completed diffusion-weighted MRI; fractional anisotropy (FA) values were extracted from major white matter tracts throughout the brain. Fifty-five participants also performed an Affective Stroop task during functional MRI. Regression analyses were performed to examine unique associations between racial discrimination experiences, response to threat-relevant images (Stroop) and FA after accounting for other potentially contributing factors, such as trauma exposure and PTSD.

Results: In response to threat-related cues in the Affective Stroop, racial discrimination was associated with significantly increased response in the ventromedial prefrontal cortex ($p < .05$ with voxelwise FWE); this finding remained significant after controlling for PTSD and trauma exposure. With respect to white matter microstructure, racial discrimination was negatively correlated with FA throughout the brain ($ps < .004$), even after accounting for PTSD, trauma exposure, and poverty; correlations were particularly strong for the corpus callosum, anterior cingulum bundle, and superior longitudinal fasciculus ($ps < .001$).

Conclusions: These findings suggest that, even after accounting for other potential contributing factors, racial discrimination was robustly associated with increased function in modulatory brain regions as well as decrements in white matter microarchitecture across a number of pathways. Results suggest that the chronic stress of racial discrimination may lead to heightened engagement of emotion regulation/cognitive control resources; over time, this increased modulation of emotion may serve to degrade white matter connections. I will discuss how these findings suggest a pathway through which racial discrimination may increase risk adverse brain health outcomes in Black Americans.

Disclosure: Nothing to disclose.

27.2 Racial Disparities in Neighborhood Disadvantage and Brain White Matter Microstructure During Late Childhood

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Background: Adverse and negative life experiences can have deleterious effects on threat-related neurocircuitry that plays a

role in adult psychopathology. However, there are significant racial/ethnic disparities in exposure to negative life experiences such that Black children are disproportionately burdened compared to White children. Limited research to date has investigated the potential for these disparities to produce race-related differences in white matter pathways that support threat processes during childhood.

Methods: Diffusion tensor imaging (DTI) and demographic data from Black and White children in the Adolescent Brain and Cognitive Development (ABCD) study ($n=9,382$) were used to investigate race-related differences in threat processing related white matter pathways. Fractional anisotropy (FA) and mean diffusivity (MD) values from canonical threat pathways (e.g., cingulum bundle and uncinate fasciculus) were extracted as indices of white matter microstructure. We assessed race-related differences in FA and MD of these tracts and the relationship between white matter microstructure and neighborhood disadvantage indexed via the area deprivation index (ADI). We further assessed differences in racial discrimination during childhood that may be related to white matter microstructure.

Results: Of participants that answered yes or no, more Black children reported experiencing racial discrimination compared to White children and Black children had greater ADI scores compared to White children. Black and white children showed significant differences in FA of threat-related circuitry such as the parahippocampal cingulum which has previously been linked to trauma and stress-related disorder psychopathology. Multiple regression models including child race and ADI showed significant relationships of both ADI and race on between parahippocampal cingulum. Follow-up models did not reveal significant race by ADI interactions, but sub-sample analysis including racial discrimination and potential interactions only revealed significant effects of ADI on FA.

Conclusions: Our results complement a growing literature on the impact of structural inequities on the brain. Neighborhood disadvantage appears to directly affect neurocircuitry known to play a role in threat-related processes and may contribute to race-related differences in the microstructure of these tracts. The disparate levels of disadvantage between Black and White children may partially explain differences in white matter microstructure of the parahippocampal cingulum which is known to be important for posttraumatic stress disorder and other trauma related psychopathology. Further longitudinal work is needed to fully disentangle the neurobiological consequences of racial structural inequities.

Disclosure: Nothing to disclose.

27.3 The Effects of Racism Across the Life Course: Mechanisms of Depression Linking Social Influences With Methylation-Based Health Indicators Among Black Americans

Sierra Carter

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Background: Black youth often confront environments besieged with reduced opportunities, financial obstacles, environmental toxicity, and a societal legacy of oppression that affects many aspects of their daily lives. This can produce early and sustained stress, potentially “weathering” youth by accelerating their epigenetic aging and inducing behavioral and biological changes that influence health outcomes many years later. Repeated experiences of stress related to racism is believed to result over time in physiological changes that may be deleterious to physical health. Depressive symptoms may be a marker of feelings of defeat, aloneness, and coping that is inadequate to situational demands, leading to physical dysregulation. Although experiences

of racism-related stressors are common among Black youth and associated with worse mental health there is an overreliance on cross-sectional designs that raise important questions about the direction of these effects as well as the persistence of the effects over time to effect physical health outcomes. This presentation will discuss study findings among 360 Black youth that longitudinally examined: (1) associations between early life racial discrimination and depressive symptoms, testing within-person concurrent/lagged effects; (2) early life racial discrimination forecasting young adult depression (age 20-29) and the emergence of latent classes membership linked to both early discrimination and multifaceted indices of cellular-level accelerated aging.

Methods: The study sample will include Black youth participants (Mean approximate age at first wave=10.9; with follow up assessments waves at approximately age 15, 20, and 29) from the longitudinal Family and Community Health Study. Self-report interviews included demographic characteristics, experiences of racial discrimination, and depressive symptoms. Biomarkers were extracted from antecubital blood draws from participants at age 29.

Results: Results revealed that there were significant positive within-person concurrent associations at all longitudinal waves of the study, indicating that at times when Black youth reported experiencing more racial discrimination than they typically did, they also reported more depressive symptoms than they typically did. In contrast, the within-person lagged association from depressive symptoms to racial discrimination was not significant. Wald tests indicated that the significant within-person lagged path from racial discrimination to depressive symptoms was significantly stronger than the non-significant path from depressive symptoms to racial discrimination (Wald $\chi^2(1)=8.949, p < .01$). With regard to further analyses related to accelerated aging, early life experiences of racial discrimination did forecast young adult depression and the emergence of a latent class of Black youth with sustained depressive symptoms (vs. lower levels of depressive symptoms) at age 20-29 that was a significant mechanism towards accelerated aging at age 29.

Conclusions: The current study provides a preliminary guide to the development of prevention-oriented interventions by investigating the importance of incorporating racism-related stress assessment, and chronic depressive symptoms, in efforts to maximize treatment benefits for Black youth. The current research findings also set the stage for examining resilience to racial discrimination and the factors that may help protect against the development of chronic elevation in depressive symptoms across young adulthood.

Disclosure: Nothing to disclose.

PANEL

28. Prenatal Programming of Neurodevelopment and Mental Illness Risk

28.1 Key Role for Maternal Microbes in Prenatal Neuroinflammation and Subsequent Social Behavior

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Background: Preclinical, Clinical, and Epidemiological studies show that exposure to prenatal stress has long term deleterious consequences on offspring including neuroinflammation and altered behaviors. Increasing attention is focused on the maternal

microbiome as contributors to neuroinflammatory changes through immunomodulatory pathways. Microglia have emerged as essential players in neurodevelopment, and whether microglia shift to a pro-inflammatory phenotype with prenatal exposures, such as stress, is an open question. In this study we address the contribution of maternal microbial changes on fetal microglia number and function.

Methods: Pregnant C57/BL6 females were randomly assigned to stressed or non-stressed control group. The stressed group was restrained between embryonic day (E) 10-E16. Placentas and fetal brains were collected on E17.5. Microglia were isolated. RT-PCR, immunohistochemistry, and multiplex ELISA were used to examine inflammation levels. A second cohort of pregnant females was treated with antibiotics to deplete microbes during pregnancy and prenatal stress.

Results: Prenatal stress lead to increased number of microglia in the fetal hippocampus, as measured by IBA-1+ staining ($n = 8-10/\text{group}$; $p < 0.05$). In addition, there was an increase in levels of the pro-inflammatory cytokines IL-1 β and IL-6 in fetal microglia ($n = 8-10/\text{group}$; $p < 0.05$) exposed to prenatal stress. This increase in cytokine production was evident in adult microglia as well ($n = 7-14$ animals, $p < 0.05$). Antibiotic treatment depleted maternal microbes ($p < 0.001$) and prevented increased fetal neuroinflammation.

Conclusions: Utilizing prenatal stress in a rodent model, we have demonstrated disruptions in microglial inflammation and function in utero, which are microbe dependent and which may contribute to alterations in adult behaviors and contribute to psychiatric illness.

Disclosure: Nothing to disclose.

28.2 Lasting Effects of Preconception Stress on Placental Adaptation and Offspring Neurodevelopment

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Background: Lifetime adversity, such as experiencing recurrent stressors, trauma, or discrimination, prior to conception is a predictor of adverse perinatal and offspring neurodevelopmental outcomes. However, little is known about the biological mechanisms involved in storing, maintaining, and perpetuating this signal across generations. The cumulative effects of stress experienced across the lifespan precipitate a state of chronic stress termed allostatic overload. As pregnancy is a time of incredible metabolic demand, increased preconception allostatic load may impair maternal adaptation to pregnancy and ultimately have detrimental effects on offspring development. We have developed a novel mouse model of maternal preconception stress (MPS) where female, but not male, offspring are hypersensitive to stress as adults. We hypothesize that the increased metabolic demand of pregnancy unmasks latent programming from preconception adverse experiences that alter signaling at the maternal:fetal interface, leading to changes in offspring neurodevelopment in a sex-specific manner.

Methods: Adult female mice were exposed to chronic multimodal stress from 4-10 weeks of age, prior to mating. Maternal blood, placentas, and fetal brains were collected at embryonic day 12.5, coinciding with full differentiation of the placenta and development of the hypothalamus, to assess lasting effects of MPS on gene expression at the maternal:fetal interface. Extracellular vesicles (EVs) were also isolated from maternal plasma and assessed for protein content both at baseline and during pregnancy. The placenta is the major contributor of EVs in maternal circulation allowing a unique window in placental signaling from circulation.

Results: MPS dams exhibited a dramatic shift in EV protein content toward proteins involved in metabolism, specifically cellular and glucose metabolism. These changes were mirrored in the transcriptional signatures MPS placentas, but more pronounced in males. Given the involvement of glucose metabolism in the placenta and the sex specificity of the adult phenotype, we investigated the involvement of O-GlcNAc transferase (OGT) and its associated protein modification. MPS placentas reduced O-GlcNAcylation, specifically in annexin A2, a protein abundant in the placenta, secreted EVs, and associated with defects in decidualization and preeclampsia. Within the fetal compartment, MPS offspring brains reduced expression of genes involved in neuronal development relative to controls. As a major determinant of nutrient availability and fetal development, changes in placental signaling may be mirrored in the fetal compartment. Indeed, MPS males showed increased concordance in gene expression between the placenta and fetal brain relative to MPS females (127 vs 6), which may contribute to the sex-specificity of the adult phenotype.

Conclusions: Taken together, these data suggest a lasting effect of lifetime adverse experiences prior to conception, perpetuate programmatic changes to metabolic signaling in the maternal compartment, ultimately altering placental adaptation to pregnancy and sex-specific fetal brain development at a critical timepoint.

Disclosure: Nothing to disclose.

28.3 Placental Mechanisms Associated With Schizophrenia Risk Genes

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Background: We have previously found that genomic risk for schizophrenia interacts with early life complications (ELCs) associated with placental pathophysiology [PMID: 29808008], and that fractionated genomic risk scores for schizophrenia, based on placental gene-expression loci, are linked with early neurodevelopmental outcomes in individuals with a history of ELCs [PMID: 33558239]. These associations are stronger in males, consistent with a higher expression of the schizophrenia risk genes in placentae from male compared with female offspring. Objective of this study is to identify the genes that, in placenta, mediate the relationship between genomic risk for schizophrenia, ELCs, and neurodevelopmental outcome.

Methods: Full-term placentae RNA-sequencing data ($N = 146$, female=73) and summary statistics from the latest schizophrenia GWAS (PGC3: 69,369 people with schizophrenia and 236,642 controls) were used for:

- the analysis of the relationship between genetic risk for schizophrenia and gene expression in placenta, at the level of specific isoforms (eQTL study);
- Whole Genome Coexpression Network Analysis (WGCNA), to identify placental pathways of convergence of genetic risk for schizophrenia, in the whole sample and stratifying by sex;
- Transcriptome Wide Association Study (TWAS) and Summary-data-based Mendelian Randomization (SMR) to identify placental gene transcripts that could mediate the association of genetic risk factors with schizophrenia, in the whole sample and stratifying by sex.

Results: More than one third of the loci with GWAS-significant associations with schizophrenia ($p < 5e-08$) harbors at least one placental eQTL linked with the genetic risk variants. The vast majority of associated with schizophrenia risk SNPs (~78%) are

placenta specific, because similar associations are not detected in brain. The WGCNA indicates a different architecture of transcript coexpression in males and female placentae, with four and three modules enriched for placental schizophrenia risk genes in male and female placentae respectively. Finally, with the TWAS, we detected 100 genes robustly associated with schizophrenia in placenta in the whole sample (Bonferroni-corrected p -value <0.05), 36 of which were prioritized with eQTL cross-validation (p -value <0.05). The majority of these genes (~94%) were not TWAS-significant in previous analysis in brain. The same analysis stratified by sex highlights 105 (38 prioritized with eQTL cross validation) and 88 (25) TWAS genes in female and male placentae, many of which (57%) are sex-specific. These associations are replicated with same directionality with SMR. The placental genes associated with schizophrenia, and their coexpression modules, are associated with biological processes relevant for the implantation and the development of placenta, such as endoplasmic reticulum response to stress, protein translation and folding, and mTOR signaling.

Conclusions: Our analysis indicates that risk for schizophrenia may unfold through placenta gene expression, implicating biological processes relevant for the early stages of placenta development. The identification of placental mechanisms of risk for schizophrenia can facilitate the development of strategies of prenatal prevention of schizophrenia, aimed at preserving the contribution of placenta to brain development. The use of placental and genomic biomarkers could allow the identification of high-risk individuals, who will benefit from postnatal strategies of prevention, based on interventions aimed at breaking the developmental cascade of events that can lead to schizophrenia.

Disclosure: Nothing to disclose.

28.4 Genetic Patterning for Child Psychopathology is Distinct From Adults and Implicates Fetal Cerebellar Development

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Background: Recent work from our group and others demonstrates the importance of the prenatal environment to risk for psychopathology in childhood. How genetic loading for psychiatric disorders influences such risk in children, including via prenatal mechanisms, remains less clear. Leveraging data from two neurodevelopmental cohorts, the Adolescent Brain Cognitive Development (ABCD) Study and Generation R (GenR) Study, we evaluated effects of polygenic risk scores from the PGC on dimensional psychopathology measures in children, and explored intermediate biological mechanisms through triangulation with gene expression and structural MRI data.

Methods: Unrelated ABCD participants of European ancestry ($n = 4,413$) were genotyped and assessed at age 9-10 across 21 U.S. sites for dimensional child psychopathology (Child Behavior Checklist, CBCL) and underwent structural MRI in 3T magnets with a unified protocol. GenR participants of European ancestry ($n = 1,850$), enrolled in the Netherlands, were genotyped and assessed with CBCL at age 10 and 13. Disorder-specific polygenic risk scores (PRS: Schizophrenia, Depression, Bipolar, Autism, ADHD, Tourette Syndrome, OCD, Anorexia) were calculated using the most recent published PGC summary statistics. Cross-disorder Neurodevelopmental (NDev), Compulsive, and Mood and Psychotic factor PRS were calculated from PGC-based genomic structural equation modeling, as in Lee et al, Cell, 2019. Top genes (FDR $p < .05$) were annotated with FUMA and developmental expression patterns were assessed using BrainSpan data. All ABCD MRI scans were visually inspected by a trained rater and 1,296 were

discarded due to motion or other artifact. Total cerebral cortical, white matter, and subcortical volumes were calculated with Freesurfer, and cerebellar subfield and total gray matter volumes were calculated with SUIT.

Results: In the ABCD cohort, NDev PRS predicted a broad range of dimensional psychopathology (CBCL total score, $p = 2.6E-9$, r^2 change = .008; internalizing, $p = 7.2E-5$; externalizing, $p = 3.4E-8$), with greater sensitivity than disorder-specific or other cross-disorder PRS indices (p 's $< .001$). These findings replicated among 10-year-olds (p 's $< .05$) and strengthened further at age 13 (p 's $< 5.0E-5$) in the GenR cohort. NDev genes were more highly expressed in the cerebellum ($p = 2.1E-7$) than the cerebral cortex ($p = 5.7E-5$). Cerebellar expression of these genes peaked in fetal life, and was significantly higher than at postnatal time points ($p = 4.1E-8$). Among ABCD participants, only cerebellar gray matter volume interacted with NDev PRS to influence CBCL total score, such that CBCL was most sensitive to cerebellar volume among children with increased PRS ($p = .016$). This effect was strongest in midline regions (vermis).

Conclusions: The genetic underpinnings of psychiatric symptoms in school-aged children differ from those underlying adult psychopathology, and their effects are instantiated during fetal brain development. They reflect a neurodevelopmental gene set that predicts a diffuse range of dimensional symptoms, and that shows peak expression in the fetal cerebellum. Longitudinal follow-up of these cohorts will enable a dynamic understanding of how polygenic risk tracks with adolescent brain development and newly emergent symptoms, and the extent to which these patterns reflect prenatal programming.

Disclosure: Nothing to disclose.

PANEL

29. Control-Alter-Delete: Epigenetic and Transcriptional Mechanisms in Reward Circuits and Neuropsychiatric Disorders

29.1 Cell Type-Specific Functions of an Epigenetic Factor in Neuronal Excitability and Drug Seeking Behavior

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Background: Epigenetic factors have emerged as key regulators of circuit adaptations that underlie relapse vulnerability in individuals suffering from substance use disorders (SUDs). Histone deacetylase 5 (HDAC5) in the nucleus accumbens (NAc) is regulated during active cocaine use, and HDAC5 functions in the NAc to limit cocaine seeking behavior triggered by multiple external and internal drug-cues (Taniguchi et al, 2017, Neuron). However, how, when, and where HDAC5 functions within the NAc to regulate gene transcription, circuit plasticity and illicit drug seeking behavior remains unclear.

Methods: We employed the rat heroin intravenous self-administration (SA) model combined with viral-mediated strategies to increase or decrease NAc HDAC5 to examine its effects on context-associated seeking, discrete cued reinstatement or heroin-primed reinstatement of drug seeking in wildtype, D1R-cre or D2R-cre transgenic rats. We used novel, cre-dependent viral constructs to assess cell type-specific roles of HDAC5 in heroin vs. sucrose SA behavior. Cell type-specific gene expression was assessed using cre-dependent vTRAP (viral translating ribosome affinity purification) and microarray analysis from NAc in D1R- or D2R-cre rats. Notable differentially expressed genes (DEGs) were

confirmed independently by qRT-PCR. Ex vivo patch-clamp electrophysiological recordings were performed in D1R vs. D2R-cre rats expressing cre-dependent control vs. nuclear HDAC5 viruses.

Results: Viral-mediated knockdown of NAc HDAC5 (shRNA) had no significant effects on heroin-taking behaviors (acquisition), but it increased drug-paired lever pressing during context-associated seeking (Ext day 1), and after extinction training, it increased both discrete cued and heroin-primed drug seeking. Viral-mediated expression of nuclear HDAC5 in NAc had no effects on heroin-taking behaviors, but it suppressed context-associated seeking (EXT day 1), cued reinstatement, and heroin-primed reinstatement. NAc HDAC5 had no effects on any sucrose SA behavior, including cued and primed reinstatement. Following establishment of stable heroin SA, we observed that NAc HDAC5 failed to suppress any form of drug seeking. Interestingly, cre-dependent expression of nuclear HDAC5 in NAc dopamine D1 receptor-positive medium spiny neurons (D1-MSNs) suppressed cued, but not drug-primed, heroin seeking, whereas nuclear HDAC5 expression in D2-MSNs suppressed drug-primed, but not cued, heroin seeking. vTRAP and microarray analysis of HDAC5 DEGs in D1- and D2-MSNs revealed numerous HDAC5 candidate target genes, including multiple genes linked to neuronal excitability. Consistent with this observation, nuclear HDAC5 expressed in D1- or D2-MSNs reduced intrinsic excitability in both cell types, but without altering glutamatergic synaptic transmission.

Conclusions: Together our cocaine and heroin SA findings reveal that NAc HDAC5 functions to limit the formation and/or strength of memories linking drug experience with diffuse and discrete, external and internal cues. Our findings suggest that HDAC5 specifically regulates illicit drug seeking (opioid and cocaine) without altering natural reward taking or seeking behaviors, and it plays cell type-specific roles in D1- and D2-MSNs to regulate external vs. internal cued drug seeking. Moreover, HDAC5 regulates NAc MSN intrinsic excitability, which presumably permits or regulates drug-specific plasticity in NAc circuitry that underlies drug-cue associations that frequently act as potent triggers of drug seeking and relapse-like behavior.

Disclosures: NeuroEpigenix, LLC: Stock / Equity (Self).
EpiVario: Grant (Self)

29.2 Leveraging Single-Cell Multi-Omics to Identify Coordinated Drug-Responsive Genetic Programs in Brain Reward Circuitry

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Background: Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. However, even with well-studied drugs such as cocaine, drug-induced transcriptional responses remain poorly understood due to the cellular heterogeneity of the NAc, the locus-specific nature of transcriptional and chromatin reprogramming, and complex drug actions via multiple neurotransmitter systems.

Methods: Here, we leveraged single-nucleus RNA-sequencing (snRNA-seq) and Assay for Transposase Accessible Chromatin (snATAC-seq) to generate a comprehensive molecular atlas of cell subtypes in the NAc, defining both sex-specific and cell type-specific responses to acute and repeated cocaine experience in a rat model system. Activity-dependent transcriptional and chromatin dynamics were modeled with bulk RNA/ATAC-seq or snRNA-seq in primary rat striatal neurons after stimulation with dopamine (1 μ M), the Drd1 receptor agonist SKF38393 (1 μ M), or

potassium chloride (10 or 25mM). To test the functional effects of dopamine-regulated gene programs, we engineered a large-scale CRISPR/dCas9 activation strategy and characterized transcriptional and physiological responses using high-throughput electrophysiology (in primary neurons) and locomotor sensitization assays (in vivo).

Results: Using an integrated snRNA-seq transcriptional atlas of the NAc, we identified robust transcriptional responses to acute cocaine in Drd1-expressing medium spiny neurons (MSNs). This cell class harbored more than twice as many differentially expressed genes (232) as any other cluster, including expression of activity-regulated transcripts such as Fos, Fosb, and Junb. In primary striatal neuron cultures, we identified similar transcriptional programs downstream of Drd1 receptor activation or direct neuronal depolarization with KCl. Notably, neuronal activation also produced large-scale chromatin reorganization, with thousands of newly accessible regions marking putative enhancer elements that were heavily enriched for AP1 transcription factor motifs. Next, using multi-omic single-nucleus profiling after repeated cocaine exposure in vivo, we again observed that Drd1-MSNs contained more differentially accessible chromatin regions than all other cell types, with all newly accessible regions containing AP1 transcription factor motifs. Additionally, using combined multi-omic profiling of NAc tissue collected following withdrawal from extended access cocaine self-administration models, we identify enduring cocaine-dependent chromatin changes. Finally, we show that direct activation of a core dopamine-driven gene program with a multiplexed CRISPR strategy initiated a secondary synapse-centric transcriptional profile, altered striatal physiology in vitro, and enhanced cocaine sensitization in vivo.

Conclusions: Taken together, these results define the genome-wide transcriptional response to cocaine with cellular precision, and highlight the mechanisms by which drugs of abuse initiate experience-dependent chromatin remodeling. These findings demonstrate that drug-responsive gene programs can potentiate both physiological and behavioral adaptations to drugs of abuse.

Disclosure: Nothing to disclose.

29.3 Molecular Profiling Across Reward Circuits of the Human Brain Reveals Insights Into Genetic Risk for Substance Use and Neuropsychiatric Disorders

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Background: The hippocampus (HPC), nucleus accumbens (NAc), amygdala (AMY), dorsolateral prefrontal cortex (DLPFC) and subgenual anterior cingulate cortex (sgACC) constitute key nodes of the brain's reward circuitry, and perturbations in reward signaling are well-documented in addiction and neuropsychiatric disorders. While differences in gene expression signatures in these brain regions implicate specific cell types, the molecular composition of these cell populations is not known.

Methods: Data was generated using 10x Genomics single-nucleus RNA-sequencing (snRNA-seq) in frozen postmortem human brain with nuclei purified by flow cytometry using DAPI (and NeuN for a sample subset) staining. After sequencing, data processing and QC, we analyzed a total of 72,057 high-quality nuclei across 23 unique samples in both region-specific and cross-region analyses. We compared snRNA-seq data to available single-cell datasets for corresponding regions in rodent models of behavior to define cross-species convergence and divergence across analogous cell subpopulations. We used Multi-marker Analysis of GenoMic Annotation (MAGMA) to identify human cell subtypes that harbored aggregated genetic risk for

neuropsychiatric and substance use disorders. For single molecule fluorescence in situ hybridization (smFISH), tissue was sectioned at 10 μ m and assays were performed with RNAscope technology.

Results: We generated an atlas of molecularly-defined cell types across human HPC, NAc, AMY, DLPFC and sgACC, which revealed strong patterns of similarities in specific neuronal subclasses across the five regions. Given the lack of single cell profiling resources in human NAc and AMY, we emphasized downstream cross-species comparisons and cell-type specific analyses of genetic risk to these regions. We identified distinct and potentially novel neuronal subpopulations in the human NAc, which we validated with smFISH for various subclasses of interneurons and medium spiny neurons (MSNs). We further identified robust interneuron cell populations in the AMY, including a subset unique to humans. We identified enrichment of region-specific cell subtypes, including stress-associated MSNs, in both neuropsychiatric and substance use disorders.

Conclusions: These data provide additional supporting evidence for involvement of the human NAc and AMY in risk for psychiatric illness by implicating specific neuronal subpopulations. The data highlight potential involvement of an MSN population associated with stress signaling in genetic risk for substance use. Generation of reference spatial transcriptomic data with the 10X Genomics Visium platform for corresponding regions is in progress, and will be used to enhance the snRNA-seq resource with spatial annotations.

Disclosure: Nothing to disclose.

29.4 Epigenetic Priming by H3K4me1 in VTA Confers Hypersensitivity to Future Stress

Catherine Pena

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Background: Early life stress (ELS) sensitizes individuals to experience of future stress. This stress-sensitization, or priming, may be at the root of increased lifetime risk for mood and anxiety disorders among those who experienced childhood maltreatment and other forms of early adversity. Heightened stress sensitivity is a core feature of anxiety and depressive disorders, along with reduced motivation and reward, both of which are regulated by the ventral tegmental area (VTA). Indeed, ELS increases excitability of dopaminergic neurons in VTA of rodents. To study the cellular and molecular correlates of lifelong stress vulnerability, we use a “two-hit” stress paradigm in mice in which a first hit of stress in early life increases susceptibility for depression-like behavior in response to a second stress in adulthood. This latent behavioral vulnerability is accompanied by latent transcriptional alterations in VTA. We hypothesized that such latent transcriptional alterations would be primed by post-translational histone modifications. In particular, histone 3 lysine 4 monomethylation (H3K4me1) is associated with primed chromatin. Several earlier findings indicated increased H3K4me1 in adult male VTA after ELS.

Methods: Levels of H3K4me1 in VTA were determined by Western blot (P21; $n = 7$ males and females each/group) or mod-spec (adult; $n = 3$ pooled male samples/group) in control and ELS mice. In order to test whether increased levels of H3K4me1 mediate ELS-enhanced sensitivity to adult stress, we generated an AAV to overexpress Setd7, an enzyme that monomethylates H3K4. We overexpressed Setd7 or control Gfp in VTA of standard-reared mice at postnatal day 10-15 during the stress sensitive period, allowed mice to mature to adulthood, and then tested them on a battery of behavioral tests including sucrose preference, social interaction, and splash test ($N = 7$ males and 7 females per group). Mice were subjected to sub-threshold social defeat stress and tested again to determine sensitivity to adult stress on the same

behavioral measures. We also performed RNA-seq in adult VTA after Setd7 or GFP expression and control or social defeat stress ($n = 4$ /group inc males and females). We used standard pipelines for alignment and examined differential analysis by DESeq2.

Results: ELS moderately increased H3K4me1 levels in VTA at both acute [P21; $t(1,12)=1.89$, $p = 0.041$] and adult time points ($p = 0.052$), although this effect was specific to males. We validated that our AAV-Setd7 increases both SETD7 protein levels and H3K4me1 in VTA in vivo relative to AAV-Gfp control. Juvenile Setd7 expression in VTA did not alter behavior at baseline. However, there was a significant interaction between juvenile Setd7 overexpression and adult social defeat stress exposure on social interaction ratio [$F(1,23)=4.41$, $p = 0.047$], such that social interaction was significantly reduced after subthreshold defeat among male and female mice with VTA Setd7 overexpression ($t(1,12)=3.92$, $p = 0.002$). Setd7 overexpression increased positive gene expression response to social defeat stress compared to defeated GFP mice.

Conclusions: Early life stress promotes a more open/permissive chromatin state in the VTA associated with transcriptional priming. Mimicking early life stress by increasing H3K4me1 in VTA primed an enduring sensitivity to adult stress, at the level of transcription and at the level of behavior. This provides causal evidence linking early life stress to epigenetic modifications in reward circuitry that directly mediate lifelong stress sensitivity.

Disclosure: Nothing to disclose.

PANEL

30. Lighting up Neural Circuits in Vivo: Innovative Optical Approaches to Unveil the Culprits of Psychiatric Disorders

30.1 Large Scale Voltage Imaging Analysis of Biological Neural Networks During Behavior

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Background: Recent improvements in genetically encoded voltage indicators enabled optical imaging of action potentials and subthreshold membrane voltage dynamics from single neurons in the mammalian brain. To perform high speed voltage imaging, widefield microscopy remains an essential tool for recording activity from many neurons simultaneously over a large anatomical area. However, the lack of optical sectioning makes widefield microscopy more prone to background signal contamination, and thus far voltage imaging using fully genetically encoded voltage indicators remains limited to simultaneous sampling of a few cells over a restricted field-of-view.

Methods: We here demonstrate a strategy for large scale voltage imaging using the fully genetically encoded voltage indicator SomArchon and targeted illumination. We implemented a simple, low-cost digital micromirror device based targeted illumination strategy to restrict illumination to the cells of interest, and systematically quantified the improvement of this microscopy design theoretically and experimentally with SomArchon expressing neurons in single layer cell cultures and in the brains of awake mice.

Results: We found that targeted illumination, in comparison to widefield illumination, increased SomArchon signal contrast and reduced background cross-contamination in the brain. Such improvement permitted the reduction of illumination intensity, and thus reduced fluorescence photobleaching and prolonged imaging duration. When coupled with a high-speed, large area

sCMOS camera, we routinely imaged tens of spiking neurons simultaneously over minutes in the brain.

Conclusions: Thus, the widefield microscopy design with an integrated targeted illumination system described here offers a simple solution for voltage imaging analysis of large neuron populations in behaving animals. The ability to simultaneously record intracellular membrane voltage dynamics from a large number neurons offers new opportunities to study the neural network mechanisms of neurological and psychiatric disorders.

Disclosure: Nothing to disclose.

30.2 Cracking Hypothalamic Circuits That Drive Survival Behaviors Using Novel Optical Methods

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Background: The diverse collection of genetically-distinct cell types in the lateral hypothalamus (LH) is crucial for orchestrating a variety of motivated behaviors that facilitate survival. A pivotal role of the LH in regulating appetitive and reward-related behaviors has been evident for decades. However, the contributions of LH circuits to other survival behaviors has been less explored. Here we examine how two lateral hypothalamic neuron populations identified by the expression of the calcium-binding protein parvalbumin (PVALB; LH-PV) or leptin receptor (LH-LEPR), modulate nociception and motivation in mice, respectively.

Methods: We used a combination of optogenetics, chemogenetics, electrophysiology, single-photon fluorescence endomicroscopy, and behavioral assays to manipulate and measure the activity of these genetically-defined neuronal subpopulations in awake behaving mice.

Results: We find that photostimulation of LH-PV neurons suppresses nociception, whereas LH-LEPR neuronal activation promotes appetitive but not consummatory behaviors. Moreover, using functional imaging, we demonstrate that LH-PV neurons respond to acute thermal stimuli and a persistent inflammatory irritant. Furthermore, we monitored calcium dynamics in LH-LEPR neurons during reward associations and observed time-locked activity changes during appetitive cues.

Conclusions: Together, these results directly implicate LH-PV neurons in modulating nociception and identify LH-LEPR neurons as a lateral hypothalamic cell type specifically encoding for appetitive behaviors in mice, thus expanding the repertoire of survival behaviors regulated by LH circuits.

Disclosure: Nothing to disclose.

30.3 Spying on Neuromodulation by Constructing New Genetically-Encoded Fluorescent Sensors

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Background: Acetylcholine (ACh), dopamine (DA), and serotonin (5-HT) are involved in many distinct crucial physiological and pathological processes in diverse organs. A longstanding yet largely unmet goal is to measure ACh, DA and 5-HT changes reliably and specifically with high spatiotemporal precision. We have developed a family of G-protein-coupled Receptor Activation-Based sensors (GRAB sensors) responding to ACh, DA or 5-HT with sensitivity, specificity and spatiotemporal resolution. Here, we will introduce our ongoing progress on development and application of new generation GRAB sensors.

Methods: We used a three-step approach to engineer and optimize GRAB sensors. First, a cpEGFP (for green sensors) or cpmApple (for red sensors) was inserted into the third intracellular loop of ACh, DA or 5-HT receptors. Based on preliminary results, we subsequently focused on the receptor-cpEGFP/cpmApple chimera due to its superior membrane trafficking and high affinity for the ligand. Second, the position of the cpEGFP or cpmApple insertion and the linker residues were systematically screened. Finally, mutations were introduced to expand the response range. After screening, we expressed GRAB sensors in cultured neurons and living animal for further characterization.

Results: We optimized a family of GRAB sensors responding to ACh, DA or 5-HT with high sensitivity, specificity and spatiotemporal resolution.

The green ACh3.5 sensor expressed in HEK293T cells exhibited maximum 670% $\Delta F/F_0$ fluorescence changes with an EC₅₀ of 1.9 μ M and the red rACh1h sensor expressed exhibited maximum 240% $\Delta F/F_0$ fluorescence changes with an EC₅₀ of 0.4 μ M in response to extracellular ACh. Further, both sensors exhibited negligible responses to a variety of tested neurotransmitters.

A pair of D1R based GRABDA (DA2.5 and DA3m) sensors exhibited maximum ~800% and ~1000% $\Delta F/F_0$ fluorescence changes with an EC₅₀ of 300 nM and 800 nM in response to extracellular DA in HEK293T cells. The D2R based red DA sensors rDA1.2a had an EC₅₀ of 150 nM. The application of 100 μ M DA elicited ~300% increase in fluorescence of rDA1.2a. Further, although NE is structurally similar to DA, the DA sensors were 10- to 20-fold more selective for DA over NE.

The newly HTR4 based 5-HT2h sensor showed a high affinity for 5-HT (EC₅₀ ~100 nM), fast on kinetics (τ_{on} ~100 ms), high specificity and spatial resolution and a minimal impact on cellular physiology and thus is well suited for detecting physiologically relevant endogenous 5-HT release. We also developed a red r5-HT2.0 sensor with a ~300% peak $\Delta F/F_0$ response to 5-HT.

Finally, we demonstrated the utility of the GRAB sensors in detecting endogenous ligand release in response to a variety of stimuli and under various behavioral conditions in different animal models.

Conclusions: Here, we will present our ongoing progress on development and application of GRAB sensors for monitoring ACh, DA and 5-HT. These sensors can be applied to many different animal species from invertebrate to vertebrate, with high chemical specificity and large signals. These tools show the power of real-time mapping with longitudinal in vivo imaging of modulators' dynamics under both physiological and pathological conditions, offering the community new tools in understanding potential alterations in psychiatric disorders. In addition, new sensors for monitoring biomolecules including other monoamines, lipids, nucleotides and peptides are also being developed.

Disclosure: Nothing to disclose.

30.4 Micro- and Nano-Scopic Decoding of Neuromodulatory Transmission

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Background: Neural communication orchestrates a variety of behaviors, yet despite impressive efforts, delineating transmission properties of neuromodulatory communication remains a daunting task due to limitations of available monitoring tools.

Methods: Recently developed genetically encoded neurotransmitter sensors, when combined with superresolution and deconvolution microscopic techniques, enable the first micro- and nano-scopic visualization of neuromodulatory transmission. I will

introduce this image analysis method by presenting its biophysical foundation, practical solutions, biological validations, and broad applicability. Experimental results are collected *ex vivo* or *in vivo* from mice of both sexes and *in vitro* from de-identified mouse cell- and human cell-induced neuron systems.

Results: Our preliminary analysis showed that the parameters of fundamental synaptic properties of cholinergic transmission, including the transmitter diffusion extent, number of release sites, release pool size, release probability, quantal size, and refilling rate, in rodent and human neurons are statistically identical. The results suggest that acetylcholine acts in mouse neurons similar to human neurons. Likewise, the pilot experimental analysis of synaptic parameters are pointing to the same pattern for other neuromodulatory transmissions, such as dopaminergic, serotonergic and adrenergic transmissions. Importantly, these new data unveil unexpected fine control and precision of rodent and human neuromodulation.

Conclusions: The findings raise the prospect of rapid advances in the understanding of neuromodulatory transmissions essential for resolving the physiology or pathogenesis of various behaviors and diseases.

Disclosure: Nothing to disclose.

PANEL

31. Neurosteroids: GABAergic, Epigenetic and Immune Regulation in Mood and Alcohol Use Disorders

31.2 The Endogenous Neurosteroid (3 α ,5 α)3-Hydroxypregnan-20-One (3 α ,5 α -THP, allopregnanolone) Moderates Inflammatory Signaling via Multiple Pathways With Sex Differences and Relevance to Alcohol Use Disorders

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Background: Peripheral and brain inflammation are increasingly recognized as critical mediators in the initiation and progression of alcohol use disorders with pronounced elevations of both toll-like receptor (TLR)4 and TLR7 pathways. We have previously shown that 3 α ,5 α -THP and pregnenolone inhibit TLR4 signal activation (Balan, 2019), which enhances drinking in alcohol-preferring (*P*) rats (Aurelian, 2019). In addition, 3 α ,5 α -THP reduces ethanol drinking, tolerance and withdrawal in *P* rats (Morrow, 2020). 3 α ,5 α -THP inhibits MyD88-, but not TRIF-dependent TLR signal activation and the production of TNF α , MCP1, IL-1 β , and IL-6 through its ability to block TLR-MyD88 binding (Balan, 2021). However, its effects on human macrophages and the potential difference between males and females, are unknown.

Methods: Human monocyte/macrophages cultured from peripheral blood mononuclear cells of male (3-5/group) and female (3-5/group) healthy subjects were used to study the effects of neurosteroids on TLR4 and TLR7 inflammatory pathways. The cultures were treated with LPS (1 μ g/ml, 24h) or Imiquimod (IMQ) (30 μ g/ml, 24 h) alone or together with 3 α ,5 α -THP, pregnenolone (PREG) or 3 α ,5 α -THDOC (1 μ M) and examined for TLR pathway activation.

Results: Both 3 α ,5 α -THP and PREG inhibit the LPS activated TLR4 signaling pathway assessed by elevations of TNF- α and MCP-1 in the cells derived from both males and females. 3 α ,5 α -THP inhibited the LPS effect on TNF- α in both males (Two-way ANOVA: $F(1,40)=4.934$, $p=0.0321$) and females (Two-way ANOVA: $F(1,42)=8.402$, $p=0.0059$). The reduction in TNF- α was $33.3 \pm 13.1\%$ in males (Tukey's post hoc test: $p=0.0086$) and $41.6 \pm 6.9\%$ in

females (Tukey's post hoc test: $p=0.0010$). Likewise, no sex differences were obtained for PREG inhibition of the LPS-induced increase of TNF- α ($27.1 \pm 4.6\%$ and MCP-1 $25.6 \pm 4.3\%$ inhibition). In contrast, 3 α ,5 α -THDOC, inhibited the LPS activated TLR4 signal in macrophages cultured from female, but not male subjects. 3 α ,5 α -THDOC (1 μ M) inhibited the LPS effect on TNF- α ($40.2 \pm 12.9\%$, Two-way ANOVA, Tukey's post hoc test: $p=0.0306$) and MCP-1 ($40.4 \pm 3.3\%$, Two-way ANOVA Tukey's post hoc test: $p<0.0001$) in female cells, but not in male cells.

The TLR7 agonist IMQ increased the levels of pIRF7, pSTAT1 and IL-6, both in male- (pIRF7: $34.5 \pm 3.9\%$; pSTAT1: $49.8 \pm 21.3\%$, IL-6: $74.5 \pm 29.2\%$) and female-derived cells (pIRF7: $48.9 \pm 3.3\%$, pSTAT1: $36.5 \pm 6.8\%$, IL-6: $77.9 \pm 18.4\%$). The IMQ-activated TLR7 signaling pathway is inhibited by 3 α ,5 α -THP in females, but not males. 3 α ,5 α -THP inhibited the IMQ effect on pIRF7 ($41.6 \pm 5.9\%$, One-way ANOVA Tukey's post hoc test: $p=0.0003$), pSTAT1 ($34.3 \pm 11.6\%$, t-test: $p=0.0486$) and IL-6 ($60.2 \pm 13.0\%$, Two-way ANOVA, Tukey's post hoc test: $p=0.0241$), in the immune cells of females, but not males.

Importantly, 3 α ,5 α -THP or PREG did not alter the expression of pathway members in cells that were not treated with the TLR agonists LPS or IMQ. 3 α ,5 α -THDOC, by contrast, increased the level of MCP-1 in the agonist-untreated steady state non-activated cells from male ($22.3 \pm 4.3\%$) and female subjects ($27.5 \pm 11.5\%$). This effect suggests a direct activation of the TLR4 pathway as well as innate inflammatory actions.

Conclusions: The data indicate that the therapeutic potential of 3 α ,5 α -THP involves modulation of proinflammatory MyD88-dependent TLR signaling pathways resulting in diminished pro-inflammatory signal activation in human immune cells, including sex specificity for inhibition of TLR7 pathway signals.

Disclosure: Sage Therapeutics: Advisory Board, Grant (Self)

31.4 Epigenetic PPAR-Alpha Regulation Triggers Inflammation and Behavioral Deficits in Stress and Alcohol Addiction Rodent Models

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Background: Social behavioral changes, including social isolation or loneliness, as well as alcohol addiction greatly afflict the general world population during the COVID-19 pandemic, and increase risk for stress-related disorders, such as major depressive disorder, posttraumatic stress disorder (PTSD), and suicide that share a large neuroinflammatory etiological component. A newly discovered molecular target involved in emotional behavior regulation, the peroxisome-proliferator activated receptor (PPAR)- α is a ligand-activated nuclear receptor and a transcription factor that following its stimulation by endogenous or synthetic ligands, induces neuroprotective effects by modulating neuroinflammatory responses and improves anxiety and depression-like behaviors associated with upregulation of neurosteroid biosynthesis. PPAR- α is also a target to decrease alcohol drinking in animal models of alcohol use disorder (AUD).

Methods: Aggressive behavior and fear responses of socially isolated mice were analyzed using the resident-intruder test and a contextual fear conditioning setup. Extraction, derivatization, and quantification of allopregnanolone, of its equipotent isomer pregnanolone and congeners were performed by HPLC-combined with gas chromatography-mass spectrometry. Real-time PCR following total mRNA extraction and cDNA synthesis was performed using Applied Biosystems Real-Time PCR System. DNA methylation levels of the PPAR-alpha gene were analyzed by methyl-DNA immunoprecipitation (MeDIP) using the MagMeDIP kit.

Results: Both protracted social isolation stress (4 weeks) and chronic alcohol administration induced hippocampus PPAR- α expression downregulation likely resulting from epigenetic chromatin modifications, which may underlie decreased neuroactive steroid biosynthesis and increased inflammatory processes associated with abnormal behavior in vulnerable (aggressive) but not in resilient (non-aggressive) socially isolated (SI) mice. Decreased PPAR- α mRNA and protein expression in hippocampus of SI mice was associated with deficient neurosteroid biosynthesis and increased levels of methylated cytosines of site-specific PPAR- α gene fragments, signifying a stress-induced epigenetic modification. This associated with increased histone deacetylases (HDAC)1, methyl-cytosine binding protein (MeCP)2, and decreased ten-eleven translocator (TET)2 mRNA expression, which favor hypermethylation. The epigenetic changes in PPAR- α expression resulted in increased expression of the pro-inflammatory markers, TNF- α and MCP1, mediated by TLR-4 and NF- κ B signaling specifically in SI aggressive mice and alcohol dependent rats.

Conclusions: This study contributes the first evidence of a brain PPAR- α epigenetic regulation through enhancing DNA methylation mechanisms. PPAR- α may constitute a marker for severe inflammatory-based psychiatric disorders and targeting epigenetic marks linked to PPAR- α expression may offer a valid therapeutic approach.

Disclosure: Nothing to disclose.

STUDY GROUP

32. Ethical Issues in the Use of Placebos in Long-Term Schizophrenia Clinical Trials: A Discussion With Ethical and Clinical Experts

Stephen Marder*, Suze Berkhout, Nina Schooler, Christoph Correll, Ryan Lawrence, Donald Goff, M. Mercedes Perez-Rodriguez, Paul Appelbaum, William Carpenter

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Study Group Summary: This workshop will explore one of the most perplexing dilemmas, which sits at the intersection of ethical and scientific practice: how to respond when asked whether an individual will need to continue their antipsychotics for the rest of their lives. Drawing on data from academic and industry trials, clinicians can make reasonable predictions about the risks of discontinuing antipsychotics for the first two years after patients are stabilized. Unfortunately, beyond this two-year period this very vital question is difficult to answer because of a lack of long-term placebo-controlled trials. This issue has become more compelling as new research without placebo controls has suggested that very long-term treatment with antipsychotics can (1) impair functional outcomes; (2) damage physical health; and (3) decrease brain volume. Parsing harm from benefit in the longer-term trajectories of schizophrenia treatment continues to be a struggle.

This workshop will bring together experts in clinical trials for schizophrenia and experts in research ethics to grapple with this challenging issue, focusing on whether and how the use of placebo in long-term trials might be justified. The panel and workshop participants will explore together whether consensus can be reached about issues of clinical equipoise and informed consent, risk and benefit, and wider questions of what values guide the production of medical knowledge. From a clinical perspective, these questions include identifying whether an antipsychotic can gain approval for long-term maintenance without placebo; whether there are clinical and biological factors

that can identify potential candidate patients/participants for drug discontinuation; whether relapse is the wrong endpoint (i.e. that exacerbation of symptoms should be utilized); and whether there are safety measures that can minimize the risk of drug discontinuation. Clinical experts in long-term treatment of schizophrenia including Nina Schooler, William Carpenter, Christoph Correll, Donald Goff, and Mercedes Perez-Rodriguez will guide these discussions. Experts in research and clinical trial ethics include Suze Berkhout, Ryan Lawrence, and Paul Appelbaum, who will facilitate discussions around what constitutes an acceptable level of risk for research participants in placebo-controlled trials, what can ensure meaningful informed consent in the context of novel trial designs, and at what point equipoise has been answered—particularly when ethical standards conflict with best practices in generating scientific evidence.

This workshop will involve a dynamic, open format: rather than offer didactic talks, each panelist contributor will comment on a range of clinical or ethical questions and trial design, pushing the boundaries and implications of each others' positions, while inviting the audience for further contributions. At its conclusion, the workshop will facilitate a thorough and fulsome discussion of trial design, standards for subject selection, meaningful outcome measures, and the broader values implicated in the science of long-term schizophrenia trials.

Disclosures: Merck, Boehringer Ingelheim, Otsuka: Consultant (Self)

Roche: Advisory Board (Self)

Uptodate, Oxford University Press: Royalties (Self).

STUDY GROUP

33. Microbiome in Brain Health and Diseases Across the Lifespan: Exciting New Directions for Integrative Research in Diverse Populations

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Study Group Summary: In recent years, research has uncovered complex interactions between microbiota living in different spaces within the human body and brain. Microbiota-brain axis has emerged as a key regulator of immune and stress-related responses. There is growing interest in how microbial-brain interactions contribute to neurobiological and behavioral disruptions but can also promote mental health.

Programming of the characteristics of microbiota in different spaces in human body and brain begins in early life, with critical periods of microbial colonization occurring in tandem with growth and maturation of neurons in the developing brain. In contrast, a decline in microbial diversity associated with aging parallels a decrease in neuronal complexity. Animal studies support bidirectional interactions between microbiome and brain. Alterations in intestinal and other body area microbiota and in microbiota-brain communication have been implicated in a number of neuropsychiatric diseases. However, the precise nature of and mechanisms underlying these associations remain unclear.

This Study Group aims to foster a discussion of challenges and proposed solutions to advancing scientific knowledge of gut-brain communication, identifying causal relationships and mechanistic pathways leading to development of interventions. Participants include microbiome researchers studying animal models and clinical samples, encompassing the entire lifespan from embryos to centenarians. They will describe new data on microbial

abnormalities in autism spectrum disorders (Hsiao), schizophrenia (Nguyen), substance use disorders (Paulus), and suicidality (Dickerson). Also debated will be the role of the microbiome in early developmental trajectories and its influence on health outcomes including behavior (Godoy-Vitorino), longevity samples in Blue Zones (Tomás), and psychosocial determinants of health like loneliness and wisdom (Jeste). Recently obtained data will be presented on dietary interventions (Kelly) as well as fecal microbial transplant (Krajmalnik-Brown) to reduce psychopathology. The Study Group participants come from various states in the US, Puerto Rico, and Costa Rica.

Scientific progress in this field requires thoughtful integration of basic and clinical sciences to foster translational research on topics like the following:

1. Microbial taxonomic diversity is associated with healthy aging. Would increasing such diversity prevent physical and cognitive decline in diseases like schizophrenia that are associated with accelerated biological aging?
2. Microbial genome is more modifiable than human genome. Can alterations in microbial genome impact human behavior?
3. What types of future prebiotics and probiotics will significantly improve mental illnesses?
4. Can fecal microbiota transplantation become a standard treatment for certain neuropsychiatric disorders?

Research on microbiome-brain axis holds great promise to advance precision medicine approaches in neuropsychiatry. Microbiome-related biomarkers can enhance our understanding of clinical heterogeneity and lead to novel methods for prediction, early detection, and prevention of illnesses. The Study Group presenters are at the forefront of this emerging science and will discuss directions for innovative research including interventions to treat mental illnesses and enhance well-being at individual and societal levels.

Disclosure: Nothing to disclose.

PANEL

34. Targeting PDE 4 Treating Substance Use Disorders: Rodent and Human Evidence of PDE4 Inhibitor Efficacy and Safety

34.1 The FDA-Approved Drug Apremilast Suppresses Alcohol Intake

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Background: Alcohol Use Disorder (AUD) is a complex psychiatric disease with far reaching impacts on society, including >95,000 associated deaths annually in the United States and a net economic cost of \$249 billion annually. Despite a growing knowledge of important genetic and molecular mechanisms, pharmacological treatment options for AUD have not advanced significantly since the U.S. Food and Drug Administration (FDA) approval of acamprosate in 2004. Substantial work supports immune and inflammatory pathways as critical regulators of AUDs at all stages of the disease; namely binge drinking, increased motivation to drink, and alcohol dependence. In particular, the cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase, PDE4, has gained attention as a potential molecular target for treating AUD. We rigorously tested the FDA-approved PDE4 inhibitor, apremilast, in mouse models of AUD.

Methods: The effects of apremilast were evaluated in mouse models of excessive alcohol drinking (listed in order of increasing chronicity for each experiment): 1) binge-like drinking, 2) motivation for self-administration, 3) drinking despite negative consequences, 4) stress-facilitated escalation of drinking, and 5) dependence-induced escalation of drinking. We studied the role of PDE4 in the nucleus accumbens (NAc) on drinking behavior and physiology by determining in experiment 6) whether administration of apremilast into the NAc would be sufficient to reduce binge-like drinking and 7) whether apremilast differentially alters physiology in two types of medium spiny neurons (MSNs; dopamine receptor D1 or D2 expressing MSNs), which comprise two major output pathways from the NAc.

Results: In male and female mice selectively bred to drink to intoxication, 20 and 40 mg/kg apremilast reduced binge-like drinking and blood alcohol levels (Exp 1), motivation to drink alcohol in an operant self-administration progressive ratio test (Exp 2), and quinine-adulterated alcohol drinking in an operant self-administration test (Exp 3).

In high drinking male and female C57BL/6J mice, apremilast reduced non-dependent and dependence-induced escalation of drinking (Exp 5), as well as stress-facilitated escalation of drinking (Exp 4). Lastly, intra-NAc apremilast was sufficient to reduce binge-like drinking (Exp 6) and increase excitability of D1-expressing MSNs in the NAc (Exp 7).

Conclusions: These results demonstrate that apremilast reduces excessive alcohol drinking across a spectrum of models for AUD and support its importance as a potential therapeutic for AUD. This collaborative work was carried out as part of the NIH funded consortium, "Integrative Neuroscience Initiative on Alcoholism".

Disclosure: Nothing to disclose.

34.2 Ibudilast, a Neuroimmune Modulator, Decreases Biomarkers of Inflammation in Individuals With Alcohol Use Disorder: A Preliminary Study

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Background: Ibudilast, a neuroimmune modulator which selectively inhibits phosphodiesterases (PDE)-3, -4, -10, and -11, shows promise as an alcohol use disorder (AUD) pharmacotherapy. Our group has previously shown that ibudilast reduces heavy drinking and attenuates neural alcohol cue reactivity in individuals with AUD. However, the biological mechanism underlying these effects are currently unknown. This presentation will highlight novel data demonstrating ibudilast's effect on peripheral markers and neural metabolite markers of inflammation in individuals with AUD.

Methods: Non-treatment-seeking individuals with AUD were randomized to receive ibudilast ($n = 24$) or placebo ($n = 28$) for 2 weeks. Blood sampling for inflammatory marker assays was collected at study randomization, after 1-week, and 2-weeks of medication. Plasma concentrations of pro-inflammatory cytokines and anti-inflammatory cytokines were measured using a multiplex immunoassay. After 1-week of treatment, participants underwent multi-voxel magnetic resonance spectroscopy (MRS) to measure metabolite concentrations. MRS data underwent stringent quality control and subjects with data not meeting quality control standards were removed. Metabolite levels were calculated using SVFit. Inflammatory marker analyses were conducted in a multi-level framework in SAS using PROC MIXED, where the effect of medication, time, and their interaction were examined. Age, sex, smoking status, body mass index, drinking prior to randomization, and baseline inflammatory levels were included as covariates.

Analyses for MRS metabolite concentrations were tested in SAS using PROC GLM, where the effect of medication was examined. Age, sex, and smoking status were included as covariates.

Results: Ibudilast increased IL-8 relative to placebo ($F(1,40)=7.47$, $p=0.009$). There was a trend interaction between medication and time for CRP ($F(1,40)=3.50$, $p=0.06$), such that at the 2-week timepoint ibudilast reduced CRP relative to placebo. There was also a trend towards ibudilast decreasing the TNF- α /IL-10 ratio ($F(1,40)=3.71$, $p=0.06$). Ibudilast decreased Choline (Cho) in the bilateral superior frontal white matter (left: $F(1,42)=6.88$, $p=0.01$; right: $F(1,42)=7.72$, $p=0.008$). Ibudilast also decreased creatine (Cr) in the left pregenual anterior cingulate cortex (ACC; $F(1,31)=4.63$, $p=0.04$). There was a trend toward ibudilast decreasing Myo-Inositol (ml) in the left pregenual ACC ($F(1,31)=0.07$). Ibudilast increased N-acetylaspartate (NAA) in the right superior frontal cortex ($F(1,39)=6.39$, $p=0.02$).

Conclusions: These preliminary findings begin to elucidate a biological mechanism underlying ibudilast for the treatment of AUD; namely, ibudilast increases an anti-inflammatory cytokine (IL-8), improves a marker of neuronal health (NAA), and decreases inflammatory markers in the brain (Cho, ml, and Cr) and in the periphery (CRP and TNF α /IL-10 ratio). These results suggest that ibudilast may work through an anti-inflammatory mechanism to reduce inflammation in individuals with an AUD.

Disclosure: Nothing to disclose.

34.3 4B or Not 4B? Evidence of the Potential Therapeutic Utility of a Selective PDE4B Inhibitor for Reducing Alcohol- and Methamphetamine-Taking in Mice

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Background: Neuroinflammation is a causal factor in drug/alcohol (EtOH)-taking behavior, as determined in various animal models. Tolerability issues accompanying the targeting neuroinflammation via non-selective inhibition of phosphodiesterase 4 (PDE4) may limit their therapeutic utility for reducing drug-taking and -craving in humans. As targeting specific PDE4 isozymes may prove to be a tolerable approach, we examined the effects of a PDE4B-selective inhibitor, A33, on EtOH and methamphetamine (MA) intake by female and male mice of genetically distinct C57BL/6 substrains that differ in their EtOH intake, MA behavioral responsiveness and innate immune response.

Methods: The dose-response function (0–1.0 mg/kg) for A33's effects upon binge EtOH intake was determined under a modified Drinking-in-the-Dark (DID) procedure (10, 20 and 40% EtOH) in female and male C57BL/6J (B6J; 12F, 11M) and C57BL/6NJ (B6NJ; 8F, 7M), followed by a series of experiments to examine for off-target motor effects. In a follow-up study, the potential interaction between EtOH and 1.0 mg/kg A33 was characterized in naïve mice using a rotarod assay, followed by determination of the effects of repeated pretreatment with 1.0 mg/kg A33 on binge-drinking of 20% EtOH ($n=6$ /sex/strain). In a final study, B6J and B6NJ mice ($n=8$ /sex/strain) were trained to orally self-administer 100 mg/L MA under operant-conditioning procedures and then the A33 dose-response functions characterized for MA reinforcement and intake, once responding stabilized.

Results: Despite higher baseline EtOH intake in B6J vs. B6NJ mice, A33 pretreatment reduced binge-drinking under both multi-bottle [A33 effect: $F(4,52)=6.79$, $p<0.0001$] and single-bottle DID procedures [A33 effect: $F(4,80)=4.77$, $p=0.002$], with no overt tolerance detected upon repeated pretreatment (no Day effect or interactions, $p's>0.44$). A33 (1.0 mg/kg) increased sucrose intake in B6NJ mice of both sexes [A33 effect: $F(1,13)=16.34$, $p=0.001$] and in B6J females [A33 X Sex: $F(1,21)=6.21$, $p=0.02$], and the

time spent on the rotarod by experimentally naïve mice injected with 2 g/kg EtOH [A33 effect: $F(1,23)=5.17$, $p=0.03$]. In A33/EtOH-experienced mice, A33 pretreatment (1.0 mg/kg) did not alter spontaneous motor behavior or EtOH's sedative-hypnotic effects under several assays (rotarod, locomotor activity, sedation; no A33 effects or interactions, $p's>0.1$). B6J also responded for, and consumed more, 100 mg/L MA than B6NJ mice [Strain effects: $F(1,44)>7.43$, $p's<0.01$] and both indices were reduced dose-dependently by A33 pretreatment [A33 effects: $F(4,164)>12.0$, $p's<0.0001$].

Conclusions: These data provide the first evidence that selective PDE4B inhibition with A33 reduces both EtOH and MA intake in mice, with minimal off-target effects and no overt development of tolerance. The drug is equally effective in male and female subjects, and in subjects with distinct innate immune responsivity that differ in baseline drug intake. If relevant to humans, such findings pose PDE4B as a potential target for intervening in active drug-taking behavior.

Disclosure: Nothing to disclose.

34.4 Roflumilast During Forced Abstinence Reduces Relapse to Methamphetamine

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Background: Methamphetamine (METH) is a psychostimulant with high abuse potential. Currently, there are no pharmacological treatments specific for METH abuse or stimulant use disorder generally. Although phosphodiesterase inhibitors have shown some promise, current animal models have not examined their use in abstinence from psychostimulant abuse.

Methods: Adult male rats were used in an IV self-administration operant model followed by a forced abstinence period during which roflumilast, a phosphodiesterase 4 inhibitor or vehicle was administered. Rats self-administered (+) Methamphetamine HCL (0.1 ml of 0.1 mg/kg) for 6 hr daily on a FR1 schedule over 14 days. A yoked control rat would receive a non-contingent infusion of 0.1 mL of heparinized saline. After a 7-day forced abstinence period, either roflumilast (1.5 mg/kg, $p.o$) or vehicle every other day was administered by the investigator. The rats were assigned according to a 2 X2 design with variables of saline or Meth X roflumilast or vehicle. After the last treatment day, rats were reintroduced to the self-administration chamber they were in for the 14-day self-administration period. Two relapse tests were conducted in separate groups of rats: (1) Cue-reinforced METH seeking wherein a cue light was activated with each active lever press, but no drug was delivered and (2) METH-reinforced METH taking test wherein a cuelight was activated with each active lever press in addition to the delivery of 0.1 ml of 0.1 mg/kg of METH on a FR1 schedule. The relapse test was a single 6 hour session performed between 10 AM and 4 PM.

Results: Rats escalated METH-reinforced active lever pressing and METH intake over 14 days ($p<0.05$). During the cue-reinforced METH seeking relapse test, METH rats had increased active lever pressing compared to yoked saline control rats (METH, Least square mean LSM = 50.83, SEM = 2.07; Saline, LSM = 12.53, SEM = 2.07; $F(1,38)=170.56$, $p<0.001$).

Roflumilast reduced relapse to cue-reinforced METH seeking behavior compared to vehicle treatment during abstinence ($p<0.001$). The pattern of active lever pressing during the relapse test showed that the roflumilast group had fewer cue-reinforced active lever presses compared to METH x Vehicle (METH x Vehicle, LSM = 2.967, SEM = 0.16; METH x Roflumilast, LSM = 1.27, SEM = 0.15; $F(1,437)=58.84$, $p<0.001$) and decreased more over time, as

indicated by a significant two-way interaction between treatment and time ($F(23,437)=8.64$, $p < 0.001$).

Roflumilast treatment during abstinence also reduced relapse to METH-reinforced METH taking (Roflumilast, $M = 3.35$, $SEM = 0.64$; Vehicle, $M = 5.40$, $SEM = 0.52$; $t(9)=-2.42$, $p < 0.05$). During the relapse test, roflumilast treatment during abstinence reduced METH intake compared to last day of METH self-administration values (Day 14) and had decreased intake relative to vehicle (Pre-treatment Day 14, $LSM = 0.31$, $SEM = 0.02$; Roflumilast $LSM = 0.14$, $SEM = 0.03$; Vehicle, $LSM = 0.23$, $SEM = 0.03$; Day 14 vs Roflumilast, $t = 5.05$, $p < 0.001$; Day 14 vs Vehicle, $t = 2.42$, $p = 0.051$; Roflumilast vs Vehicle, $t = 2.08$, $p = 0.051$).

In separate groups rats trained to self-administer sucrose pellets, roflumilast during abstinence did not affect relapse to sucrose self-administration.

Conclusions: The study is the among the first to report the use of a pharmacological agent during abstinence to reduce relapse to METH, and the first to identify a pharmacological agent to reduce relapse to both METH seeking and METH intake. Roflumilast reduced METH seeking and METH taking while leaving natural reward intact. The findings suggest that phosphodiesterase inhibition during abstinence may be useful for the treatment of METH use disorder.

Disclosure: Nothing to disclose.

PANEL

35. Obsessive-Compulsive Disorder: Linking the Critical Circuit Elements

35.1 The Ventrolateral Prefrontal Cortex as Part of the OCD Network: Circuits and Functional Connections

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Background: The orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), regions strongly implicated in OCD, are part of a complex network that underlie behavioral flexibility. The lack of this flexibility is a key feature of OCD. These areas are strongly connected to the ventrolateral prefrontal cortex (vlPFC) and insula, both of which are also associated with OCD. Together they constitute a network that links motivation, salience, value-encoding, and stimulus-response processing, providing the basis for behavioral flexibility. An important issue is how information flows between these structures. Here we studied the connections of the vlPFC, with a particular focus on its interface with the ACC and insula, the two nodes of the salience network, and the OFC. We used a new cross species and multimodal approach to demonstrate that the anatomic connections of the vlPFC is reflected in resting state functional activity in both nonhuman primates (NHPs) and humans.

Methods: Following retrograde injections into different vlPFC regions, labeled cells were quantified throughout the frontal cortex using StereoInvestigator software (MicroBrightField). To compare the input pattern across injection sites, we calculated the percent input to each site from each frontal cortex area. We then used a seed-based functional connectivity analysis in NHP resting-state data to determine the relationship between the anatomy and functional connectivity in the same species. Finally, we placed seeds in homologous regions in the human brain to analyze resting state functional connectivity in humans. All animal experiments were carried out in accordance with the Institute of Laboratory Animal Resources Guide for the Care and Use of

Laboratory Animals and approved by the University Committee on Animal Resources.

Results: Consistent with the literature, area 44 is most tightly connected to motor control areas. Rostral and caudal area 45 differ somewhat in their connections. While both are linked to the dorsolateral prefrontal cortex, areas 9 and 46, rostral area 45 is also connected to motor control regions and the caudal region is connected to the OFC. vlPFC area 47/12 has the most diverse connections. Rostral 47/12 is most tightly linked to OFC, motor control regions, and area 9. Mid47/12 is connected most strongly with OFC, dorsolateral PFC. Caudal 47/12 stands out with its close connections to the ACC, OFC, insula, and motor control areas. Moreover, the results also show high correlations of connectional strengths between rsMRI and vlPFC anatomic connections in both nonhuman and human primates.

Conclusions: Results suggest that area caudal vlPFC area 47/12 occupies a unique position to modulate other OCDnet nodes. It is centrally placed to mediate not only between the ACC, insula, and OCD, but also, through its connections with motor control areas, regulate action plans. Importantly, the vlPFC is part of the dorsal and ventral attention networks. This combined with the possibility that the caudal 47/12 is part of the salience network by virtue of its strong connections with the ACC and insula, places the vlPFC at the junction between these three cognitive networks and thus in a position to regulate behavioral flexibility and information seeking.

Disclosure: Nothing to disclose.

35.2 Neural Networks for Information Seeking

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Background: One of our most fundamental strategies for coping with an uncertain future is to seek information about what rewards and hazards the future holds. To date, little is known about how the brain regulates information seeking about punishments. This is striking given how our individual strategies for coping with uncertain future aversive punishments impact our everyday lives and society as a whole, depending on whether we eagerly seek knowledge or 'stick our heads in the sand' to avoid knowledge about them. Aberrant information seeking is a key signature of OCD and other disorders. Understanding the precise mechanisms of information seeking could be key for developing targeted and precise individualized treatments.

Methods: Monkeys' ($n = 2$, male) preferences were measured from choices among options that predicted rewarding and aversive outcomes with different probabilities and informativeness. Generalized linear models (GLMs) estimated the subjective value of information, juice reward, and aversive air puffs. Monkeys' gaze was obtained using eye tracking. Standard electrophysiology obtained the spiking of neuronal ensembles. Because the prefrontal cortex regulates information seeking through the basal ganglia and the lateral habenula, we will also show neural recording and neuromodulation data in these brain areas in an expanded task that has been readily implemented by our group in humans.

Results: Decision attitudes toward punishment and reward information are not tied to each other – individuals with similar preferences for reward information can have strikingly different attitudes toward punishment information. Anterior cingulate (ACC), as well as an interconnected subregion of the ventrolateral prefrontal cortex (vlPFC), contained neural populations that anticipated opportunities to gain uncertainty-resolving information. vlPFC integrated attitudes toward punishment and reward, encoding the overall preference for information to guide decision

making. ACC-vlPFC reflected individual differences in the monkeys' preferences, and trial-by-trial fluctuations in neural signals anticipated information seeking. To discover how this network controls decisions, we manipulated the activity of (i) regions of basal ganglia that receive inputs from the ACC-vlPFC and (ii) the lateral habenula that integrates inputs from the basal ganglia to control motivated behavior. Targeted neuromodulation changed the subjective value of information and mediated decision-making processes under uncertainty in highly precise manners. Because humans and monkeys use similar mental algorithms to control information seeking, these results pave the way for novel opportunities to deconstruct the circuits of cognition and develop neuromodulation to correct aberrant behaviors in disorders such as OCD.

Conclusions: Informational attitudes about rewards and punishments are dissociable at both the behavioral and neuronal levels. We identified an ACC-vlPFC network containing neurons that selectively encode opportunities to gain information to resolve uncertainty and reflected individual differences. The computations that assign value to information are similar in monkeys and humans and are expressed through the basal ganglia – lateral habenula circuits. Direct modulation of the habenula and related basal ganglia circuits could be a viable way to mediate decision making processes in patients with cognitive disorders, such as OCD.

Disclosure: Nothing to disclose.

35.4 Defining the Target of Ventral Capsulotomy for Intractable OCD

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Background: Recent meta-analyses have confirmed our initial studies of the safety and efficacy of bilateral ventral anterior limb of the internal capsule lesions (vALIC) for intractable OCD. This work demonstrated that 57% of OCD patients who had failed all nonsurgical options had a 35% or greater decrease in YBOCS score. Recent advances in neuroanatomical methods that combine anterograde and retrograde tracers and high-resolution diffusion imaging (DI) in the same animal, as well as advances in interpreting false negatives and positives in human DI have opened up the possibility of defining which white matter connections are critical to lesion in order to achieve a therapeutic response. Defining these fiber tracts also have implications for furthering our understanding of which prefrontal cortical networks and their connections are likely to be involved in the symptoms of OCD.

Methods: Two samples of male and female patients with intractable OCD were treated with a staged gamma knife lesion procedure that initially targeted either the ventral most fibers of the vALIC containing OFC corticostriatal thalamic loops (CSTC) ($n = 10$) or that targeted the fibers above those containing vlPFC cingulate and frontopolar (CSTC) loops ($n = 15$). Following a nine month period, nonresponders received a second lesion in the alternate location. Prepost resting state fMRI and diffusion imaging was obtained. Results a new study of thirteen intractable OCD patients undergoing laser guided thermal ventral capsulotomy confirmed the efficacy of the combined nonstaged lesion.

Twenty-six patients with prepost imaging were entered into a study to correlate lesion placement with outcome. The spatial location of pre post YBOCS residuals was plotted to examine the relationship of location with outcome.

Results: At an average of 9 months followup neither single lesion placement was clinically effective. Zero out of ten patients met criteria for response with a single ventral most lesion (mean

prepost YBOCS change) and only one of 13 patients met criteria for response with the dorsal ventral single shot treatment. The combined ventral capsulotomy using fMRI guided laser thermography was highly effective and comparable to gamma ventral capsulotomy. Prepost imaging studies pointed to the importance of lesioning the connections of the OFC and medial prefrontal CSTC loops for treatment outcome and suggested there is individual variation in where these loops run in the vALIC at the capsulotomy target site.

Conclusions: The efficacy and safety of ventral capsulotomy for intractable OCD was confirmed in a new study using LITT. Improvement in mean YBOCS scores at followup, as well as responder rates, appear comparable to published studies of gamma and thermal ventral capsulotomy for intractable OCD.

Two studies examining the effect of staged single lesions in the ventral capsule failed to show efficacy. Imaging studies have demonstrated that there is significant variation in individuals in the course of corticofugal fibers in the ventral capsule. Further studies are needed to demonstrate which fibers should be targeted within individuals to maximize efficacy and safety.

Disclosure: Nothing to disclose.

STUDY GROUP

36. Developing Novel Treatments for Psychiatric Illnesses: Can Drug Development Tool Qualification Advance CNS Drug Development?

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Study Group Summary: There are many challenges in developing drugs for the treatment of psychiatric disorders, many related to diagnostic heterogeneity, which impacts patient selection and assessment of treatment benefits in trials. Drug development tools (DDTs) are methods, materials, or measures that have the potential to advance drug development. The 21st Century Cures Act established a process for FDA qualification of DDTs. Accepted DDTs are publicly listed and can be implemented for their qualified contexts of use (COUs) in any drug development program. The DDT qualification process has been successful in other fields of medicine; however, there have been fewer DDT submissions in psychiatry. This study group will focus on understanding how to develop, qualify, and use DDTs in psychiatric trials as well as how to overcome challenges that impede development.

Biomarkers and clinical outcome assessments (COAs) are two types of DDTs with FDA qualification programs. COAs are instruments that measure or reflect how patients feel, function, or survive, and biomarkers are defined characteristics that are indicators of normal biological processes, pathogenic processes, or responses to an exposure or intervention. Biomarker categories include susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety.

The study group will highlight experiences and lessons learned from researchers, pharmaceutical developers, FDA, NIMH, consortia, and other stakeholders in the DDT ecosystem. Kolb and Graham will describe examples from the Biomarkers Consortium portfolio, focusing on analytic and clinical validation of biomarkers and tools for CNS disorders. Dage, Graham, Kolb, and Pandina will provide perspectives from the pharmaceutical industry on the use

of novel DDTs in CNS drug development. Cannon and McPartland will discuss their experiences obtaining accepted letters of intent from FDA for the development of DDTs for enriching clinical trials for patients at high risk for developing psychosis and for autism, respectively. Berman, Horner, Leptak, and Reasner will discuss the Biomarker and COA Qualification Programs and provide guidance from reviewing DDTs for psychiatry and other therapeutic areas. Lisanby will provide a NIMH perspective on DDT development.

Key questions to discuss include:

Which psychiatric indications would benefit most from the development of DDTs?

How can researchers identify a potential biomarker that may be worth developing as a DDT?

What do qualified DDTs look like in other medical fields, and how can we apply their successful experiences to psychiatry?

How do competitors become collaborators to develop DDTs?

What are the organizations that facilitate pre-competitive DDT development?

How do researchers choose and refine the COU for a DDT?

How do pharmaceutical companies view different biomarker measurement methods (e.g., neuroimaging, EEG, blood tests, etc.)?

What have we learned about selecting COAs and biomarkers for use in clinical trials?

Can COAs and biomarkers that are not submitted to qualification programs still be used in drug development?

What is the regulatory path for DDTs, and how can stakeholders seek guidance from FDA on DDT qualification?

Collaboration is key for successful DDT development. Therefore, this study group offers an ideal venue for multiple stakeholders to discuss the challenges and possibilities associated with DDTs.

Disclosure: Nothing to disclose.

PANEL

37. The RDoC Paradigm: Advances in the Study of Brain/Behavioral Mechanisms

37.1 Mapping Dimensions of Neural Circuits to Symptoms, Behaviors and Treatments Across Mood and Anxiety Disorders

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Background: There have been tremendous advances in the use of functional neuroimaging to characterize human neural circuit function involved in emotional and cognitive functions that are impaired in depression and anxiety. Yet, we lack a means to quantify circuit function and dysfunction at the individual subject level at a means of underlying the circuit heterogeneity underlying depression and anxiety and that has clinical relevance for informing treatment decisions.

Methods: A system for quantifying subject-level function in three task-free and three task-evoked circuits was developed and tested in primary and generalizability samples of depression and anxiety. This system included standard definitions for each region and a method for computing circuit scores based on the activation of these regions and connectivity between them, and expressed in standardized units relative to healthy reference sample acquired under the same conditions. In a separate sample, circuit score contributions to distinguishing response to antidepressant and behavioral interventions were assessed. In the primary sample, regression models were used to assess the extent of one-to-one mapping between subject-level circuit scores and clinical

symptom and behavior measures, and using the Benjamini-Hochberg procedure to control the false discovery rate. The reproducibility of these associations in regard to both consistency within confidence intervals and effect size were evaluated in the generalizability sample. Stepwise logistic regression models were used to assess the contribution of circuit scores to treatment response for both antidepressants and behavioral intervention.

Results: In the primary and generalizability samples ($n = 250$), task-free salience and default mode circuit function was found to map onto symptoms of anxious avoidance (salience; $t = -2.98$, $FDRp = 0.008$, Standardized beta effect size = -0.26), threat dysregulation (salience; $t = -2.43$, $FDRp = 0.011$, Standardized beta effect size = -0.23), and negative emotional biases (default mode; $t = -2.59$, $FDRp = 0.009$, Standardized beta effect size = -0.25) and anhedonia (default mode; $t = -2.50$, $FDRp = 0.010$, Standardized beta effect size = -0.24) – core characteristics that cut across diagnoses. More regionally specific dysfunctions within task-evoked cognitive control and affective circuits implicated symptoms of cognitive and valence-congruent emotional functions. In the treatment sample ($n = 205$), distinct profiles of circuit dysfunction within both task-free and task-evoked circuits differentiated response to antidepressants (negative affect; chi-square = 4.85 ; $p = .028$, Standardized interaction beta effect size = 2.82) as compared to behavioral intervention (attention; chi-square = 18.83 ; $p = .005$, Standardized interaction beta effect size = 5.14).

Conclusions: The functional image processing system developed and tested in this study offers one means by which our field can acquire cross-study, cross-site imaging samples and use such data to refine our understanding of circuit-phenotype relations and to pursue trials using circuit metrics as clinically interpretable outcomes.

Disclosure: Laureate Institute for Brain Research: Advisory Board (Self)

37.2 Disentangling Depression Heterogeneity Toward Understanding Risk and Prevention Pathways for Dementia: A Presentation of Meta-Analytic, Population-Based, and Clinical Trial Data

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Background: A depressive episode at any point in life is a risk factor for dementia. While there is overlap between the cognitive processes and neural circuits affected by depression and dementia, it is unclear which patients might be 'driving' these findings, and to what extent antidepressant treatment might moderate risk. Delay or prevention of dementia via effective treatment of depression would be critical for public health. Here, we present three large 'n' studies offering an opportunity to interrogate brain circuits to address this question.

Methods: The first study included meta-analytic data from 14,318 participants. We compared younger and older adults with MDD to control participants. An Activation Likelihood Estimation (ALE) analysis and coordinate-based network mapping were used to identify brain circuits. Meta-regressions examined impact of age of onset and antidepressant treatment.

The second study examined UK Biobank participants ($N = 19,932$) split into 5 groups: those with lifetime major depressive episode only, non-phobic anxiety disorders only, both depressive and anxiety disorders, trauma- and stressor-related disorders, and controls. We used linear models to test for group effects on functional connectivity (FC) and cortical thickness (CT). We then compared the resulting patterns of case-control t-statistics using Pearson correlations across imaging features and permutation testing.

The third used baseline data in $n=330$ participants from a clinical trial. We assessed FC in 5 groups at-risk for dementia: remitted MDD, non-amnesic mild cognitive impairment (naMCI), MDD + naMCI, amnesic MCI (aMCI), and MDD + aMCI. Dual regression was conducted, followed by group-ICA from the Smith atlas, and PALM (Permutation Analysis of Linear Models).

Results: In the first study our ALE results implicated bilateral parahippocampus (e.g. $z\text{RIGHT}=5.2$, $p\text{FWE}<0.001$) and anterior cingulate (e.g. $z\text{RIGHT}=3.6$, $p\text{FWE}<0.005$) in MDD and anterior cingulate (e.g. $z\text{RIGHT}=3.7$, $p\text{FWE}<0.005$) in LLD. Meta-regressions showed late onset was associated with widespread structural abnormalities and antidepressant treatment was associated with changes in anterior cingulate ($t=3.8$, $p\text{FDR}=0.03$) and DLPFC ($t=3.0$, $p\text{FDR}=0.04$).

In the second study greatest case-control differences were found in MDD and comorbid MDD and anxiety, followed by anxiety and stress disorders. MRI signatures of lifetime anxiety and MDD were highly concordant (Pearson's $R=0.68$, $p\text{PERMUTATION}<0.001$ for FC; $R=0.49$, $p<0.001$ for CT), as well as for those with both disorders ($p<0.005$), primarily in altered connectivity of frontoparietal ICA components.

In the third study for within-network FC we found no difference between participant groups. For between-network FC, we found a significant difference between the DMN and the superior parietal lobe (SPL); driven by the AD group (compared to MDD and HC groups ($p<0.05$)) following FDR correction. None of the remitted MDD groups were different from healthy controls.

Conclusions: Late-life depression appears to include additional brain circuit risk for dementia, moderated by antidepressant treatment. Depression (including comorbid anxiety) creates neural risk for dementia (rather than stress disorders). Remission from depression is not associated with a brain circuit profile consistent with dementia.

Disclosure: Nothing to disclose.

37.3 A Neurobiological Phenotype for Increased Comorbidity Load and Worse Prognosis in the Anxiety Disorders

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Background: The current diagnostic system emphasizes discrete categories that may not map on to underlying dimensions of psychopathology. For instance, comorbidity in the anxiety disorders is the norm and it is associated with increased disability, higher risk of suicide, lower remission rates and greater chance of relapse. Epidemiological and genetic data suggest that anxiety disordered patients fall along a spectrum, ranging from those with focal fear, low comorbidity and low negative affectivity on one end, to those with diffuse anxiety, high comorbidity and high negative affectivity on the other. fMRI work has indicated heightened threat reactivity along this spectrum; however evidence suggests that an EEG marker of motivated attention to threatening stimuli, the late positive potential (LPP) becomes blunted in individuals with more diffuse and comorbid anxiety. Using multiple neurobiological measures, we tested a novel hypothesis – that an EEG-fMRI brain profile can account for comorbidity's deleterious effects on outcome, beyond what would be expected if comorbidity was simply the sum of its parts.

Methods: A total of one-hundred and ten individuals ($n=64$ female) were recruited. Seventy-eight of these individuals had in common at least one focal fear diagnosis (specific phobia or performance-only social anxiety) but varied in number of comorbid internalizing disorders: low comorbid (0 or 1 comorbidities, $n=44$); high comorbid (2 or more comorbidities, $n=34$). Thirty-two psychiatrically healthy controls were recruited for

comparison. fMRI BOLD measurement of threat neurocircuitry and the LPP provided complementary and unique measures of negative emotion generation during a picture-viewing paradigm.

Results: More comorbid individuals showed heightened negative > neutral "alarm" (e.g., BOLD activation in the amygdala, insula), but reduced negative > neutral motivated attention (e.g., LPP), compared to less comorbid individuals. To test whether the combination of heightened alarm and reduced motivated attention (HARM-A) was associated with increased internalizing psychopathology, interactive effects were examined. Results showed that individuals with high levels of amygdala activation in combination with small LPPs had higher levels of latent internalizing psychopathology [amygdala activity X LPP, $\Delta F(1, 51)=3.28$, $\beta=-.27$, $p=.05$, $\Delta R^2=.06$], controlling for main effects of alarm and motivated attention, with similar results found for the interaction between left amygdala-insula connectivity X LPP, [$\Delta F(1, 51)=4.63$, $\beta=-.29$, $p=.04$, $\Delta R^2=.08$]. Prospective analyses showed that this same neurobiological phenotype (HARM-A – e.g., amygdala X LPP) was associated with increased dysphoria 18 months later [left amygdala: $\Delta F(4, 26)=1.56$, $\beta=-.46$, $p=.04$, $\Delta R^2=.19$; right amygdala: $\Delta F(4, 26)=1.51$, $\beta=-.41$, $p=.04$, $\Delta R^2=.19$], controlling for baseline dysphoria and main effects of alarm and motivated attention.

Conclusions: A neurobiological phenotype characterized by excessive "alarm" and reduced motivated attention, HARM-A – might reflect a common, synergistic, pathophysiologic process that is a better predictor of comorbidity load, and downwards trajectory than any existing diagnosis, or single-method metric, like fMRI threat detection/amygdala reactivity.

Disclosure: Aptinix Inc.: Consultant (Self)

37.4 Brain Mechanisms Mediating Resilience to Environmental Adversity: Application to the COVID-19-Pandemic

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Background: We have proposed (Buckholtz and Meyer-Lindenberg, Neuron 2012), that transdiagnostic dimensional constructs may relate to brain mechanisms mediating risk for mental illness. In recent work, we have extended this approach to resilience mechanisms. The ongoing pandemic provides an unprecedented case study in which mental health and well-being are adversely affected by threats to health, economics, and social cohesion, triggering broad societal interest in resilience. In this talk we will present unpublished work bringing neuroscience into this conversation.

Methods: Data are based on the ongoing longitudinal MARS and PEZ studies. Methods have been published previously (e.g. Reichert et al. Nat Neurosci 2019, Holz, N. E., et al. Neuropsychopharmacology 2015) and encompass ecological momentary assessment (EMA), geolocation and geostatistics, as well as structural and functional neuroimaging at 3T. Sample sizes are $i0$ for longitudinal pandemic data and several hundreds of participants for resilience mechanism studies. PEZ is an epidemiologically representative sample of the German population in our research area; the MARS study is enriched for early adversity. As such both sexes are represented, minority group representation is assured by oversampling to overcome response bias.

Results: Our findings indicate that resilience factors including nature exposure, non exercise activity, and social contact converge on neural systems of executive and emotional control, centered on dorsolateral and anterior cingulate regions and the subcortical structures (asuch as amygdala) that they regulate. During two lockdowns in Germany due to the pandemic in Spring and Fall of 2020, mixed models showed three-way interactions between time point, social contacts and neurobiobehavioral risk

moderated by amygdala volume, neuroticism and polygenic risk for schizophrenia. Well-being during lockdowns were mediated by emotional control brain mechanisms, while executive control was a more important mediator in the interim.

Conclusions: Our data indicate convergent systems of brain resilience to environmental adversity and suggest that these mediate well-being during periods of social isolation due to physical distancing in the COVID-19-Pandemic.

Disclosures: American Association for the Advancement of Science, Elsevier, Thieme: Honoraria (Self)

Lundbeck Foundation, Lundbeck A/S, Janssen Cilag: Consultant (Self)

Brain Mind Institute Lausanne: Board Member (Self).

PANEL

38. Genetics of Intermediate Phenotypes in Psychosis

38.2 Toward Primary Prevention of Psychotic Disorders Based on Genetic and Neurobiological Measures

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Background: Primary prevention requires reliable prediction of susceptibility before any symptoms are present. For two decades, prevention of psychosis has focused on persons at the first presentation of symptoms, termed “Clinical High Risk” patients. This is secondary prevention. As a first step toward primary prevention, we did multivariate analyses on a battery of measures where published data supports abnormalities prior to appearance of initial psychosis symptoms, and determined if these measures would satisfactorily predict psychotic disorders. These neurobiological and behavioral measurements included cognition, eye movement tracking, auditory event related potentials (ERPs), and polygenic risk scores for schizophrenia (PRS).

Methods: The Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) measured this battery in an ancestry-diverse series of consecutively recruited adult outpatients with a psychotic disorder and healthy controls. Participants include all genders, 16 to 50 years of age, 261 with psychotic disorders (Schizophrenia (SZ) 109, Bipolar with psychosis (BPP) 92, Schizoaffective disorder (SAD) 60), 110 healthy controls.

Results: Sensitivity, specificity, and Area Under the Curve (AUC) of Receiver Operating Characteristic of 85%, 62%, and 86%, respectively, were obtained for both regression methods. These prediction metrics demonstrate a promising diagnostic distinction based on premorbid risk variables. There were also statistically significant pairwise interactions between measures in the ERM model.

Conclusions: The strong prediction metrics of both types of analytic model provide proof-of-principle for multivariate biologically-based laboratory tests as a first step toward primary prevention studies. Prospective studies of adolescents at elevated risk, vs. healthy adolescent controls, would be a next step toward development of primary prevention strategies.

Disclosure: Nothing to disclose.

38.3 Genetic Clues to Heterogeneity in ASD and Schizophrenia

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Background: Exome sequencing studies of rare, coding variation have identified more than 300 genes associated with intellectual disability (ID), ASD, and/or schizophrenia. In tandem, genome-wide association studies (GWAS) have characterized the role of common, inherited variation in shaping risk for neuropsychiatric diseases. The success of these activities provides opportunity to leverage genetic and phenotypic data together to help understand heterogeneity in the etiology and phenotypic presentation of DSM-defined outcomes. Dissection of case heterogeneity will identify individuals that share etiologic routes to their diagnosis, which could eventually have treatment implications.

Methods: This work employs results from very large (total $N > 250,000$) genetic studies of ID, ASD, and schizophrenia, as well as deeply phenotyped ASD data sets. We examined the rate of disruptive de novo variants in ID/ASD/SCZ associated genes, in individuals diagnosed with each of those disorders. We compare the rates, identifying genes in both the ASD- and schizophrenia-associated gene lists that differ in their average phenotypic preferences. We then use the polygenic transmission disequilibrium test, to understand the extent to which common and rare variant risk for ASD co-localizes. We further use polygenic risk scores to understand sex differences in liability to ASD diagnosis.

Results: Some ASD associated genes, including ANK2 and GIGYF1, remain associated with ASD at a genome-wide significant level when including in the analysis only ASD cases without ID. This is not true for the majority of ASD-associated genes, as most are more strongly associated with ID than ASD (61 of 71 ASD-associated genes have $p < 0.01$ for ID). ASD-associated genes with a schizophrenia association of $p < 0.01$ are less likely to also be associated with ID than expected by chance ($p < 0.03$), suggesting emerging stratification of the ASD-associated gene list via cross-disorder comparison. Common polygenic risk for ASD is over-transmitted to ASD-affected children from their unaffected parents using PRS constructed only from SNPs that lie within ID/ASD associated genes ($p = 0.005$). Polygenic predictors of greater educational attainment and IQ are also overtransmitted using this approach ($p < 0.001$), suggesting that co-localization of ASD's common and rare genetic influences may not map to equivalent phenotypic effects. The unaffected mothers of children with ASDs carried more common, polygenic risk for ASD themselves than the unaffected fathers ($p < 1e-07$). As this can only occur through ascertainment effects, it suggests that women are on average able to carry more genome-wide risk for ASD without meeting criteria for an ASD diagnosis.

Conclusions: The strong returns of genetic studies of ID, ASD, and schizophrenia now permit examination of variability among associated risk factors. Such comparisons will identify variability in pathways to disease, a critical component to the characterization of complex and heterogeneous neuropsychiatric outcomes.

Disclosure: Nothing to disclose.

38.4 Multi-Omics Reveals New Molecular Traits to Interpret Schizophrenia GWAS Results

Chunyu Liu

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Background: Psychiatric genetics has achieved significant progress in the past fifteen years with the help of advanced genotyping and sequencing technologies. Hundreds of common single nucleotide polymorphisms (SNPs), dozens of rare copy number variants (CNVs) have been associated with schizophrenia through genome-wide association studies (GWAS). Turning associations to causations and mechanistic interpretation are still two major challenges. Molecular traits, including gene expression,

protein abundance in the brain, are valuable intermediate phenotypes that can help to interpret the GWAS findings.

Methods: Multi-omics refers here to expression quantitative trait loci (eQTL), translation QTL (tQTL), and protein QTL (pQTL) data. We used the PsychENCODE BrainGVEx data, which has sample sizes ranging from 200–400 depends on the -omics measures. The first-trimester fetal brain data is from the Human Developmental Biology Resource (HDBR) with 134 samples. We analyzed frontal cortex from postmortem brains and fetal brains to map loci of quantitative traits. Both supervised and unsupervised methods were used to deconvolute gene expression in major neural cell types for both adult and fetal brains. Subsequently, we performed prediXcan/metaXcan to impute the corresponding molecular traits on the PGC schizophrenia GWAS. Mendelian Randomization (MR) was used to identify molecular traits that mediate the genetic effects for disease risk.

Results: We identified thousands of eQTL, tQTL, pQTL of bulk tissue of adult frontal cortex, of fetal brains, and of subtypes of major neural cells. There is a significant sharing among QTLs of the different molecular traits. All molecular traits contribute to the GWAS signals of schizophrenia. Meanwhile, different molecular traits all have their own unique trait-, cell-type-specific QTLs, with the trait-specific contribution to GWAS. New risk genes were revealed through these analyses.

Conclusions: SNPs associated with various molecular traits helped to uncover mechanisms of some of the GWAS signals of schizophrenia and likely causal variants and genes.

Disclosure: Nothing to disclose.

PANEL

39. Shaping Our Social World: Neural Mechanisms and Circuits of Social Motivation and Their Contextual Modulation

39.2 Dorsal Raphe Dopamine Input Dictates Central Amygdala Representations of Social Stimuli

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Background: Affiliative social connections facilitate well-being and survival in numerous species. Engaging in social interactions requires positive and negative motivational drive, elicited through coordinated activity across neural circuits. However, the identity, interconnectivity, and functional encoding of social information within motivational neural circuits remains poorly understood.

Methods: Here, we focused on the downstream projections of dorsal raphe nucleus (DRN) dopamine neurons using dopamine transporter (DAT)-Cre transgenic male mice (DRNDAT), allowing us to target this subpopulation of cells which we previously implicated in 'negative drive'-induced social motivation (Matthews et al., 2016). Using optogenetics, anatomical tracing, ex vivo electrophysiology and in vivo calcium imaging, we explored how the projections of DRNDAT neurons affected social motivation and the neural dynamics of the different downstream targets.

Results: We show that three prominent DRNDAT projections – to the bed nucleus of the stria terminalis (BNST), central amygdala (CeA), and posterior basolateral amygdala (BLP) – play separable roles in behavior, despite substantial collateralization ($n = 13$ mice, 2970 cells). Photoactivation of the DRNDAT-CeA projection promoted social behavior ($n = 21$ mice; $p = 0.027$) and photo-stimulation of the DRNDAT-BNST projection promoted exploratory behavior ($n = 22$ mice; $p = 0.0298$), while the DRNDAT-BLP projection supported place avoidance ($n = 12$ mice; $p = 0.0455$), suggesting a negative affective state. Downstream regions

showed diverse receptor expression ($n = 12$ mice), poisoning DRNDAT neurons to act through dopamine, neuropeptide, and glutamate transmission. Furthermore, we show ex vivo that the effect of DRNDAT photostimulation on downstream neuron excitability dependent on the anatomical target (recorded cells: BNST $n = 10$, CeA $n = 36$, BLP $n = 48$; amplitude EPSP $p = 0.03$; amplitude IPSP $p = 0.001$), suggesting cell-type-specific modulation. Finally, we performed simultaneous microendoscopic calcium imaging of CeA neurons with stimulation of DRNDAT terminals in CeA. Preliminary results using unsupervised machine learning reveal functionally distinct clusters of CeA neurons that respond differently to DRNDAT photostimulation ($n = 3$ mice, 73 cells).

Conclusions: Our findings support a role for DRNDAT projections in promoting distinct features of the response to novel social stimuli – orchestrating a coordinated, flexible response through recruitment of specific downstream circuits. This highlights the breadth of DRNDAT influence over downstream targets, the signaling complexity of this system, and its potential to underlie a shift in both behavior and affective state. Uncovering the neural circuit mechanisms which incline individuals towards sociability is key to understanding the basic human need for social connection and the neural representation of a loneliness-like-state.

Disclosure: Nothing to disclose.

39.3 A Cortical-Hypothalamic Circuit Decodes Social Rank and Promotes Dominance Behavior

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Background: How do we know our social rank? Most social species, from insects to humans, self-organize into social dominance hierarchies. The establishment of social ranks serves to decrease aggression, conserve energy, and maximize survival for the entire group. Despite dominance behaviors being critical for successful interactions and ultimately, survival, we have only begun to learn how the brain represents social rank and guides behavior based on this representation. The medial prefrontal cortex (mPFC) has been implicated in the expression of social dominance in rodents, and in social rank learning in humans. Yet precisely how the mPFC encodes rank and which circuits mediate this computation is not known.

Methods: We developed a trial-based social competition assay in which mice compete for rewards, as well as a computer vision tool to track multiple, unmarked animals. With the development of a deep learning computer vision tool (AlphaTracker) and wireless electrophysiology recording devices, we have established a novel platform to facilitate quantitative examination of how the brain gives rise to social behaviors. During this novel reward competition assay we recorded from 998 mPFC single units and used supervised machine learning to determine if social rank was encoded in mPFC. We then used optogenetics to photo-identify and manipulate mPFC cells that project to the lateral hypothalamus (mPFC-LH) and mPFC cells that project to the basolateral amygdala (mPFC-BLA) during social competition.

Results: Overall, individual mPFC cells showed patterns of activity that differed with rank during social competition, but not when animals performed the task alone. Dominant mice had more cells that were responsive to reward-seeking behavior (dom $n = 127$, sub $n = 63$ cells; $p = 0.01$), while subordinate mPFC cells had stronger responses to the competitor's reward seeking behavior (dom $n = 63$, sub $n = 59$ cells; $p = 0.0013$). To explore rank differences at the population level, we analyzed mPFC population dynamics in a lower dimensional state-space. Population dynamics were highly separated by rank and competitive success.

($n = 13$ iterations, 507 dom cells and 491 sub cells; $p = 1.6 \times 10^{-25}$). Moreover, a classifier was able to decode social rank. Next, to identify potential mPFC circuits involved in social rank encoding, we used phototagging to record two subpopulations of mPFC cells. Removing mPFC-LH cells, but not mPFC-BLA cells, from the population data decreased the accuracy of social rank decoding ($n = 50$ iterations with 43 mPFC-LH neurons; $p = 0.004$; and 10 mPFC-BLA neurons; $p = 0.091$). To directly test the hypothesis that mPFC-LH neurons modulate social dominance, we used optogenetics to stimulate mPFC-LH neurons during the social competition task. mPFC-LH stimulation in subordinate mice during the reward competition increased trials won (ChR2 $n = 9$, eYFP $n = 6$; $p = 0.03$).

Conclusions: Altogether we present a novel behavioral paradigm and tool to study social dominance behaviors. Population dynamics in the mPFC were predictive of social rank and competitive success. Finally, we demonstrate that mPFC cells that project to the lateral hypothalamus contribute to the prediction of social rank and promote dominance behavior during the reward competition. Thus, we reveal a cortico-hypothalamic circuit by which mPFC exerts top-down modulation of social dominance.

Disclosure: Nothing to disclose.

39.4 Prolonged Partner Separation Erodes Transcriptional Signatures of Pair Bonding in Prairie Voles

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Background: The loss of a spouse is often cited as the most traumatic event in a person's life, and recovery requires adapting to the absence of a salient source of motivation and reward. For most people, the severity and maladaptive effects of grief subside over time via a currently understudied neuromolecular adaptive process. Like humans, socially monogamous prairie voles (*Microtus ochrogaster*) show behavioral and neuroendocrine stress phenotypes upon partner loss, and given time, they can form a new bond, a key indicator that they have adapted to the loss of their partner. This presentation will highlight new data testing the hypothesis that extended partner separation erodes pair bond behaviors and transcription, representing a potential mechanism that enables new bond formation.

Methods: We paired male prairie voles with an opposite-sex (OS, $n = 16$) or same-sex (SS, $n = 15$) vole for 2 wks. All pairs were then separated, and we performed partner preference and resident intruder tests 48 hrs and 4 wks post-separation to measure affiliative preference and selective aggression, respectively. For transcriptional studies, we paired animals for 2 wks and then collected nucleus accumbens tissue from OS and SS-paired animals that remained paired or were separated for 48hrs or 4wks ($n = 5 - 9$ /group). For all analyses, we compared transcriptional profiles in OS versus SS paired voles to control for the effects of social context (paired vs isolated).

Results: OS and SS paired males showed a partner preference after 2 wks of pairing (one way t-test relative to null; OS: $T_{15} = 5.14$, $p < 0.001$, SS: $T_{14} = 2.014$, $p = 0.064$) Partner preference remained evident for both groups after being separated for 48 hrs (OS: $T_{15} = 3.908$, $p < 0.001$, SS: $T_{14} = 2.149$, $p = 0.050$) or 4 weeks (OS: $T_{15} = 3.908$, $p < 0.002$, SS: $T_{14} = 3.477$, $p = 0.004$). Both groups showed similar latency to aggression towards an intruder male after 48 hr (log-rank test; $\chi^2 = 1.7$, $p = 0.900$) with SS males increasing latency to aggress after 4 wks of separation (log-rank test; $\chi^2 = 4.2$, $p = 0.040$).

We compared differentially expressed genes (DEGs) in OS and SS-paired voles following 2 wks or 6 wks of pairing. We observed significant overlap in the up- and down-regulated transcripts

between timepoints (Fisher's exact test; up: 104 shared; $p = 5.359 \times 10^{-31}$; down: 46 shared, $p = 7.051 \times 10^{-14}$). RRHO2, a threshold-free approach that identifies significant overlap in ranked gene lists, revealed highly concordant gene expression profiles across pairing timepoints. We asked whether this signature remains intact following separation. Analysis of shared DEGs between pair-bond-intact voles and those separated for 48 hours showed significant overlap (87 shared; $p = 6.78 \times 10^{-19}$), which decreased after 4 weeks of separation (18 shared, $p = 0.532$), results that were further confirmed via RRHO2 analysis.

Conclusions: Partner separation results in erosion of neuro-transcriptomic signatures of pair bonding despite intact pair bond behavior. Combined with our prior work indicating that voles are capable of forming a new bond 4 wks post-separation, but not earlier, our data indicate that the erosion of pair-bond transcription may prime the vole to be able to form a new bond.

Disclosure: Nothing to disclose.

STUDY GROUP

40. How Can We Better Support Black and Other Under-Represented Scientists?

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Study Group Summary: Race and ethnicity are major contributing factors to exclusion and inequities in our universities and other scientific enterprises. In recent months, we have heard calls for equity and justice from our trainees, our colleagues, our institutions, and our scientific societies. Many scientists, including majority-group scientists, have good intentions about rectifying injustice in our scientific enterprises. Intentions, however, are cheap. Guidance and concrete plans are needed to put intentions into actions. ACNP membership comprises a powerful group of scientists who run some of the most sought-after neuroscience laboratories in academia, industry, and the government, as well as administrators who hold leadership positions in these enterprises, with access to resources and the power to influence policy. While the membership, no doubt, accepts that it is incumbent on them to actively promote equity in their scientific and professional lives, they can benefit from learning about the nuances of existing problems and different actionable ideas and steps. Accordingly, this study group will focus on potential action plans for improving the success of under-represented scientists in our field. Attention will be paid to three related themes: increasing representation and engagement, providing equitable access to and distribution of research funding, and more effective mentoring of trainees and junior faculty. The overarching aim of the discussion about these themes will be to provide actionable guidance to support the advancement of Black and other underrepresented scientists. The study group participants include individuals representing a wide range of expertise and backgrounds who have written about the topic, are actively involved in shaping institutional policies, and/or have an established track record of successful mentoring of URM trainees. They include: Dr. Marguerite Matthews, scientific program manager at NIH/NINDS involved in shaping policy and funding options related to a multitude of programs relevant to the missions of ACNP including the NIH Blueprint and NIH BRAIN Initiative; Dr. Kafui Dzirasa, a physician scientist and associate professor of psychiatry and behavioral science at Duke, who has written and spoken extensively and eloquently on how race and

ethnicity are the major fault-lines that contribute to exclusion and inequities in academia; Dr. Damien Fair, professor and director of the Masonic Institute for the Developing Brain at University of Minnesota and a MacArthur fellow who has a long-standing track record of promoting neurodiversity and advocacy for equitable education and mentoring of URM trainees; and Dr. Michael Taffe (professor of psychiatry at UCSD) and Dr. Nicholas Giplin (professor of physiology, LSU) who have written about solutions to overcome racial inequity in NIH funding. Representatives of institutional leadership to provide administrative insight for the feasibility of proposed solutions will include Dr. Sophia Vinogradov, chair of the Department of Psychiatry at University of Minnesota, Dr. Carlos Zarate, president-elect of ACNP, and Dr. Joshua Gordon, director of NIMH.

Disclosure: Nothing to disclose.

MINI PANEL

41. Molecular, Genetic and Imaging Markers of Resilience to Post Traumatic Stress

41.1 Increased mGluR5 Availability Following Traumatic Stress is Associated With Greater Fear Expression in Rats: An in Vivo [18F]FPEB and PET Imaging Study

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Background: Evidence suggests some individuals may be more susceptible to developing posttraumatic stress disorder (PTSD), while others may be more resilient. Identifying predictive biomarkers of vulnerability would aid in the discovery of improved PTSD treatments. Clinical neuroimaging and postmortem findings suggest a role for the metabotropic glutamate receptor 5 (mGluR5) in PTSD pathology. Further elucidating the nature of the relationship between mGluR5 and disease etiology requires prospective and mechanistic studies which are not feasible in clinical populations. Therefore, we utilized a rodent model to assess the utility of mGluR5 as a biomarker of traumatic-stress vulnerability.

Methods: Rats were exposed to traumatic stress [$n = 16$ males (M), $n = 12$ females (F)] on Day 1 of a stress-enhanced fear learning (SEFL) paradigm. Contextual fear memory (Day 2) was used to classify rats as resilient (RES) or vulnerable (VUL). Novelty-induced fear, stress sensitization (Day 3), and stress-enhanced fear memory (Day 4) were assessed relative to no-trauma exposure controls (CON: $n = 7$ M, $n = 4$ F). Positron emission tomography (PET) pre and post-SEFL was used to calculate [18F]FPEB non-displaceable binding potential (BPND), with amygdala, hippocampus, prefrontal cortex (PFC), and striatum as ROIs. The %change in mGluR5 availability pre vs post was calculated as Δ BPND. Label free quantitative LC MS/MS was performed to identify differentially expressed proteins in the PFC of CON ($n = 3$ M, $n = 4$ F), RES ($n = 7$ M, $n = 6$ F) and VUL ($n = 5$ M, $n = 6$ F). The IPA platform was used for functional analysis.

Results: VUL rats displayed the most freezing on SEFL Day 1 vs CON and RES (both $p < 1.0E-4$) and demonstrated stronger contextual fear memory vs RES ($p < 1.0E-4$). VUL rats also displayed greater novelty-induced fear ($p = 3.6E-2$) and stress sensitization ($p < 1.0E-4$) vs CON. For SEFL (RES + VUL), there was a significant positive correlation between Δ BPND and freezing during SEFL Day 1 for all ROIs ($n = 32$, $r = 0.424$ - 0.538 ; $p = 3.9E-2$ - $7.0E-3$). PFC Δ BPND was significantly associated with contextual fear memory ($n = 32$, $r = 0.50$, $p = 1.0E-2$). Top enriched pathways for M-SEFL

(RES + VUL) vs M-CON included synaptic LTD ($p = 3.31E-13$), CRH signaling ($p = 2.88E-11$), and Gq signaling ($p = 1.51E-10$), with all pathways predicted to be activated (z Score= 3.16 - 3.64). Top enriched pathways for F-VUL vs F-CON included glutathione metabolism ($p = 1.14E-04$), axonal guidance ($p = 8.03E-4$), and acute phase response ($p = 2.51E-03$).

Conclusions: Greater freezing during the SEFL procedure and stronger contextual fear memory were associated with a larger increase in mGluR5 availability, particularly in the PFC, suggesting upregulation of mGluR5 may be involved in the etiology of PTSD related phenotypes. The exploratory proteomics analysis indicated the SEFL procedure in males resulted in an upregulation of GPCR and glucocorticoid signaling, while the vulnerable phenotype in females is associated with changes in second-messenger signaling and cellular stress response pathways, highlighting potentially important differences in male and female responses to trauma and stress.

Disclosure: Nothing to disclose.

PANEL

42. Neuromodulators in Disease-Relevant Affective Processing

42.1 Regulation of Binge Alcohol Drinking-Induced Socio-Affective Disturbances by Lateral Habenula Serotonin 5HT2c Receptors

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Background: Binge alcohol drinking is a severe public health problem that is often a precursor to alcohol dependence. While some individuals engage in binge drinking to relieve symptoms of anxiety or depression, repeated cycles of binge drinking may exacerbate these symptoms, leading to further increases in drinking and potential transitions to dependence. Recent work suggests that increased anxiety-like behavior associated with alcohol dependence is regulated by serotonin 5HT2c receptors in the lateral habenula (LHb) in male rodents. However, whether LHb 5HT2c also regulates affective symptoms induced by non-dependent binge alcohol drinking remains unexplored in either males or females.

Methods: Adult male and female C57BL6/J, 5HT2c-Cre, or 5HT2c-flox mice were subjected to 3 weeks of Drinking in the Dark (DiD) or water drinking. One week following drinking, affective behaviors were tested in the 3 chamber sociability test, acoustic startle test, and open field test. In-vivo calcium imaging of LHb 5HT2c neurons was performed using GCaMP7f fiber photometry, while in-vivo measurement of 5-HT release onto LHb-5HT2c neurons was performed using GRAB-5HT fiber photometry. Knockdown of LHb 5HT2c was achieved by injecting AAV8-Cre into the LHb of 5HT2c-flox mice. LHb 5HT2c neurons were chemogenetically manipulated by injecting AAV8-DIO-hM3Dq into the LHb of 5HT2c-Cre mice.

Results: DiD increased anxiety-like behavior in the open field test in both sexes, but reduced social recognition only in females ($p = 0.008$) and increased acoustic startle responses only in males ($p = 0.02$). Neuronal tracing and histology revealed that the LHb receives 5-HT inputs from the caudal aspect of the dorsal raphe nucleus (DRN), LHb 5HT2c neurons express vGlut2, and LHb 5HT2c neurons project back to the DRN. In males, DiD had no effect on the responses of LHb 5HT2c neurons to alcohol, social interaction, or acoustic startle stimuli. However, in females, DiD increased the responsivity of LHb 5HT2c neurons to alcohol consumption

($p = 0.04$), suggesting stimulus-specific plasticity in these neurons as a result of DiD exposure. DiD had no effect on stimulus-evoked 5HT release onto Lhb 5HT2c neurons in either sex. Chemogenetic activation of Lhb 5HT2c neurons reduced binge alcohol consumption, sucrose consumption, social behavior, and acoustic startle responses in both sexes. Ongoing experiments will determine whether knockdown of Lhb 5HT2c prior to DiD protects against binge drinking-induced affective disturbances.

Conclusions: Together, these data suggest that sex-specific affective disturbances induced by binge drinking are driven, at least in part, through Lhb-5HT2c. This may ultimately have important implications for the development of pharmacological treatments for alcohol use disorders.

Disclosure: Nothing to disclose.

42.2 Intersection of Opioid and Nociceptive Networks in the Cingulate Cortex

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Background: Pain is an unpleasant emotional experience. Recent work from our lab and others have identified stable populations of neurons activated by acutely noxious stimuli in the amygdala and in the anterior cingulate cortex (ACC) key to this affective facet of pain. Further, opioids, the current standard of care for chronic pain, in the ACC play a role in ameliorating perception of the aversive quality of pain through mu opioid receptors (MOR). We hypothesize that MOR-expressing and nociception-active neurons in the ACC overlap and represent a crucial population in mediating affective nociceptive behavior. We used single nucleus RNA sequencing (snRNAseq) to identify nociception-active cell types in the ACC expressing MOR. Localizing nociception-active ACC neurons and manipulating ACC MOR activity during nociception provides further insight into this novel affective pain target.

Methods: ACC tissue for snRNAseq was collected in neuropathic pain or control mice ($n = 5$ /condition, male). All mice experienced a noxious thermal stimuli prior to tissue collection to induce expression of immediate early genes (IEG). Next, single nuclei were isolated, cDNA libraries prepared, sequence, and aligned. Single nuclei clustering was performed in Seurat_v3. Well-characterized, a priori markers of cortical cell types were used to identify the subpopulations represented by each cluster (Slc17a7 for excitatory neurons, Gad1/2 for inhibitory interneurons). 14,220 individual nuclei (7,011 control, 7,209 neuropathic) were analyzed. MOR and nociception-active populations were identified by Oprm1 and 139 different IEGs, respectively.

To localize ACC nociception-active neurons, neurons activated by a noxious stimulus were labeled with tdTomato using a TRAP2 (Targeted Recombination in Active Populations):Ai9 line ($n = 6$, male and female); ACC nociception-active neurons were quantified with ImageJ.

In a preliminary study, ACC MOR neurons were chemogenetically inhibited during evoked behavioral responses mechanical and noxious thermal stimuli (Oprm1-Cre line; $n = 5-7$; male and female).

Results: We identified 22 unique clusters from all major cell types (neurons and glia), including 8 glutamatergic neuron (Slc17a7) and 4 GABAergic interneuron (Gad1/2) clusters. We found Slc17a7 neuron clusters were the most transcriptionally active to the noxious stimuli, notably three clusters with single genetic identifiers: Otof, Figf, Npr3. The Figf cluster was also Oprm1 + , suggesting this cell type is well-positioned to influence nociceptive affective processes. Next, we determined the location of nociception-active neurons within the ACC. TRAP2:Ai9 histology

revealed that nociception-active neurons are present throughout the ACC, with prominent labeling in layer 2/3 as well as 5. Finally, we assessed the role ACC MOR neuron activity on affective nociceptive behavior. Chemogenetic inhibition of ACC MOR neurons reduced responding to acute mechanical, but not noxious thermal, stimuli in control and neuropathic pain mice, suggesting ACC MOR activity contributes to chronic pain allodynia.

Conclusions: We provide insight into the cell type and location of nociception-active and MOR neurons in the ACC, and insight into the behavioral effect of MOR ACC activity neurons during nociception. Future studies will use intersectional approaches to manipulate MOR/nociception-active neurons during behavior, which we hypothesize mediates the affective analgesic effects of opioid therapies. Identifying specific networks underlying the therapeutic effects of opioids can aid the development of analgesics with improved selectivity.

Disclosure: Nothing to disclose.

42.3 Biased Signaling Modifies the Rewarding Properties of Mu-Opioid Receptors

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Background: Overdose deaths involving opioids have skyrocketed nationally over the last 20 years. One major difficulty in addressing this epidemic is that both the therapeutic (i.e., analgesic) and addictive properties of opioids act via mu-opioid receptors (MOPRs). However, growing evidence suggests that these different properties may be mediated by dissociable intracellular signaling mechanisms (G-protein signaling vs. beta-arrestin signaling). Recently, we have shown that MOPRs exert their rewarding, but not analgesic, effects via a lateral dorsal raphe to nucleus accumbens circuit (LDRN-mNACSh). Here, we sought to determine how G-protein or arrestin signaling specifically control MOPR modulation of reward. By isolating these MOPR mechanisms, we can design more effective therapeutic opioids that reduce, or even avoid, their abuse potential.

Methods: Male and female adult (8-16 weeks) mice were used for all studies. Behaviorally, mice were tested (7-13/group) on a food intake task in which they were allowed to freely consume sucrose pellets for one hour. Mice were tested while ad libitum or after an acute 24 hour food deprivation. Mice were also tested on a lickometer task in which they were allowed intermittent access to a sucrose solution. Mice were tested while ad libitum or after an acute 18 hour water deprivation. Statistically, we used parametric ANOVAs/t-tests. Effect sizes and confidence intervals were also calculated to supplement findings. Several mice (3-6/group) were also used for anatomical validation.

Results: MOPR knockout mice (OPRM1 KO) ate and licked less after food or water deprivation compared to wildtype mice. In contrast, beta-arrestin 2 knockout mice (Arrb2 KO) did not show overall deficits in food intake or lickometer tests, indicating that arrestin does not primarily mediate MOPR modulation of reward behaviors. Further analysis of lick microstructure showed that the reductions in licks in OPRM1 KO mice was driven by fewer initiations of lick bouts ($p = 0.018$), whereas lick bout durations were similar between KO and wildtype mice ($p = 0.231$). Arrb2 KO mice also performed fewer bouts ($p = 0.014$), but had lick bout durations that were nearly twice as long as wildtype mice ($p = 0.089$). Perhaps indicating that arrestin may play a role in how reward behaviors are expressed. To further isolate the contribution of arrestin signaling in MOPR mediated behaviors, we selectively expressed a G-protein biased mutant MOPR in OPRM1 KO mice in the LDRN-mNACSh circuit. We found that this selective rescue

partially restored food intake ($p=0.11$) and lick behavior compared to wildtype mice. Furthermore, we found that this rescue induced a similar lick microstructure phenotype as there Arrb2 KO mice, wherein they showed increased lick bout duration but not lick bout initiation ($p < 0.001$). Ongoing studies include the development of G-protein specific CRISPR/Cas9 viral vectors for selective disruption of different G-protein subunits, as well as selective restoration of arrestin signaling in Arrb2 KO mice. Future experiments will also test how exogenous opioid rewards (e.g., morphine) are affected by G-protein or arrestin signaling.

Conclusions: Conclusion: These results show that both G-protein and arrestin signaling contribute to MOPR mediated reward behaviors, and do so in a complementary fashion. Specifically, G-protein signaling appears to be necessary for reward consumption initiation, whereas arrestin is necessary for reward consumption cessation. These results have major implications for therapeutic opioid drug development.

Disclosure: Nothing to disclose.

42.4 Cannabinoid Modulation of Hyper-Reward Responsivity and Hyper-Exploration in Mice With Reduced Dopamine Transporter Expression Model of Bipolar Mania: Revealing Mechanisms From Clinical Observations

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Background: Bipolar disorder (BD) is a life-shortening disease affecting 2-5% of the world, driving 1 in 3 to attempt suicide. Treatment side-effects and lack of specificity means novel therapies are urgently needed. People with BD are ~7 times more likely to use cannabis vs. the general population, perhaps attempting self-medicate given lower anandamide (AEA) expression seen in BD, but disentangling such effects are difficult in human studies. Mice with reduced DAT expression recreate hyper-reward responsiveness and hyper-exploration in mice consistent to people with BD, but AEA levels have yet to be determined. Here, we tested the hypotheses that: 1) DAT KD mice would also exhibit reduced AEA levels, while 2) Δ^9 -tetrahydrocannabinol (THC) and 3) cannabidiol (CBD) (the two main components of cannabis), would remediate the hyper-reward responsive and hyper-exploratory profile of DAT KD mice.

Methods: Multiple cohorts of mice tested, DAT mutant mice produced via heterozygote breeding pairs, or C57BL/6J mice (DAT background strain). Cohort 1: Female and male DAT WT and KD mice for AEA analysis. Cohort 2: Male C57BL/6 mice treated with vehicle or CBD (3 or 30 mg/kg), for 5 or 15 days for AEA analysis. Cohort 3: Female WT and KD mice treated with vehicle or THC (3 mg/kg) prior to exploration testing. Cohort 4: Female and male DAT WT and KD treated with vehicle or THC (0.3 or 3 mg/kg) for 4 days prior to motivation testing. Cohort 5, Female and Male DAT WT and KD mice treated with vehicle or CBD (3 or 30 mg/kg) for 15 days prior to exploration and motivation testing

Results: Cohort 1: DAT KD mice exhibited significantly lower striatal AEA levels than WT mice irrespective of sex. Cohort 2: C57BL/6 mice treated with CBD (30 mg/kg) over 15 days increased AEA levels, no effect after 5 days. Cohort 3: THC reduced activity and rearing in DAT KD mice vs. their vehicle-treated controls. Cohort 4: Vehicle-treated DAT KD mice exhibited higher breakpoint than WT mice while 4-day THC (3 mg/kg) treatment increased breakpoint irrespective of sex and gene. Cohort 5: 15-day CBD treatment significantly lowered hyperactivity and hyper-exploration in male DAT KD mice, with no effect in females, while no gene or drug effects was seen in motivation.

Conclusions: DAT KD mice exhibited reduced AEA levels like people with BD. Chronic CBD treatment (15-days at 30 mg/kg),

increased AEA levels in male C57BL/6J mice and normalized hyper-exploratory behavior in male DAT KD mice. Acute THC treatment normalized the hyper-exploratory behavior in DAT KD mice but 4-day treatment induced hypermotivation. Data on the impact of chronic THC treatment on hyper-reward responsiveness and hyper-exploration, in addition to effects of such CBD and THC treatment on AEA levels in DAT KD mice are being collected enabling direct comparisons of their effects. These data indicate the potential for cannabinoids to normalize BD-relevant behavior and reveal a potential biomarker for treatment responsiveness, normalizing AEA levels.

Disclosure: Nothing to disclose.

MINI PANEL

43. Clinical Applications of Neurofeedback for Post-Traumatic Stress Disorder and Depression

43.1 Beyond the Amygdala: Mechanisms of Posterior Cingulate Cortex Downregulation and Symptom Decreases in Post-traumatic Stress Disorder Using Real-Time fMRI Neurofeedback

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Background: Intrinsic connectivity networks in the human brain, including the default mode network (DMN), frequently display disrupted functioning among those affected by post-traumatic stress disorder (PTSD). The posterior cingulate cortex (PCC) is the main hub of the posterior DMN and typically shows hyperactivity in PTSD when individuals are recalling and re-experiencing trauma memories. Critically, the therapeutic normalization of pathological activation in the PCC with real-time fMRI neurofeedback (NFB) has yet to be explored in PTSD.

Methods: Using real-time fMRI NFB, we investigated the mechanisms of PCC downregulation during trauma/stressful word presentation over 3 NFB training runs and a transfer run without NFB [total $n=29$ (PTSD $n=14$, healthy controls $n=15$)]. Additionally, we examined the predictive accuracy of machine learning models in classifying PTSD and healthy controls during NFB training based on neural activation.

Results: We found that both the PTSD [$F(1, 13)=37.6, p < .0001, \eta^2=.743$] and healthy control [$F(1, 14)=33.67, p < .0001, \eta^2=.706$] groups were able to downregulate the PCC with similar success over NFB training and in the transfer run. We observed reduced symptoms of reliving over NFB training in the PTSD ($p=.016$) and healthy control ($p=.008$) groups, where the PTSD group additionally showed reduced symptoms of distress ($p=.010$). Importantly, downregulation was associated with unique within-group decreases in activation within the bilateral dorsomedial prefrontal cortex, the bilateral postcentral gyrus, the right amygdala/hippocampus, the cingulate cortex, and the bilateral temporal pole/gyri. By contrast, downregulation was associated with increased activation in the right dorsolateral prefrontal cortex among healthy controls as compared to PTSD. Here, right dorsolateral prefrontal cortex activation was negatively correlated to PTSD symptom severity scores and difficulties in emotion regulation. Moreover, anterior insula and cerebellum (lobule VI/crus I) activation was positively correlated to PTSD symptoms. Finally, machine learning models were able to accurately classify PTSD and healthy participants based on neural activation during NFB training with over 80% balanced accuracy (ROC = 0.85, $p < .001$ permutation testing).

Conclusions: This is the first study to investigate PCC downregulation with real-time fMRI NFB in both PTSD and healthy individuals. Our results reveal acute decreases in symptoms over training and provide converging evidence for EEG-NFB targeting brain rhythms linked to the PCC. Future clinical trials of real-time fMRI NFB investigating PCC downregulation in PTSD are warranted to leverage the effects of multiple training sessions.

Disclosure: Nothing to disclose.

43.2 Who Can Regulate? Factors Associated With Successful Amygdala Neurofeedback Learning in Depression

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Background: Patients with major depressive disorder (MDD) show hypoactive amygdala responses to positive stimuli, including positive autobiographical memories. By providing real-time fMRI neurofeedback regarding amygdala activity, patients with MDD are able to increase their amygdala response during positive memory recall. This results in significant symptom improvement. However, approximately 30% of participants are unable to increase their amygdala response with training. Here, we combine data from multiple experiments to examine whether demographic, clinical, cognitive, and neural factors are related to neurofeedback learning success.

Methods: This analysis includes 52 participants who received amygdala neurofeedback. Participants come from 3 different clinical trials of amygdala neurofeedback where the same baseline information was collected (NCT02079610, NCT02709161, NCT03428828). Participants received two neurofeedback training sessions where they were instructed to increase the level of a thermometer representing their amygdala activity while recalling positive autobiographical memories. Each session started with a baseline run during which no neurofeedback was provided and ended with a transfer run where no neurofeedback was provided but participants were told to use what they had learned during training. Neurofeedback success was defined as a significant increase from baseline to the final transfer run. The following variables measured prior to training were examined to determine if they were related to neurofeedback success: age, sex, length of current depressive episode, number of previous depressive episodes, depression severity assessed by the HDRS and BDI-II, anhedonia assessed by the SHAPS, Alexithymia assessed by the TAS, rumination assessed by the ATQ, current mood state assessed by the POMS, and baseline amygdala activity during positive memory recall prior to neurofeedback training.

Results: There was a strong correlation between baseline amygdala activity and neurofeedback success ($r = -0.63, p < 0.001$). There were no other significant correlations with neurofeedback success ($r_s < 0.183$ ps > 0.301). Finally, being male was also associated with less neurofeedback success relative to females ($t(50) = 2.05, p = 0.047$).

Conclusions: Male sex and high amygdala activity during positive memory recall prior to training were associated with less neurofeedback success. Our results suggest that our deficit targeting intervention is only effective in those who present with this deficit (blunted amygdala activity during positive autobiographical memory recall). Furthermore, men with MDD may have different mechanisms underlying their depression that require different interventions. The lack of significant correlation with any other demographic or clinical feature suggests that this intervention is appropriate for all females with depression so long as they present with blunted amygdala activity during positive autobiographical memory recall.

Disclosure: Nothing to disclose.

43.3 Amygdala and Social Cognition Circuits During and Following Neurofeedback in Depressed Youth

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Background: Many adolescents show recurring depressive episodes, resulting in economic and human suffering due to treatment-resistant depression (TRD). The goal of the present study was to determine the effect of a novel neurofeedback procedure on the circuitry of visual self-recognition among adolescents with and without depression. The amygdala and hippocampus (AMYHIP) govern self-processing, emotion regulation and recall of emotional memories. They are reciprocally connected to midline cortical structures (MCS) to enable both self-processing and emotion regulation. Disrupted functional connectivity between these areas results in blunted affect, inappropriate emotional responses, and impaired processing of affective memories in depressed patients. Given the disrupted connectivity between AMYHIP and MCS in depression and their roles in self-processing and emotion regulation, the amygdala and hippocampus were the present study's loci of neurofeedback as well as of examination after versus before the neurofeedback procedure.

Hypotheses (H): (H1) Control and depressed youth would display different AMYHIP connectivity with MCS. (H2) Depressed participants would display connectivity patterns more similar to control youth during self vs. other face processing after neurofeedback. (H3) Depressed youth's connectivity patterns would change in ways unlike control youth. (H4) AMYHIP hemispheric differences would be present due to hypothesized unique emotion regulation functions enabled by the left versus right AMYHIP during emotionally salient mental activities.

Methods: Right-handed adolescents ($N = 53$), with ($N = 34$) and without ($N = 19$) depression, completed the Emotional Self-Other Morph Neurofeedback task (ESOM-NF). Participants also completed a self vs. other recognition task (ESOM-Q) before and after the ESOM-NF task. The highest peak of activity in the left and right amygdala were used as seeds for psychophysiological interaction (PPI) analyses. There were no significant areas associated with connectivity to the hippocampus. ESOM-Q data was subjected to a 2nd level GLM analysis: two between-group effect of diagnosis (with vs. without depression) by two within-group effect of time (time 1 vs. time 2) by two within-group effect of amygdala hemisphere (left vs. right). Variables that differed between diagnosis groups (IQ) were added as a covariates.

Results: Group by time interaction: Cortical to amygdala connectivity varied as a function of time between depressed and healthy adolescents. During ESOM time 1, depressed youth showed significantly higher cortico-amygdalar connectivity as compared to controls. However, depressed youth showed significantly lower cortico-amygdalar connectivity during ESOM time 2.

Group by hemisphere interaction: Cuneus-amygdala connectivity differed within hemisphere and between groups. Depressed youth showed lower left amygdala to cuneus connectivity as compared to controls. However, depressed youth showed significantly higher right amygdala to cuneus connectivity as compared to controls.

Conclusions: Increased right amygdala-cortical connectivity in depressed youth during self-processing suggests implicit emotion regulation, while increased left amygdala-cortical connectivity in healthy youth suggests explicit emotion regulation. In summary, neurofeedback resulted in altered amygdala functional

connectivity in both depressed and healthy control youth during self-recognition tasks.

Disclosure: Nothing to disclose.

PANEL

44. Mechanisms of Neurodevelopmental Risks in Childhood: Interactions of Stress and Environmental Toxicants

44.1 Interacting Effects of Prenatal Maternal Stress and Pyrethroid Exposure on Brain Development Relevant to Neuropsychiatric Risk: Mechanisms of Maternal Hepatic Inflammation, Reduced Metabolism, and Changes to Placental Structure and Function

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Background: Prenatal exposure to pyrethroid insecticides is a risk factor for neuropsychiatric problems in children. Despite widespread exposure, there is a gap in knowledge about mechanisms by which pyrethroids alter brain development, including whether pyrethroids reach the fetal brain to have a direct impact. Increased effects of prenatal pyrethroids and unique mechanisms involved in their effects may arise from exposome-related combinations—i.e. co-occurrence with other common exposures such as stress. In particular, how stress and pyrethroids together may influence indirect pathways that affect the brain via the placenta is unknown.

Methods: To address these questions, CD1 mouse dams were treated with 10mg/kg α -cypermethrin ($n = 12$) or corn oil vehicle ($n = 12$) via oral gavage for four days during a period of forebrain neurogenesis and migration, embryonic days 11 to 14 (E11-E14). Half of dams underwent three times daily restraint stress (45 min) on the same days; tissues from E14 were assessed. Prolonged α -cypermethrin exposures (E6-E16) at a range of dose 0.3-10 mg/kg ($n = 10$ per group) were also used to investigate placental mechanisms.

Results: The combination of α -cypermethrin and maternal stress reduced offspring forebrain volume, delayed microglia cellular development, and delayed tangential migration of GABAergic progenitors into the cortical plate. RNA sequencing of migrating GABAergic progenitors identified 60 differentially expressed genes unique to maternal α -cypermethrin and stress exposure, implicating biosynthetic and metabolic processes which may reflect placental nutrient transport.

We found that increased inflammation (IL-6, $p < 0.01$; IL-1 β , $p < 0.001$) in maternal liver when α -cypermethrin and stress exposure were combined predicted ($r = 0.58$, $p < 0.05$) the over two-fold increased level of α -cypermethrin in serum of stressed dams (Mann-Whitney; $p < 0.05$), suggesting that stress has impacts through increasing the effective “dose” of pyrethroid by impairing metabolism.

Despite this, α -cypermethrin measurement in fetal body and amniotic fluid found very low levels (20-30 or 300 times lower respectively than in maternal serum), implicating indirect mechanisms by which offspring brain could be affected, potentially through placental dysfunction.

Therefore, we investigated maternal exposure to a range of pyrethroid dose to determine links between increasing dose, placenta changes, and neurodevelopmental outcomes. Indeed, forebrain growth and cellular markers of development such as microglial morphology showed dose-dependent delays. Some impacts of α -cypermethrin on placenta were non-linear with

respect to dose: cytokine levels and macrophage number. However, others were dose-dependent and correlated with neurodevelopmental delays: labyrinth zone thickness reduction and Depp1 transcriptional increase. In addition, module-trait correlation analysis of α -cypermethrin induced changes showed altered placental chemokine gene expression trend correlated with delayed fetal brain microglia changes ($r = 0.63$, FDR corrected $p = 0.06$).

Conclusions: Maternal α -cypermethrin exposure, when combined with stress exposure, had increased impacts on offspring brain development through increased maternal toxicant level, which was correlated with placental structural changes, oxidative stress, and chemokine pathways. These placental mechanisms may underlie neuropsychiatric risk linked to pesticide exposure.

Disclosure: Nothing to disclose.

44.2 Associations Between Ambient Fine Particulate Matter, Maternal Lifetime Stress and Infant Temperament: Mechanistic Insights Through the Application of Mitochondrial DNA Whole Genome Sequencing of the Placenta

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Background: Prenatal ambient fine particulate matter (PM_{2.5}) and maternal psychosocial stress have been shown to impact neurodevelopment including infant temperament. Both exposures have been associated with changes in placental mitochondrial DNA (mtDNA) copy number suggesting disrupted mitochondrial placental function may play a role. We have shown that maternal psychosocial stress is associated with increased mtDNA mutations; it is unclear if PM_{2.5} exposure or the co-exposure of PM_{2.5} and stress impact mutational load and subsequently infant temperament.

Methods: This study examines the impact of PM_{2.5}, maternal lifetime psychosocial stress, and mtDNA mutational load at birth on infant temperament in an urban cohort ($n = 304$). Mothers' daily exposure to PM_{2.5} over gestation was estimated using a satellite-based spatio-temporally resolved prediction model. Lifetime exposure to potentially traumatic stressors was ascertained using the Life Stressor Checklist-Revised. Whole placental mtDNA sequencing samples was performed to identify total, nonsynonymous, and gene-specific mutational loads. Mothers completed the Infant Behavior Questionnaire-Revised when the children were 6 months old and three dimensions were derived: Extraversion (Ext), Negative Affectivity (NA), and Orienting and Regulation (OR). Bayesian Distributed Lag regression models were used to statistically model and visualize the PM_{2.5} timing-dependent pattern of associations with mtDNA mutational load. A Cross-validated Ensemble of Kernels method was used to test for interactive effects between PM_{2.5} and psychosocial stress. Weighted quantile sum (WQS) regression was used to develop a weighted mtDNA mutational load index to predict infant temperament using sums of empirically weighted percentiles.

Results: Increased prenatal PM_{2.5} exposure was associated with a greater amount of nonsynonymous mutations with critical windows of exposure being identified in mid to late pregnancy; the association was the strongest with co-exposure to psychosocial stress. Gene-specific analyses revealed the strongest associations among genes coding for NADH dehydrogenase and subunits of ATP synthase; mutations among NADH dehydrogenase genes were also affected by psychosocial stress in addition to cytochrome C oxidase genes. Increases in the weighted mtDNA mutational load index were significantly associated with increases

in Ext ($\beta = 3.05$, $SE = 0.65$, $P < 0.0001$), NA ($\beta = 3.26$, $SE = 0.74$, $P < 0.0001$), and OR ($\beta = 3.30$, $SE = 0.89$, $P = 0.0003$). This was mainly driven by mutations among NADH dehydrogenase genes which account for 56%, 44%, and 37% of the effect on Ext, NA, and OR, respectively. Overall, stress-related mutations were a stronger predictor of temperament (WQS weights from 19–28%) compared to PM2.5 (9–14%).

Conclusions: Prenatal PM2.5 exposure and psychosocial stress are associated with increased placental mitochondrial mutational load, particularly in mid to late pregnancy. Given that both PM2.5 and psychosocial stress are predominantly linked to increased mutations among NADH dehydrogenase genes (Complex 1 of the electron transport chain), and subsequently mutations among these genes are a main driver of temperament outcomes, further work is needed to tease out the role of NADH dehydrogenase in early neurodevelopment.

Disclosure: Nothing to disclose.

44.3 Effects of Prenatal Air Pollution and Maternal Stress on Social Behavior: Roles for Microbiota, Microglia, and Dopamine

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Background: A wealth of epidemiological work suggests that perinatal exposure to air pollution is associated with risk for autism spectrum disorders (ASD). Moreover, psychosocial stressors activate the maternal immune system, making mothers more sensitive to toxicants. Yet, the mechanism by which stress and pollutants synergize to produce risk has yet to be determined. ASD is characterized by impaired social interaction and social communication and is male-biased. Importantly, ASD is often accompanied by gastrointestinal dysfunction, and fecal microbiota transfer therapy has yielded promising amelioration of behavioral symptoms in ASD. In a novel mouse model of combined prenatal diesel exhaust particles (DEP) and maternal stress (MS) we have found that male but not female offspring have deficits in social behavior, changes in the gut microbiome, and altered neuroimmune interactions within the mesolimbic reward system. Here, we aim to investigate the causal links between the microbiome, brain, and social outcomes.

Methods: First, we aimed to test whether restoring healthy gut microbiota could rescue social behavior following DEP/MS. Thus, we used a) a cross-fostering procedure to assess intervention at birth and b) co-housing with naïve cage mates at weaning to assess intervention later in life. These manipulations have been shown to shift the composition of the gut microbiome. In cross-fostering experiments, DEP/MS exposed male and female pups were fostered on the day of birth to either a DEP/MS or a VEH/CON exposed dam. For co-housing, DEP/MS exposed male offspring were housed at weaning with either 3 littermates or 3 wild-type cage mates. In both experiments, social behavior was assessed during adolescence using a 3-chambered social preference test and 16S sequencing was used to assess the gut microbiome. Second, we used a chemogenetic approach to test whether activation of the dopamine system could rescue social behavior. DAT-cre mice were prenatally exposed to either VEH/CON or DEP/MS. At postnatal day 23, males of both treatments received stereotaxic microinjection of either AAV-hSyn-DIO-mCherry (control virus) or AAV-hSyn-DIO-hM3Dq-mCherry (virus encoding the excitatory DREADD receptor) into the ventral tegmental area. Clozapine-N-oxide (CNO) was administered peripherally 30 min before social behavior testing 10 days later.

Results: Our results show that cross-fostering of DEP/MS exposed male pups to VEH/CON dams on the day of birth

prevents deficits in sociability ($t(1,13) = 3.334$, $p < 0.01$). Similarly, co-housing with naïve cage mates reverses social behavior impairments in male offspring ($t(1,20) = 2.177$, $p < 0.05$). Finally, chemogenetic activation of VTA dopamine neurons restores sociability in DEP/MS-exposed male offspring ($F(2,26) = 4.253$; $p < 0.05$).

Conclusions: These results suggest that the gut microbiome may causally contribute to the changes in social behavior observed in male offspring following DEP/MS exposure. Furthermore, driving activity of the mesolimbic dopamine system is sufficient to rescue these social behavior impairments. Importantly, this work also suggests that intervening during either the perinatal or adolescent period may be effective at reducing social behavior impairments. We are currently investigating whether microglia act as key intermediaries between the gut microbiome and the dopamine system in the developmental sculpting of these social circuits.

Disclosure: Nothing to disclose.

44.4 Prenatal Exposure to Air Pollution and Early Life Stress on Infant Temperament, Hippocampal Subregional Volumes, and Visual-Spatial Reasoning

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Background: Socioeconomic disparities place children from low-income family and neighborhood settings at high risk for exposure to stressful life events and air pollution, both of which have been linked with internalizing symptoms and poor academic achievement. Herein we study if specific dimensions of early life stress are associated with children's temperament phenotypes, internalizing behaviors, and hippocampal subfield volumes and if prenatal exposure to air pollution magnifies these effects. We also investigate associations between hippocampal volumes and visual-spatial reasoning.

Methods: Forty Hispanic/Latinx and non-Hispanic/Latinx Black children, age 7–9 years old, enrolled in the Sibling Hermanos birth cohort followed in the Columbia Center for Children's Environmental Health completed a structural MRI scan and cognitive assessment. Air pollution was estimated via the sum of eight airborne polycyclic aromatic hydrocarbons (PAH) during the 3rd trimester of pregnancy. Maternal report of psychosocial stressors (perceived stress, psychological distress, social support, intimate partner violence, neighborhood quality, material hardship) and children's temperament was measured at child age 5 (EAS Survey). Children's internalizing problems (INT) were assessed at age 7 (Children's Behavioral Check List). Left and right whole hippocampus as well as CA1, CA3, and CA4/dentate gyrus hippocampal (Hi) subfield volumes were extracted using Freesurfer 6.0. Wechsler Abbreviated Scale of Intelligence-2nd edition Performance Intelligence Quotient (PIQ) measured visual-spatial reasoning. Multiple linear regression tested associations between left and right hippocampal volumes, and the stress by prenatal air pollution interaction on whole and subregional hippocampal volumes, residualized for age, sex, and total intracranial volume, false discovery rate (FDR) corrected. Multiple linear regression controlling for age and sex tested PAH-related hippocampal associations with PIQ, associations between PAH, temperament, and INT, and if temperament mediated associations between PAH and INT.

Results: Maternal perceived stress was the only stress dimension that associated with hippocampal subfields; prenatal PAH moderated this association with strongest effects in CA3 ($\beta = -.59$, 95% Confidence Interval [CI]: $-.95, -.22$, $pFDR = .03$). Children with

higher prenatal PAH and higher perceived stress had smallest right hippocampal subfield volumes. Right CA3 volume was positively associated with PIQ ($\beta = .38$, 95% CI: $-.05, .71$, $p = .02$). Prenatal PAH associated with shyness at age 5 ($\beta = .30$, 95% CI: $.14, .56$, $p = .01$), which was associated with INT at age 7 ($\beta = .49$, 95% CI: $.29, .68$, $p < .001$), and shyness mediated effects of prenatal PAH on INT ($\beta = .18$, 95% CI: $.08, .32$, $p = .02$).

Conclusions: We extend prior findings and show that prenatal PAH exposure magnifies effects of early life stress on child behavior to include effects on hippocampal subfields. Altered hippocampal volume associated with visual-spatial reasoning, which contributes to social and academic functioning. We extend classic developmental psychology models of behavioral inhibition as a risk for internalizing/anxiety symptoms by including prenatal chemical exposures as risk factor for behavioral inhibition. The interactive, deleterious effects of early life stress and prenatal air pollution exposure underscore the need to study mixtures of chemical and social exposures.

Disclosure: Nothing to disclose.

PANEL

45. Opioid Regulation of Prefrontal Cortical Ensembles and Circuitry

45.1 The Prefrontal Cortical Dynorphin / Kappa-Opioid Receptor System and Emotional Processing

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Background: The endogenous dynorphin/kappa-opioid receptor system is implicated in mediating stress- and drug-induced maladaptive behaviors relevant to a plethora of neuropsychiatric disorders, such as exaggerated threat reactivity. Dynorphins and kappa-opioid receptors are heavily expressed in limbic circuits that control affective behavior including the medial prefrontal cortex (mPFC). However, there is a critical knowledge gap in our understanding of the anatomical architecture and function of dynorphin-expressing neurons in the mPFC in mediating responsiveness to threats.

Methods: Here, we used an interdisciplinary approach to dissect the architecture and function of the dynorphin / kappa-opioid receptor system in the mPFC during conditioned threat. We utilized a combination of anatomical and electrophysiological approaches to delineate how the dynorphin/kappa-opioid receptor system is embedded in mPFC circuits. In-vivo single cell imaging and fiber photometry, as well as the novel kappa-opioid receptor sensor kLight, were used to identify how threats activate mPFC dynorphin-expressing neurons and increase dynorphin peptide release. Transgenic and viral approaches were used to knockdown prodynorphin expression and peptide release and determine the functional consequence on threat responsiveness.

Results: Dynorphin is expressed in sub-populations of excitatory projection neurons that project to the amygdala, lateral hypothalamus, ventral tegmental area, paraventricular nucleus of the thalamus, and nucleus accumbens, as well as a subset of inhibitory neurons that express somatostatin. These diverse types of mPFC dynorphin cells are differentially embedded in mPFC circuits (Two-way ANOVA; $F(150,650)=4.377$, $p < 0.0001$). mPFC dynorphin neurons are preferentially modulated by footshocks relative to the global population of mPFC neurons (Two-way ANOVA, $F(560,7840)=3.92$, $p < 0.0001$). Moreover, we characterized the kappa-opioid receptor sensor, kLight, in brain slices and

in-vivo. kLight was utilized in conjunction with in-vivo fiber photometry to demonstrate that endogenous dynorphin release occurs in response to footshock-predictive cues. Finally, knock-down of dynorphin expression in the mPFC accelerates passive freezing responses to footshocks and conditioned cues, suggesting that mPFC dynorphin release gates passive responsiveness to threats (Two-Way ANOVA; $F(6,60)=2.389$, $p = 0.039$).

Conclusions: Collectively, these studies provide a framework wherein dynorphin cell activity can modify local mPFC micro-circuits and downstream limbic regions interconnected with the mPFC. mPFC dynorphin neurons are activated by threats and release dynorphin peptides to drive passive fear responses to threats. These results elucidate a novel role of the dynorphin/kappa-opioid receptor system in gating active responsiveness to threats and provide a mechanism by which dysregulation of this system in cortical circuits can contribute to heightened stress reactivity/fear/anxiety in neuropsychiatric disorders. These results also provide a novel therapeutic target for the treatment of heightened stress reactivity in neuropsychiatric disorders.

Disclosure: Nothing to disclose.

45.2 Hyperexcitability of Drd1+ and Drd2+ Prelimbic Neurons Projecting to Nucleus Accumbens After Abstinence From Heroin is Normalized by Cue-Induced Relapse

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Background: There is little information about changes in excitability of prefrontal (PL) neurons projecting to the nucleus accumbens (NAc) that express Drd1 vs. Drd2 dopamine receptors or how such changes may be affected by relapse. Here wildtype (WT), Drd1-Cre+, and Drd2-Cre+ rats were trained to self-administer heroin and patch clamp recordings of PL->NAc neurons were conducted in prefrontal slices after 7 days of forced abstinence (no extinction training) with or without a relapse test.

Methods: Male and female Long Evans wildtype (WT), Drd1-Cre+, and Drd2-Cre+ rats were implanted with a jugular catheter and their NAc core was infused with AAVrg-hSyn-eGFP (WT rats) or AAVrg-hSyn-DIO-eGFPV (Cre+ rats). After recovery, they were trained to self-administer heroin ($n = 30$) on a FR1 schedule or they received yoked saline ($n = 20$). In Experiment 1, all WT rats underwent 7d homecage abstinence without a relapse test to compare the excitability of PL->NAc neurons under saline or heroin-abstinent conditions. In Experiment 2, all rats underwent 7d homecage abstinence with a subset of Drd1-Cre+ ($n = 7$) and Drd2-Cre+ ($n = 6$) rats undergoing a cue-induced relapse test. In both experiments, immediately after decapitation under isoflurane anesthesia, whole-cell patch clamp recordings of eGFP positive PL->NAc neurons in oxygenated aCSF containing 100 μ M picrotoxin were performed. Mean sEPSC amplitudes were analyzed from an average sEPSC trace computed from 50-100 individual sEPSCs. Mean sEPSC frequencies were analyzed from 20-s long trace segments. A repeated measures two-way ANOVA was used to analyze action potential step firing. In Experiment 1, intrinsic excitability measurements from saline-treated and heroin-treated WT rats were compared using two-tailed unpaired t-tests. In Experiment 2, one way ANOVAs for each genotype were followed by Tukey's pairwise comparison tests when there was a significant F-value.

Results: In Experiment 1, AP firing, sEPSC amplitude, and sEPSC frequency of PL->NAc neurons were significantly greater in WT heroin rats than in yoked saline controls. There were no differences in rheobase between groups. In Experiment 2, Drd1 + PL->NAc neurons in heroin-abstinent rats exhibited greater

action potential firing than in Drd1+ PL- > NAC neurons of saline-treated rats. Moreover, both measurements of sEPSCs in PL- > NAC neurons were significantly greater in heroin-abstinent Drd1+ rats than in saline-treated rats. In PL- > NAC neurons of Drd2+ rats, the only measurement that differed between heroin-treated vs. saline-treated groups was a significant increase in sEPSC frequency. Following cued relapse, Drd1+ PL- > NAC neurons exhibited significantly smaller sEPSC amplitudes and fewer frequency events than Drd1+ PL- > NAC neurons in heroin-abstinent rats. However, these measurements were not different in Drd2+ rats after heroin-abstinence vs. heroin-relapse. There were no differences in rheobase nor were there any detectable sex differences in either genotype under any condition.

Conclusions: This study demonstrates that neuroadaptations in PL- > NAC neuronal excitability are expressed predominantly by Drd1+, but not Drd2+, PL- > NAC neurons after abstinence from heroin. Further, these changes are normalized by cue-induced relapse, suggesting that intrinsic excitability is enhanced in PL- > NAC neurons by abstinence and relieved by drug seeking.

Disclosure: Nothing to disclose.

45.3 Rescue of Prefrontal Hypoactivity During Reinstatement of Heroin Seeking

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Background: Cue-induced activation of the dorsomedial prefrontal cortex (dmPFC) predicts relapse to drug seeking in human addicts and mediates drug seeking in rodent models. Despite this knowledge, no studies to date have longitudinally tracked the activity of single dmPFC excitatory output neurons to determine how their activity adapts across drug use, extinction/withdrawal, and relapse. Furthermore, how unique neuronal ensembles are engaged during cue-induced drug seeking remains unclear. Here we examine the characteristics and neuromodulatory mechanisms that engage dmPFC neuronal ensemble dynamics during cue-induced drug seeking.

Methods: Using 2-photon calcium imaging in mice ($n = 8$ mice; mixed sex), we measured the activity of single dmPFC excitatory output neurons (expressing the calcium indicator GCaMP6s; $n = 902$ –1083 neurons recorded per day) from the onset of i.v. heroin self-administration through extinction and reinstatement. To do so, we used a newly developed head-fixed heroin self-administration assay that allows for heroin taking and seeking during two-photon calcium imaging of dmPFC excitatory output neurons. After imaging, we use PCA-based spectral clustering to identify how unique groups of neurons differentially encode behavioral variables related to drug seeking. Finally, by combining chemogenetics with two-photon recordings, we examined the necessity of locus coeruleus (LC) noradrenergic inputs for the observed dmPFC ensemble dynamics and for cue-induced reinstatement of drug seeking (Gi-DREADD and tdTomato control; $n = 6$ /group).

Results: Data reveal that within our model dmPFC excitatory output neurons display reductions in activity across heroin self-administration (after the first day of acquisition), with this hypoactivity extending through extinction training. The reduced activity is selectively rescued to basal levels (pre-heroin) during cue-induced reinstatement. Spectral clustering revealed the existence of 4 'neuronal ensembles', and the activity of these ensembles could each predict active lever pressing during cue-induced reinstatement. The ensembles were specifically activated (ensemble 1, 2) or inhibited (ensemble 3, 4), in anticipation active lever pressing. Considering the global increase in activity among

dmPFC output neurons during reinstatement (among all ensembles), we hypothesized that the neuromodulator noradrenaline could contribute to the rescue in overall activity as well as active lever pressing related ensemble dynamics. Thus far, we find that chemogenetic inhibition of LC-dmPFC noradrenergic axons abolishes cue-induced heroin seeking behavior. Ongoing analysis will identify the function of LC-dmPFC noradrenergic activity for engaging the downstream dmPFC neuronal ensembles during cue-induced reinstatement.

Conclusions: These data identify unique ensembles of dmPFC excitatory output neurons which become hypoactive across heroin self-administration and extinction, re-activated to basal levels during cue-induced reinstatement, and differentially engaged (activated or inhibited) in anticipation (within a seconds) of active lever pressing during reinstatement. Although the mechanisms that contribute to this rebound in activity remain unclear, ongoing experiments test the hypothesis that LC-dmPFC noradrenergic neurons may provide a critical neuromodulatory role.

Disclosure: Nothing to disclose.

45.4 Machine Learning Identifies a Novel Synaptic Regulator in the Human Orbital Frontal Cortex as a Potential Target for Heroin Addiction Relevant to Drug-Seeking and Reversal Learning

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Background: The use of opioid drugs and related overdose deaths continue to rise in epidemic proportions that have only been exacerbated by the COVID pandemic. Most medications for opioid use disorder focus on opioid pharmacology emphasizing a need for new treatment interventions lacking addictive potential. Neurobiological evidence has emphasized the critical role of the prefrontal cortex in regulating drug craving and cognitive control central for perpetuating the cycle of abuse. Our research strategy focused on postmortem molecular studies of the human prefrontal cortex to guide complementary mechanistic insights in animal models that can subsequently inform the development of new treatment targets.

Methods: In this project, we leveraged machine learning approaches to query RNA-sequencing datasets obtained from human post-mortem orbitofrontal cortex (OFC) tissue to classify subjects as either belonging to control or heroin use groups based on their gene expression profiles. We subsequently used translational rodent models of heroin addiction and cognitive flexibility to investigate the relationship of identified transcripts to heroin-related and neurocognitive behaviors.

Results: Three feature (gene) importance metrics from machine learning analyses highlighted expression of SHISA7, an auxiliary subunit of the GABAA receptor, as being predictive of heroin users. SHISA7 was reduced in the OFC human heroin users as well as in the OFC of rats that self-administered heroin. Furthermore, Shisa7 expression correlated with heroin-seeking behavior. Viral overexpression of Shisa7 in the OFC after heroin self-administration augmented heroin-seeking as well as improved reversal learning, demonstrating the direct relevance of this transcript to heroin-related and cognitive behaviors. Computational analyses showed that Shisa7 specifically integrated in gene network ensembles critical for synaptic plasticity that are dysregulated with heroin use.

Conclusions: Though not previously emphasized in neuropsychiatric disorders, SHISA7, identified using a machine learning-based strategy, appears to be a novel synaptic regulator related to

heroin addiction and cognition with particular relevance to heroin-seeking behavior. Key components of the Shias7 network are druggable targets for treatment development.

Disclosure: Nothing to disclose.

PANEL

46. Negative Urgency and Drug Addiction

46.1 Negative Urgency, Central Amygdala, and Mechanisms of Individual Vulnerability to Continued Alcohol Self-Administration Despite Negative Consequences in Rats

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Background: Addiction develops only in a vulnerable minority of substance users. This implies that discovery of novel treatments needs to rely on an understanding of mechanisms behind individual differences in vulnerability for clinically relevant behaviors. We recently reported (Augier et al, Science 2018) that a key feature of alcohol addiction, choice of alcohol over natural reward, is found in a vulnerable minority of rats, and results from altered GABA-ergic transmission in the central nucleus of the amygdala (CeA). Here, we examined mechanisms of individual vulnerability for another key feature of alcohol addiction, continued use despite adverse consequences ("compulsivity"). A whole brain search once again identified a population of GABA-neurons within CeA. These cells gate alcohol self-administration when the alcohol reward is associated with punishment. In compulsive rats, deficiency in behavioral inhibition under punished conditions are present despite elevated levels of anxiety-like behavior, and are best understood as "negative urgency". The involvement of CeA identified through these studies is consistent with recent human brain imaging findings of networks involved in alcohol addiction.

Methods: We used a footshock-punished alcohol self-administration procedure to screen a large population ($n > 300$) of outbred rats, to identify those showing compulsivity, operationalized as punishment-resistant self-administration. Unsupervised clustering was used to identify a vulnerable subpopulation in which compulsivity emerged as a stable trait. A whole-brain search for neural activity associated with compulsive self-administration was carried out using Fos-mapping in compulsive, non-compulsive and yoked controls. Principal component analysis was used to identify networks of correlated neuronal activity. A viral vector - based Fos-TRAP system was used to tag neuronal ensembles whose activity was associated with compulsive self-administration. This provided subsequent chemogenetic control of neuronal activity through selective expression of an inhibitory hM4Di DREADD, and allowed the causal role of neuronal activity in these cells to be evaluated. Confocal microscopy was used to characterize activated ensemble members within CeA, and a virally mediated shRNA knock-down was used to examine the mechanistic role of their phenotypic marker, PKCdelta.

Results: Punishment resistant self-administration was initially unimodal, but became bimodal over the course of 14 days. Compulsivity emerged over time as a stable trait in a subpopulation (30%) of rats, and was associated with activity of a brain network that included central nucleus of amygdala (CeA). Activity of PKCdelta+ inhibitory neurons in the lateral subdivision of CeA (CeL) accounted for ~75% of variance in punishment-resistant alcohol taking. Chemogenetic inhibition of neurons activated during punishment-resistant self-administration suppressed alcohol taking (vector type x condition: $p < 0.001$; $\eta^2 = 0.4$). So did a

virally mediated shRNA knock-down of PKCdelta in CeA ($p < 0.001$; $\eta^2 = 0.2$).

Conclusions: These findings identify a novel mechanism for a core element of alcohol addiction, and point to a novel candidate therapeutic target. The PKCdelta inhibitory neurons of lateral CeA interact with SOM-positive cells to gate CeA outputs to downstream effector structures. These include the PAG, a structure that has been previously implicated in compulsive alcohol self-administration, and mediates behavioral inhibition in face of aversive stimuli.

Disclosures: Brainsway, Aelis Farma, Indivior, Camurus: Consultant, (Self)

Janssen: Grant (Self).

46.3 Negative Urgency: Construct, Alcohol Model and SNPs

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Background: Negative urgency, the propensity to act rashly under distress, is implicated in disordered eating and addiction. Negative urgency is thought to promote use under an affective dysregulation, negative reinforcement model of addiction, as it may impair the ability to resist urges to use during withdrawal and preoccupation/anticipation stages. Data support a key role for negative urgency in problematic alcohol, tobacco, cocaine, and food use. With negative urgency, use occurs without forethought of harm, and, ultimately, perhaps compulsively despite negative consequences. Translational targets for negative urgency are unclear due to lack of preclinical models or gene association studies. Here, we report a negative urgency model of alcohol drinking based on frustrative exposure to alcohol cues. We also study human gene variants previously linked to negative urgency, but here in relation to pathological drinking and obesity phenotypes.

Methods: Male and female Wistar rats were exposed to chronic, intermittent ethanol vapor (CIE; 8 wks; 14 hr on/day; 200-250 mg% blood ethanol concentration) or air control ($n = 8-10$ /group). During the last 3 weeks and thereafter, rats received scheduled, intermittent (MWF), 1-hr, 2-bottle choice ethanol access (2BC; 10% w/v vs. water) at 6-hr withdrawal. The effects of frustrative alcohol cues were tested by comparing acute (15-min) alcohol intake of rats that did or did not receive 20-min pre-exposure to empty alcohol bottles plus alcohol scent. Intake was studied in clean bedding vs. familiar cages in a 2 (CIE) X 2 (Test cage) X 2 (Frustrative cues) design. We used REGENIE association analyses of UK Biobank participants ($n = 481,626$) to study 57 SNPs previously linked ($p < 0.0001$) to negative urgency. Covariates were age, sex, Townsend deprivation index, and 10 principal components for ancestral lineage. Cases had received an ICD-9 or ICD-10 alcohol-related hospitalization diagnosis or cause of death or had an AUDIT-P > 12 . Controls were those with no alcohol ICD diagnosis. Non-cases with an AUDIT-P = 4-12 were excluded.

Results: A significant ($p < 0.001$) Test cage main effect reflected that rats drank less alcohol in the potentially unsafe, clean test cage than in their home cage. A CIE X Frustrative cues interaction ($p < 0.05$) reflected that pre-exposure to empty alcohol bottles differentially increased 15-min ethanol intake of CIE rats. This effect was larger in the unfamiliar test cage, restoring intake to levels that did not differ from home cage intake. Some SNPs associated ($ps < 0.05$) with pathological alcohol use after Firth correction (rs9956835, rs17703595, rs34026507, rs1958886, rs1371614). Others associated ($1E-8 < ps < 1E-4$) with body fat or waist circumference (rs56078238, rs1371614, rs6847460, rs8012774).

Conclusions: Pre-exposure to frustrative alcohol cues increased drinking of post-dependent rats in a new cage setting, a negative urgency model of hazardous intake after frustration stress. SNPs linked to negative urgency also may associate with alcohol-related hospitalizations and deaths as well as obesity measures; gene-set analyses will be discussed.

Disclosure: Nothing to disclose.

46.4 Exploring the Role of Sensory Feedback in Promoting Motivation to Gamble and Game Immersion Across Rats and Humans

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Background: Problem gambling is often comorbid with substance misuse, and a subset of gamblers report engaging in gambling behavior in order to escape negative mood states. The sound and light stimuli used in electronic gambling machines may facilitate this escape behaviour, leading to a state of immersion or “dark flow”. The studies presented here in both rats and humans aimed to capture elements of this phenomenon in laboratory-based gambling tasks, and investigate the neurocognitive basis for this effect.

Methods: 156 male and female undergraduate students were randomized to play a highly-realistic slot machine simulator in one of three sensory feedback conditions - Plus, Neutral, or Minus - while wearing an eye-tracker. The three conditions differed solely in the frequency and intensity of sensory stimulation (reward-concurrent sounds and visuals). Subjects also completed questionnaires designed to assess immersion and mood, including the Depression, Anxiety, and Stress Scales (DASS). The hypotheses and analysis plan were pre-registered on OSF. Male and female rats completed a gambling-like paradigm based loosely on the Iowa Gambling Task used clinically. In each 30 minute session, rats chose between four options that varied in the magnitude and probability of sugar pellet rewards versus time-out penalties. In order to maximise their sugar pellet profits, rats had to avoid the tempting “high risk high reward” options, associated with larger potential per-trial gains but longer and more frequent time-outs, and instead opt for smaller trial-by-trial wins with less chance of shorter punishments. Some animals learned the cued version of this task in which audiovisual cues were delivered concurrently with rewards, and some could choose at the start of each trial whether any reward obtained would be cued or uncued. A small number of male rats were implanted with telemetry devices able to record blood pressure, heart rate, and body temperature while the rGT was performed.

Results: In healthy volunteers, immersion during game play was predicted by the total DASS score. Immersion scores also increased with sensory stimulation in males, but not females. When given the option, animals chose cued trials more frequently than uncued trials, even though risky choice was higher in the presence of win-paired cues. Rats were also more impulsive, as measured by premature responses made prior to presentation of the four “gambling” options, and collected their winnings faster on cued trials. Body temperature was also higher in male rats performing the cued task, yet heart rate variability was lower.

Conclusions: Our finding that DASS scores predicted immersion on the slot machine simulator is consistent with the hypothesis that gambling-induced immersion may be a form of escape. The observation that increasing the intensity of sensory cues only facilitated immersion in males was unexpected, but may reflect differences in motivation to gamble across genders. The pattern of telemetry data from male rats is consistent with the

view that game play in the presence of cues is more engaging or arousing while also making animals less sensitive to trial-to-trial “ups and downs”. The fact that all animals generally prefer cued over uncued trials matches previous observations that people prefer electronic gambling products featuring sensory cues. Furthermore, the elevated impulsivity and motivation for reward observed on cued trials suggests the cues facilitate behavioural disinhibition.

Disclosure: Nothing to disclose.

STUDY GROUP

47. Irritability: Translational Approaches to Pathophysiology and Treatment Development

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Study Group Summary: Irritability, defined as a decreased threshold for anger in response to frustration or threat, is the hallmark symptom of common psychiatric disorders in children and adults (i.e., oppositional defiant disorder, intermittent explosive disorder, disruptive mood dysregulation disorder). In addition, it is a widely-prevalent and disabling feature of multiple other psychiatric disorders across the lifespan (e.g., PTSD, MDD). Presence of irritability in these disorders is associated with poorer prognosis and suicidality. Yet the biological mechanisms underpinning irritability and its related constructs (frustration, anger attacks, hostility, and aggression) remain understudied. There are few preclinical models and the neurocircuitry of irritability remains poorly understood. There is an urgent need to develop new therapies because commonly used medications may be ineffective or worsen irritability, and current psychotherapeutic approaches are not always feasible or effective.

Key gaps in our knowledge that have hindered the development of new treatments include:

1. How do we define and operationalize irritability and related constructs (e.g., frustration, anger attacks, hostility, and aggression)?
2. How do we measure these constructs across the lifespan (children, adolescents, adults, elderly) using analogous tools?
3. How do we design ethologically valid translational experiments in animals and humans for irritability and related constructs?
4. What are some promising strategies to develop new treatments for irritability and related constructs?

Our panel of researcher and clinicians are diverse across career-stage, gender, theoretical perspectives, geography, and ACNP membership-status. They will engage the audience in addressing these knowledge gaps. Dr. Leibenluft will begin the study group with a broad overview of affective-neuroscience informed conceptualizations of irritability. Next, clinically-focused presentations will discuss the syndromic features of irritability in pediatric (Dr. Wakschlag) and adult (Dr. Fava) samples, and how these relate to longer-term clinical outcomes (Dr. Jha). These presentations will also discuss the challenges of operationalizing and measuring irritability across the lifespan, and highlight the potential role of

informants and ecological momentary assessments. The next set of presentations will focus on preclinical models of aggression (Dr. Russo) and aberrant responses to threat (Dr. Kenwood) and frustrative nonreward (Dr. Eshel) along with analogous studies in humans (Drs. Tseng and Brotman) that have informed neurocircuit mechanisms of irritability in youths. Dr. Brotman will also discuss the development of novel psychotherapeutic approaches. These neuroimaging presentations will also discuss challenges and opportunities of using large-scale multimodal data in studying irritability (Dr. Satterthwaite). Finally, Dr. Trivedi will discuss the neurocircuit mechanisms that predict improvement in irritability with currently available treatments, and the implications of these data for pharmacologic treatment development.

We anticipate vigorous discussion among the panel members and the audience resulting in broad recommendations to the field for generating data needed to guide discovery of novel treatments for irritability and related constructs.

Disclosure: Nothing to disclose.

PANEL

48. Psychosis in Neurodegenerative Disorders and Dementia in Schizophrenia: Where Does the Twain Meet?

48.1 Impact of Alzheimer's Disease and Related Disorders Neuropathology on Neuropsychiatric Symptoms

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Background: The impact of Alzheimer's disease and related dementias neuropathologies on neuropsychiatric symptoms is unclear. Awareness of the impact of specific dementia subtype neuropathologies on neuropsychiatric symptoms eventually may lead to improvement in the clinical management of these symptoms.

Methods: All brains with neuropathological diagnoses were examined in the National Alzheimer's Coordinating Center V.10 collection for patients in whom the Neuropsychiatric Interview-Questionnaire had been administered during life. 1,808 brains from 39 sites were examined. Ignoring clinical diagnosis, ordinal or logistic regression analyses evaluated the effects of 8 neuropathological diagnoses on 12 Neuropsychiatric Interview-Questionnaire domains, correcting for multiple comparisons in all analyses. For neuropsychiatric symptoms (NPS), average Neuropsychiatric Interview-Questionnaire domain scores over time was the primary measure and positive Neuropsychiatric Interview-Questionnaire domain score at any time-point was secondary.

Results: Delusions and hallucinations were more common in Alzheimer's disease than those without Alzheimer's disease (36% versus 17% and 26% versus 10%, respectively); similar results were obtained for Lewy body disease (36% versus 27% and 29% versus 17%, respectively). In Lewy body disease, delusions increased from brainstem ($\beta = 0.53$, 95%CI 0.27-1.02) to limbic ($\beta = 1.48$, 95% CI 1.14-1.91, $p < .01$) to neocortical pathology ($\beta = 2.34$, 95% CI 1.73-3.15, $p < .001$), as did hallucinations ($\beta = 0.23$, 95% CI 0.07-0.76, $p < .05$ to $\beta = 1.69$, 95% CI 1.27-2.27, $p < .01$ to $\beta = 4.49$, 95% CI 3.27-6.16, $p < .001$). Overall, apathy was the most prevalent neuropsychiatric symptom, reaching 80% in hippocampal sclerosis. Infarcts/lacunae and microinfarcts showed few associations with NPS. Frontotemporal lobar degeneration was associated with increased apathy, increased disinhibition, and decreased psychotic features and agitation compared to those without frontotemporal lobar

degeneration. Hippocampal sclerosis was associated with increased apathy (OR 2.60, 95%CI 1.86-3.66, $pFDR < .05$) and disinhibition (OR 2.15, 95% CI 1.63-2.84, $pFDR < .05$); these associations persisted after excluding frontotemporal lobar degeneration and vascular neuropathologies. In pathologies with semi-quantitative ratings, increasing pathology was associated consistently with increased neuropsychiatric symptoms. The majority of autopsies demonstrated more than one type of dementia neuropathology with concomitant Alzheimer's and Lewy body pathology being most common.

Conclusions: The findings support the inclusion of neuropsychiatric symptom criteria for Lewy body disease (visual hallucinations) and behavioral variant frontotemporal lobar degeneration (apathy, disinhibition) diagnoses. The consistent associations of increased neuropathology with more severe NPS have clinical implications. The novel findings of increased apathy and disinhibition in hippocampal sclerosis suggest that the impact of this understudied neuropathology on NPS merits further investigation.

Disclosures: Acadia, Eisai, Sunovion, Genentech, Biogen, BxCel, Green Valley: Advisory Board, (Self).

48.3 Distinct Patterns of Neurodegenerative Atrophy and Neuropathology Predict Nature and Type of Hallucination and Delusion Symptoms

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Background: Understanding the biological foundations for psychosis has the potential to make treatments more precise, individualized, and effective. Psychosis occurs in a subset of patients with every major neurodegenerative disease (NDG), but the specific relationships among specific psychotic symptoms, structural brain changes, and neuropathological changes have not been widely investigated. We compared prevalence rates of psychotic symptoms in a large autopsy-based cohort to systematically identify differences in nature or content of psychosis. We then analyzed how specific psychotic symptoms correspond to focal changes in structural gray matter morphology.

Methods: We studied 372 patients with autopsy-confirmed NDG, characterizing the specific psychosis content subtype and frequency via retrospective chart review. Patients included 111 with Alzheimer's disease (AD), 59 with LBD and concomitant AD (LBD/AD), 133 with frontotemporal lobar degeneration (FTLD) with tau inclusions (including progressive supranuclear palsy, corticobasal degeneration, or Pick's neuropathology), and 69 with FTLD-TDP, including Types A-C. Patients underwent T1 MP-RAGE structural magnetic resonance imaging scanning, and voxel-based morphometric (VBM) analysis (SPM12 with VBM12 toolbox default parameters) to examine brain-behavior correlations of psychotic features.

Results: Of 372 patients, 111 had psychosis during their disease. Hallucinations were significantly more common in patients with LBD/AD pathology (Braak Parkinson stage 5-6 LBD), including misperception, peripheral hallucinations, hallucinations that moved, hallucinations of people/animals/objects, delusions regarding a place or misidentification, and the feeling of a presence. Patients with FTLD-TDP were significantly more likely to experience delusions, including paranoia, delusions of misidentification, and self-elevating delusions such as grandiosity and erotomania, compared to patients with AD and FTLD-tau. Patients with hallucinations were significantly more likely to have structural damage to the nucleus accumbens and fusiform gyrus than those without hallucinations. Patients with delusions were more likely to

have atrophy in the right rostral caudate, pallidum, putamen, and cerebellum than patients with the same pathologies without delusions.

Conclusions: The nature and content of psychosis can meaningfully assist prediction of underlying NDG pathology. Also, in the context of NDG, damage to brain structures involved in reward processing (nucleus accumbens) and resolving ambiguity during decision-making (basal ganglia) predicts new-onset psychotic symptoms.

Disclosures: University of California, San Francisco: Employee (Self), Quest Diagnostics: Grant (Self).

48.4 High Prevalence of Rare, Damaging Variants and Early-Onset Dementia in a Cohort of Chronically Institutionalized, Severely Affected Patients With Schizophrenia

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Background: Chronically institutionalized individuals with schizophrenia are known to have poor outcomes and higher rates of dementia compared to community samples. To date, there has been little genetic characterization of chronically institutionalized individuals and the etiology of the dementia in schizophrenia remains unknown. We hypothesized that because of the severity of their illness, chronically institutionalized (> 5 years) patients with schizophrenia would have an increased burden of rare, damaging genetic variants compared to typical schizophrenia and controls. Here, we present genetic and cognitive data on a cohort of patients with severe, extremely treatment-resistant schizophrenia (SETRS).

Methods: The whole genome sequencing component of this study included 90 individuals with SETRS, 189 individuals with typical schizophrenia, and 3,327 controls that passed quality control and ancestral pruning. We compared the burden of rare, damaging missense and loss-of-function variants between SETRS, typical schizophrenia, and controls across intolerant genes depleted of functional variation in the general population. We selected this gene set as the rare variant risk for schizophrenia has been previously shown to be concentrated exclusively among intolerant genes. We assessed the cognitive functioning of 148 SETRS participants using the Montreal Cognitive Assessment (MOCA) and the Clinical Dementia Rating Scale. Individuals were carefully screened to ensure that they did not meet diagnostic criteria for intellectual disability prior to disease onset.

Results: SETRS participants (mean [SD] age, 60.5 [9.9] years; 96 [64.9%] male) had an average duration of 24.6 [12.4] years of lifetime hospitalization in state inpatient facilities. SETRS individuals had a high burden of rare loss-of-function (odds ratio [OR], 1.95; 95% confidence interval [CI], 1.35-2.75; $P = 2.9 \times 10^{-4}$) and damaging missense variants in intolerant genes (OR, 2.62; 95% CI, 1.70-3.88; $P = 1.6 \times 10^{-5}$). 50% of SETRS individuals carried at least one rare, damaging missense or loss-of-function variant in intolerant genes compared to 32.8% of typical schizophrenia individuals (OR, 2.04; 95% CI, 1.19-3.53; $P = 8 \times 10^{-3}$) and 25.7% of controls (OR, 2.89; 95% CI, 1.86-4.52; $P = 1.3 \times 10^{-6}$).

The average MOCA score for the cohort was 9.86 [6.44] out of 30 (severe dementia) with 146/148 (98.6%) scoring below the standard 26-point cutoff for dementia and 143/148 (96.7%) with the more stringent cutoff of ≤ 21 . Among individuals ≤ 65 years old, the average MOCA score was 10.3 and 94.9% of individuals had a score ≤ 21 , consistent with a very high prevalence of early-onset dementia. Similarly, the average CDR score was 2.11 out of 3 (mean 2.05 in ≤ 65 years old), consistent with moderate to severe

dementia and 140/148 (94.6%) participants had a score of 1 (mild dementia) or greater.

Conclusions: Extremely ill patients with schizophrenia who require long term hospitalization represent a distinct phenotypic subtype of schizophrenia with high rates of rare, damaging genetic variation and early-onset dementia.

Disclosure: Nothing to disclose.

STUDY GROUP

49. Encouraging Ethical Data Use, Analysis and Interpretation in Biomedical Research

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Study Group Summary: Health disparities persist among racial and ethnic groups despite decades of research investigating their underlying causes. For example, although the overall incidence of major depression is lower for Black than for white individuals, Black individuals are less likely to receive treatment and more likely to experience chronic depression. Research is critical to untangle the factors that contribute to these and many other health disparities to ultimately inform interventions to address them. However, there is also a longstanding history of using evidence of racial differences to reinforce deterministic and racist ideas in biological and psychological science. Even studies that purport to identify “gaps” in minoritized racial and ethnic groups intending to eliminate them should consider underlying contextual factors that can contribute to outcomes. Further, they should refrain from deterministic interpretations that fail to consider the possibility of developmental change that could result from transformations in the social and emotional contexts in which people live. As researchers, we must be mindful of the interpretation of our analyses and take precautions to avoid contributing to and perpetuating racism in science, especially with biological data (e.g., brain imaging and genetics). For even if “race”-related differences remain when controlling for other contextual variables (e.g., neighborhood deprivation) and indicators of systemic racism (e.g., segregated housing), such residual effects could nonetheless reflect other unmeasured consequences of racism.

As accessibility to population-based biomedical research, such as the Adolescent Brain Cognitive Development, Human Connectome, and Environmental Influences of Child Health Outcomes studies, and opportunities for leveraging increasingly complex datasets to explain behavior, predict outcomes, and investigate mechanistic pathways to understand health and disease are expanding, enhancing researcher knowledge of responsible data use is essential, especially for trainees and early stage investigators. Best practices should address factors such as study design, analytic approaches, interpretation, and communication that can impact individuals and communities.

The objective of the session will be to facilitate a discussion about strategies for encouraging ethical science that consider underlying individual, community, structural, and societal factors that can contribute to outcomes throughout development. Our panelists’ areas of expertise range from community to computational level research across the lifespan. The group is chaired by a BIPOC member of ACNP and a NIDA Scientific Program Manager of the largest study of emerging psychopathology in an ethnically/geographically diverse sample. The speakers comprise an

ethnically diverse group of scientists and scientists studying the Ethical, Legal and Societal Aspects of neuropsychiatry. This dovetails nicely with the BIPOC group submission focusing on considerations related to study design and initiation. ACNP is the ideal setting for this discussion, with opportunities to hear from basic, clinical and translational neuroscientists about strategies for encouraging ethical data use, analysis and interpretation and promoting health disparities research while preventing continued stigmatization and marginalization of individuals and communities.

Disclosure: Nothing to disclose.

PANEL

50. Mechanisms and Modulation of Compulsive Behaviors

50.1 Hyperactivity of Indirect Pathway Projecting Spiny Projection Neurons Drives Compulsive Behavior

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Background: Compulsive behaviors are hallmark symptoms of Obsessive Compulsive Disorder. Aberrant striatal activity has been linked to compulsive behavior in correlative studies in humans and causal studies in rodents. Despite this, it is not understood how the major opposing cell-types in the striatum, D1- and D2-spiny projection neurons (SPNs), contribute to striatal hyperactivity to drive compulsive behavior. Using head-mounted miniscopes, we first sought to determine the role of D1- and D2-SPNs in mediating compulsive behavior in mice with a highly penetrant compulsive grooming phenotype (Sapap3-KOs). After identifying D2-SPN hyperactivity at the onset of compulsive grooming, causal manipulations reducing indirect-pathway projecting SPN (iSPN) activation were conducted.

Methods: Male and female mice were used for all experiments. Cohort 1: Sapap3 KOs and WT s ($n = 9,11$) were injected with AAV-GCaMP6m and implanted with GRIN lenses in CS to visualize striatal calcium activity during grooming behavior in both D1 and D2-SPNs. Cohort 2 and 3: D1-cre/Sapap3-KOs and WT s ($n = 12,11$) or A2A-cre/Sapap3-KOs and WT s ($n = 7,8$) were injected with DIO-GCaMP6m to image D1 or D2-SPNs. SPNs were segmented using CNMFe and fluorescence converted to a Z-score using the mean and SD across the entire session. Fluorescence was averaged across peri-grooming periods for spectral clustering. Clustering was performed on all cohorts simultaneously. Imaging (Cohort 4) and optogenetic inhibition (Cohort 5) of iSPNs in was performed via retrograde GCaMP6m unilaterally (imaging) or ArchT (or mCherry control) bilaterally in the globus pallidus externa (GPe) with lenses/fibers in CS. Fluoxetine (FLX; 18 mg/kg) treatment was administered via drinking water for 4 weeks followed by a 2-week washout.

Results: For all cohorts, KOs had increased grooming time and bouts compared to WT s . Spectral clustering revealed 8 grooming clusters. Cohort 1: Assessing all SPN subtypes together, KOs displayed increased grooming onset-associated calcium activity relative to WT s . This increase was associated with a larger percentage of individual SPNs activated at the onset of grooming in KOs. Cohort 2: D1-SPN activity was not elevated at grooming onset. No increase in grooming onset-activated neurons was detected in D1-SPNs. Cohort 3: Activity of D2-SPNs were elevated at the onset of grooming. An increase in the percentage D2-SPNs activated at grooming onset was identified in KOs compared to WT s . Increases in the proportion of D2-SPNs from KOs

participating in clusters associated with grooming onset (cluster 3 and cluster 4) as well as a reduction in the proportion of grooming-onset inhibited cells were found. Cohort 4: FLX treatment significantly reduced compulsive grooming, which rebounded following washout. Calcium event rates and the proportion of grooming-onset activated iSPNs were reduced following FLX. Cohort 5: Optogenetic inhibition of iSPNs in KOs produced a reduction in total grooming time during laser on periods in ArchT but not mCherry controls.

Conclusions: Sapap3-KOs have increased grooming-onset striatal activity manifest through alterations in the makeup of clusters of striatal SPNs. Surprisingly, D1-SPN activity was not increased at grooming onset while D2-SPN activity was increased in KOs at the onset of grooming and associated with increases in grooming-onset activated clusters and reduction in grooming inhibited functional clusters. Pharmacological and optogenetic inhibition of putative D2 iSPNs reduced compulsive grooming behavior. These data point to a novel model in which D2-SPN hyperactivity may promote compulsive grooming behavior.

Disclosure: Nothing to disclose.

50.2 Ketamine Increases Activity of a Fronto-Striatal Projection That Regulates Compulsive Behavior

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Background: Obsessive-Compulsive Disorder (OCD), characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions), is associated with dysfunction in fronto-striatal circuits. There are currently no fast-acting pharmacological treatments for OCD. However, recent clinical studies demonstrated that an intravenous infusion of ketamine rapidly reduces OCD symptoms.

Methods: To probe mechanisms underlying ketamine's therapeutic effect on OCD-like behaviors, we used the SAPAP3 knockout (KO) mouse model of compulsive grooming. We injected SAPAP3 KO mice with ketamine or saline and measured grooming behavior across 7 days (WT-ketamine=13, WT-saline=14, KO-ketamine=12, KO-saline=11). We then used fiber photometry to assess the effect of ketamine on grooming-related neural activity in the fronto-striatal circuit formed by dorsomedial prefrontal cortex (dmPFC) projections to the dorsomedial striatum (DMS) (WT=11, KO=10). We used optogenetic stimulation and inhibition of this dmPFC-DMS projection in wild-type (WT) ($N = 8-18$) and KO mice ($N = 7-15$) to demonstrate causal control of grooming behavior. Both sexes were included in all experiments.

Results: Here we recapitulate the fast-acting therapeutic effect of ketamine on compulsive behavior (grooming duration: 2-way RM ANOVA, interaction $P = 0.0081$, time $P = 0.5614$, experimental group $P < 0.0001$, subject $P < 0.0001$), and show that ketamine increases activity of dorsomedial prefrontal neurons projecting to the dorsomedial striatum in KO mice (peak amplitude: 2-way ordinary ANOVA, interaction $P = < 0.0001$, treatment $P = < 0.0001$, genotype $P = 0.2720$). Optogenetically mimicking this increase in fronto-striatal activity reduced compulsive grooming behavior in KO mice (grooming duration: 2-way RM ANOVA, interaction $P = 0.0430$, laser $P = < 0.0001$, genotype $P = 0.0018$). Conversely, inhibiting this circuit in wild-type mice increased grooming (grooming duration: 2-way RM ANOVA, interaction $P = 0.0395$, laser $P = 0.0841$, virus $P = 0.0010$). Finally, we demonstrate that ketamine blocks the exacerbation of grooming in KO mice caused by optogenetically inhibiting fronto-striatal activity (grooming

duration: 2-way RM ANOVA, interaction $P=0.0221$, laser $P=0.0167$, experimental group $P=0.0612$).

Conclusions: These studies demonstrate that ketamine increases activity in a fronto-striatal circuit that causally controls compulsive grooming behavior, suggesting this circuit may be important for ketamine's therapeutic effects in OCD.

Disclosure: Nothing to disclose.

50.3 Experimental Manipulation of the Orbitofrontal Cortex Impacts Neural Activation, Connectivity, and Behavioral Markers of Human Compulsive Behavior: A Theta Burst Stimulation Study

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Background: Compulsive behaviors (CBs) have been conceptualized as a failure to override habitual behaviors that have been “stamped in” through repetition and negative reinforcement due to short-term distress reduction. CBs have been strongly linked to orbitofrontal cortex (OFC) function in animal models and human studies, but human studies have largely been limited by correlational designs (e.g., cross-sectional group comparisons). Furthermore, brain regions function not in isolation, but as components of widely distributed brain networks—such as those indexed via resting state functional connectivity analysis—that conjointly contribute to behavioral outcomes.

Methods: In this study of 69 patients with CB disorders, we examined the impact of OFC/frontopolar neuromodulation on 1) CBs performed in response to an idiographically designed stressful laboratory probe, 2) cerebral blood flow in the focal/target brain region, and 3) resting state functional connectivity between OFC seed areas and the rest of the brain, using a multiband-multiecho sequence to improve OFC signal-to-noise. Patients were randomized in a double-blind, between-subjects design to receive a single session of neuromodulation targeting the left OFC—intermittent Theta Burst Stimulation (iTBS; expected to increase OFC activity), or continuous TBS (cTBS; expected to decrease OFC activity) (both conditions: 600 pulses at 110% target RMT). In both conditions, brain modulation was paired with a subsequent computer task providing practice in overriding a clinically relevant habit (an overlearned shock avoidance behavior), delivered during the expected window of OFC increase/decrease.

Results: cTBS, relative to iTBS, exhibited a beneficial impact on acute laboratory behavioral assessments of CBs at +90min post-TBS. Furthermore, following this single, very brief (40sec) session of cTBS, these acute behavioral effects persisted at +1-week. cTBS and iTBS modulated OFC/frontopolar activation in hypothesized directions, according to a measure of cerebral blood flow. In addition, in whole-brain analyses, iTBS, relative to cTBS, increased resting state connectivity between a right OFC (BA47) seed region and two other areas: dorsomedial PFC (DMPFC) and occipital cortex. Within a priori striatal regions, connectivity was also increased between this right BA47 seed and dorsal and ventral striatum. Connectivity effects were correlated with OFC/frontopolar target engagement measures and with subjective task difficulty during habit override training. All findings described: $p < .05$, adjusted for multiple comparisons (details below).

Conclusions: Experimental modulation of OFC, within the behavioral context of habit override training, impacted laboratory markers of CB vulnerability, both acutely and at 1-week follow-up. Neuroimaging findings confirmed target engagement and helped reveal both focal and neural network-level impacts of neuromodulation, when paired with this specific behavioral context. Findings may serve as an initial precursor to mechanistic

intervention development, including potentially synergistic neuro-behavioral treatment combinations.

Disclosure: Nothing to disclose.

PANEL

51. From Genes to Memes: Inflammatory Modulation as a Target for Transdiagnostic Treatment of Mood and Anxiety Disorders

51.1 Reward Circuits and Symptoms of Anhedonia as Modifiable Targets for Therapy in Depressed Patients With High inflammation: Evidence From a Dopaminergic Challenge Study

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Background: A significant portion of adult patients with depression exhibit increased inflammation, which has been associated with low functional connectivity (FC) in corticostriatal reward circuits and symptoms of anhedonia. Preclinical and clinical evidence suggests that these changes in circuitry may be due in part to the effects of inflammation on the availability and release of dopamine. For example, our previous work in non-human primates demonstrated that inflammation decreased dopamine availability and release, which was correlated with effort-based sucrose consumption and reversed by the dopamine precursor levodopa (L-DOPA). Accordingly, low FC in reward circuits and symptoms of anhedonia in patients with major depression (MD) and evidence of chronic low-grade inflammation may serve as targets for interventions that reverse the impact of inflammation on the brain, including L-DOPA which increases dopamine.

Methods: We tested the hypothesis that FC in ventral striatum (VS) to ventromedial prefrontal cortex (vmPFC) circuitry, both at rest and during reward processing, would be increased by L-DOPA compared to placebo in MD patients with higher versus lower levels of inflammation (plasma C-reactive protein [CRP] and cytokines). Using a double-blind, randomized cross-over challenge, 40 medically stable, unmedicated male and female adult outpatients with a primary diagnosis of MD underwent resting state and task (Monetary Incentive Delay Task [MIDT]) fMRI following acute L-DOPA/carbidopa (250/50mg) or placebo administered one week apart. Motivation was assessed by Effort Expenditure for Rewards Task (EEfRT) and momentary assessments of anhedonia symptoms were collected with a modified Snaith-Hamilton Pleasure Scale.

Results: A differential resting state VS-vmPFC FC response to L-DOPA versus placebo was observed in patients with increasing levels of inflammation whereby patients with $CRP > 2$ mg/L ($n = 19$) exhibited a significant L-DOPA-related increase in FC compared to those with $CRP \leq 2$ mg/L ($n = 21$, $p < 0.05$ before and after controlling for covariates). This change in FC also correlated with a composite factor comprised of inflammatory cytokines and their soluble receptors ($r = 0.37$, $p < 0.05$). Similar relationships were observed for VS-vmPFC FC during reward processing (anticipation of win, $p < 0.05$, but not loss), and the difference in FC during expectation of win versus loss (L-DOPA minus placebo) significantly correlated with the difference in resting state FC in this circuit ($r = 0.48$, $p < 0.01$). The percent of hard choices on the EEfRT positively correlated with FC during rest ($r = 0.32$, $p < 0.01$), and there was an interaction between CRP and treatment for the association between FC and symptoms of anhedonia after L-DOPA ($p < 0.05$). Only patients with $CRP > 2$ mg/L exhibited relationships between higher FC and lower symptoms of anhedonia after L-DOPA ($r = -0.46$, $p = 0.05$).

Conclusions: These data from MD patients administered L-DOPA, combined with our translational work in non-human primates, suggest a role for decreased dopamine in inflammation-related circuit deficits and symptoms of anhedonia in patients with high CRP. Furthermore, FC in reward circuitry may serve as modifiable imaging biomarker for the efficacy of pharmacological, behavioral and/or psychosocial interventions designed to reduce inflammation or its impact on the brain and behavior.

Disclosure: Nothing to disclose.

51.4 Behavioral Interventions for Insomnia and Inflammatory and Viral Transcription Profiles in Immune Cells Over One Year in Older Adults: A Randomized Controlled Trial

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Background: Sleep disturbance is associated with elevated inflammatory activation and compromised defenses from viral infection. Treatment of insomnia with either cognitive behavioral therapy for insomnia (CBT-I) or a mind-body intervention (Tai Chi Chih, TCC) modifies gene transcription profiles immediately post-intervention in older adults with insomnia, but it is not known whether these effects are durable over one year follow-up. We hypothesized that the treatment of insomnia with either CBT-I or TCC, as compared to an active comparator education control, Sleep Education Therapy (SET) would lead to sustained changes in gene expression profiles, indicating reduced inflammatory and elevated viral responses.

Methods: Methods: In this randomized trial, 123 older adults with insomnia were randomly assigned to cognitive behavioral therapy for insomnia (CBT-I), tai chi chih (TCC), or sleep education therapy (SET) an active comcondition (SS) for two hour sessions weekly over 4 months with follow-up at 16-months. We measured genome-wide transcriptional profiling at baseline and month 16 months

Results: Genes with a 50% or greater average difference (>1.5 fold) between CBT-I or TCC, compared to SET, controls were calculated across the set of 26,641 transcripts. A total of 479 upregulated and 362 downregulated transcripts met this threshold criterion in CBT-I compared to SS, and at total of 429 upregulated and 475 downregulated transcripts were present in TCC compared to SS. Promoter-based bioinformatics analysis (TELis) inferred gene-regulatory commonalities among genes associated with treatment, by quantifying the prevalence of specific transcription factor binding motifs (TFBM) in gene promoter sequences. Analyses revealed different patterns of TFBM prevalence among the TCC compared to the SS controls, and similar patterns in the CBT-I compared to the SS controls. Specifically, CBT-I compared to SET controls exhibited significantly lower pro-inflammatory NF- κ B, AP1, and CREB transcription factor activity (p 's < 0.05). TCC compared to SET also exhibited lower pro-inflammatory AP1 and CREB (p 's < .05), while NF- κ B was lower in TCC compared to SET but not statistically significant (p = .22). The anti-inflammatory glucocorticoid receptor (GR) was differentially altered in CBT-I and TCC when compared to SET, with significant increased activity in TCC (p < 0.05), but no difference in activity in CBT-I compared to SET (p = 0.46). Anti-viral IRF2 and ISRE activity was significantly increased in the CBT-I compared to SS controls (p < 0.05), with trend differences in TCC compared to SET (p = 0.1).

Conclusions: Treatment of insomnia with either of two behavioral interventions, CBT-I or TCC, results in a sustained downregulation of inflammatory signaling. Additionally, CBT-I or TCC, resulted in a sustained up regulation of anti-viral interferon activity. However, the anti-viral interferon response did not hold for the TCC group compared to controls. The anti-inflammatory

glucocorticoid receptor activity was elevated in the TCC group compared to SS, as well as CBT-I. These results provide further support linking insomnia in older adults with elevated leukocyte expression of proinflammatory genes and suggest that the treatment of insomnia has durable effects to reverse activation of inflammatory signaling pathways and down-regulation of anti-viral immunity found in those with insomnia. Treatment of insomnia has the potential to reduce the risk of aging related inflammatory diseases and to augment resistance to viral infection.

Disclosure: Nothing to disclose.

PANEL

52. Can Inflammation Be Useful as a Novel Classifier of Schizophrenia Subtypes?

52.1 Stratifying by Inflammatory Status Reveals Novel Neuropathology in Neurogenic Niche in Schizophrenia

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Background: Inflammation regulates neurogenesis, and we recently identified reduced neurogenesis in the subependymal zone (SEZ), the birthplace of inhibitory interneurons, in schizophrenia and bipolar disorder compared to controls. Here, we asked: "What is the extent of inflammation in the neurogenic region and does it vary with diagnosis?", "How does the transcriptome vary with inflammatory status?" and "What is the relationship of inflammation to neuropathology within the neurogenic niche?"

Methods: SEZ tissue was dissected from caudate sections cut ~1.5 mm deep to lateral ventricle from $n = 93$ male and female human brains (controls, schizophrenia and bipolar disorder). Total RNA was isolated and cDNA was synthesized and mRNA was measured via qPCR. We defined those with low and high levels of inflammation using a two step recursive cluster analysis of IL6, IL6R, IL1R1 and SERPINA3 mRNAs. cDNA sequencing libraries were constructed with total RNA and paired-end sequencing of 100 bp read lengths was done with NovaSeq 6000. After QC steps, sequence alignment and differential expression analysis, Ingenuity Pathway Analysis (IPA) was conducted. Immunohistochemistry and counting of CD163 + macrophages was performed. Between group differences were assessed using Chi-square or ANCOVA, with Fisher's least significant difference (LSD) post hoc tests.

Results: More schizophrenia (37%) and bipolar disorder cases (32%) were in high inflammation subgroups compared to controls (10%), $\chi^2(2) = 6.29$ $p < 0.05$. Across the high inflammation subgroups, microglia mRNAs were reduced (IBA1, P2RY12, P2RY13, $F(4,74-76) \geq 3.60$, $p \leq 0.01$), while mRNAs for perivascular macrophages (CD163), pro-inflammatory macrophages (CD64), monocytes (CD14), natural killer cells (FCGR3A) and adhesion molecules (ICAM1) were increased (all $vF > 26.7$, $p \leq 0.003$, all post hoc $p < 0.004$). The most significant transcriptional change in schizophrenia was increased CD-163 mRNA (log2 fold change = 1.71, $q < 0.0000000001$). Macrophages were found in perivascular sites throughout the neurogenic zone and macrophage cell density was increased in high inflammation schizophrenia (64%, ANCOVA (PMI), $F(4,78) = 3.71$, $p = 0.008$). IPA confirmed that up-regulated genes were overrepresented in complement, acute phase response signaling, agranulocyte adhesion and diapedesis pathways (all $p \leq 0.0003$). When comparing those with schizophrenia in the high and low inflammation subgroups, changed transcripts were associated with tissue fibrosis including an increase in collagen involved in the extracellular matrix stiffening (fibrosis).

Conclusions: High inflammation subgroups in major psychiatric disorders have increased macrophages and suppressed microglia in the neurogenic zone that may lead to fibrosis and a reduction of newborn neurons.

Disclosure: Nothing to disclose.

52.2 Inflammation Subtypes in Psychosis and Relationships With Genetic Risk for Psychiatric and Cardiometabolic Disorders

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Background: Elevated peripheral inflammation is common in psychosis and may be related to genetic factors, although these relationships are not well-described. Cardiometabolic disorders (CMDs) are common in psychosis, related to inflammation, and have known genetic contributions. We examined signatures of peripheral inflammation in psychosis and their relationships with cognition, symptoms, and polygenic risk for schizophrenia (SCZ), bipolar disorder (BP), major depressive disorder (MDD) and CMDs in participants from the Bipolar Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study.

Methods: Fifteen inflammatory and microvascular markers were assessed in the serum of 122 persons (86 psychosis, 36 controls-HC) of European ancestry. Symptoms were assessed with the positive and negative syndrome scale (PANSS) and cognition with the Brief Assessment of Cognition in Schizophrenia (BACS). A combination of unsupervised exploratory factor analysis and hierarchical clustering was used to categorize inflammation. A higher inflammation subtype was defined by elevated inflammation factor scores in a group of seven markers (CRP, IFN γ , IL1 β , IL8, IL10, TNF α , and VEGF). PsychChip genotyping and imputation was also performed resulting in 4,322,238 SNPs. Polygenic risk scores (PRS) for coronary artery disease (CAD), type-2 diabetes (T2D), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), waist-to-hip ratio (WHR), SCZ, BP, and MDD were calculated for our participants using publicly available GWAS significant ($p < 5E-8$) summary statistics for each trait. Principal component analysis generated six factor loadings for the matrix of CMD PRSs combined. Regression models examined inflammation relationships with individual PRS and CMD-PRS factor loadings. Permutation-computed empirical p -values (EMP) accounted for overfitting and false discovery rate (FDR) for multiple comparisons. Functional module detection identified biological mechanisms linked to PRS-inflammation associations.

Results: High inflammation status was identified in $n = 33$ (38%) of those with psychosis and $n = 8$ (22%) of HC. High inflammation status was associated with lower BACS scores ($p = 0.038$) with a trend toward higher PANSS total scores ($p = 0.076$) in those with psychosis. The first principal component of the CMD-PRS-matrix was a significant predictor of high inflammation status ($R^2 = 0.12$, EMP = 0.002) in all participants with a large effect in those with psychosis ($R^2 = 0.18$, EMP = 0.001). The network of functional interactions among genes included in the primary CMD-PRS component resulted in eight functional modules, two of which contained enrichment for inflammation or immune processes.

Conclusions: Consistent with previous findings, a subtype with elevated inflammation was identified in 38% of those with psychosis. Inflammation status was associated with greater genetic risk for CMDs, but not SCZ, BP, or MDD. No significant associations were observed between CMD-PRS and cognition or symptoms. These findings identify potential genetic factors that may predispose some individuals with psychosis to higher inflammation that may then adversely impact cognition and symptoms.

Disclosure: OptumRx: Consultant (Self)

52.3 Increased Peripheral Complement Levels Predict Temporal Lobe Cortical Thinning in Schizophrenia

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Background: There is growing evidence for complement system involvement in the pathogenesis of schizophrenia, although the extent of complement system disturbances across its multiple pathways has not been fully reported. It also remains unclear whether complement abnormalities are characteristic of all patients with schizophrenia or whether they are representative of a subgroup of patients. The aim of the present work was to quantify and compare a range of complement factors, receptors and regulators in peripheral blood of healthy controls and people with schizophrenia and to determine the extent to which these peripheral inflammation markers relate to brain structure.

Methods: Seventy-five healthy controls and 90 patients with schizophrenia or schizoaffective disorder were included in the study. Peripheral blood samples were collected from all participants and mRNA expression was quantified for 20 complement related genes, as well as for pro- and anti-inflammatory cytokines. Structural MRI was also performed with T1-weighted scans used to determine regional cortical thickness measures.

Results: There were significant increases in peripheral mRNA encoding receptors (C5ar1, CR1, CR3a), regulators (CD55, C59) and protein concentrations (C3, C3b, C4) in people with schizophrenia relative to healthy controls. C4a expression was significantly increased in a subgroup of patients displaying elevated peripheral cytokine levels. A higher inflammation index derived from mRNA expression predicted cortical thinning in the temporal lobe (superior temporal gyrus, transverse temporal gyrus, fusiform gyrus, insula) in patients with schizophrenia and healthy controls even after correcting for multiple comparisons.

Conclusions: Analysis of all three major complement pathways supports increased complement activity in schizophrenia and also shows for the first time that peripheral C4a upregulation is related to increased peripheral proinflammatory cytokines in schizophrenia. Our region-specific, brain neuroimaging findings linked to increased complement mRNA expression suggests a role for the complement system in schizophrenia and healthy controls. Further studies are required to clarify clinical and neurobiological consequences of aberrant complement activity in schizophrenia and related psychoses.

Disclosure: Astra Pharma: Grant (Spouse)

52.4 A 3-Site Study of MRS Glutamate, GABA, PET Microglial Radioligand Binding and Plasma Cytokine Concentrations in Recent Onset and Established Schizophrenia

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Background: The UK MRC SPRING study was designed to: i) test two groups of non-dopaminergic theories of schizophrenia, GABA-glutamate excitation-inhibition (E/I) neurotoxicity hypotheses and neuro-inflammation hypotheses, and ii), determine whether they reflect subtypes, different stages of the illness or are joint aspects of pathogenesis. The novel aim was to assess the relevant processes in the same individuals early and late in the course of schizophrenia in three centres -Manchester, Nottingham and Cardiff - to ensure reproducibility and a large sample.

Methods: Male and female patients aged 18–55 yrs and meeting DSM-IV criteria for schizophrenia spectrum disorders were recruited, a Recent Schizophrenia group (RS) within 5 years of onset and less than 12 weeks of medication, and an Established Schizophrenia group (ES) with more than 10 years of treatment ($n = 20$ patients per group per centre). Matched RC and EC control groups were recruited ($n = 10$ per group per centre). Clinical assessments included Positive and Negative Syndrome Scales (PANSS) and WAIS IQ (FSIQ), and confounder variables see below. 1H MRS was carried out at 7T in Nottingham and at 3T in Manchester and Cardiff in 27ml volumes of the anterior cingulate (ACC) and occipital cortex. [^{11}C](R)-PK11195 PET radioligand binding to the microglial translocator protein (TSPO) was measured in the ACC and other voxels (PMID:32606376). Plasma cytokine samples were taken at screening.

Results: Diagnosis main effects and interactions.

1. Glutamate in ACC was markedly reduced in ES patients compared to RS and controls ($\text{RC} = 0.08 \pm 0.16$, $\text{RS} = 0.23 \pm 0.25$, $\text{EC} = 0.19 \pm 0.47$, $\text{ES} = -0.47 \pm 0.29$; Diag xPhase $p = 0.017$).
2. GABA in occipital cortex was reduced in both recent and established patients ($\text{RC} = 0.22 \pm 0.35$, $\text{RS} = 0.11 \pm 0.21$, $\text{EC} = 0.32 \pm 0.22$, $\text{ES} = -0.27 \pm 0.34$; Diag $p = 0.034$).
3. TSPO binding potential in ACC was not affected by diagnosis but significant reductions were seen in putamen ($\text{RC} + \text{EC} = 0.10 \pm .012$, $n = 21$; $\text{RS} + \text{ES} = 0.06 \pm 0.01$, $n = 41$; Diag $p = 0.015$), insula and thalamus.
4. CRP and IL-6 were increased in patients compared to controls but significantly more so in the established patients (CRP: $\text{RC} = -0.14 \pm 0.18$, $\text{RS} = -0.09 \pm 0.15$, $\text{EC} = -0.05 \pm 0.22$, $\text{ES} = 0.40 \pm 0.11$; Diag $p = .01$, Diag x Phase $p = 0.03$).

Clinical correlations.

Decreased TSPO in ACC and other regions correlated significantly with increases ($r = >0.4$) in PANSS positive symptoms in the ES group. Positive symptoms were associated with lower ACC GABA. FSIQ scores were lower with increased IL-6 and CRP levels.

Confounds of age, exposure to antipsychotics, duration of illness, and BMI correlated with each other and variably with IL-6 and CRP. None correlated with positive or negative symptoms.

Conclusions: There was no MRS evidence of glutamate disinhibition in RS. Reductions in ES are compatible with neurodegeneration but they did not relate to measures of inflammation, symptoms or confounds. Reductions in occipital GABA content in RS and ES are compatible with GABA deficiency in schizophrenia. Changes in PET TSPO and cytokines and their functional correlates point to non-inflammatory immune dysfunction in early pathogenesis and possible secondary inflammatory mechanisms in later stages of illness.

Disclosure: P1vital Ltd: Consultant (Self)

MINI PANEL

53. Neuroendocrinology of Irritability in Women Across the Reproductive Lifespan

53.1 Temporal Dynamics of Differential Mood Sensitivity to Steroid Manipulation in Peripartum-Onset Depression: Evidence for Rapid, Marked, and Sustained Differences in Anger/Irritability

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Background: Experimental paradigms demonstrate that reproductive mood disorders (e.g., peripartum-onset mood disorder) are

characterized by hormone sensitivity—an abnormal neurobiological response to normal changes in estradiol and progesterone that leads to affective symptoms during reproductive transitions. However, given the diverse effects of steroids, the pathophysiology of this hormone sensitivity remains to be discovered. One way of narrowing the range of candidate mechanisms may be to characterize the temporal dynamics of hormone-sensitive symptom development in the context of hormone manipulation models, including the lag, rate, magnitude, and duration of different affective responses. In the present study, we sought to characterize the temporal dynamics of the hormone-sensitive affective response in the context of an experimental model of pregnancy.

Methods: Participants were 30 parous females with ($N = 15$) or without ($N = 15$) a history of peripartum-onset depression. After a baseline month of leuprolide-induced hypogonadism (maintained throughout study), we administered 8 weeks of pregnancy-level addback of estradiol (oral micronized started at 4mg/day, titrated up to 10mg/day) and progesterone (oral micronized started at 400mg/day, titrated up to 800mg/day). After careful phenotyping to identify groups of hormone-sensitive (HS+) and non-hormone-sensitive (HS-) individuals using a 30% change threshold on the Inventory for Depression and Anxiety Symptoms (laboratory-administered), we used multilevel models to describe group differences in the development of various affective symptoms as measured using the Daily Record of Severity of Problems.

Results: Twenty-nine participants could be categorized as HS+ ($N = 10$) or HS- ($N = 19$). All emotional and behavioral symptoms showed greater symptom emergence during hormone addback among HS+ participants; however, most physical symptoms (insomnia, headache, swelling/bloating/weight gain, and joint/muscle pain) failed to show any group differences in symptom provocation. The hormone-sensitive affective response was detectable in the first week (Total Symptom Score: $\gamma\text{GROUP} \times \text{WEEK}[\text{BLvsWEEK1}] = 1.40$, $\text{SE} = .50$, $t(3109) = 2.78$, $p = .0054$). This early group difference was also reflected at the item level, with 10 of 21 symptoms showing a significant Group X Week in first or second week of addback (anger/irritability, depressed/blue, hopelessness, mood swings, increased appetite/overeating, overwhelm, and breast tenderness). Anger/irritability and hypersomnia showed the fastest absolute rate-to-peak within the HS+ group. Anger/irritability and overwhelm were the two most persistent hormone-sensitive symptoms, showing significant group differences across all eight weeks of addback. In area under the curve contrasts, anger/irritability demonstrated the largest effect size for group differences in total symptom development across addback ($d = 1.87$), followed by difficulty concentrating ($d = 1.37$), worthlessness/guilt ($d = 1.27$), and overwhelm ($d = 1.26$).

Conclusions: Across metrics, anger/irritability emerged as the most prominent hormone-sensitive symptom, demonstrating early differentiation from controls, an early symptom peak, and the largest absolute difference between groups. These results point to rapid development of anger and irritability following rising hormones as an early indicator of (and potentially a primary process in) peripartum mood changes.

Disclosure: Nothing to disclose.

53.2 Biomarkers of Emotional Regulation of the Postpartum Parent-Infant Dyad

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Background: Feeling a lack of emotional regulation, the ability to exert control over one's own emotional state, is a common concern of postpartum individuals, particularly in feeling unable to control decreased interest, worry, irritability, and restlessness.

Heart Rate Variability (HRV), measures representing the beat-to-beat variation, not only reflect aspects of the Autonomic Nervous System (ANS) function but also emotional regulation. Measures of HRV are thought to reflect vagal activity. There is evidence the gut microbiome is associated with development of anxiety and mood changes. The objective of this work is to study HRV and microbial composition relate to maternal reported symptoms of mood and anxiety and infant stress reactivity.

Methods: Self-assessment of symptoms included the Edinburgh Postnatal Depression Scale (EPDS), Generalized Anxiety Disorder-7 (GAD-7) and the Perceived Stress Scale (PSS) were collected alongside fecal samples from mother and infant in the postpartum visit. HRV was measured before, during, and after the Trier Social Stress Test (TSST) administered to the mothers and a heel stick administered to the infants. Reactivity was calculated from the difference between measures during stress and at baseline. Maternal microbial composition was characterized by 16S rRNA sequencing and alpha-diversity was calculated by Faith's PD, observed OTUs, and Shannon. A factor analysis was used to assess which symptoms from the EPDS, GAD-7 and PSS were likely to group from the UNC cohort with a UIC cohort of perinatal individuals. The Mood and Anxiety Disorders Questionnaire (MASQ)-90 was also obtained and those groupings applied to this analysis. Early life adversity (ELA) was measured by the Adverse Childhood Experiences. Sleep quality was also assessed with the Pittsburgh Sleep Quality Index.

Results: In a subset of the larger cohort of 94 perinatal individuals, 40 postpartum parent-infant dyads had maternal and infant HRV data. Pearson correlations did not find an association between total scores on the EPDS, GAD-7 or PSS and maternal HRV before, during, or after the stressor. Measures of maternal alpha-diversity also did not associate with HRV, but showed a trend towards lower alpha diversity and lower quality sleep. Maternal MASQ General Distress Mixed (GDM) which includes irritability, restlessness, sleep difficulty, and worry showed lower vagal tone after the stressor; as did a similar grouping of symptoms from the factor analysis. Individuals with higher maternal MASQ Anhedonia (AD) showed higher reactivity. AD and GDM correlations were made stronger (AD $R = 0.47$, $p = 0.003$ and GDM $R = 0.28$, $p = 0.09$) when only considering those with ELA. Greater maternal vagal reactivity ($R = -0.51$, $p = 0.019$) was associated with lower infant vagal reactivity. Maternal AD and AA were associated with lower infant vagal tone reactivity (AD $R = 0.45$, $p = 0.03$ and AA $R = -0.43$, $p = 0.018$). Maternal alpha-diversity associated with lower infant vagal tone and higher heart rate at baseline.

Conclusions: Maternal vagal tone reactivity associates with infant reactivity and this is also associated with maternal symptoms indicating greater difficulty with emotional regulation. A less diverse maternal microbial composition was associated with these findings. Maternal ELA is also an important consideration. Future work will look at HRV and maternal microbial composition in pregnancy to see if this precedes the postpartum relationships. Mother-infant interactions will also be helpful in understanding how mother's emotional regulation impacts the development of her infant's emotional regulation.

Disclosure: Abbvie: Stock / Equity (Spouse)
Sage Therapeutics: Grant (Self)

53.3 Effects of Estradiol on Irritability and Neural Reward Circuit During the Menopause Transition

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Background: Sex steroid changes interact with antecedent vulnerability to trigger irritability and neural system dysregulation

in susceptible women in the context of reproductive transitions. Here we present data from two pharmaco-fMRI studies investigating the effects of experimentally controlled reproductive steroid exposure on irritability and reward circuit activation in perimenopausal women.

Methods: In Study 1, women with current perimenopause-onset major depressive episode (MDE; $n = 15$) and euthymic perimenopausal women ("controls"; $n = 18$) were treated with transdermal E2 (100 µg/day) for 3 weeks. In study 2 (data collection underway), with current perimenopause-onset major depressive episode (MDE; $n = 10$) were treated with the tissue selective estrogen complex (TSEC) Duavee (conjugated estrogens/bazedoxifene, 0.45mg/20mg) for 3 weeks. In both studies, irritability was assessed with the Inventory of Depression and Anxiety (IDAS) III Temper Scale. fMRI sessions, conducted at baseline and post-treatment, included the monetary incentive delay (MID) task. Scans were performed using a Siemens Magnetom Prisma 3T scanner. Whole-brain functional images were acquired using a multi-slice, interleaved pulse sequence (TR = 2000 ms; TE = 25 ms; FOV = 256 mm; acquisition matrix = 256 x 232 x 144 mm; flip angle = 80°; voxel size = 4 x 4 x 4 mm; 36 axial slices) sensitive to blood-oxygen-level-dependent (BOLD) contrast. Data were preprocessed using FSL version 6.0.4 (Oxford Center for Functional Magnetic Resonance Imaging of the BRAIN (FMRIB), Oxford University, U. K.).

Results: In Study 1, results of GEE comparing irritability in MDE and controls during E2 treatment revealed significant group ($\chi^2(1,35) = 21.98$, $p < .0001$), visit ($\chi^2(3,35) = 10.10$, $p = 0.0177$), and interaction effects ($\chi^2(3,35) = 10.36$, $p = 0.0158$). Compared with controls, those with MDE showed a greater decrease in irritability, with the largest decrease from baseline observed at the end of the third treatment week ($p < 0.025$). The degree to which E2 treatment reduced variability in serum E2 levels, measured weekly, was associated with lower levels of irritability at post-treatment ($r(33) = 0.53$, $p < .002$). Following E2 treatment, women with MDE showed greater increased activation in the right nucleus accumbens and paracingulate gyrus during reward onset, compared with controls (cluster corrected $p < .05$). In Study 2, results of GEE comparing irritability over the course of the intervention revealed significant visit effects multivariate $F(3,27) = 4.34$, $p < .02$. In addition, we assessed remission (scale of <7 on Hamilton Depression Rating Scale) at the end of intervention and 9/10 women in our pilot study reported scores reflecting remission at week 3. Data collection in Study 2 is ongoing and fMRI analysis is underway.

Conclusions: Findings support the role of sex steroids in regulating irritability in perimenopausal women. Steroid changes were associated with regulation of the neural reward circuitry, which may mediate hormone-related affective dysfunction.

Disclosure: Nothing to disclose.

PANEL

54. Impact of Unpredictable Parental and Environmental Signals on Neural Circuit Maturation and Mental Health

54.1 Patterned Sensory Signals During Sensitive Periods Enable Brain Circuit Maturation: Synapses, Microglia, Behaviors

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Background: Brain circuits, comprised of neuronal ensembles communicating via synapses, execute complex behaviors involved

in mental health and disease. During sensitive developmental periods, activity, largely in response to sensory signals, governs which synapses are strengthened or pruned, and this selective sculpting enables circuit maturation. We have identified reduction of excitatory synapses onto stress-sensitive hypothalamic neurons after predictable barrages of sensory stimuli to neonatal rats, and, in contrast, enduring exuberant excitatory innervation of the same cells after exposure to unpredictable chaotic sensory input. We further demonstrated that these changes in excitatory synapse density on CRH-expressing neurons in the paraventricular hypothalamic nucleus are important, as they promote muted or protracted responses to stress throughout life.

Methods: To probe the mechanisms by which excitatory synapse density is augmented by unpredictable patterns of sensory input (FRAG) early in life, employ multiple methodologies in vivo and in vitro centered on the role of microglia. Employing a suite of transgenic mice we used live two-photon imaging to determine microglial process dynamics, selective chemogenetic manipulation of microglia, confocal and electron microscopy and hormonal and behavioral assays in both sexes.

Results: We identified disrupted synapse pruning by microglia as a mechanism for aberrant sculpting of the innervation to stress-sensitive neurons. Microglial process dynamics, assessed using 2-photon microscopy ($t_{16} = 2.79$, $p = 0.01$), and engulfment of synaptic elements by microglia ($t_{13.87} = 2.22$, $p = 0.04$), were attenuated in FRAG mice versus controls, related to deficient signaling of the microglial phagocytic receptor MerTK. Accordingly, selective chemogenetic activation of FRAG mouse microglia rescued microglial process dynamics and reduced excitatory synapses density to control levels. Notably, such early-life microglial activation ameliorated the augmented and prolonged stress responses in adult FRAG mice.

Conclusions: Together, the data indicate that unpredictable patterns of sensory inputs prevent selective pruning of synapses, perhaps via absence of selective Hebbian plasticity. They establish microglial actions during development as powerful contributors to the enduring, experience-dependent sculpting of stress-related brain circuits, which, in turn, governs life-long behaviors.

Disclosure: Nothing to disclose.

PANEL

55. From Basic Science to Clinical Practice: A New Era for Brain Stimulation Treatment of Addictive Behaviors

55.2 Dosing by Design: Using Functional and Structural Architecture to Improve TMS Outcomes

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Background: Transcranial Magnetic Stimulation (TMS) has emerged as a promising treatment for various psychiatric disorders. The optimal dose and stimulation location for each patient, however, remains elusive. Using the scaffolding of a large clinical trial, we retrospectively analyzed the influence of neural architecture and functional topography on treatment outcomes in a TMS trial for alcohol use disorder.

Methods: In the Parent Study (randomized, double-blind, enrolled from 2016-2019), 51 heavy alcohol users were randomized to receive real or sham stimulation to the medial prefrontal cortex during an intensive outpatient treatment program (3600 pulses cTBS, 110% rMT, 10 visits; 36,000 pulses total; left frontal pole). Longitudinal functional and structural MRI data were

acquired for each individual at baseline and 3 follow ups (up to 4 scans per individual). In the present study, anatomical data were used to calculate the amplitude of the realized TMS electric field at the cortex for each individual (SIMNIBS v3.1) and baseline functional MRI data were used to calculate the overlap between the TMS-induced field and individual functional maps. Multivariate linear regressions and clustering analyses were used to calculate the independent and synergistic impact of these factors on treatment outcomes.

Results: Individuals for whom the TMS-induced electric field intersected spatial maps of brain regions significantly activated by drug cues (FWE corrected clusters $p < 0.05$) had the highest sobriety over the 4 month duration of the experiment ($F(2, 49) = 14.58$, $p = 0.02$) and a greater change in depression symptoms (as measured by the Beck Depression Inventory; $F(1,66) = 5.016$, $p = 0.028$), anxiety (as measured by the Spielberger Anxiety Inventory; State- $F(1,66) = 3.655$, $p = 0.06$, Trait $F(1,66) = 7.746$, $p = 0.007$) relative to individuals with non-overlapping TMS-electric fields and functional MRI activity.

Conclusions: In this prospective clinical trial, the individuals with the best clinical outcomes were those in whom the TMS-induced electric field overlapped with their specific pattern of cue-induced BOLD signal within the medial prefrontal cortex. These data suggest that, instead of merely using a fixed stimulation location and motor-cortex-based dosing, patients treatment outcomes may be maximized by incorporating structural and functional architecture into dosing protocols.

Disclosure: Nothing to disclose.

55.3 It's High Time for a New Approach to Treating Cannabis Use Disorder: Investigating the Therapeutic Potential for Non-Invasive Brain Stimulation in Heavy Cannabis Users

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Background: Neuroimaging studies have shown that cannabis use disorder (CUD) is associated with reduced brain activity in the dorsomedial prefrontal cortex/anterior cingulate cortex (DMPFC/ACC). This region is part of the Salience Network which is critical for monitoring and adapting cognition and behavior by weighting and integrating goal-related conflicts and errors. Reduced activity in this region may be related to a tendency to choose riskier outcomes in the face of conflict, such as relapsing to cannabis use despite adverse consequences. One way to treat CUD and reduce relapse risk may be by increasing activity in the DMPFC/ACC using non-invasive brain stimulation (NIBS). Transcranial magnetic stimulation (TMS) is a NIBS technique that can selectively alter and normalize cortical and subcortical brain activity. Specifically, high-frequency, excitatory repetitive TMS (rTMS) can increase cortical excitability. The purpose of this double-blind, active sham-controlled feasibility and proof-of-principle study was to (1) determine the feasibility and tolerability of the procedures in cannabis smokers, and (2) to determine if 11 days of high-frequency, excitatory deep rTMS to the DMPFC/ACC could reduce cannabis self-administration.

Methods: Seventeen adult male and female non-treatment-seeking cannabis users were randomized to receive 11 daily sessions of active or sham DMPFC/ACC rTMS (Brainsway H7 coil, 10Hz, 1200 pulses, 110% rMT) while inpatient for 19 days. Cannabis self-administration was assessed before and after rTMS treatment: The first session occurred after 3 days of monitored abstinence (before rTMS) and the second session followed 11 days of rTMS. During each session, participants had 6 opportunities throughout the day (every 1.5 hr) to choose between smoking

cannabis (5.5% THC; up to 3 puffs/choice) or receiving money (\$1/puff to their study earnings). For interim analysis, we tested (1) feasibility/tolerability (as measured by study completion, full-dose rTMS, and no adverse events), and (2) “proof-of-principle” test of treatment effects.

Results: All 17 participants completed the full study, tolerated full-dose rTMS and all study procedures well, and did not endorse any significant adverse events. Individuals in the active rTMS group ($n = 9$) cut their cannabis intake to ~half their baseline use (-4.7 ± 5.8 choices), with 78% ($n = 7/9$) showing a decrease from baseline of at least 3 puffs (range: 3–18 puffs). The sham rTMS group ($n = 8$) showed no changes in self-administration (-0.9 ± 3.7 choices), with 75% ($n = 6/8$) showing the same or slightly increased use, thus reflecting a trend toward greater reductions in cannabis use following active vs. sham deep rTMS. This study is ongoing (goal of completing $n = 15$ per group).

Conclusions: To our knowledge, this is the first study to assess the effects of rTMS on cannabis self-administration. While data collection is still ongoing, these preliminary results indicate that (1) high-frequency deep rTMS to the DMPFC/ACC may influence cannabis self-administration, and (2) these procedures were feasible and well tolerated in this population. Upon completion, this study will contribute to the further development of therapeutic NIBS for CUD, including those employing novel rTMS-based approaches.

Disclosure: Nothing to disclose.

55.4 Using a New Trick to Tame an Old Dog: A Preliminary Study of Repetitive Transcranial Magnetic Stimulation (rTMS) for Cannabis Use in Schizophrenia

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Background: Rates of problematic cannabis use in schizophrenia are high, with ~25% diagnosed with cannabis use disorder (CUD), compared to ~3% in the general population, which negatively impacts psychosocial functioning. These patients have greater difficulty quitting cannabis that may reflect putative deficits in the dorsolateral prefrontal cortex (DLPFC), which may constitute a target for treatment development. Neuromodulatory treatments including repetitive transcranial magnetic stimulation (rTMS) warrant consideration in this regard.

Our primary objective determined effects of active versus sham high-frequency (20-Hz) rTMS applied to bilateral DLPFC on cannabis use in outpatients with schizophrenia and CUD. Secondary outcomes included cannabis craving/withdrawal, psychiatric symptoms, and cognitive function.

Methods: A preliminary double-blind, sham-controlled randomized rTMS trial enrolling $N = 24$ outpatients. Nineteen participants were randomized to receive active ($n = 9$) or sham ($n = 10$) rTMS (20-Hz) 5x/week for 4 weeks. Cannabis use and psychotic symptoms were monitored weekly. A cognitive battery was administered pre- and post-treatment.

Results: No significant differences in cannabis use between active and sham treatments were found; however contrast estimates indicated greater reductions in the active group (GPD: Estimate=0.33, $p = 0.21$). A trend toward greater reduction in craving over time was found in active vs. sham (Estimate=3.92, $p = 0.06$). Reductions in PANSS positive (Estimate=2.42, $p = 0.02$) and total (Estimate=5.03, $p = 0.02$) symptoms were found in active vs. sham groups. rTMS improved sustained attention (Estimate=6.58, $p < 0.05$), and suppressed increased tobacco use that was associated with cannabis reductions (Treatment x Time: $p = 0.01$). rTMS was safe and well-tolerated with high treatment retention (>90%).

Conclusions: Our preliminary findings suggest that rTMS applied to bilateral DLPFC is safe and potentially efficacious for treating CUD in schizophrenia. Further evaluation of neuromodulation methods to address co-occurring psychosis and addiction by targeting DLPFC dysfunction associated with schizophrenia is suggested.

Disclosure: Nothing to disclose.

PANEL

56. Psychiatric Comorbidity in Alzheimer's Disease: From Neural Circuits to Therapeutic Interventions

56.2 Depressive-Like Behaviors in Mouse Models of Alzheimer's Disease: Role of Serotonergic Systems

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Background: Neuropsychiatric symptoms (NPS) may be an early biomarker of Alzheimer's disease (AD) that can be used to aid diagnosis and early intervention. Earlier studies have reported marked loss of serotonin (5-HT) neurons and the presence of tau tangles in the raphe nuclei in the early stages of AD, but the precise contribution of these neuropathological changes to depression is unclear. The locus coeruleus (LC) also develops tau pathology and may contribute to NPS. The goal of the present study is to assess the contribution of tau pathology in the dorsal raphe nucleus (DRN) and LC to depressive and anxiety-like behaviors in mouse models of AD.

Methods: We used two AD models, the htau line which expresses all six isoforms of human wild-type tau, and a viral vector (AAV) that expresses P301L-tau under the control of a CAG promoter. Htau mice or age-matched C57BL/6J controls were assessed for depressive-like behaviors in social interaction, sucrose preference, and forced swim tests at 4 months of age. They were also assessed for anxiety-like behaviors in the open field and elevated plus maze at 4 months and cognitive function in the Barnes maze at 6 months. In another cohort of male C57 mice, AAV expressing P301L-tau or GFP was injected into the DRN or LC at 8–12 weeks of age. Four weeks later, depressive- and anxiety-like behaviors were assessed. At the end of behavioral testing, brains were extracted for immunohistochemical analysis of phospho-tau and tryptophan hydroxylase 2 (Tph2) or tyrosine hydroxylase (TH).

Results: Depressive behaviors were observed at 4 months of age in male and female htau mice relative to C57 mice in the social interaction test ($F(1,16)=28.77$, $p < 0.001$) and the sucrose preference test ($F(1,20)=8.31$, $p < 0.01$). There were no significant differences in the forced swim test in either sex. In the elevated plus maze, there was an increase in time spent in the open arms in male mice only ($t_{30}=2.25$, $p < 0.05$), which is suggestive of reduced anxiety. In the open field, there was an increase in distance moved in the males ($t_{32}=3.54$, $p < 0.01$), but not in center time. We did not observe significant differences in cognitive function in the Barnes maze in either sex. In mice that were injected with P301L-tau directly into the DRN, we observed main effects of tau on depressive-like behaviors in the social interaction ($t_{36}=6.493$, $p < 0.001$) and sucrose preference tests ($F(1,18)=7.372$, $p < 0.05$). No differences were observed in the forced swim test. In the EPM ($t_{14}=2.56$, $p < 0.05$) and open field tests ($t_{17}=2.616$, $p < 0.05$), there was an increase in distance moved. There were no effects of P301L-tau in the DRN on cognitive function in the Barnes maze or contextual fear recall test.

In mice injected in the LC, we did not observe any differences in depressive- and anxiety-like behaviors or cognitive function. In both htau mice and mice injected with P301L-tau in the DRN or LC, we observed significant tau pathology.

Conclusions: These results suggest that tau pathology in the DRN may be driving depressive symptoms in AD prior to the onset of cognitive decline. Surprisingly, tau pathology in the LC was not associated with NPS in our model, although previous studies suggest it is involved in sleep disturbances. Ongoing histology and electrophysiology studies will examine tau-induced alterations in Tph2 and TH neuronal function.

Disclosure: Nothing to disclose.

56.3 Changes in Cholinergic Structure and Function in Middle Age Women and the Relationship to Alzheimer's Disease Risk

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Background: Cholinergic system integrity appears to be critical for maintaining normal cognitive functioning in aging. Women are at increased risk for AD. Understanding the neurobiological factors related to individual differences in cognition at menopause is critical for understanding normal cognitive aging and determining risk factors for AD. We have shown that estrogen's interaction with the cholinergic system is important for cognitive functioning in postmenopausal women. What is not known is how changes in cholinergic system functioning influences cognition as well as AD biomarkers like amyloid, tau, and neurodegeneration. Understanding this relationship may lead to individual risk profiles that can be observed earlier in the aging process while novel treatment (e.g. newer cholinergic approaches) and prevention strategies may be effective.

Methods: Decreased cognitive performance during a temporary cholinergic blockade may be an indicator of susceptibility to the negative effects of hormone withdrawal on the brain and risk for age-related cognitive impairment and/or dementia. We take a multimodal approach to assessing the relationship between cholinergic integrity and AD biomarkers in middle-aged and older normal women including functional brain activity during cholinergic blockade, structural anatomy of the cholinergic basal forebrain, cortical cholinergic projections using the novel cholinergic PET radiotracer [18F]FEOBV, amyloid (flobetapir) PET imaging, CSF/blood sampling for amyloid, tau, and neurodegeneration markers such as NFL.

Results: While no benefit of estrogen therapy alone was seen post menopause, with anticholinergic blockade the beneficial effect of estradiol become manifest and is more prominent in younger postmenopausal women aged 50-60 compared to older women aged 70-80. Significant heterogeneity in individual responses is seen on both attention and memory tasks with 50% of women showing either compensatory or impaired responses suggesting individual differences in risk profile. Postmenopausal cognitive symptoms are associated with increased functional connectivity and decreased medial temporal/hippocampal volume. Preliminary data from cholinergic PET imaging in normal postmenopausal women shows that reduced [18F]FEOBV SUVR correlates ($p < .01$) with age and increased amyloid PET signal, with age and amyloid PET SUVR having an additive negative effect on cholinergic integrity. In addition, [18F]FEOBV SUVR directly correlates ($p < .01$) with cholinergic basal forebrain volume, particularly CH4.

Conclusions: Menopause-related cognitive changes may correlate with both cholinergic functional integrity and established AD

biomarkers that portend increased risk for late-life cognitive impairment or dementia. Preliminary evidence suggests that some otherwise normal postmenopausal women have increased sensitivity to cholinergic blockade, altered brain activation, decreased basal forebrain cholinergic system (BFCS) volume and cholinergic PET SUVR. These indications of early cholinergic dysfunction may be associated with early biomarkers of AD and otherwise cognitively women who show elevated amyloid PET SUVR values or other AD biomarker may have increased risk for AD.

Disclosure: Nothing to disclose.

56.4 Effects of Long-Term Alcohol Consumption in Male and Female PS19 Mice

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Background: The PS19 mouse is a humanized mouse line encoding the P301S mutation associated with neurodegenerative tauopathy. Alcohol consumption remains a prevalent public health issue with increased heavy consumption in older populations and in recent years. Thus, we examined how long-term alcohol consumption altered affective behaviors, learning and physiology in aged PS19 mice and their wildtype (WT) littermates.

Methods: 3 month old naive, and alcohol drinking (20% intermittent access, 16 weeks) male and female PS19 and WT littermates were used. Behavioral tests: open field, elevated plus maze (EPM), light-dark (LD) box, novelty induced suppression of feeding (NSF) test, cue and contextual fear conditioning, and novel object recognition test. Whole-cell electrophysiology was performed in the LC (Schmidt et al., 2019).

Results: Female mice consumed significantly more alcohol ($P < 0.0001$, $F(1,23)=33.69$). During the drinking male mice showed altered weight gain with a significant time x genotype ($p < 0.01$, $F(15,677)=2.173$) and time x treatment ($p < 0.05$, $F(15,677)=1.875$) interactions, and a strong trend for a time x genotype x treatment interaction ($p = 0.0695$, $F(1,52)=3.434$) such that alcohol male PS19s exhibited decreased weight gain.

We found a significant interaction in distance traveled in the open field in male mice ($p < 0.05$, $F(1,35)=5.290$), due to a deficit in male WT animals distance traveled ($p < 0.05$). Over time, there was a trend for a time x treatment ($p = 0.0638$, $F(2,70)=2.864$) and genotype x treatment interactions ($p = 0.0727$, $F(1,35)=3.423$). Females did not show any differences.

In the EPM, male mice had an effect of genotype for time in the open arms ($p < 0.01$, $F(1,31)=8.438$). In the LD box males had an effect of genotype on both latency to enter the light ($p < 0.05$, $F(1,28)=7.515$) and time in the light ($p < 0.05$, $F(1,28)=4.407$). Females did not show any differences.

In the NSF test, female mice had an effect of genotype with an increase in latency to feed ($p < 0.05$, $F(1,21)=4.632$). Males did not show any differences.

Due to hyperactivity in male PS19 animals, we compared the water and alcohol drinking male PS19 animals in fear behavior. Alcohol male PS19 animals exhibited decreased cued recall ($p = 0.0589$, $F(1,11)=4.440$). Female mice did not exhibit any differences.

Testing for novelty preference, male mice showed a genotype x alcohol interaction ($p < 0.05$, $F(1,26)=5.334$), with a male PS19 consuming alcohol exhibiting a deficit ($p < 0.05$). Female mice showed a significant genotype by alcohol consumption interaction ($p < 0.05$, $F(1,27)=6.630$), however, female WT alcohol consuming animals showed a preference deficit compared to their female PS19 alcohol counterparts ($p < 0.05$).

As the locus coeruleus (LC) as it is the first site of neurodegeneration in Alzheimer's Disease, we found that in 9 month old PS19 female mice there is a significant decrease in the spontaneous discharge of LC neurons of naïve PS19 animals vs. their WT littermates ($p < 0.05$, $t = 2.340$, $df = 10$). Ongoing studies are examining LC electrophysiological function in male and female naïve PS19 animals and water vs. alcohol consuming PS19 animals.

Conclusions: In this study we found several differences in behavior between male and female PS19 animals consuming alcohol. Male PS19 mice exhibited "behavioral disinhibition" like phenotypes in the EPM and LD box, and altered learning, reminiscent of what we and others have previously observed in male mouse models of stress and substance use disorder (Mozhui et al., 2010; Bravo et al, 2020). Surprisingly, even though female animals of both genotypes consumed more alcohol than their male littermates, we found few behavioral differences.

Disclosure: Nothing to disclose.

PANEL

57. Electrophysiology as a Translational Biomarker for Treatment Development in Psychiatric and Neurological Disorders: Insights From Cross-Species EEG Research

57.1 Cross-Species EEG Markers of Cognitive Flexibility Using a Probabilistic Reversal Learning Task

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Background: Cognitive flexibility, or the ability to update action-outcome expectations in an uncertain environment, is impaired in several psychiatric and neurological disorders, including depression, schizophrenia, and Parkinson's disease. Non-human animal procedures that accurately reflect neurophysiological and behavioral markers of cognitive flexibility as measured in humans are needed to successfully develop effective clinical treatments for these cognitive deficits, which are presently lacking. We measured neurophysiological (EEG) and behavioral markers of cognitive flexibility in both humans and rats using a functionally equivalent cross-species probabilistic reversal learning (PRL) task. We also assessed the ability of the dopaminergic drug modafinil to modulate these neurophysiological and behavioral measures across both species.

Methods: Rats - Male and female Wistar rats ($n = 15$) were implanted with intracranial and extracranial recording electrodes over frontal and parietal areas and tested in an operant PRL task. Rats received modafinil (0, 4, 8, 16, 32, 64 mg/kg) prior to testing. Humans - EEG data from 96 equidistant scalp electrodes were recorded from male and female participants ($n = 45$) during performance of a computer-based PRL task. A separate group of participants ($n = 26$) received modafinil (0, 100, 200 mg) prior to testing. PRL Task - During testing, subjects were required to choose between two stimuli - a target stimulus that was reinforced on 80% of responses and a non-target stimulus that was reinforced on 20% of responses. The target or non-target assignment of the stimuli reversed if the target stimulus was selected on eight consecutive trials, irrespective of feedback.

Results: Humans and rats both performed several reversals [humans: 13.5 ± 0.75 (mean $\pm$ SEM); rats: 7.3 ± 0.73], reflecting cognitive flexibility. This was accompanied by a higher probability to repeat reinforced target responses, reflecting sensitivity to positive outcomes, relative to a lower probability to abandon

unreinforced target responses, reflecting sensitivity to negative outcomes, across species [humans: $t(44) = 13.84$, $p < 0.001$; rats: $t(14) = 8.4$, $p < 0.001$]. A feedback-related negativity (FRN) emerged in frontal (e.g., FCz in humans; ACC and lateral OFC in rats) areas when negative relative to positive feedback was presented [humans: $F(1,45) = 14.83$, $p < 0.001$; rats: $F(1,9) = 19.29$, $p < 0.01$]. There was no effect of modafinil on neurophysiological or behavioral outcomes in humans, while higher doses produced impairments across both sets of outcomes in rats. Reinforcement learning analyses revealed more positive Q and prediction error values associated with target relative to non-target responses in both species [Q - humans: $t(44) = 26.74$, $p < 0.001$; rats: $t(14) = 7.41$, $p < 0.001$; PE - humans: $t(44) = 12.2$, $p < 0.001$; rats: $t(14) = 6.23$, $p < 0.001$].

Conclusions: Our results demonstrate a frontal FRN effect in both humans and rats performing a conceptually and procedurally analogous PRL task used to assess cognitive flexibility. The FRN reflects an error signal when a target response was not followed by a positive outcome (i.e., a negative prediction error). Modulation of the neurophysiological and behavioral markers of cognitive flexibility was only evident after treatment with large doses of modafinil in rats that likely exceeded the doses administered to humans. These results demonstrate feasibility in recording task-based neurophysiology in a similar manner across species and implementing identical analytical methods to both human and rodent behavioral and neurophysiological data.

Disclosure: Nothing to disclose.

STUDY GROUP

58. So You Studied a Female Mouse, Now What? Reconciling Sex Differences in Animals With the Role of Gender in Mental Health

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Study Group Summary: We have just passed the five-year anniversary of the NIH's "Considering Sex as a Biological Variable" policy implementation, requiring all grant applicants to use both male and female animals in their proposed work. Despite some early resistance, many preclinical neuroscientists have taken the mandate seriously and adapted their experimental designs to include males and females. Perhaps unsurprisingly, these researchers have identified sex-dependent behavioral or mechanistic outcomes in work that is related to better understanding and treating psychiatric illnesses. The challenge now becomes, how do we interpret, communicate, and translate these findings in a way that recognizes the complex contributions, interactions, and dissociations of sex and gender in mental health? New insights across sexes in animal models will continue to broaden our understanding of what is possible in the brain, but identifying how our findings might translate to people of all genders will require careful intention, thought, and interpretation, resisting oversimplification. We believe that the ACNP attendees would benefit greatly from a discussion on this topic. Our panel brings together scientists with a range of perspectives on these issues. We represent diversity with respect to model organism (rodent, non-human primate, and human), career stage (Postdoc, Assistant, Associate, and Full Professors), location, and demographics (4/7 women, 2/7 non-white, 3/7 LGBTQ).

Disclosure: Nothing to disclose.

STUDY GROUP

59. Race and Racism in Neuropsychopharmacology Research: Dissecting the Study, Team, and Interpretation of the Science

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Study Group Summary: In 2020, one of America's worst kept secrets was exposed— that systemic racism persists at every level. This study panel is a coordinated effort to continue relevant discussions initiated by Black, Indigenous, and People of color (BIPOC) members of ACNP who hosted an inaugural event at the 2020 meeting. As the U.S. struggles to address structural racism, scientific granting agencies including the National Institutes of Health (NIH) have initiated efforts with the goal of improving minority health. Multiple requests for applications and notices of special interest were announced focused on research that directly addresses the impact of structural racism and discrimination on minority psychosocial, behavioral, and physical health. Historically, the predominantly underrepresented minority scientists (URMs) performing health disparities and intervention-based research have struggled to secure R01-level funding because these topics are underappreciated by reviewers. This differential success rate based on topic choice is one key driver of the funding gap. Now this research is considered timely and important, but as a new “hot topic” predictable pitfalls must be avoided to safeguard against introducing additional disparities in the research enterprise itself. For example, while individuals new to disparities research should not be discouraged to compete for these NIH announcements, there should be ample support for integrated teams with the established experience to successfully conduct disparities research. In parallel, NIH reviewers may need supplemental training to effectively judge scientific merit of such projects, or better yet, individuals with vetted experience must be given a seat at the table establishing strategic program priorities, defining key review variables, and ensuring proper study interpretation. The goal of this session is to facilitate a discussion of how neuropharmacology/psychiatry research must address race and racism within the research itself, the formation of the study teams, and interpretation and application of results. Dr. Crystal Barksdale, Program Chief at National Institute of Mental Health Minority Mental Health Research Program, will discuss the policy perspective including efforts to diversify research priorities and workforce. Dr. Ruth Shim, Professor of Psychiatry at University of California Davis, will provide the researcher's perspective with over a decade of experience conducting research related to minority mental health. Dr. Oliver Rollins, Assistant Professor of American Ethnic Studies at University of Washington will aim his sociological lens at neuroscience research including ethical dilemmas that may arise related to misinterpretation of data. Drs. Cynthia Rogers (Member, Chair), Nii Addy (Associate Member, Co-Chair), Marisa Spann and Sade Spencer (Associate Members, Sponsors), BIPOC members of ACNP, will lead an interactive discussion. Deliverables from this session include the identification of potential strategies to ensure more studies related to health disparities will in fact reduce rather than expand health disparities and further marginalize or discourage participation of URMs in research. Overall, this timely study panel will facilitate larger discussions and action steps within and beyond the ACNP conference to ensure careful, culturally informed consideration of race and racism in neuropsychopharmacology research.

Disclosure: Nothing to disclose.

MINI PANEL

60. Neurobiological Correlates of Antipsychotic Efficacy in Psychotic Disorders**60.1 Neuroimaging Candidate Markers for Predicting Response to Antipsychotic Treatment in Psychosis Spectrum Disorders**

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Background: Treatment response biomarkers are intended to characterize patients in context of a given treatment before it is started. A growing number of studies use a myriad of neuroimaging techniques that are geared towards discovering biomarkers predicting subsequent response to antipsychotic treatment in psychosis spectrum disorders. Our group has conducted several multimodal neuroimaging studies following patients longitudinally with the overarching goal to capture the neural correlates of treatment with risperidone, a commonly used antipsychotic medication. We found that a number of baseline measures including brain neurochemistry, functional connectivity and white matter integrity have potential to be leveraged for prediction of subsequent response to antipsychotic treatment.

Methods: We will present unpublished neuroimaging data of two cohorts of unmedicated/ medication-naïve psychosis spectrum patients followed longitudinally while treated with risperidone. The first cohort consisted of 71 antipsychotic-medication naïve first episode patients and the second cohort consisted of 63 unmedicated patients with schizophrenia. Treatment response was calculated as percent change in BPRS positive scores between baseline and endpoint. Resting state data (acquisition parameters: cohort 1: A > P and P > A; TR/TE = 1550/37.80ms, 2mm isotropic voxels, 225 acquisitions in each direction; cohort 2: TR/TE = 2000/30ms, 6mm slice thickness, 1mm gap, 225 acquisitions). To obtain connectivity maps, we placed seeds in the dorsal striatum, a principal site of antipsychotic drug action, and in the hippocampus, a brain region implicated in the schizophrenia pathophysiology. Analyses were performed using small volume correction ($p < 0.01$), and then cluster corrected using TFCE. We also acquired MRS data in cohort two ($n = 61$) in the bilateral anterior cingulate cortex (ACC; 2.7x2x1cm³) and left hippocampus (2.7x1.5x1cm³) using a PRESS sequence (TR/TE = 2000/80ms; 256 averages in the ACC and 640 averages in the hippocampus).

Results: Resting state connectivity of the striatum to the was found to be predictive of response to antipsychotic treatment in both groups. Importantly, caudate dysconnectivity to areas of the default mode network were predictive of better subsequent treatment response in both cohorts ($p < 0.01$). Resting state connectivity of the hippocampus, similarly shows consistent spatial patterns of brain regions predictive of subsequent treatment response ($p < 0.01$). We will also show findings of a longitudinal study using magnetic resonance spectroscopy to quantify neurometabolite levels using linear regression analyses suggesting that Glx levels in the hippocampus and NAA levels in the anterior cingulate cortex ($R^2 = 0.15$, $F = 2.37$; $p = 0.08$ and $R^2 = 0.14$, $F = 2.27$, $p = 0.09$ respectively) may be relevant in predicting clinical response to antipsychotic medication.

Conclusions: Taken together, our data are promising in that various neuroimaging techniques have shown potential to be leveraged for treatment response biomarker development. Future studies testing utility of these putative markers at the single subject level, and testing if an aggregate approach (i.e.

combination of multiple imaging modalities) will increase overall performance and clinical utility of neuroimaging data will move the field closer to realizing a precision medicine approach in the management of schizophrenia spectrum disorders.

Disclosure: Neurocrine Biosciences: Advisory Board (Self)

American Board of Psychiatry and Neurology: Consultant (Self)

National Institute of Mental Health: Grant (Self).

60.2 Breakthrough Psychosis as a Model to Study the Mechanisms of Treatment Responsiveness Over the Course of Treatment: A Hypothesis Generating Study

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Background: Most individuals with psychotic disorders respond to antipsychotic medication in the early phase of illness, but over 80% experience relapses of their symptoms, which over time accounts for accrued disability. Non-adherence with antipsychotic medication is the most common cause of relapse, although it may also occur despite ongoing maintenance treatment.

Since non-adherence at the time of relapse is common and often uncertain, we have focused previous work on relapse in individuals treated with long acting injectable (LAI) antipsychotics, for whom drug delivery can be easily confirmed. This phenomenon, known as Breakthrough psychosis on Antipsychotic Maintenance Medication (BAMM), occurs in ~25% per year among those with continuous treatment. Currently, there are indirect data that could justify opposite hypotheses for the mechanisms of relapse in BAMM (i.e., primarily striatal vs extra-striatal dysfunction). This work aims to generate data that can be used in subsequent hypothesis confirmatory studies, to investigate the mechanisms involved in the failure to sustain treatment responsiveness.

Methods: We conducted a cross-sectional study of individuals with a DSM-IV psychotic disorder presenting to the emergency department with acute worsening of their psychotic symptoms (at least 1 item of the BPRS psychosis subscale moderate or worse). We compared between individuals with BAMM ($n = 23$), and those who declared antipsychotic discontinuation prior to relapse ($n = 27$). Antipsychotic plasma levels were used to confirm adherence status, and healthy controls ($n = 26$) were included as a reference. The outcome of interest was the striatal connectivity index (SCI), a previously validated composite score reflective of resting state connectivity in 91 functional connections of the striatum predictive of treatment response in schizophrenia. In previous literature, lower SCI values reflect most aberrant striatal resting state function, and greater probability of treatment responsiveness. We acquired for each individual >10 minutes of resting state fMRI, to generate functional connectivity maps. Region of interest (ROI) analyses were conducted to calculate SCI values for each participant, taking the connectivity strength of those 91 connections. This metric was entered as dependent variable in a linear regression adjusted for sex and age for which group (i.e., BAMM vs after discontinuation) was the independent variable.

Results: Individuals in the BAMM group had significantly lower SCI values than healthy controls (Cohen's $d = 0.99$, $p < 0.001$), and non-adherent individuals upon relapse (Cohen's $d = 0.58$, $p = 0.032$), whereas non-adherent individuals had also trend level lower SCI values than healthy controls (Cohen's $d = 0.44$, $p = 0.09$). These differences essentially remained unchanged after removing individuals with psychosis other than schizophrenia, and in analyses without global signal regression. Looking at the 91 functional connections that make up the SCI, only that of ventro-

rostral putamen with left insula in BAMM vs healthy controls survived correction for multiple comparisons ($\beta = 0.23$, $p = 0.031$).

Conclusions: These data generate the hypothesis that relapse of psychotic symptoms may be characterized by striatal dysfunction, and that the degree of it may be significantly worse when relapse occurs despite ongoing antipsychotic treatment. Subsequent hypothesis confirmatory studies including responders to antipsychotic treatment and additional approaches to study striatal function seem justified by these data.

Disclosures: Alkermes Pathways Research Award: Grant (Self)

TEVA: Consultant (Self)

UpToDate: Royalties (Self).

60.3 Using Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) Data to Predict Clozapine Responders

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Background: Successful treatment of psychosis is often difficult. Individuals non-responsive to antipsychotic medications include up to 30% of all schizophrenia cases. At the point of non-response, the next option is treatment with clozapine. However, clozapine is a drug associated with serious side effects and difficult treatment logistics. The B-SNIP has used data to generate a hypothesis and create a model to predict which individuals with psychotic disorders will respond to a clozapine trial. We propose that a feasible EEG-based biomarker test to define a clozapine responder a priori will increase the utilization of one of the most effective drugs in the psychosis treatment armamentarium.

Methods: The current B-SNIP data with available medication characterization include $n = 614$ psychosis probands (schizophrenia, $n = 303$, schizoaffective disorder, $n = 206$, psychotic bipolar I disorder, $n = 105$). The B-SNIP data include a Structured Clinical Interview for DSM-IV to arrive at a diagnosis, extensive clinical workup, including carefully collected medication data; several EEG paradigms are acquired with broad potential for EEG characterization. One EEG characteristic often deviant in psychosis is Intrinsic EEG Activity (IEA), neural activity not specifically stimulus-related. It is quantified using data from a 9sec ITI period, so the participant is alert but has no structured task or processing. We analyzed the relationship between the medications used to treat psychosis probands and the IEA characteristics of their EEG.

Results: Our findings demonstrate that while most antipsychotics do not affect the IEA, clozapine has a clear and powerful effect on IEA in all individuals, i.e., it is associated with higher IEA across all clozapine-treated probands vs. those not on clozapine. We examined this effect across psychosis Biotypes: in Biotype1 (B1), the clozapine-induced increase in IEA "normalized" this measure (perhaps because B1 group has innately low IEA): IEA in B1-off clozapine vs. healthy controls = -0.47 (Glass Δ), B1-on clozapine = 0.03, B1 Δ change = 0.50. Likewise, in Biotype2 (where IEA is high), clozapine was associated with an increased IEA: B2-off clozapine vs. controls = 0.60, B2-on clozapine = 1.22, B2 Δ change = 0.62. We also examined relationships between symptoms and Biotype on- vs. off-clozapine status. We made the hypothesis that the normalization of IEA in B1 will bring with it improvement in psychotic symptoms but that B2 would not benefit from clozapine effects on IEA. We posit that these effects are based on the "attractor network model" of drug action in psychosis as impacted by the pharmacological properties of clozapine. Therefore, we are currently conducting a randomized multi-site trial treating B1 and B2 psychosis cases with clozapine vs. risperidone ($n = 160$ completers are planned).

Conclusions: The randomized clinical trial of clozapine (vs. risperidone) in psychosis B1 vs. B2, based on the B-SNIP biomarker approach, is ongoing. Depending on the usefulness of the biomarkers that B-SNIP has collected, we may find applications of these in clinical practice. Then, if positive, we will have to design

ways to employ biomarker data for individuals seeking treatment, much like an individual with heart failure gets cardiac function tests to guide optimal treatments.

Disclosure: Nothing to disclose.