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ABSTRACTS COLLECTION

ACNP 62nd Annual Meeting: Panels, Mini-Panels and Study Groups

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Panel

1. Prolonged Exposure to Drugs of Abuse: Molecular Mechanisms and New Treatment Targets

1.1 Cell-Type Specific Insights: Epigenetic Reprogramming and Striatal Gene Responses in Cocaine Withdrawal

Philipp Mews

Chobanian and Avedisian School of Medicine at Boston University, Boston, Massachusetts, United States

Background: A hallmark of addiction is drug-induced disruption of gene programs across brain circuits that direct motivated behaviors, making individuals vulnerable to relapse even after prolonged abstinence. Chronic cocaine exposure induces lasting changes in gene regulation within the brain's motivation and reward systems, linked to an increased relapse risk. These changes are thought to involve chromatin modifications in the nucleus accumbens (NAc), a brain region governing motivated behaviors. However, the molecular processes underpinning these maladaptive gene activities are not fully understood. This study explores a novel epigenetic mechanism whereby chronic cocaine exposure triggers enduring transcriptional reprogramming within distinct neuronal subtypes in the NAc, specifically the D1 and D2 medium spiny neurons (MSNs).

Methods: We used fluorescence-activated nuclei sorting (FANS), ATAC-seq, and RNA-seq to assess cocaine-induced molecular changes in D1 and D2 MSNs, in mice. Additionally, we used mass spectrometry and ChIP-seq for histone modification profiling to distinguish immediate and long-term chromatin and gene expression changes after chronic cocaine exposure and prolonged withdrawal.

Results: Our study revealed that chronic cocaine causes lasting chromatin changes in D1 medium spiny neurons (MSNs), including a significant reduction of the histone variant H2A.Z. These epigenomic changes are linked to abnormal gene expression upon cocaine relapse. Selectively reducing the histone chaperone ANP32E in D1 MSNs prevents cocaine-induced H2A.Z depletion and inhibits cocaine conditioned place preference, while its reduction in D2 MSNs enhances cocaine-related reward learning.

Conclusions: Our study highlights the importance of investigating cell-type-specific epigenome regulation in understanding cocaine's lasting impact on the brain. We link extended cocaine withdrawal to reduced H2A.Z, increased genome accessibility, and latent gene priming in D1 MSNs. Reducing ANP32E in D1 MSNs prevents cocaine-induced H2A.Z depletion and inhibits cocaine's rewarding effects. Our findings posits histone variant exchange as a potential therapeutic target to counteract the deleterious effects of drugs of abuse on brain function and behavior.

Disclosure: Nothing to disclose.

1.2 Abstract not included.

1.3 Choroid Plexus and Nicotine Addiction

Paul Kenny

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Background: Nicotine stimulates neuronal nicotinic acetylcholine receptors (nAChRs) expressed by neurons located in brain motivation circuits, actions critical in establishing the tobacco habit in human smokers. nAChRs are also expressed by non-neuronal cells in brain, the functional relevance of which has not been explored.

Methods: Whole-brain c-Fos mapping and functional magnetic resonance imaging (fMRI) were used to identify brain sites in which neural activity was modified by nicotine. Single cell RNA-sequencing (scRNAseq) and next-generation RNA-sequencing (RNAseq) were used to characterize transcriptional responses to nicotine. Foxj1-Cre::Cas9 mice were used in CRISPR experiments. Conditioned place preference (CPP), nicotine drinking, and intravenous nicotine self-administration procedures were used to assess behavioral actions of nicotine.

Results: c-Fos mapping and fMRI revealed that periventricular brain regions were highly responsive to nicotine. scRNAseq and RNAseq showed that non-neuronal cells in these regions were responsive to nicotine, particularly choroid plexus cells. Expression of the Chrna4 gene, which encodes the α4 nAChR subunit, in choroid plexus cells was modified by nicotine. We used the CRISPR/Cas9 system in Foxj1-Cre mice to cleave Chrna4 into choroid plexus. Chrna4 deficiency in choroid plexus decreased aversion-related and increased reward-related behavioral responses to nicotine.

Conclusions: Non-neuronal cells show robust changes in gene expression in response to behaviorally relevant doses of nicotine. nAChR-mediated signaling in choroid plexus cells is modulated by nicotine. Remarkably, CRISPR/Cas9-mediated genomic cleavage of α4 nAChR subunits in choroid plexus rendered mice less sensitive to nicotine aversion and more sensitive to nicotine reward. These findings highlight the pressing need to better understand the actions of nicotine and other drugs of abuse on non-neuronal cells in the brain. These findings also suggest that signaling processes in non-neuronal cells may play important roles in the addiction-relevant processes.

Disclosure: Co-founder of Eolas Therapeutics: Patent (Self).

1.4 Pattern of Prolonged Cocaine Self-Administration Determines Alterations in Dopamine and Acetylcholine Circadian Rhythms

Mark Ferris

Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States

Background: After decades of critical research, there remain no FDA-approved treatments for cocaine use disorder. This has prompted the need for expanding preclinical models and exploring more comprehensive neurobiological outcomes for CUD. Here we used a recently developed preclinical model that varies pattern of cocaine intake and is shown to be a critical modulator of brain and behavioral outcomes. In these rats, we measured dopamine (DA) and acetylcholine (ACh) signaling/activity, as well as demand curves for cocaine across several time-points across the 24-hour day.

Methods: Male, Sprague-Dawley rats self-administered (SA) intravenous cocaine (0.75 mg/kg) in one of 3 conditions: short (2 hr) continuous access (ShA), long (6 hr) continuous access (LgA), or intermittent access (IntA). After 14 days of cocaine SA, rats were euthanized either midway through their dark cycle or midway through their light cycle for neurochemical assessment of real-time DA and ACh signals using fast scan cyclic voltammetry or fiber photometry, as well as for assessment of cholinergic interneuron activity using slice electrophysiology. In a separate set of rats, behavioral economics procedure for cocaine was used to assess cocaine demand across several times of day following the 3 SA conditions.

Results: Diurnal (light/dark) variation in DA and ACh signaling and activity observed in naïve rats was disrupted IntA, but not ShA and LgA conditions. DA rhythms in IntA rats were increased and flattened across the light/dark cycle compared to naive, ShA, and LgA rats. LgA showed an overall decrease in DA release across all time-points but the rhythm across time was maintained. Pharmacological and optogenetic interrogation of circuits points to disruption of ACh modulation of DA as the mechanism for IntA mediated DA changes and shifts in cocaine demand.

Conclusions: This work shows that cocaine-induced diurnal disruptions of DA release is mediated by corresponding changes in acetylcholine (ACh) signaling from striatal cholinergic interneurons via nicotinic ACh receptors on dopamine terminals. We demonstrated that the rhythms of ACh / DA interactions are greatly disrupted following IntA, but not LgA and ShA conditions. Thus, pattern of cocaine intake determines changes in biological rhythms that are critical for learning, motivation, and implicated in CUD.

Disclosure: Nothing to disclose.

Study Group

2. My Way or the Highway: Methodological Reporting Checklists to Promote Transparency and Reproducibility in Brain Studies, Do They Help or Add Burden and Suppress Innovation?

Tony George*, Hamed Ekhtiari, David Moher, Thomas Nichols, Shari Wiseman, Dost Ongur, Sarah Lisanby, Charlotte Stagg

University of Toronto, Toronto, Canada

Study Group Summary: There is an ongoing discussion among researchers, the open science community, funding and regulatory agencies, and journal editors on the necessity or effectiveness of reporting checklists to improve transparency, repeatability/reproducibility (repeating the same methods to test replicability of the results) and data sharing opportunities. There is a concern that endorsing methodological checklists developed by a group of researchers will push the field to one way of doing research and suppress innovation or diversity within the research methodologies. Meanwhile, lack of precise reporting of methodological details in publications is very frequent as tested in multiple studies.

In this study group, we open up an opportunity for a discussion among researchers involved in developing reporting checklists, editors of major journals in the field, and regulatory and granting agencies on the potentials and threats of developing, using, encouraging and endorsing checklists. We will also discuss the best practices to develop methodological checklists to be dynamically updated with a democratized and rigorous scientific methodology. Monitoring adherence to the checklist in upcoming publications via live systematic reviews and the pros and cons of using reporting checklists to design upcoming studies will be discussed.

In this study group a diverse set of speakers from US, Canada and UK, share their experiences in developing, supporting, endorsing and applying checklists in various levels. David Moher will discuss the emergence of CONSORT in 1996, a guideline for reporting randomized trials, and the subsequent experience of CONSORT with a preview of CONSORT 2023, which incorporates elements of the Template for Intervention Description and Replication (TIDieR) checklist. He will also discuss PRISMA, a guideline for reporting systematic reviews, one of the mostly highly cited publications in medicine.

Thomas Nichols will talk about the creation of "Statement on Neuroimaging Research and Data Integrity" in the Committee on Best Practices in Data Analysis and Sharing (COBIDAS) in the Organization for Human Brain Mapping (OHBM). Hamed Ekhtiari will discuss the methodologies adopted to develop ContES Checklist and FDCR Checklist within the International Network of Neuroimaging Neuromodulation (INNN) and how to measure the adherence to the checklists. A group of editors in chief of the major journals in the field, Tony George (Neuropsychopharmacology), Shari Wiseman (Nature Neuroscience), Charlotte Stagg (Brain Stimulation) and Dost Ongur (JAMA Psychiatry) will discuss the standards of checklists developments, current gaps in the field and technical considerations of endorsement of checklist and encouraging authors and reviewers to adhere with the checklists.

Sarah Lisanby (NIMH) will share her experiences in developing methodological checklists and guidelines in neuromodulation and how to consider these checklists in the request for proposals and grant submissions within NIH. The panel will be open for further discussions by the audience and the speakers will conclude with discussion on a roadmap for the next steps.

Disclosure: Nothing to disclose.

Study Group

3. Exploring Advances in the Neuroscience of Eating Disorders: A Multidisciplinary Study Group

Martin Paulus*, Joanna Steinglass, Laura Berner, Sarah Stern, Carolyn Rodriguez, Mark Chavez

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

Study Group Summary: In the past decade, there have been major advances in the neuroscience of eating disorders. Eating disorders are highly prevalent (up to 20% of the population have experienced a DSM-5 eating disorder by early adulthood) and are associated with high rates of morbidity and mortality (anorexia nervosa alone has a standardized mortality ratio 6 times higher than expected). Interest in the neuroscience of eating disorders is growing. However, there are relatively few research groups dedicated to this work, which has likely contributed to a slower pace of scientific advancement. The need to advance research in this area is particularly urgent given increases in adolescent eating disorders since the COVID pandemic, estimated as high as 15%. The proposed workgroup aims to stimulate a discussion among ACNP meeting participants to boost programs of research in eating disorders with more methodological, subject matter, and socio-demographic diversity.

Traditional accounts of eating disorders have centered on blunted reward processes in anorexia nervosa and high levels of impulsivity in bulimia nervosa. However, clinical complexity (e.g., reinforcing aspects of dietary restriction, rigidly controlled intake between binge-eating episodes) highlights a need for more nuanced models and methods. In the last decade, we have identified frontsostriatal dysfunction and decision-making alterations underlying dietary restriction and binge eating. These findings have opened new pathways for research in eating disorders.

The primary aim of the Study Group is to facilitate a comprehensive and multi-disciplinary dialogue on the latest developments, persistent hurdles, and prospective directions in neuroscience psychiatric research on eating disorders. This will be achieved through:

1. Reviewing recent advances in clinical and preclinical research, with a particular focus on neuroimaging, neuromodulation, and computational modeling methods.
2. Exploring translational opportunities by discussing phenotypically similar disorders, like substance use and obsessive-compulsive disorders, while considering the potential for broader inclusion of other psychiatric disorders in future discussions.
3. Incorporating diverse perspectives not only from researchers but also from representatives from funding agencies to enrich the discourse and ensure a holistic understanding of the challenges and opportunities in the field.
4. Encouraging open discussions among attendees with different backgrounds, allowing for the exchange of innovative ideas and fostering potential collaborations.
5. Emphasizing the translation of our mechanistic understanding of eating disorders into practical clinical interventions, aiming to significantly improve patient outcomes.

The panel will include two clinical researchers in eating disorders (Drs. Steinglass and Berner) who will review recent advances and challenges in human work; a preclinical researcher (Dr. Stern), who will review the latest animal models of eating disorder behaviors; and two researchers with expertise in substance use disorders and obsessive compulsive disorder, respectively (Drs. Paulus and Rodriguez), who will discuss opportunities for translation. The program officer managing NIMH's eating disorder portfolio (Dr. Chavez) will provide insight on his Institute's perspectives.

Disclosures: UptoDate: Honoraria (Self). Spring Health: Board Member (Self). Roche Pharmaceuticals: Consultant (Self). Engrail Therapeutics: Employee (Spouse/Partner).

Study Group

4. Navigating Restrictive Legislation: Ethical and Practical Considerations for Conducting Unbiased Neuropharmacological Research

Sade Spencer*, Nicholas Gilpin, Kristen Brennand, Jessica Nielson, Jeff Boissoneault, Cynthia Rogers

The University of Minnesota, Minneapolis, Minnesota, United States

Study Group Summary: This study group will focus on the ethical and practical considerations that neuropharmacologists, both researchers and clinicians, must consider when conducting research or providing care in the face of restrictive legislation. The panelists will explore the direct and indirect impacts of local and national legislation and policies. Those direct effects include, but are not limited to, restrictions on access to drugs, constraints on funding, and legal barriers to conducting research. Those indirect consequences might be represented by impacts on graduate and medical student matriculation or large-scale restrictions on entire research domains (e.g., embryonically derived stem cells). The diverse group of panelists will discuss the ethical implications of conducting research under these conditions including the potential for biases and conflicts of interest. In addition, the panelists will share practical strategies for maintaining the integrity of research, protecting the safety of researchers, and engaging with affected communities in antagonistic or restrictive environments. This study group will be of broad interest to the attendees and membership of ACNP as an international organization that encourages collaboration between researchers and practitioners to foster the advancement of scientific inquiry and treatment of mental health conditions, especially given that these collaborations may be occurring across political boundaries. The study group will also discuss and consider challenges and opportunities to engage with policymakers to affect future legislative decisions.

Our objective is to bring together basic scientists, behavioral health researchers, clinicians, and ethics and policy experts to discuss the practical implications of recent legislation on research and practice.

Disclosure: Nothing to disclose.

Panel

5. Imaging Studies of Infancy and Early Childhood Provide New Insights Into the Developmental Origins of Mental Health

5.1 Mapping Subcortical Brain Development and Cognition in Infancy and Early Childhood: A Global, Multi-Cohort Study

Ann Alex

Michigan State University, East Lansing, Michigan, United States

Background: Infancy and early childhood (birth to six years) is a dynamic and critical period in human brain development. The Organization for Imaging Genomics in Infancy (ORIGINs) was established to facilitate large-scale collaborative studies of brain structure and function during this period. The current study was designed to (1) map development of subcortical and intracranial volumes in diverse, global populations, (2) determine how socio-demographic factors and adverse birth outcomes shape neuro-developmental trajectories, and (3) identify neural correlates of variation in cognitive development.

Methods: We assembled and harmonized ICV and subcortical volume data from 8 large and diverse pediatric cohorts from 4 countries. The dataset included 2108 children (3607 observations) for mapping brain trajectory and 1238 children (2530 observations) for cognitive development. Age-related growth was analyzed using nonlinear mixed models with an asymptotic function. Cognitive development was analyzed using linear mixed models and correlations between brain phenotypes and cognitive scores using Pearson correlations.

Results: ICV and subcortical structures follow a nonlinear growth pattern. The amygdala was the first subcortical volume to mature, while the thalamus exhibited protracted development. Males had larger brain volumes than females, and children born preterm or with low birthweight showed catch-up growth with age. Socioeconomic factors exerted region and time specific effects. Regarding cognition, males scored lower than females; preterm birth affected all developmental areas tested, and SES affected visual reception and receptive language. Brain-cognition correlations revealed region specific associations.

Conclusions: Our study illuminates how sex, adverse birth outcomes, and SES influence neurodevelopment and cognitive outcomes in socially and ethnically diverse cohorts and lays the foundation for large-scale studies of hormonal and genetic effects on this critical developmental period. Several specific follow-up studies will be briefly discussed.

Disclosure: Nothing to disclose.

5.2 Novel Insights Into Potential Impacts of Environmental Risk Factors on Early Brain Development

Wei Gao

Cedars-Sinai Medical Center, Los Angeles, California, United States

Background: There is emerging evidence demonstrating impacts of a series of environmental risk factors on early brain development. In particular, prenatal drug exposure (PDE), maternal stress/anxiety, and poverty have all been linked to altered functional brain development in affected newborns and long-term abnormal developmental outcomes. However, there still are many unexplored territories. In this work, we looked into a new angle for each of the three risk factors on newborn offspring functional connectivity (FC), including the timing effects of PDE, the potential mediation role of anxiety on effects of maternal stress, and a novel measure of prenatal family income, changing slope, to reveal new insights into their developmental impacts.

Methods: PDE study participants included neonates with prenatal drug exposure (PDE, $n = 81$) and drug-free controls (CTR, $n = 28$). The Timeline Follow Back (TLFB) was conducted to assess frequency of opioid and other drug use in each trimester to assess timing effects. Maternal stress/anxiety and poverty study participants were 56 mom–infant dyads. Prenatal stress was measured using a Life Events Interview while prenatal anxiety was assessed using State-Trait Anxiety Inventory. Family income changing slope was calculated through linear regression of the reported values from the three prenatal timepoints. For both studies, newborn (< 1-month old) resting-state fMRI scans were acquired during natural sleep. Regions of interest (ROIs)-based study was conducted in the maternal stress/anxiety study while seed-based analysis (i.e., amygdala) was conducted for both the poverty and PDE studies.

Results: Higher prenatal stress was associated with decreased left amygdala–left ACC FC values and decreased right amygdala–left ACC FC values. The effect of prenatal stressful events on infant left amygdala–left ACC was mediated by prenatal anxiety symptoms. Prenatal family income changing slope was correlated with FC between right amygdala and right middle/inferior temporal gyrus. We are actively generating preliminary results on the timing effects of PDE.

Conclusions: Our results may reveal novel insights into the timing effects of PDE, mediation effects of maternal anxiety, and impacts of prenatal income changing slope on offspring functional network development.

Disclosure: Nothing to disclose.

5.3 Genetic Liability for Autism Shapes the Developing Brain

Jessica Girault

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

Background: Mounting evidence suggests neuroimaging biomarkers in infancy serve as important predictors of autism spectrum disorder (ASD), and new evidence suggests that heritable quantitative autistic traits (QATs) in family members explain variation in brain development prior to symptom onset in infants. Here I present a body of work demonstrating a proof-of-principle for incorporating familial QATs with infant neuroimaging to understand links between ASD genetic liability and brain development.

Methods: Analyses utilize a sample of 385 (59% male) infant siblings of children with ASD (probands), who are at high likelihood (HL) for ASD and a comparison sample of 107 (58% male) typically developing (TD) infants. MRIs were collected at 6, 12, and 24m of age. Clinical best estimate diagnoses for ASD were made at 24m ($n = 89$ ASD, 77% male). All HL infants had proband QATs and 315 HL and TD infants had QATs available for one or both parents. Longitudinal mixed models quantified associations between familial QATs and infant brain development in a set of a-priori MRI phenotypes. Main effects of proband/parent QATs were investigated as well as QAT x group (HL-ASD, HL-nonASD, TD) interactions.

Results: QATs in probands and mothers (but not fathers) were associated with trajectories of total brain volume and surface area from 6-24 months of age in the HL-ASD group. Proband traits were related to cortical regions, fiber pathways, and functional connections involved in visual processing at 6m.

Conclusions: Results reveal associations between QATs in family members and brain development prior to symptom onset in infants later diagnosed with ASD. In addition to findings with overall brain size, regional results coalesced around the structure and connectivity of visual system at 6m. This work sets the stage for future investigations into the etiology of ASD by identifying presymptomatic neuroimaging biomarkers which reflect inherited liability for the disorder.

Disclosure: Nothing to disclose.

5.4 Early Childhood Development of Cortical Structure-Function Coupling

John Gilmore

University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States

Background: Cortical structure-function (S-F) coupling, the relationship between white matter and functional networks, is abnormal in schizophrenia and other psychiatric disorders. While there is strong evidence that the functional connectome is highly related to the white matter connectome in older children and adults, little is known about structure-function relationships in early childhood, the period of rapid development of these connectomes.

Methods: The development of cortical S-F coupling in children in the UNC Early Brain Development Study who were longitudinally scanned at 1, 2, 4 and 6 years of age (N = 360) and in a comparison sample of adults from the Human Connectome Project (N = 89). S-F coupling of 78 cortical regions was determined using Spearman's rank correlations between the regional profiles of the white matter connectome and functional connectome matrices. We also determined the participation coefficient (PC), a graph measure of how well connected a node is to network communities in the brain.

Results: The strongest S-F coupling in 6 year olds were found in regions involved in default, visual, limbic, ventral attention, and sensorimotor networks. These regions also exhibited the strongest coupling in 4 year olds, and many were also regions of highest S-F coupling in 1 and 2 year olds especially default (L and R Front Med Orb; L and R Ant Cingulum, R Precuneus) and visual regions (L and R Calcarine, R Cuneus). Interestingly, 4 regions (L and R Ant Cingulum, L Mid Cingulum, L Calcarine) were among the strongest S-F regions in 1 year olds and adults. We found significant negative correlations between S-F coupling and participation coefficients for structural networks in 1, 2, 4, and 6 year olds (1 year: $r = 0.273$, $p = 0.013$), and for functional networks in 1 and 2 year olds (1 year: $r = -0.327$, $p = 0.007$). There we no significant relationships in adults.

Conclusions: Overall regional patterns of S-F coupling are relatively stable from 1 to 6 years and while S-F coupling patterns continue to mature after age 6, some aspects of adult regional S-F coupling patterns are established in early childhood. In 1- and 2-year-olds, regions with more local connections have higher S-F coupling than regions with more distributed connections, though this relationship diminishes with age and maturation of networks.

Disclosure: Nothing to disclose.

Panel

6. Translating Insights From Postmortem Brain Studies Into Knowledge of Disease Mechanisms and Novel Treatment Strategies

6.1 Enhancing Gene Expression Prediction in Major Psychiatric Disorders via Co-Expression Models

Giulio Pergola

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

Background: Imputed gene expression based on common variants is instrumental to understanding the biology of psychiatric risk. By identifying trans-eQTLs via co-expression across different brain regions, we aimed to generate a platform for Transcriptome-Wide Association Studies with enhanced gene expression imputation, particularly for genes depleted for cis-eQTLs.

Methods: We developed the trans "Module Quantitative Trait Loci Eigengene" (MODULE) model to generate polygenic scores associated with the eigenvalue of the co-expression module as a predictor of single-gene expression. We trained MODULE on genotype and gene expression data of the Lieber Institute for Brain Development from tissue homogenate RNA-sequencing in the dorsolateral prefrontal cortex (DLPFC) (N = 593), amygdala (N = 463), hippocampus (N = 237), caudate (N = 214) and subgenual anterior cingulate cortex (sACC) (N = 512 EA). We included adults of European Ancestry (EA) (mean ages across regions: 45.9-49.6 years; female ratios across regions: 23%-31%).

We derived module eigenvalues from 25 published co-expression networks and we tested the performance of network-derived predictors on the Genotype-Tissue Expression (GTEx) cohort (DLPFC: 191, amygdala: 133, hippocampus: 182, caudate: 250, and ACC: 165) (age across regions: 20 – 79 years; female ratios across regions: 26%-30%). We combined predictions within brain regions and compared the performance of MODULE with the cis-based EpiXcan model.

Results: Prediction models performed similarly across brain regions, with average variance explained by EpiXcan of 2.6%-3.4% across 7,545-8,154 genes, and 2%-3% by MODULE across 12,872-12,987 genes. The two techniques predicted 6,285-7,810 genes in common, i.e., most EpiXcan predicted genes, but MODULE afforded many more predictions despite lower explained variance. Notably, 11,701 predicted genes overlapped among the trans-models across brain regions, with the number of uniquely predicted genes ranging from 26 to 153 per region.

Conclusions: This framework effectively expands the number of imputed genes that can be deemed heritable with remarkable across-regions consistency. Smaller effect sizes of trans-eQTL predictions are expected. Our approach is promising to enhance Transcriptome-Wide Association Studies for schizophrenia, bipolar disorder, and major depression.

Disclosure: Nothing to disclose.

6.2 Abstract not included.

6.3 Abstract not included.

6.4 Abstract not included.

Panel

7. Beyond Pavlovian Fear Conditioning: Diverse Symptoms of PTSD

7.1 Chronic Stress Alters Ventral Hippocampal Circuits Associated With Cognitive Flexibility

Jennifer Donegan

Dell Medical School at the University of Texas at Austin, Austin, Texas, United States

Background: Post-traumatic stress disorder (PTSD) is a psychiatric condition that develops after a traumatic event. In addition to heightened arousal and avoidance, people with PTSD also display cognitive deficits. Cognitive flexibility, the adaptive ability to modify behavior in the face of a changing environment, is impaired in people with PTSD and increasing cognitive flexibility is associated with symptom improvement. People with PTSD show alterations in the hippocampus and we have previously

demonstrated a key role for the hippocampus in cognitive flexibility. In the current experiments, we examine the effect of chronic stress, a risk factor for PTSD, on the structure and function of hippocampal circuits and determine their role in cognitive flexibility.

Methods: In a rodent model with hippocampal hyperactivity, the ventral hippocampus (vHipp)-medial prefrontal cortex (mPFC) or vHipp-nucleus accumbens (NAc) pathway were chemogenetically inactivated before cognitive flexibility was measured using the attentional set shifting test. Previously, we found that vHipp parvalbumin (PV) interneurons also regulate cognitive flexibility. To determine the innervation of vHipp pyramidal cells, eGRASP was used to label synaptic connections between pyramidal cells and PV cells in animals exposed to chronic stress. To determine whether these anatomical differences result in changes in physiology, we used in vitro electrophysiology to measure the intrinsic activity of PV cells after chronic stress.

Results: First, chemogenetic inhibition the vHipp-mPFC pathway and vHipp-NAc pathway differentially affect cognitive flexibility. Next, we found that chronic stress alters the number of synaptic connections formed between PV interneurons and pyramidal cells that project to mPFC and NAc. Then to determine if these anatomical differences result in functional changes, we used in vitro electrophysiology to demonstrate that chronic stress alters the intrinsic properties of PV interneurons in the vHipp.

Conclusions: Our results suggest that the vHipp plays a key role in regulating cognitive flexibility. Further, chronic stress alters vHipp circuits. Characterization of these circuits may lead to the identification of new molecular targets for the treatment of specific symptoms of PTSD and other psychiatric disorders associated with vHipp dysfunction.

Disclosure: Nothing to disclose.

7.2 Role of the Paraventricular Thalamus in Stress Enhanced Fear Sensitization

Denisse Paredes

University of Texas at Austin, Austin, Texas, United States

Background: Extreme stress causes long-lasting changes in affective behavior manifesting in conditions such as post-traumatic stress disorder (PTSD). Pavlovian fear conditioning has been a dominant paradigm for studying the effects of trauma through an associative learning framework. However, stress also causes long-lasting nonassociative fear sensitization, often overlooked in Pavlovian fear conditioning studies. I will present research on a mouse model of stress-induced fear sensitization in which we use a range of methods, including immediate early-gene mapping, fiber photometry, and chemogenetics, to identify the paraventricular thalamus (PVT) as an essential brain locus for stress-induced fear sensitization.

Methods: Male and female 129 sv/ev mice were stressed (4 shocks, 1mA) and tested for stress-induced sensitization using two behavioral tests: 1) sensitized spontaneous fear in response to a novel tone, 2) sensitized fear conditioning (contextual fear conditioning in a novel context). In one study, the PVT was chemogenetically silenced during stress with Gi- DREADDs. In another, fiber photometry assessed bulk calcium activity of the PVT during stress and behavioral assays of fear sensitization. Finally, the PVT was chemogenetically activated with Gq-DREADDs during behavioral assays.

Results: Silencing the PVT during stress blocked stress-induced sensitization of spontaneous fear to the novel tone ($t13 = 2.291$, $p = .0393$, $n = 7$-8), but had no effect on contextual fear conditioning. In the fiber photometry experiment, stressed mice exhibited increased Ca++ responses in PVT during novel tone presentation ($t7 = 3.588$, $p = 0.0089$, $n = 8$). DREADD-induced activation of the PVT enhanced fear to the novel tone ($F1,35 = 13.94$, $p = 0.0007$, $n = 17$-20/group), but had no effect on contextual fear conditioning.

Conclusions: Our results demonstrate that (1) after stress, PVT is hyperactive in response to weak threats, (2) PVT activation is necessary for induction of fear sensitization by a stressor, (3) PVT hyperactivity is sufficient to induce fear sensitization, and (4) PVT hyperactivity mediates sensitization of spontaneous fear responses but plays no role in stress-induced sensitization of fear learning. We identify the PVT as potentially encoding a stress memory that mediates long-term sensitization of spontaneous but not learned fear.

Disclosure: Nothing to disclose.

7.3 Inhibition of Hippocampal or Thalamic Inputs to the Nucleus Accumbens Reverses Stress-Induced Alterations in Dopamine System Function

Hannah Elam

Vanderbilt University, Nashville, Tennessee, United States

Background: Symptoms of psychosis are observed in some patients diagnosed with post-traumatic stress disorder (PTSD), yet little is known about the biological underpinnings that contribute to psychosis within PTSD. Symptoms of psychosis are thought to be driven by aberrant regulation of the mesolimbic dopamine system. We have previously demonstrated that modulating afferent regulation of the mesolimbic dopamine system may be a viable therapeutic option for patients with PTSD and comorbid psychosis. Two such afferent regions are the ventral hippocampus (vHipp) and paraventricular nucleus of the thalamus (PVT), which work in concert to regulate ventral tegmental area (VTA) dopamine neuron activity through a multisynaptic circuit that begins with convergent inputs to the nucleus accumbens (NAc). Indeed, activation of vHipp-NAc or PVT-NAc projections significantly increases VTA dopamine neuron population activity, defined as the number of neurons firing spontaneously. These data suggest that hyperactivity in the vHipp or PVT, which are stress-sensitive brain regions, may contribute to psychosis-like behavior, and that inhibition of these specific circuits may alleviate stress-induced, psychosis-like phenotypes.

Methods: In this study, we induced stress-related pathophysiology in Sprague Dawley rats using the two-day inescapable foot shock procedure. We used local field potential recordings to examine how coordinated neuronal activity was altered by stress within circuits of interest. Finally, we utilized in vivo electrophysiology to examine how foot shock stress altered the firing rate of PVT and vHipp neurons and to examine the effects of stress on VTA dopamine neuron population activity.

Results: We observed a significant increase in coherent activity between the PVT and NAc up to 48 hours after foot shock stress. In addition, stress-induced increases in VTA dopamine neuron population activity was observed, which was reversed following chemogenetic inhibition of either vHipp-NAc or PVT-NAc projections.

Conclusions: Taken together these results suggest that increased coordinated activity from the PVT to NAc, following stress, may contribute to psychosis-like symptoms but that targeting the either the PVT or vHipp may be viable options for the treatment of comorbid psychosis related to PTSD.

Disclosure: Nothing to disclose.

7.4 Dissociable Contributions of the Amygdala and Ventral Hippocampus to Stress-Induced Changes in Defensive Behavior

Denise Cai

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

Background: Severe stress can produce multiple persistent changes in defensive behavior. While much is known about the circuits supporting stress-induced associative fear responses, how circuit plasticity supports the broader changes in defensive behavior observed after severe stress remains unclear. It is often assumed that many of the defensive behavioral changes observed in the aftermath of stress are fundamentally associative in nature. It could be the case that multiple memory systems – associative and non-associative – support the enduring consequences of stress on defensive behavior. However, a direct biological dissociation of such memory systems has remained elusive.

Methods: We used anisomycin to inhibit protein synthesis and chemogentic inhibition system (PSAM/PSEM) to inhibit neural activity in BLA and vHC.

Results: We found that stress-induced protein synthesis in the BLA and vHC support distinct changes in defensive behavior. Anisomycin in the vHC after trauma reduced subsequent time in the dark side of the light-dark test ($p < 0.05$), whereas anisomycin in the BLA was without effect. Anisomycin in the BLA or vHC reduced associative fear of the trauma environment ($p < 0.05$). Anisomycin in the BLA reduced freezing in the novel stressor test relative to controls ($p < 0.05$), whereas anisomycin in the vHC was without effect. For intracranial infusions, NT:veh = 23, T:veh = 40, T:ani-BLA = 19, and T:ani-vHC = 20 mice.

We found that distinct stress-induced defensive behaviors require activity of the BLA and vHC. Inhibition of either the BLA or vHC was able to reduce trauma memory recall ($p < 0.05$). Inhibition of the vHC, but not the BLA, was able to attenuate stress-induced increases in time spent in the dark side in the light-dark test ($p < 0.05$). In a drug-free test, there were no differences in trauma memory recall. Inhibition of the BLA, but not the vHC, during the novel stressor was able to reduce subsequent freezing when placed back in this environment ($p < 0.05$). For Ctrl = 9, PSAM-BLA = 10, and PSAM-vHC = 7 mice.

Conclusions: Here, we find that stress-induced plasticity in the ventral hippocampus (vHC) and basolateral amygdala (BLA) support doubly dissociable defensive behavioral changes. These findings highlight that multiple memory-systems support stress-induced defensive behavior changes.

Disclosure: Nothing to disclose.

Panel

8. Precision Neuromodulation: Controlling the Where (Anatomy), When (Physiology), and What (Cognitive State)

8.1 Testing the Variability and Stability of Individualized TMS Treatment Targets for PTSD Using Resting State Functional Connectivity

Sanne van Rooij

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Background: The right (r) amygdala has been implicated in the development and maintenance of posttraumatic stress disorder (PTSD) symptoms. Therefore, treatments targeting the amygdala and improving prefrontal regulation of an overactive amygdala are of great interest. Transcranial Magnetic Stimulation (TMS) is a safe neurostimulation treatment that can target prefrontal regions, but cannot stimulate the amygdala directly. Here we use resting state functional connectivity (RSFC) to identify a region in the right dorsolateral prefrontal cortex (rDLPFC) that is positively connected with the r amygdala and test target variability and stability.

Methods: In this ongoing sham-controlled TMS clinical trial for PTSD (current N = 17, 76% women, 29% Black), pre-TMS fMRI scans were collected and RSFC was used to define the area within the rDLPFC most strongly positively connected with the r amygdala. Using neuronavigation, this individualized rDLPFC target was stimulated twice daily with 1Hz TMS (1800 pulses/session) over ten weekdays. To test TMS target variability and stability, we compared this target between subjects (variability) and with two other targeting approaches using pre-TMS RSFC. First, the peak for negative RFSC with the r amygdala was defined to test variability between positive and anti-correlation (e.g., as used in the currently FDA-clear SNT protocol). Second, the peak for the positive RSFC target was defined after fear neurocircuitry was engaged by fMRI tasks, i.e., fearful faces and fear conditioning, in the same pre-TMS scan. Within subject repeated measures ANOVAs were conducted to compare X, Y, Z MNI target coordinates between subjects and the three targeting approaches.

Results: Significant variability was observed in target locations between participants ($p < 0.001$), and for positive RSFC compared to negative RSFC ($p = 0.02$), but stability of the target for positive RSFC after fear neurocircuitry engagement was found ($p > 0.05$).

Conclusions: Data from the first clinical trial for PTSD using RSFC for individualized TMS targets shows significant variability in targets between participants and for positive vs negative targeting, suggesting the relevance of RSFC-based individualized targeting. The target location did not change after engaging the fear neurocircuitry, providing important data for the stability of this TMS target.

Disclosure: Nothing to disclose.

8.2 Individualizing TMS Targeting for Pediatric Populations

Christine Conelea

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Background: The efficacy of transcranial magnetic stimulation (TMS) for adult psychiatric conditions has led to interest in extending this method to younger patients. Adult research suggests that individual differences in brain anatomy, physiology, and function can contribute to variability in TMS outcomes. In youth with psychiatric disorders, these differences can be more pronounced, and accurate and reliable MRI measurement of these brain features can be challenged by issues of tolerability and movement. Accordingly, our group conducted a series of studies focused on methods to enable individualized TMS targeting in pediatric patients using MRI data and electric field modeling.

Methods: First, we developed a pipeline to computationally define individual TMS targets within the supplementary motor area (SMA) for a clinical trial in Tourette Syndrome (12-21 years, N = 34 to date; 38% female, 5% nonbinary). Second, we generated patient-specific, whole-brain resting-state functional connectivity network maps for N = 23 of these youth to identify the extent to which targets fell in different functional networks across patients. Third, we acquired fMRI data from a transdiagnostic sample of youth (12-18 years, N = 15 to date, 62% female, 6% nonbinary) to determine whether briefer scans with signal-to-noise improvements in image acquisition (NORDIC

denoising, Vizoli et al., 2021) can reveal reliable individual-specific networks to guide TMS targeting.

Results: Study 1: TMS targets were defined as the coil position and orientation within SMA with the highest correlation between fMRI finger tapping task activation and modeled induced electric field. Correlation values ranged from r = -.24-.48 and there were individual differences in target location. Study 2 revealed variable SMA functional organization, such that our targeting approach selected coordinates within ventral attention (n = 8) and cingulo-opercular networks (n = 13). Initial feasibility data from study 3 show good tolerability and low motion with novel MRI acquisition procedures.

Conclusions: Findings confirm that individual differences in anatomy, function, and network topography can result in variable TMS target selection for children and adolescents. Methodological decisions related to MRI acquisition procedures and quantification of TMS targets can also drive variability.

Disclosure: Nothing to disclose.

8.3 Controlling the When: Precision Oscillation-Locked Neurostimulation

Alik Widge

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Background: Rhythmic, sinusoidal electrical oscillations are ubiquitous in the brain. They have been argued to coordinate spiking ensembles, facilitate communication across regions, and govern gating of sensory information to behavior. It is not yet clear which of these links are true/causal, nor how we could leverage that knowledge for new treatments. In recent years, we and others have suggested that a useful approach is phase-locked neurostimulation: locking pulses/trains to specific phases of endogenous rhythms, to constructively or destructively interfere with them.

Methods: I will briefly overview others' pilot results with phase locked invasive electrical stimulation in Parkinson disease, where it has unique symptom control effects. I will then present our lab's toolkit (TORTE) for performing oscillation-locked stimulation experiments using the same code and systems across humans and animals. We have used TORTE to test phase-locked stimulation in three preparations: rat cortico-amygdala connections associated with defensive/threat responses, human cortico-hippocampal connections associated with memory (in epilepsy patients), and modulating human DLPFC excitability with TMS locked to the phase of DLPFC alpha oscillations.

Results: In all three preparations, we verified good phase locking (mean error under 1º, circular variance under 65º), then delivered 30 minutes of phase-locked stimulation (about once per second) In rats (n = 3), we increased theta band coherence between PFC and amygdala (ES = 0.8), and in a pilot behavior study (n = 1), avoidance behavior in a platform-mediated avoidance test decreased (from 75% to 25% of total time during a threat stimulus). In human hippocampi (n = 4), stimulation increased excitability (height of evoked potential peak, $p < 0.001$ for permutation test). The TMS experiment is ongoing, but in the first patient, we similarly see an increase in long-interval cortical inhibition (LICI) specifically with TMS locked to the alpha trough.

Conclusions: In multiple preparations, preliminary results suggest that (A) we can target stimulation to specific brain oscillations and (B) doing so has unique physiologic effects not possible with phase-blind stimulation. I will discuss next translational steps, particularly our efforts to make this open-source toolkit widely available for rigorous, larger-N research.

Disclosures: Medtronic: Other Financial or Material Support (Self). Abbott: Consultant (Self). DBS: Patent (Self).

8.4 Augmenting Virtual Reality Exposure for Warzone-Related PTSD Using Transcranial Direct Current Stimulation

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Background: Despite scientifically proven efficacious, many individuals with posttraumatic stress disorders (PTSD) fail to optimally benefit from exposure therapy. These suboptimal outcomes can be explained through the underlying neurobiology of PTSD. Namely, PTSD reflects a disorder in the processing of traumatic fear memories due to hyperactivity in amygdala-based threat reactivity, exacerbated by a failure to down-regulate because of hypoactivity in the ventromedial prefrontal cortex (VMPFC). Furthermore, varied contextual cues make precision during exposure difficult and likely contributes to variability in clinical response. To improve exposure-based outcomes, we investigated whether noninvasive neuromodulation, i.e., transcranial direct current stimulation (tDCS), could enhance VMPFC-based threat inhibition during standardized virtual reality (VR)-based exposure, with the goal to improve clinical outcomes and augment the inhibition of threat responses in Veterans with PTSD (NCT03372460).

Methods: Fifty-five Veterans with PTSD received either 2mA VMPFC-targeted tDCS with the anode placed over EEG coordinate Fp1 (n = 26) or sham (n = 29) during six, 25-minute sessions of standardized warzone VR exposure, delivered over 2-3 weeks. Severity of symptoms was assessed at baseline, mid-treatment, end-of-treatment, and at one- and three-month follow-up. Skin conductance was assessed continuously throughout each VR exposure session to quantify habituation between sessions.

Results: Veterans who received active tDCS during VR exposure, versus sham, reported a greater reduction in PTSD symptom severity from baseline to primary endpoint at one-month follow-up ($t = 2.43$, $p = 0.019$), which continued throughout the 3-month follow-up period ($t = 2.65$, $p = 0.014$), such that 75% of patients in the active tDCS group reported a level of symptoms indicative of remission, whereas this was true for only 36% in the sham group. Likewise, active tDCS significantly augmented psychophysiological habituation to VR events over sessions compared to sham ($F = 4.02$, $p < 0.001$).

Conclusions: The synergistic application of tDCS plus a brief course of standardized VR exposure offers clinical benefit without the need to personalize the exposure experience, which could improve treatment adherence and completion.

Disclosure: Nothing to disclose.

Panel

9. Emerging Roles for the Paraventricular Thalamus (PVT) Circuit in the Origins of Mental Illness: A Cross-Species, Trans-Disciplinary Discussion

9.1 Abstract not included.

9.2 The PVT as a Critical Neural Node Underlying Individual Differences in Motivated Behaviors

Shelly Flagel

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Background: Individuals make choices and prioritize actions using complex processes that assign value to stimuli or cues in the

environment. For some, these stimuli can attain inordinate control and promote maladaptive behaviors. This occurs via Pavlovian learning, such that stimuli that predict reward acquire motivational properties and become attractive and desirable. In humans and rats, this propensity to attribute incentive value to reward cues has been associated with externalizing behaviors and distinct patterns of brain activation. The paraventricular nucleus of the thalamus (PVT) has emerged as a key node that encodes the motivational value of reward-cues. Here we examine the role of subcortical afferents from the lateral hypothalamus (LH) to the PVT in this regard.

Methods: Male Sprague-Dawley rats were used.

Experiment 1: A dual vector approach was used to selectively express inhibitory G(i)-DREADD in neurons projecting from the lateral hypothalamus (LH) to the PVT. Rats underwent 7 sessions of Pavlovian conditioning, consisting of 25 trials of lever-cue (CS) presentation followed by reward (food, US) delivery. Clozapine-N-oxide (5 mg/kg) was administered prior to sessions 5-7 and the effects of Gi-DREADD activation were assessed.

Experiment 2: Rats received an infusion of fluorogold in the PVT, underwent 5 sessions of Pavlovian conditioning, and were exposed to lever-cue presentation prior to sacrifice. Hybridized chain reaction fluorescent in situ hybridization (HCR-FISH) was used in combination with immunohistochemistry to assess activity in LH-PVT neurons.

Results: Experiment 1: Inhibition of the LH-PVT pathway increased the incentive value of a reward cue in rats with an inherent predisposition towards Pavlovian incentive learning ($n = 5$-15/Group, Group x Treatment, $p = 0.003$; Treatment within Group, $p = 0.02$). There was no effect on goal-directed behaviors.

Experiment 2: Rats with an increased propensity to attribute incentive value to reward cues had greater cue-induced neuronal activity in orexinergic neurons projecting from the LH to the PVT ($n = 9$-10/Group, $p < 0.001$).

Conclusions: These findings demonstrate a role for orexinergic neurons in the LH-PVT pathway in cue-motivated behaviors and support the notion that the PVT encodes the motivational power of cues, and, in turn, can promote maladaptive and aberrant decision-making.

Disclosure: Nothing to disclose.

9.3 Functional Connectivity of the Paraventricular Thalamus Circuit in Humans: Links to Sex, Development, and Psychopathology

Michael Yassa

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Background: Adverse experiences are associated with mental illness, including depression and posttraumatic stress disorder (PTSD), with dysregulation of emotional and motivational circuits being central features. The paraventricular nucleus of the thalamus (PVT) is thought to encode adverse emotional memories and adjudicate behavioral strategies during motivational conflict between threat/fear and reward. Since these processes are commonly aberrant in mental illnesses, understanding the role of the PVT in humans is of high clinical relevance.

Methods: We investigated two cohorts using 3T fMEI:

1. a birth prospective cohort ($n = 178$). Early-life experiences were assessed, including unpredictability of maternal sensory signals during interactions between mothers and their infants at ages 6 and 12 months. Children were imaged at ages 9-17, and depressive symptoms were quantified using the Children's Depression Inventory (CDI).
2. The second cohort involved adult participants (ages 18-45, total $n = 75$; 63F). We used the Beck Depression and Anxiety Inventories to calculate anhedonia factor scores.

In both cohorts, we delineated PVT seed-to-voxel and seed to ROI connectivity controlling for nearby thalamic nuclei.

Results: PVT' connectivity was predominantly with the default mode network, including nucleus accumbens (NAc), amygdala, medial prefrontal cortex (mPFC) and subgenual anterior cingulate cortex (sgACC).

In the developmental cohort, PVT-mPFC connectivity was higher in females but linearly declined with age across both sexes. The strength of connectivity of PVT-sgACC was associated with unpredictable maternal signals ($n = 83$; $T = -4.16$, $p < 0.005$; FDR-corrected). Relationships between the Childhood Depression Index and PVT regional connectivities were differentiated by sex.

In the adult cohort, anhedonia factor scores were predicted by PVT-NAc connectivity, yet only in males ($R = 0.53$, $p = 0.043$) and not in females ($R = 0.096$, $p = 0.52$). This relationship in males was higher in those with more psychiatric symptoms ($R = 0.69$, $p = 0.018$).

Conclusions: Based on data from several cohorts, we can conclude that (a) the functional connectome of the PVT circuit is recoverable in human 3T data, (b) PVT-prefrontal connectivity is higher in females than males but decline linearly as a function of age, (c) PVT circuit connectivity is associated with early life unpredictability, as well as psychiatric symptoms in adolescents and adults.

Disclosure: Nothing to disclose.

9.4 Investigating the Role of the Human Paraventricular Nucleus of the Thalamus in Fear Memory and Posttraumatic Stress Disorder

Daniel Stout

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Background: Post-traumatic stress disorder (PTSD) is a debilitating psychiatric disorder that develops after experiencing or witnessing a traumatic event. Studies in experimental models have shown that the paraventricular nucleus of the thalamus (PVT) is involved in the regulation of long-term fear memory, a hallmark symptom of PTSD. However, the role of PVT in human fear memory and in PTSD remains unclear.

Methods: We employed magnetic resonance imaging (MRI) in concert with diagnostic, clinical assessments. A sample of 53 Veterans (32% women), with PTSD ($n = 30$) and trauma-exposed controls (TEC; $n = 23$) completed a 2-day fMRI fear learning paradigm and resting-state fMRI (rs-fMRI). We conducted a Group (PTSD vs. TEC) x Day (Day 1-acquisition vs. Day 2-recall) mixed-effects analysis of variance on PVT activity and controlled for the surrounding midline thalamus. For rs-fMRI, a PVT seed-to-whole-brain connectivity analysis was conducted (pTFCE-FEW < 0.05). Significant clusters were then correlated with self-reported PTSD symptom severity.

Results: The day of imaging had a significant effect. PVT activity was significantly greater on the more remote, recall Day 2 compared to Day 1, $F(1,49) = 12.22$, $p = .001$. We also observed a significant main effect of Group, $F(1, 49) = 5.61$, $p = .022$. Specifically, individuals with PTSD have overall greater PVT fear memory activity compared to the trauma exposed control group. Exploratory analyses indicated that PVT fear memory activity increased from Day 1 to Day 2 in both the TEC group ($p = .031$) and in the PTSD group ($p = .026$). For rs-fMRI, increasing levels of

PTSD symptom severity was associated with decreasing functional connectivity between the PVT and the right hippocampus, and this association remained significant after controlling for connectivity between the rest of the midline thalamus and the right hippocampus, $t = -2.02$, $p = .048$.

Conclusions: These findings suggest that the human PVT plays a critical role in the retention of conditioned fear memory up to 24 hours after initial acquisition. We provide evidence via multimodal neuroimaging of alterations of PVT function in individuals with PTSD that could signify altered encoding and facilitated consolidation of fear memories into long-term memory. This work sets the stage for exploring the neural circuits underlying long-term retention of fear memories in humans and their implication for the pathophysiology and treatment of PTSD.

Disclosure: Nothing to disclose.

Study Group

10. Will the Promise of Translational Neuropsychopharmacology Research Ever Deliver? The Lion's Roar; the Kitten's Purr

Jacqueline McGinty*, Michael Nader, Eric Nestler, Victoria Arango, Sandra Comer, Rita Goldstein, William Stoops, Kathleen Brady

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Study Group Summary: Preclinical and clinical neuropsychopharmacology researchers strive to understand the organization of the brain and the adaptations that take place in individuals with mood and substance use disorders (SUDs) in order to develop effective therapeutics to treat these disorders. SUDs offer a particularly unique challenge because they can impact brain structure and function, are often associated with co-morbidities (e.g., HIV, hepatitis, anxiety, depression), may change sensitivity to stressors in the environment, etc. Every year brings new discoveries that characterize more pathways in the brain, more cell types (neurons, glia), more genes and proteins, and more functional connectomic relationships implicated in these disorders. These discoveries may prompt the development of more therapeutic targets and novel approaches to treatment. Yet despite numerous reports that manipulating a particular gene, receptor, or brain pathway decreases relapse to drug seeking or improves symptoms putatively related to a mental health disorder, the gap between the research claims (the lion's roar) and the effective treatments (the kitten's purr) persists or may, in fact, be growing. Could this gap be exacerbated because of the built-in cross-sectional nature of most rodent and human post-mortem interrogations that eliminates the ability to study within-subject markers of progression (e.g., addiction severity, initial vs. long-term recovery)? An advantage of human studies is that they allow longitudinal within-subject designs, further adapting a whole-brain approach and studying behavior in naturalistic settings. If translated back and used for medication/intervention development and testing, such studies could advance the field by, for example, identifying non-invasive scalable biomarkers of brain function and structures. A disadvantage of human studies is that many conclusions are correlative stemming from restricted ability to intervene physically in the brain to understand the function of individual genes, proteins, and pathways. However, identification and manipulation of major "hubs" in the circuitry that controls drug seeking or regulates mood disorders in both animals and humans may yield more effective treatments. This Study Group, composed of senior preclinical and clinical investigators, will discuss the following critical questions pertaining to this overarching challenge for neuropsychopharmacology research.

1. How does more information about the function of single cells/pathways in rodents and nonhuman primates translate into improved drug treatments?
2. How do interventions with viral gene constructs (i.e., DREADDs) and optogenetics translate into new treatment approaches?
3. How does machine learning/AI applied to multi-scale data (derived across measures/scales: cognitive/emotional function; brain measures; peripherally derived biomarkers, etc.) translate into neuropsychiatric diagnoses or outcome predictions?
4. How do we close the gap between research discoveries and effective treatments?

By engaging in this discussion, this Study Group hopes to facilitate scientific interactions that progress from thinking about the brain and its disorders into actions that improve brain health.

Disclosure: Nothing to disclose.

Study Group

11. Creating a Multicomponent-Driven Biomarker Framework for Disease Staging in Psychiatric Disorders: Development, Integration, and Clinical Utility

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Study Group Summary: Biomarkers offer the potential for improving diagnosis and identifying individuals in pre-symptomatic stages of the illness, in addition to predicting, monitoring, and guiding treatment development. Much progress has been made in the identification, development, and replication of neuroimaging, electrophysiological, cognitive, and genomics biomarkers for use as tools in clinical research on psychiatric disorders and within industry to facilitate the development of interventions. And there is great interest in digital health technologies (DHTs, e.g., wearables, smartphone apps) that are enabling collection of objective measures with high temporal resolution that can be acquired in the home and in the community settings. Given the recent interest in the potential of multi-component biomarkers[1] to advance understanding of disease and treatment development by the FDA[2] and by the National Academies Forum on Neuroscience and Nervous System Disorders[3], this study group will focus on opportunities and challenges for integrating multiple types of biomarker data to better capture the complexity of psychiatric disorders, different domains of function and pathophysiology, and their utility for different contexts of use in clinical research and in treatment development.

Consortia are playing an important role in developing standardized instrumentation, data collection methods, and data processing and analysis pipelines for biomarkers (e.g., neuroimaging, neurophysiological, genomics/polygenic risk score, cognitive, DHT derived biomarkers) to enable the collection of high-quality data that is reliable and scalable. This study group will consider examples of consortium approaches to create a multi-component biomarker-driven framework for diagnosis of prodromal stages of the illness, staging, and tracking of disease

progression and for use in treatment development using examples of ongoing efforts in Alzheimer's Disease (AD), Parkinson's disease, and in early-stage schizophrenia.

1. In a recent FDA public meeting referenced below, a multi-component biomarker definition was proposed as a "defined characteristic or characteristics that include two or more biomarker measurements evaluated through an algorithm as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or therapeutic".
2. FDA Public Meeting: Identification of Concepts and Terminology for Multi-Component Biomarkers, https://www.fda.gov/drugs/news-events-human-drugs/fda-public-meeting-identification-concepts-and-terminology-multi-component-biomarkers-03232022
3. National Academies' Forum on Neuroscience and Nervous System Disorders, Multimodal Biomarkers for Central Nervous System Disorders: Development, Integration, and Clinical Utility - A Workshop, https://www.nationalacademies.org/our-work/multimodal-biomarkers-for-central-nervous-system-disorders-development-integration-and-clinical-utility-a-workshop

Disclosure: Nothing to disclose.

Study Group

12. The Landscape of Early Neurocognitive Changes: Implications for Clinical Trials and Real World Applications

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Study Group Summary: Early intervention may help prevent AD/ADRD, but there are significant limitations in the early prediction of cognitive and functional decline using available clinical research tools. The Landscape of Early Neuropsychological Changes in AD/ADRD Project, led by the National Institute of Aging, convened 35 experts from September 2022 to April 2023 for a series of webinars to discuss the current state-of-the art, emerging methods, and gaps in measurement of early changes in AD/ADRD. This study group will focus on issues raised by this project, specifically those most relevant to the methodologies of current and next generation AD/ADRD early intervention and prevention trials. Study group participants include experts in diverse neuropsychiatric and neurocognitive assessment strategies that are critical for detection and measurement of changes linked to AD/ADRD, and possess experience spanning novel web-based and ambulatory testing, ecological momentary assessment, measurement of subjective cognitive change, and passive monitoring methods using mobile devices and the internet of things, including motor vehicles.

Major questions to be addressed include: (1) How do we assess neuropsychological changes across the lifespan? What are the optimal methods, intervals, and durations of assessment to optimize estimates of change trajectories? What sampling strategies will help increase generalization of study findings broadly and with sensitivity to individual and cultural differences? (2) How do we best capture subjective cognitive changes and neuropsychiatric symptoms that may presage AD/ADRD pathological processes? How do we integrate patient- and care partner-reported outcomes to identify individuals who might otherwise not be identified by traditional, performance-based cognitive measures? (3) How do we integrate clinical and laboratory measures with more ecologically valid real world measures to detect early signs of functional changes? Can these sources comprise face-valid indicators of clinically significant effects, and be more meaningful, feasible, and accessible for diverse populations? (4) How do we integrate digital tools, including more precise, "real-time", longitudinal, and temporally-dense measurement into AD/ADRD prevention trials? What are the psychometric and pragmatic tradeoffs between repeated measures and decreased time for assessment at each interval? Can these measures leverage wearable, sensor, and digital computing technologies to capture diverse aspects of physiology, physical activity, sleep patterns, cognitive and social engagement, and other behavioral factors to more accurately capture early markers of AD/ADRD risk/resilience as they change in the real world? What evidentiary thresholds will be required to justify using these strategies in clinical trials?

Study group participants will discuss the key methodological gaps for detecting early neuropsychological changes in AD/ADRD, consider if and how these can be addressed by current tools, and then focus on how specific novel measurement approaches can inform development of the next generation of measures and methods for AD/ADRD prevention trials. The study group will further address how current and future efforts can better address fundamental values of inclusion, integration, openness, and accessibility to ensure that progress serves as many communities and individuals as possible.

Disclosures: Karuna Therapeutics: Advisory Board (Self). Prodeo LLC: Honoraria (Self).

Panel

13. Neuromodulation for OCD: New Directions for Old Tricks

13.1 Frontopolar Connections: Where Do Their Fibers Go, Who Do They Talk To, and How Do They Relate To Other Frontal Connections?

Suzanne Haber

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Background: The prefrontal/anterior cingulate cortex (PFC/ACC) network is involved in behavioral flexibility and is considered dysfunctional in most psychiatric disorders, including obsessive-compulsive disorder (OCD). Their connections are the targets for invasive or noninvasive stimulation targets. The anterior limb of the internal (ALIC) and the medial subthalamic nucleus are the most frequent for invasive (deep brain stimulation or lesions) for OCD. In both approaches the goal is to modulate the network through the white matter. Noninvasive stimulation (TMS) targets the PFC/ACC directly. As with DBS, however, the white matter is preferentially stimulated over grey matter. An important goal is to understand and probe the circuits involved at each target. Here, we present the fiber organization and terminals of a relatively new target for TMS, the frontopolar region (FP), following its fibers through cortex and the ALIC, and comparing its connections with other frontal regions.

Methods: We analyzed the trajectory of cortical fibers from the frontal cortex in nonhuman and human primates, based on tracer injections in monkeys and high-resolution diffusion MRI in both nonhuman and human primates. For the monkey tracer data, we created a 3D model that contains previously charted cases,

allowing the analysis of relationships between fiber bundles from all frontal cortical regions.

Results: Dorsal vs. ventral FP fibers take different routes to the white matter and are positioned in differentially within cortical and subcortical bundles. The 3D model of the ALIC shows that the ventral vs. dorsal FP fibers are closely positioned with different PFC/ACC regions. Premotor and motor fibers travel caudal to those from PFC/ACC with little overlap. Monkey anatomic data and human dMRI data showed a similar trajectory of fibers/streamlines within the internal capsule. Finally, we show which circuits are likely to be involved at each target location.

Conclusions: Fibers from different frontal cortical areas travel within white matter bundles in specific and predictable ways. Moreover, the topography based on the anatomic results monkeys can be reliably replicated in humans. Delineating the relative positioning of fibers and those likely involved at each target is a critical step in evaluating the circuit involved and its relationship to on clinical outcomes.

Disclosure: Nothing to disclose.

13.2 Anterior Capsulotomy for Intractable OCD

Nicole McLaughlin

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Background: It is estimated that Obsessive-Compulsive Disorder (OCD) is treatment refractory in over 20% of cases. Those individuals have severe and disabling symptoms, despite all available treatments. For a subgroup of such patients, neurosurgery is a recognized option. Although psychiatric neurosurgery for OCD has been conducted for decades, there is still lack of clarity regarding which white matter pathways are responsible for clinical change.

Methods: Over the past 30 years, patients (including all races, ethnicities, and sexes) at Butler Hospital/Rhode Island Hospital have undergone anterior capsulotomy through the use of gamma knife (GK; $n = 55$) or laser interstitial thermal therapy (LITT; $n = 9$). Both groups underwent a full clinical and neuropsychological evaluation pre- and one-year post-intervention. The LITT group also completed the stop signal task (SST), which examined change in inhibitory control. This study will present the clinical outcomes of both procedures, as well as unpublished data regarding both clinical and experimental cognitive performance one-year post-surgery.

Results: Clinical outcomes have indicated that both techniques are effective in reducing OCD symptoms (GK, $p < .0001$; LITT, $p = .008$). Analysis of pre-post neuropsychological data ($n = 31$) has demonstrated no significant decline in any domain. There were significant improvements in Performance IQ ($p = .012$; $d = 0.47$), visual memory (immediate $p = .001$, $d = 0.63$; delayed $p < .001$, $d = 0.69$), naming ($p < .001$; $d = 0.75$), and speeded motor dexterity (dominant hand $p = .005$, $d = 0.56$; non-dominant $p < .001$, $d = 0.75$). Preliminary analysis of pre-post surgery performance on the SST in a subset ($n = 7$) has shown clinically significant improvements in stop signal reaction time block 1 ($p = 0.03$, $d = 1.12$) but not block 2 ($p = 0.51$); there were no significant changes in accuracy or reaction time.

Conclusions: Results indicate that anterior capsulotomy is effective using the gamma knife or LITT. There were no significant declines on traditional neuropsychological measures. In addition, preliminary performance on an inhibitory control task, which targets prefrontal-subcortical circuitry, improved post-surgery. Clinical and cognitive changes after capsulotomy will be discussed in relation to neural circuitry and implications for anatomical models of OCD and surgical targeting.

Disclosure: Nothing to disclose.

13.3 The Effects of Varying Pulse Repetition Frequencies and Duty Cycles for Transcranial Focused Ultrasound (tFUS) of the Ventral Capsule/Ventral Striatum for Obsessive-Compulsive Disorder

Darin Dougherty

Massachusetts General Hospital/Harvard University, Charlestown, Massachusetts, United States

Background: Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts and/or compulsive behaviors. Deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS) has been found to be effective for treatment-resistant OCD. However, DBS is associated with neurosurgical risks and side effects. Transcranial focused ultrasound (tFUS) is a novel brain stimulation method that has the capability to modulate deeper subcortical brain regions, such as the VC/VS, noninvasively.

Methods: In this active-control parameter exploration study, we investigated the effects of 3 different tFUS stimulation protocols on the VC/VS and the wider corticostriatal circuit (Protocol A: Pulse Repetition Frequency [PRF] = 10 Hz, 5% Duty Cycle (DC), Protocol B: PRF = 125 Hz, 5% DC, Protocol C: PRF = 125 Hz, 50% DC) as well as a control region, the entorhinal cortex (ErC). These occurred during four separate visits and were conducted in the MR environment while fMRI BOLD signal was measured and was later analyzed using SPM.

Results: These tFUS parameters had differential effects on Blood Oxygen Level Dependent (BOLD) activation in the corticostriatal network: 1. Protocol A was associated with decreased BOLD activation in the putamen ($p = 0.004$), 2. Protocol B had no effect on BOLD activation in the corticostriatal network, and 3. Protocol C was associated with a trending decrease ($p = 0.06$) in BOLD activation in the putamen. The tfUS parameters also had differential effects on Arterial Spin Labeling (ASL) perfusion: 1. Protocol A was associated with a trending decrease in VC/VS perfusion ($p = 0.17$), 2. Protocol B was associated with a trending increase in VC/VS perfusion ($p = 0.15$), and 3. Protocol C had no effect on VC/VS perfusion. Importantly, tFUS of the entorhinal cortex (ErC), included as a control region, was not associated with changes in corticostriatal BOLD activation during the reward task, nor was ErC tFUS associated with changes in VC/VS ASL perfusion.

Conclusions: These findings demonstrate the varying effects of different pulse repetition frequencies and duty cycles on BOLD activation and ASL perfusion in the corticostriatal network and their potential for treatment of OCD. Trials in patients with OCD are forthcoming based on this dose finding study.

Disclosures: Medtronic: Contracted Research (Self). Medtronic: Honoraria (Self), Celanese: Consultant (Self)., Sage, Neurable, Intrinsic Powers: Advisory Board (Self). Innercosmos: Founder (Self)

13.4 Non-Invasive Neuromodulation for OCD

Nolan Williams

Stanford University School of Medicine, Palo Alto, California, United States

Background: OCD is a highly heterogeneous clinical syndrome. More than 25% of patients show no improvement with standard of care treatment. New interventions are urgently needed. Repetitive transcranial magnetic stimulation (rTMS) is a promising alternative, 1–3 using powerful, focused magnetic field pulses to stimulate target brain areas. So far, at least two stimulation targets

have consistent evidence of efficacy in OCD: the dorsomedial prefrontal cortex (DMPFC) and the orbitofrontal cortex (OFC).

Methods: We have developed methods for discovering neurophysiological subtypes of depression based on resting state fMRI measures in relevant brain networks; diagnosing them in individual patients; and using them to predict individual differences in rTMS response.4,5 Here, we describe our application of these methods to discover novel network-based subtypes of OCD and develop prognostic neuroimaging biomarkers for predicting differential treatment response to rTMS targeting the DMPFC or OFC. The purpose of this study is to determine the overall efficacy and trajectory of response to accelerated rTMS regimens in OCD, by randomizing participants to 2 different treatment arms: DMPFC or rOFC.

Results: Stanford has enrolled 50 participants with OCD. Participants' ages ranged from 18-76. All participants successfully completed pre-treatment visits, including fMRI and EEG, before receiving rTMS treatment. The percentage of participants at Stanford to-date who responded to rTMS treatment targeting either the DMPFC or OFC is 43.2 %.

Conclusions: The preliminary results continue to be promising, and suggest that the proposed accelerated rTMS intervention could be an effective treatment strategy for some patients with OCD.

Disclosure: Magnus Medical: Advisory Board (Self)

Panel

14. Neurobiology of Social Determinants of Health and Exposomics: Impact on Mental Illnesses and Mental Health From the Womb to the Grave

14.1 Harnessing Translational Approaches to Fight the Trans-Generational Transmission of Stress

Tamar Gur

Ohio State University College of Medicine, Columbus, Ohio, United States

Background: Exposure to prenatal stress has long term consequences on offspring including aberrant gut microbiome and increased behavioral abnormalities. Our previous preclinical work pinpoints the maternal microbiome and the chemokine CCL2 as key mediators of long term neuroinflammation and reductions in social behavior. Here we address whether disrupted maternal gut microbiome extends into a prospective cohort study and identify a role for CCL2 in both clinical and preclinical work.

Methods: A prospective longitudinal study ($N = 38$) was performed in the peripartum period with maternal fecal and vaginal swabs and cord blood collected. Assessment included measures of perceived stress, anxiety, depression (CESD). PacBio full-length 16S rRNA sequencing was used to identify microbial communities. Preclinical: Intra-amniotic injections of recombinant CCL2 or saline were performed. Concentration of CCL2 in maternal and fetal tissues was measured by ELISA. Social behavior was measured in adulthood in the 3-chamber social approach paradigm.

Results: Clinical: During the 2nd trimester, perceived stress was associated with increased relative abundance of several opportunistic fecal taxa, including the Prevotellaceae family ($r = 0.534$, $p = 0.015$), At delivery, depressive symptoms were associated with increased relative abundance of opportunistic microbe Sneathia ($r = 0.710$, $p = 0.001$) and decreased relative abundance of the short chain fatty acid producer Peptoniphilus ($r = -0.440$, $p = 0.068$). Furthermore, relative abundance of the beneficial commensal microbe Lactobacillus at delivery was negatively correlated with umbilical cord concentration of CCL2 ($n = 13$, $r = -0.724$, $p = 0.012$). Preclinical: Following injection of CCL2 into the amniotic sac, CCL2 was increased in the fetal plasma, fetal liver, and fetal brain ($n = 6$-7; $p < 0.001$. Female offspring exposed to CCL2 demonstrated increased neuroinflammation in prefrontal cortex (CCL2, TNFα; $n = 6$-7; $p < 0.05$) and did not exhibit social preference ($n = 6$-7; $p = 0.134$), in contrast to the control group ($n = 6$-7; $p = 0.00029$).

Conclusions: We found stress and depressive symptoms to be associated with increased relative abundance of opportunistic pathogen. Leveraging preclinical and clinical research can expedite our mechanistic understanding of how prenatal stress is transmitted to the next generation.

Disclosure: Nothing to disclose.

14.2 Pregnancy Social Disadvantage Has Lasting Impacts on Child Psychopathology Mediated by Maternal and Child Inflammation, Neonatal Brain Development, and Parenting

Deanna Barch

Washington University, Saint Louis, Missouri, United States

Background: We have long known that childhood prenatal social disadvantage (PSD; reduced family and neighborhood economic resources) is associated with increased risk for psychopathology. In a sample of 377 mother-child dyads recruited during pregnancy, we have shown that maternal PSD is associated with reduced gestational age and birthweight, reduced gray and white matter volumes at birth, and disrupted white matter integrity at birth. Here we examine whether maternal inflammation or gut microbiome mediates the relations between PSD and outcomes in children.

Methods: 377 mothers were recruited during pregnancy and provided measures of income, neighborhood adversity, blood for cytokines and fecal samples for microbiome during the 2nd and 3rd trimesters. Offspring (male and female) were imaged at birth with structural, diffusion, and resting state measures and provided fecal samples at 4 months and followed through age 4, with mental health assessments starting at age 2.

Results: Mothers with high PSD had significantly higher IL-6. Maternal IL-6 was associated with reduced cortical-spinal tract and uncinate fractional anisotropy. Microbiome data for the highest and lowest PSD maternal/child dyads ($N = 89$) were profiled using whole metagenome sequencing. Mother and child strain-level GM structure correctly classified PSD status (81% and 85% accuracy). The top PSD discriminatory species in infants were Enterobacter nimipressuralis and Klebsiella pneumoniae, LPS-producing proteobacteria that can elicit pro-inflammatory cytokine cascades. In 181 children at age 2, PSD predicted higher ITSEA externalizing ($B = .28$, $p < .0001$) and dysregulation ($B = .23$, $p = .0002$), as well as worse cognition and language scores on the Bayley ($ps < .01$). Cortical gray volume at birth mediated the relation of PSD to these symptoms, as did parenting. Parenting moderated the relationship between PSD and both cognition and language, with parental support associated with better cognition and language in low PSD children.

Conclusions: These data show that maternal PSD is a risk factor associated with child psychopathology, and that elevated levels of maternal inflammation and offspring pro-inflammatory microbiome profiles are part of a pathway linking maternal social disadvantage to neonatal brain outcomes and subsequent mental health risk.

Disclosure: Nothing to disclose.

14.3 Social Determinants of Mental Health in Adulthood: Parasympathetic Regulation of Type I Interferon as a Mechanism of Social Risk and Resilience

Steven Cole

UCLA David Geffen School of Medicine, Los Angeles, California, United States

Background: Aberrant Type I interferon (IFN) activity has been implicated in multiple forms of psychopathology. We explored the possibility that social adversity and associated alterations in parasympathetic nervous system (PNS) activity might modulate Type I IFN activity.

Methods: Study 1 randomized 66 adults to either intentionally increase PNS activity or decrease PNS activity over a 5-wk period through daily 40 min biofeedback of Respiratory Sinus Arrythmia (RSA). Blood samples collected at baseline and wk 5 follow-up were assayed by genome-wide transcriptional profiling to quantify Type I IFN response gene activity. Study 2 examined social-environmental regulation of Type I IFN gene expression over 3.5 years of longitudinal individual development in 93 rhesus macaques randomized at birth to either adverse unstable social conditions or salutary stable social conditions. Studies involved both sexes.

Results: In Study 1, community-dwelling adults randomized to increase PNS activity via RSA biofeedback showed significantly greater Type I IFN gene expression relative to those randomized to decrease PNS activity. In Study 2, infant rhesus macaques randomized to adverse (unstable) social environments for the first 6 months of life showed 26% reduction (SE 9%, $p = .021$) in average expression of a pre-specified set of 33 Type I IFN response genes in comparison to animals living under stable social conditions. Following their subsequent transition to stable social conditions, this difference receded to non-significance ($+3\% \pm 6\%$, $p = .747$). Effects on Type I IFN were characteristic of the broader pattern of transcriptome-wide empirical differences: within the first 6 months of life, animals randomized to unstable social conditions showed systematic deviations outside the normal range of transcriptional-developmental trajectories for 681 gene transcripts; of those, 650 (95%) subsequently re-entered the range of normal variation following transition of these animals to stable social conditions.

Conclusions: PNS activity promotes Type I IFN activity, and may represent one biological pathway through which social adversity can affect mental health. Persistent gene impacts of early life adversity may be maintained by ongoing social adversity and its impact on PNS activity rather than being irreversibly embedded in biological development.

Disclosure: Nothing to disclose.

14.4 Adverse Versus Positive Social Determinants of Health in Later Life: Biological Underpinnings in Persons With Schizophrenia and Healthy Subjects

Dilip Jeste

Global Research Network on Social Determinants of Mental Health and Exposomics, La Jolla, California, United States

Background: Medicine has traditionally focused on risk factors rather than on positive, protective, and preventive factors. This also applies to social determinants of health (SDoH) including social isolation and loneliness vs. social engagement that is based on compassion and resilience. I will highlight novel data showing counteractive biological associations of adverse vs. positive SDoH on inflammatory and metabolic pathology and microbial diversity associated with aging in people with schizophrenia and in healthy comparison subjects (HCs).

Methods: We examined data from middle-aged and older adults with schizophrenia and HCs using validated clinical measures of adverse vs. positive social and psychological factors along with pro-inflammatory cytokines and metabolic markers (Hb A1c and Homeostatic Model Assessment for Insulin Resistance or HOMA-IR) in blood, plus alpha (within-individual) and beta (between-individuals) microbial diversity, using 16S rRNA.

Results: Biomarker data supported the hypothesis of accelerated biological aging in schizophrenia. Persons with schizophrenia also had a standard deviation higher level of loneliness and lower level of social engagement and resilience than HCs. In both groups, loneliness was associated with worse physical and mental health, higher levels of hs-CRP and IL-6 as well as Hb A1c and HOMA-IR, while the reverse was true for pro-social engagement and resilience. In the gut microbiome, loneliness was associated with lower levels of alpha and beta diversity, in contrast to compassion-based social engagement and resilience. The relationship between microbial pathophysiology and SDoH is likely to be bi-directional. We also identified functional pathways related to trimethylamine-N-oxide (TMAO) reductase that were altered in schizophrenia. This suggests specific molecular processes that could be impacted by changes in the gut microbiome in schizophrenia.

Conclusions: Our results suggest that health-damaging biological effects of adverse SDoH could be potentially reversed by positive SDoH such as social engagement. This points to a need to develop interventions that promote positive factors and thereby counteract and even reverse the effects of adverse SDoH in schizophrenia as well as in HCs to slow the speed of biological aging.

Disclosure: Nothing to disclose.

Panel

15. The Placenta-Brain Axis: Prenatal Molecular Mechanisms Underlying Psychiatric Risk Across the Lifespan

15.1 Extracellular Vesicle miRNAs at the Maternal-Fetal Interface May Instruct the Pathogenesis of Neurodevelopmental Disorders

Serena Gumusoglu

University of Iowa Carver College of Medicine, Iowa City, Iowa, United States

Background: Diseases of pregnancy are linked to offspring neurodevelopmental disorders (NDD) and lifelong psychiatric risk. Extracellular vesicles (EVs) are one placenta-brain mechanism which impact neurodevelopment. EVs are small packets of proteins and nucleic acids including miRNAs abundantly produced by the placenta. EVs penetrate fetal brain, where they dock and transfer their contents to affect target cells including neurons. EV miRNA content is changed by placental diseases such as preeclampsia, which is also an NDD risk factor. Here, we examined maternal EV miRNAs in a cohort of children with and without NDD to reveal post-transcriptional prenatal programming mechanisms.

Methods: EVs were purified from pregnant participant plasma samples. Participants were retrospectively selected from Iowa Perinatal Family Tissue Bank (PFTB; IRB: 200910784) if their pregnancy resulted in a child (either sex) with NDD (diagnosis of

ASD, ADHD, and/or anxiety; n = 9) or no psychiatric diagnosis (n = 11) by age 10. Placentas (n = 3) were used for placental expression studies. Exosomes were isolated and RNA purified. Expression of 368 validated human miRNAs was profiled via A-Set TaqMan low density array and Plac1 by qPCR. Target prediction and functional annotation were performed by miRSystem and miRDB.

Results: Multiple miRNAs were significantly increased (miR-499a-5p, 133b, 525-3p, 493) or decreased (miR-518e, 517c, 455-3p, 518-f) in IDD samples versus controls ($p < 0.05$). All were expressed in placental EVs. The primary gene targets (enrichment score > 1.5) of differentially-expressed miRNAs are related to neuronal systems, synaptic transmission, axonal guidance, and developmental biology. Of 797 genes with high computationally predicted target scores (> 60, miRDB), 125 are known ASD risk genes (SFARI) ($P < 0.0001$ over-representation). ASD genes (XPO1, KMT2C, DMXL2) are targeted by miR-133b and miR-455-3p. Plac1 was expressed in pregnant plasma EVs, demonstrating trophoblast origins.

Conclusions: EV-bound miRNAs in pregnancy are associated with offspring NDD. These miRNAs are expressed in placental EVs and target genes involved in brain structure/function and ASD risk. Additional work is needed in larger cohorts and preclinical models to determine relevance to particular NDDs and a causal role for placental EVs in neurodevelopment.

Disclosure: Nothing to disclose.

15.2 Placental Communication With the Brain via Extracellular Vesicles

Cheryl Rosenfeld

University of Missouri, Columbia, Missouri, United States

Background: There is evidence that the fetal brain of the mouse is especially dependent upon the placenta as a source of serotonin (5-hydroxytryptamine; 5-HT) and possibly other factors needed for its development. This functional linkage between the two organs is named the placenta-brain axis. How factors reach the developing brain remains uncertain but are postulated to be part of the cargo carried by placental extracellular vesicles (EV).

Methods: We have analyzed the protein, catecholamine and small RNA content of EV collected from culture media of undifferentiated mouse trophoblast stem cells (TSC), and TSC differentiated into parietal trophoblast giant cells (pTGC), potential primary purveyors of 5-HT. Further, we have examined how exposure of mouse and human neural progenitor stem cells (NPC) to EV from varying mouse and human trophoblast (TB) cells affect their transcriptome profile.

Results: As hypothesized, the EV from the trophoblast cells contained relatively high amounts of 5-HT, as well as lower levels of dopamine and norepinephrine, but there were no significant differences between EV derived from pTGC and from TSC. The content of miRNA and small nucleolar (sno)RNA, however, did differ according to EV source, but the primary inferred targets of the miRNA from both were mRNA transcripts enriched in the fetal brain. The snoRNA, by contrast, were upregulated in pTGC relative to TSC. Exposure of mouse and human NPC to EV from respective TB cells affects their transcriptome profile, especially of transcripts associated with neurogenesis and synaptogenesis.

Conclusions: Placenta-derived EV might, therefore, provide crucial roles in fetal brain development and be an integral part of the placenta-brain axis. Understanding how the contents of TB-derived EV affect NPC might yield new insights and potential treatment strategies for neurobehavioral disorders that originate in utero, such as autism spectrum disorders (ASD).

Disclosure: Nothing to disclose.

15.3 Abstract not included.

15.4 Abstract not included.

Panel

16. Connecting Neural and Digital Signatures of Affective Disorders: Opportunities for Personalized Measurement and Intervention in the Era of Precision Psychiatry

16.1 Integrating Neural Circuit and Behavioral Measures to Define and Personalize Treatments for a Cognitive Biotype of Depression

Leanne Williams

Stanford University School of Medicine, Stanford, California, United States

Background: Persistent cognitive impairments are a significant contributor to disability in depression, commonly persisting despite remission of mood symptoms on standard antidepressant medication (ADM). We and we urgently need interventions that specifically target mechanisms underlying cognitive impairment in depression.

Methods: The investigators first sought to identify a cognitive control biotype in a sample of 1,008 patients with MDD. Cluster analysis was used to identify a cohesive subtype defined by behavioral tests of cognitive control, validated mechanistically by functional neuroimaging of dorsolateral prefrontal (dLPFC) and related regions of the cognitive control circuit, and validated clinically by symptom-function profiles and response outcomes for standard antidepressants. To selectively treat cognitive control, we pursued a stratified medicine trial in 26 new patients with MDD enriched for C+ biotype status and treated for 8 weeks with guanfacine immediate release (GIR), selective for alpha 2a receptor agonism in the dLPFC.

Results: A 'cognitive control biotype' was present in 27% of patients, characterized by significantly reduced performance on cognitive behavioral tests and activation of the cognitive control circuit (dLPFC: $P = .003$; $d = -0.78$ [95% CI, -1.28 to -0.27]), and a specific profile of symptoms and poor psychosocial functioning ($P < .001$; $d = -0.25$ [95% CI, -0.39 to -0.11]). Response and remission rates on standard antidepressants were significantly lower for this biotype (C+) relative to patients with intact cognition (C-) (38.8% vs. 47.7%, $P = .04$). In the prospective sample, GIR significantly improved individual-level cognitive performance ($t = -4.22$, $p < .001$) and dLPFC activity ($t = -6.30$, $p < .001$). Prefrontal-amygdala connectivity improved with mood, but not cognition. Following treatment with GIR, 90% of patients achieved symptom response and the remission rate exceeded that for standard antidepressants.

Conclusions: The findings highlight the importance of assessing cognitive biotypes of depression and targeting these subtypes with selective interventions. The outcomes advance the objective to develop mechanistic experimental therapeutics for precision medicine in psychiatry, using circuit biomarkers anchored in RDoC and focusing on patients underserved by current treatments.

Disclosure: Nothing to disclose.

16.2 Predicting Affect With Mobile Phone Keyboard and Accelerometer Data in Female Subjects With Suicidal Ideation

Loran Knol

Radboud University Nijmegen, Nijmegen, Netherlands

Background: The ubiquity of smartphones provides many opportunities for passive, unobtrusive assessment of the psychomotor dynamics and daily routines of people who struggle with mental illnesses. Pioneered by our own group, keyboard and accelerometer data have been shown to yield relevant insights into both mood and cognition in clinical samples. However, relating these keyboard-derived data to self-report questionnaires that gauge participants' mood is not trivial due to discrepancies in the sampling frequencies of the different modalities. High dimensionality in one of the modalities further complicates the modelling. To this end, we aimed to fuse high-dimensional, daily self-report data with dense smartphone keyboard data collected in a group of female subjects with suicidal ideation.

Methods: We used baseline data from the ongoing CLEAR-3 trial, a randomised controlled crossover trial investigating the hormonal mechanisms involved in menstruation that contribute to suicidal ideation in people assigned female at birth. Participants installed the BiAffect keyboard on their phone, which replaced the standard iOS keyboard. BiAffect also recorded accelerometer data, from which we extracted phone movement levels and orientation. Participants additionally completed a battery of questionnaires regarding their affective functioning on a daily basis (34 items). We used temporal independent component analysis to get a time-dependent, low-dimensional representation of the questionnaire data. Linear mixed-effects regression was used to predict the independent component values from the BiAffect data.

Results: Across five, ten, and twenty independent components, we identified a component that loaded on all questionnaire items consistently. For the five-component solution, loadings were positive for positive affect and negative for negative affect. Higher phone movement rates predicted higher intensities of this general positive-affect component after Bonferroni correction ($\beta = 0.12$, $p = 0.00021$).

Conclusions: Temporal independent component analysis is an effective tool for extracting components out of time-dependent questionnaire data without collapsing the time domain. In female subjects with suicidal ideation, this method shows that the degree of phone movement during typing is informative of overall self-reported affect.

Disclosure: Nothing to disclose.

16.3 Improving the Real-Time Prediction of Suicide Among High-Risk Adolescents

Randy Auerbach

Columbia University, New York, New York, United States

Background: Recent advances in smartphone technology now afford an opportunity to track moment-to-moment affective and behavioral change captured through mobile sensing. This approach holds enormous promise to improve the real-time prediction of suicidal thoughts and behaviors (STB), which may then facilitate the development of just-in-time interventions.

Methods: Participants included adolescents ($N = 180$) ages 13-18-years-old reporting an affective and/or substance use disorder. The sample was enriched for current STB; 67% reported suicidal ideation with 27% also reporting a past year attempt. At baseline, participants completed a clinical interviews and self-report questionnaires, which were re-administered at the 1-, 3-, and 6-month follow-ups. Participants also installed the EARS app on their personal smartphones, which obtained mobile sensor and experiencing sampling data over 6 months. Mobile sensor data focused on mobility patterns: (a) entropy (stability of daily routine), (b) home stay (consecutive time spent at home), and (c) distance traveled (distance traveled each day). STB were probed through weekly surveys and follow-up interviews. For a subset of youth, structural and functional MRI data were obtained.

Results: Models tested whether entropy, home stay, and/or distance traveled patterns in the previous week predicted next week suicidal behaviors (attempt, psychiatric hospitalization, emergency department visit) or events (suicidal behaviors, significant weekly ideation, and/or weekly suicide plan). First, greater home stay, relative to one's own mean, predicted the occurrence of suicidal behaviors in the following week. Second, greater within-person deviations in entropy predicted suicidal events in the subsequent week. Third, regularized regression models including sociodemographic characteristics, clinical features, and mobility patterns predicted when suicidal events occurred with 72% accuracy. Last, exploratory models will test whether including neuromarkers markers improves prospective prediction of suicidal risk.

Conclusions: Mobile sensor data collected naturalistically from adolescents can reliably predict suicidal behaviors and events. Although further testing is required, these data may have a transformative impact in developing future suicide prevention and intervention strategies.

Disclosure: Nothing to disclose.

16.4 Passive Detection of Altered Decision-Making Associated With Mood Disorders

Olusola Ajilore

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

Background: Evidence accumulation models are computational approaches to detecting latent cognitive processes associated with decision making. Previous studies which have applied these methods to study of mood disorders using drift diffusion models have found slower rates of evidence accumulation, altered response caution, and slower non-decision times (time for stimulus perception and motor activity). The present study used data from the UnMASCK study to ascertain components of decision making, in a transdiagnostic mood disorder population, from standard neuropsychological tests as well as passively from naturalistic, smartphone keyboard data.

Methods: The study recruited a total of 88 participants (62 with a mood diagnosis, MD; 26 healthy comparison subjects). During the 30-day course of the study, participants used the BiAffect app, which allows for tracking of typing dynamics. Participants underwent standard neuropsychological testing with the NIH toolbox 2 weeks into the study and at the end of the study. For calculation of drift diffusion parameters, we utilized the Bayesian Python HDDM toolbox, which can estimate parameters for individual subjects as well as groups and can quantify the certainty related to parameter estimations. For NIH Toolbox analysis, reaction times and correct/incorrect responses were entered into the HDDM. For keyboard analysis, interkey delays (as a proxy for reaction time) and typographical errors were entered into the HDDM.

Results: Using the NIH Toolbox Dimensional Change Card Sort Task, MD participants had significantly slower drift rates (HC > MD, $Pr = 0.99$), smaller boundary separations (HC > MD, $Pr = .94$), and longer non-decision times (MD > HC, $Pr = .95$). Analyzing ~4M keystrokes over 4 weeks, similar patterns were seen in the typing data. MD participants had slower drift rates, wider boundary separations, and longer non-decision times (all Bayesian $Pr = 1.0$).

Conclusions: Aspects of decision-making derived from standard neuropsychological tests may be captured by passive, unobtrusively obtained naturalistic smartphone data. Naturalistic smartphone data revealed drift diffusion model parameters consistent with previous findings in mood disorders but has the advantage of high temporal resolution and unobtrusive data capture.

Disclosures: Embodied Labs, Blueprint Health, Sage Therapeutics: Advisory Board (Self). Otsuka: Consultant (Self)., Boehringer Ingelheim: Honoraria (Self). KeyWise AI: Founder (Self)

Panel

17. Larger Scale Data Informing the Use of ECT and Ketamine/Esketamine in Severe and Treatment Resistant Major Depressive Disorder

17.1 Abstract not included.

17.2 Long-Term Treatment With Esketamine Nasal Spray in Patients With Treatment-Resistant Depression: Final Results of the SUSTAIN-3 Study

Dong-Jing Fu

Janssen Research and Development, LLC, Titusville, New Jersey, United States

Background: Regulatory agency approval of esketamine nasal spray (ESK), combined with oral antidepressant, for treatment-resistant depression (TRD) was based on data from phase 2/3 (≤ 1 yr) studies.

Methods: Adults with TRD who participated in phase 3 "parent" studies could continue ESK treatment by enrolling in a global, open-label, long-term extension study, SUSTAIN-3 (NCT02782104). Based on their status at parent study end, eligible participants entered a 4-wk induction phase (IND) followed by an optimization/maintenance phase (OP/MA) of variable length, or directly entered the OP/MA phase of SUSTAIN-3. ESK dosing was flexible, twice/wk during IND and individualized to depression severity during OP/MA.

Results: 1148 participants were enrolled. Mean (SD, range) age was 49.6 (12.28, 19-83) years. Total exposure to ESK in SUSTAIN-3 was 3,777.0 cumulative patient-yrs. Mean (SD, range) total duration of exposure was 42.9 (24.22, 0-79) mon. About 2/3 of participants were on 84 mg, ~1/3 on 56 mg, and < 3% on 28 mg as their final dose; most participants received ESK weekly or every other wk during OP/MA.

Common treatment-emergent adverse events (AEs, ≥ 20%) were headache, dizziness, nausea, dissociation, nasopharyngitis, somnolence, dysgeusia, and back pain. Incidence of increased blood pressure-related AEs did not rise over time. No events of treatment-emergent interstitial/ulcerative cystitis, respiratory depression, or hypertensive crisis were reported. Nine participants died: COVID-19 related (n = 3), pneumonia (n = 2), completed suicide, myocardial infarction, multiple injuries, unknown cause (1 each).

Mean Montgomery-Åsberg Depression Rating Scale (MADRS) total score decreased during IND, and this reduction persisted during OP/MA (mean [SD] change from baseline to endpoint of each phase: IND -12.8 [9.73]; OP/MA 0.2 [9.93]), with 35.6% of participants in remission (MADRS ≤ 12) at IND endpoint, and 54.1%, 51.1%, 46.8%, 47.7%, and 46.9% at wks 56, 104, 160, 208, and 256, respectively.

Conclusions: Improvement in depression generally persisted among participants who remained on maintenance treatment; no new safety signals were identified during long-term treatment (up to 6.6 yrs). All-cause mortality and completed suicide rates were lower than expected based on published data from patients with TRD.

Disclosures: Janssen Research and Development, LLC: Employee (Self). Johnson and Johnson: Stock / Equity (Self).

17.3 Abstract not included.

17.4 Association of Clinical Markers With Response to Ketamine Versus Electroconvulsive Therapy in Treatment-Resistant Non-Psychotic Major Depression: Findings From the ELEKT-D Trial

Amit Anand

Harvard Medical School, Boston, Massachusetts, United States

Background: A recent large open-label randomized clinical trial (ELEKT-D trial) demonstrated that treatment with intravenous ketamine was non-inferior to electroconvulsive therapy (ECT) for non-psychotic treatment-resistant major depression (TRD)(Anand et al NEJM In press). Using data from this study, this unplanned secondary analysis evaluated whether select clinical and socio-demographic features were associated either with differential improvement with ketamine versus ECT. (NCT03113968).

Methods: Participants of the ELEKT-D trial (N = 365) who were randomized and received either ECT (9 sessions; n = 170) or ketamine (six infusions; n = 195) were included. Depression severity was assessed with the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) and the Montgomery Asberg Depression Rating Scale. Primary outcome was response (≥50% reduction) on QIDS-SR. Secondary outcomes included remission (presence of none-to-minimal symptoms) or levels of depression over time.

Results: Initial results indicate that there were no clinical features that predicted improvement with ketamine versus ECT after adjusting for multiple comparisons. In unadjusted analyses, North American Adult Reading Test (NAART) scores predicted the primary outcome. Estimated odds ratio (95% confidence interval [CI]) of response with ketamine versus ECT was 2.62 (95% CI = [1.54, 4.46], $p < 0.001$), 1.73 (95% CI = [1.12, 2.67], $p = 01$) and 1.29 (95% CI = [0.77, 2.14], $p = 0.33$) for individuals at 25th, 50th, and 75th percentile scores of NAART in this study. Additional results for predictors of secondary outcomes are being analyzed and will be presented at the meeting.

Conclusions: Performance on a quickly-administered reading test may predict improvement with ketamine versus ECT. As none of the clinical features were significant after adjusting for multiple comparisons, future studies should include systematic assessment of biomarkers to identify subgroups of individuals who improve with ketamine versus with ECT.

Disclosure: Nothing to disclose.

Panel

18. Glial and Immune Cells Contribute to Brain Function in Neuropsychiatric Disorders

18.1 Prefrontal Astrocytes Regulate Cognition via Acting on the Kynurenine Pathway

Tina Notter

University of Zurich, Zurich, Switzerland

Background: Astrocytes are an integral part of the tripartite synapse and modulate neuronal signaling. Accumulating evidence suggests that abnormalities in cortical astrocytes are involved in the pathophysiology of psychotic disorders. It remains elusive; however, how aberrant activity of cortical astrocytes contribute to behavioral and cognitive dysfunctions implicated in these disorders. The present study examined how selective activation of prefrontal astrocytes modulates behavior and cognition in mice.

Methods: Astrocyte activity was stimulated in the medial prefrontal cortex (mPFC) of adult C57BL6/N mice using chemogenetics (hM3DGq). Prefrontal astrocytes were targeted using intracerebral injection of rAAVs and activated with 1 mg/kg clozapine N-oxide. The functional role of prefrontal astrocytes in behavior and cognition was examined using a variety of behavioral tests, measurements of brain metabolites using LC-MS, and pharmacological interventions. Sample sizes were $N = 10$ except for LC-MS where $N = 5$, with $N =$ pooled mPFC samples from 2 mice. Males and females were included.

Results: Activation of prefrontal astrocytes impaired short-term memory in the Y-maze spontaneous alternation test (males: $p < 0.01$; females: $^*p < 0.05$) and temporal order memory test (males: $p < 0.001$; females: $p < 0.01$) and led to sensorimotor gating deficits in the prepulse inhibition (PPI) test (males: $p < 0.01$; females: $p < 0.05$). Prefrontal astrocyte activation also increased the locomotor response to a low dose of the NMDA receptor antagonist, MK-801 (males: $p < 0.05$), providing a link between activation of prefrontal astrocytes and functional alterations in glutamatergic signaling. In line with these findings, activation of astrocytes resulted in elevated levels of the endogenous NMDA receptor antagonist, kynurenic acid (KYNA) (males: $p < 0.01$). Finally, we found that pharmacological inhibition of KYNA production reinstated the cognitive deficits induced by chemogenetic activation of prefrontal astrocytes.

Conclusions: Our study identified a causal link between activation of prefrontal astrocytes, increased production of KYNA, and disruption of cognitive functions. These findings thus provide mechanistic insights into the pathophysiological relevance of astrocytes-related dysfunctions implicated in psychotic disorders and beyond.

Disclosure: Nothing to disclose.

18.2 Regulation of Circuit Maturation and Fear Learning by Myelination

Wendy Xin

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Background: Recent research indicates that myelin plasticity following learning is required for multiple forms of memory, including fear and spatial memories. Furthermore, studies using human postmortem tissue have identified myelination deficits as a common pathological hallmark of numerous psychiatric disorders. However, our current understanding of the relationship between myelination and neuronal circuit maturation and plasticity is limited. Therefore, we used mouse genetic approaches to visualize and manipulate myelination, first to evaluate the role of developmental myelination in circuit maturation, then to examine the cell type-specific roles for myelination in fear learning and memory.

Methods: We used lineage tracing to track the maturation of oligodendrocyte precursor cells in the visual cortex following monocular deprivation during adolescence (MD) ($n = 8$). To evaluate the role of myelination in regulating neuronal plasticity, we deleted a transcription factor required for oligodendrogenesis selectively from precursor cells and examined functional neuronal plasticity following MD ($n = 8$-9 per group). In a separate study, we used lineage tracing to determine which cell types become myelinated following contextual fear conditioning (preliminary). We then developed a novel approach to disrupt axon-myelin adhesions in genetically defined subpopulations of neurons to examine the cell type-specific role of myelination in modulating fear learning and memory (preliminary). Male and female mice were used in all studies. Group comparisons were performed using t-tests and 2-way ANOVAs where appropriate.

Results: Sensory experience altered the dynamics of oligodendrocyte generation ($p < 0.01$), and preventing oligodendrogenesis during adolescence led to enhanced neuronal plasticity in adult mice ($p < 0.001$). In preliminary studies, we also found that new myelin is formed around parvalbumin interneurons in the prefrontal cortex of mice following contextual fear conditioning. Using a novel genetic approach, we selectively disrupted axon-myelin adhesions in parvalbumin-expressing neurons, which resulted in impaired fear memory recall 24 hours later.

Conclusions: Overall, our studies indicate that oligodendrocytes and myelin play crucial roles regulating experience-dependent neuronal plasticity and fear memory.

Disclosure: Nothing to disclose.

18.3 Long-Term Impact of Prenatal Immune Stress on Microglia Responsivity and Consequences on Striatal Neural Activity and Age-Related Cognitive Decline

Lindsay Hayes

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Background: Immune mechanisms are implicated in the etiology and pathology of neurodevelopmental and neurodegenerative disorders with microglia as a key cellular driver. Epidemiologic evidence established that maternal inflammation is associated with increased risk for neurodevelopmental disorders. However, it remains elusive how maternal inflammation impacts microglia biology and leads to disease susceptibility or pathology. We examine the long-term impact of maternal immune activation (MIA) on microglia biology and disease pathology across the lifespan from neonatal to aging.

Methods: The microglia developmental trajectory, immune reactivity, and aging were evaluated by RNA sequencing. Striatal circuit activity was measured using electrophysiology of striatal medium spiny neurons. Age-related cognition was evaluated using fear conditioning. Males (M) and females (F) were included. Analyses used linear mixed effect modeling, ANOVAs, and t-tests. Microglia sequencing experiments used 4-8 mice per group, striatal electrophysiology used 10-20 cells from 3-8 mice per group, and behavior used 14-20 mice per group.

Results: MIA accelerated the maturation of MIA-microglia with an increase in homeostatic and decrease in inflammatory pathways. Direct challenge of MIA-microglia with an exogenous activator caused a systematic decrease in microglia reactivity consistent with neonatal microglia. One mechanism for the blunted microglia was through decreased transcription factor recruitment for regulation of gene expression ($p < 0.05$). The MIA-impaired microglia caused a decrease in connectivity of a subset of striatal neurons (mEPSC $p < 0.036$). Finally, we hypothesized the blunted microglia may protect mice from age-related cognitive decline. Surprisingly, only the aged females were protected from age-related cognitive decline after MIA exposure (MIA vs CON in aged F $p < 0.004$, young vs aged in MIA F $p = 0.7$).

Conclusions: The MIA results illuminate human brain imaging data which also showed reduced microglia reactivity in schizophrenia. We suggest that MIA is a tolerizing stimulus leading to an enduring innate immune memory in microglia by modulating epigenetic and gene regulation. Finally, we expand the data to implicate MIA in protection against age-related inflammation and consequential cognitive decline.

Disclosure: Nothing to disclose.

18.4 Type I Interferon Responsive Microglia Shape Cortical Development and Behavior

Caroline Escoubas Guney

UCSF, San Francisco, California, United States

Background: Microglia are brain resident phagocytes that engulf synaptic components, extracellular matrix and whole neurons. However, whether there are unique molecular mechanisms that regulate these distinct phagocytic states is unknown. Here we define a molecularly distinct microglial subset whose function is to engulf neurons in the developing brain.

Methods: Littermate controls were used when feasible. Mouse strains used: Ifnar1-/- (JAX #028288), Syn-1CRE (JAX #003966), Ifnar1 flox (JAX #028256), Cx3cr1CRE (MMRRC_0363 95-UCD)

Single cells were isolated with MACS beads and approximately 15,000 cells were sequenced and analyzed with Seurat. Biological replicates include 3 males and 3 females. IHC was performed in perfused and paraformaldehyde fixed tissues using markers including IFITM3 to identify IRMs. A total of 2-5 image per mouse and 3-6 mice from both sexes were analyzed with Fiji or Imaris software. Behavioral analysis was performed in a blinded fashion using equal numbers of male and female mice.

Results: We identified a cluster of Type I interferon (IFN-I) responsive microglia (IRMs) that expanded 20-fold in the postnatal day 5 somatosensory cortex after partial whisker deprivation, a stressor that accelerates neural circuit remodeling. In situ, IRMs were highly phagocytic and extended across multiple cell diameters to actively engulf whole neurons. Conditional deletion of IFN-I signaling (Ifnar1fl/fl) in microglia but not neurons resulted in dysmorphic 'bubble' microglia with stalled phagocytosis and accumulation of neurons with double strand DNA breaks, a marker of cell stress. Conversely, exogenous IFN-I was sufficient to drive neuronal engulfment by microglia and restrict the accumulation of stressed neurons. IFN-I deficient mice had excess excitatory neurons in the developing somatosensory cortex and displayed tactile hypersensitivity to whisker stimulation.

Conclusions: These data define a molecular mechanism through which microglia engulf neurons during a critical window of brain development. More broadly, they reveal key homeostatic roles of a canonical antiviral signaling pathway in brain development.

Disclosure: Nothing to disclose.

Study Group

19. No More Shooting in the Dark! Hopes and Challenges for Using Brain Imaging to Inform Neuromodulation Therapies in Psychiatric Disorders

Desmond Oathes, Hamed Ekhtiari, Sara Tremblay, Danielle DeSouza, Martijn Figee, A. Moses Lee, Anita Bajaj, Sarah Lisanby

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

Study Group Summary: Neuroimaging is being increasingly used to guide neuromodulation therapies in the hope that greater personalization and brain-based targeting will be the key to maximizing clinical effects. Imaging can be used in a variety of ways, including in guiding brain stimulation targeting as well as in measuring circuit engagement, optimizing dose-response and, finally, in measuring brain changes associated with symptom improvement to neuromodulation therapies.

There are also challenges associated with using neuroimaging to inform neuromodulation in psychiatric disorders. First, it is difficult to know ahead of time which brain measurements or targets are optimal without running exhaustive and costly clinical trials. Brain imaging adds a substantial cost to any clinical trial. Second, effect sizes may be small comparing image vs. non-image guided clinical effects making them hard to detect without large samples. Third, many clinics do not have straightforward access to imaging facilities and scientists or technicians to process imaging data. Fourth, there are ethical considerations when conducting sham treatments or stimulation protocols perceived as unlikely to have strong clinical effects. Finally, a lack of consensus in the field of brain imaging data for acquisition, processing methods and reporting standards hinders data aggregation for more statistically powerful analyses.

Despite these challenges, brain imaging is being used successfully to inform a variety of neuromodulation therapies. The proposed Study Group panelists will discuss clinical and brain imaging derived effects of neuromodulation as well as offer suggestions on how the field can continue to evolve, improve, and overcome barriers towards further optimization and growth. The Study Group will present research in healthy controls (Tremblay, Oathes) as well as in patients diagnosed with depression (Oathes, Tremblay, Lisanby, DeSouza, Figee), PTSD (Oathes), OCD (Figee, Lee), and addiction (Ekhtiari) that links brain imaging to clinical interventions employing a variety of neuromodulation therapies including rTMS (Oathes, Tremblay, Lisanby, DeSouza), tES (Ekhtiari), ECT (Lisanby) and DBS (Figee, Lee). A representative from a for-profit brain stimulation clinic will offer guidelines for pursuing research in that context (DeSouza). A representative from the FDA will also discuss the pathway for clearing brain imaging tools and measurements in the context of novel brain stimulation protocols in psychiatry (Bajaj). Though all successful therapies in psychiatry aim to change brain function, there is a unique mandate in brain stimulation therapies to choose in advance a brain target that is believed to mechanistically contribute to the illness or its remediation. Given the unique convergence between measurement and therapeutic intervention for brain stimulation paired with brain imaging, we believe that brain stimulation offers an ideal proving ground for demonstrating the relevance of neuroimaging to psychiatry.

Disclosure: Nothing to disclose.

Study Group

20. Plugging the Leaky Pipeline: Bolstering Physician-Scientist Recruitment, Training, and Retention in Psychiatric Research

Warren Taylor, Heather Ward, Olusola Ajilore, Anita Bechtholt, Diana Clarke, Kafui Dzirasa, Carolyn Rodriguez, Jeremy Veenstra-VanderWeele

Vanderbilt University Medical Center, Nashville, Tennessee, United States

Study Group Summary: The physician-scientist workforce has steadily declined across academic medicine over the last three decades, and psychiatry is no exception to this trend. Even with the expansion of medical scientist training programs (MSTP) and other initiatives intended to improve the pipeline, the number of physicians identifying medical research as a primary practice area has declined. Similarly, while the absolute number of physician-scientists (MD or MD/PhD) receiving NIH research project grants has stayed relatively stable over the last 15 years, the proportion of awards to physician-scientists has declined as growth in biomedical research has been fueled by non-physician PhD investigators. Importantly, these observations obfuscate other worrisome trends, including continued disparities in gender and racial background among independent physician-scientists, increasing investigator age at time of first NIH R01 funding, and continued effects of the COVID-19 pandemic on the workforce. While the work by non-physician scientists is essential for the advancement of our field, physician-scientists play a critical role in translating research into clinical populations and evaluating new treatments in clinical trials. It is not clear how to shift these trends most effectively, and ACNP is the ideal venue and audience for that discussion.

Disclosure: Nothing to disclose.

Panel

21. Amygdala fMRI Neurofeedback: From Basic Mechanisms to Clinical Applications

21.1 New and Confirmed Neurocircuitry for Neurofeedback in Adolescent Suicide Attempt and Depression: Random Covariance Modeling for Task-Based fMRI

Karina Quevedo, University of Minnesota, Minneapolis, Minnesota, United States

Background: Adolescence is a critical developmental window for self-processing and emotion regulation, disruptions to which are linked to persistent depression. A recent task-based, neurofeedback functional magnetic resonance imaging (NF fMRI) study of depressed vs. healthy adolescents elicited differential functional connectivity (FC) amongst brain regions of interest (ROIs). Previous results employed univariate models and included only two seed areas of FC (amygdala, hippocampus).

Methods: To reflect the large number of ROI's comprising self-processing and emotion regulation networks, a multivariate random covariance model (RCM) for bi-level subject and group-specific graphical models was applied to analyze the FC network of: (1) 17 pre-identified ROIs for depressed vs. healthy controls, (2) within depressed adolescents comparing those with vs. without a suicide attempt or ideation, (3) subject-specific analysis of correlation between subject FC and pre-post intervention clinical depression and rumination symptoms change, and (4) a whole-brain exploration with the AAL3 atlas. RCMs were tuned with modified BIC and significance assessed via FDR-corrected 5000-permutation tests.

Results: Corroborated (1) significant hyper- and hypo-connectivity of right vs. left amygdala-cuneus FC, respectively, in depressed vs. healthy youth. Yielded (2) that suicide attempters show higher FC (0.053) between left superior, middle, inferior temporal gyrus (BA 19, 22, 37, 39) and left amygdala ($\delta = -0.098$, $p = 0.009$) compared to non-attempters (-0.0459) ($N\_S = 19$). Suicide ideators ($N\_I = 29$) show negative cross-hemispheric differential connectivity ($\delta = -0.099$, $p = 0.0092$) between the left anterior cingulate cortex (ACC, BA 6, 8, 9, 24, 32) and right superior, middle, inferior temporal gyrus (BA 19, 22, 37, 39), vs non-ideators ($N\_I = 5$). Results in (3) yielded associations between symptoms of rumination and depression and larger circuitry. (4) New connectivity patterns were uncovered by whole-brain explorations with the AAL3 atlas.

Conclusions: The results confirmed prior preferential engagement of left amygdala - cortical circuitry during self-referential processing among adolescents with a past recent history of suicide attempts. Suggesting that this might be a biomarker of suicide attempts risk to be tested in future longitudinal research.

Disclosure: Nothing to disclose.

21.2 The Role of the Cognitive Control Network in Amygdala Neurofeedback Success

Kymberly Young

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Background: Real-time fMRI neurofeedback (rtfMRI-nf) training to increase amygdala activity during positive autobiographical memory (AM) recall results in significant symptom improvement in patients with major depressive disorder (MDD). However, the neurobiological mechanisms underlying such positive effects are unclear. Previous work using other rtfMRI-nf paradigms suggests that the cognitive control network (CCN) plays an important role in rtfMRI-nf success. As the CCN is important for self-guided motivation and internal reward processing, it may therefore be an important mechanism underlying rtfMRI-nf learning regardless of paradigm. Here, we examine whether the CCN also contributes to rtfMRI-nf learning using our positive AM paradigm.

Methods: 100 participants from 3 different clinical trials received two rtfMRI-nf training sessions ($n = 64$, experimental group, amygdala feedback; $n = 36$ control group, parietal feedback) where they were instructed to increase the level of a thermometer representing the target region's activity while recalling positive AMs. Each session started with a baseline run during which no rtfMRI-nf was provided and ended with a transfer run where no rtfMRI-nf was provided. Regulation success was defined as a significant increase from baseline to transfer. We examined changes in the CCN from baseline to transfer and correlated these changes with rtfMRI-nf success and clinical improvement.

Results: There was a strong correlation between change in CCN activity and rtfMRI-nf success overall ($r = 0.28$, $p = 0.006$). This correlation was similar in both the experimental group ($r = 0.28$, $p = 0.03$) and the control group ($r = 0.43$, $p = 0.01$; difference between correlations $z = 0.81$, $p = 0.42$). The correlation between CCN change and symptom change was not significant overall ($r = 0.5$, $p = 0.66$) or for either group (experimental $r = 0.08$, $p = 0.54$; Control $r = -0.02$, $p = 0.90$).

Conclusions: The CCN contributes to successful transfer of self-regulation after rtfMRI-nf training, regardless of assigned regulation target. This suggests that CCN activity is involved in neurofeedback regulation success generally (regardless of target) and that employing CCN activity during rtfMRI-nf training could boost success rates.

Disclosure: Nothing to disclose.

21.3 Variability in Brain Response to Feedback Signal Associated With Therapeutic Efficacy of Amygdala Neurofeedback for MDD and PTSD

Masaya Misaki

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

Background: Real-time fMRI neurofeedback (rtfMRI-NF) of amygdala activity has shown promise in correcting aberrant amygdala activity and alleviating symptoms of MDD and PTSD. Existing evidence suggests that this NF training impacts various brain activities and hippocampal volumes, which may contribute to treatment efficacy. This study investigated the whole-brain response to the feedback signal during NF training as a predictor of treatment response since adapting mental strategy according to feedback is critical for mastering brain self-regulation via reinforcement learning.

Methods: We analyzed data from left amygdala rtfMRI-NF studies, including the real NF condition of 59 MDD patients and 24 combat veterans with PTSD. Feedback signal response was evaluated using a general linear model analysis with a feedback signal time course regressor convolved with the hemodynamic response function. We used UMAP and K-means to cluster whole-brain response patterns across participants. The number of clusters was determined by the stability of the cluster structure as assessed by repeated half-split training and testing. Symptom change was assessed one week after the session. Analyses were conducted separately for MDD and PTSD.

Results: We identified three MDD and two PTSD subgroups, with no significant differences in age, sex, NF signal amplitude, or amygdala activity. However, symptom changes differed significantly between subgroups. MDD subgroups that demonstrated responses to feedback in extensive brain regions showed a significant reduction in MADRS scores, unlike those with more limited brain responses. Similarly, a PTSD subgroup with a significant prefrontal response showed a significant PCL-M reduction, whereas another with limited brain response did not show significant symptom change.

Conclusions: Variability in feedback response patterns was associated with symptom reduction, but not with NF signal amplitude or amygdala activity. This suggests that differences in response patterns may reflect individual efforts to self-regulate brain activity in response to feedback. This further suggests that the treatment effect does not solely rely on amygdala regulation. The efficacy of NF training may need to be evaluated by considering whole-brain modulatory activity in response to the feedback signal, not only regulation of the target region.

Disclosure: Nothing to disclose.

21.4 Functional Magnetic Resonance Neurofeedback Targeting the Amygdala Modulates Monosynaptic Connections With Large-Scale Brain Networks: A Cross-Species Study

Lucas Trambaiolli

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

Background: fMRI neurofeedback targeting the up-regulation of the left amygdala during autobiographical memory recall has promising results as a therapeutical tool for several psychiatric disorders. Recent evidence suggests that amygdala neurofeedback induces resting-state functional connectivity (rsFC) changes between the amygdala and regions of the salience and default mode networks (SN and DMN, respectively). Notably, the hippocampus (a core node of the DMN) is co-activated during neurofeedback training and presents changes in rsFC and volume after the neurofeedback training.

We hypothesize that these rsFC changes happen within areas anatomically connected with the amygdala by (i) direct monosynaptic connections or (ii) polysynaptic connections mediated by the hippocampus.

Methods: We used the coordinates from 16 regions of interest (ROIs) from 3 studies showing pre-to-post-neurofeedback changes in rsFC with the left amygdala. These included 6 ipsilateral and 7 contralateral ROIs of the DMN and 3 ipsilateral ROIs of the SN. We registered these coordinates to a cross-species brain parcellation and identified the homologous regions in the macaque brain.

We injected 7 bidirectional tracers in the amygdala of adult male macaques and used bright- and dark-field microscopy to identify cells and axon terminals in each ROI. We also injected tracers to validate our results in the lateral precuneus (ROI of the DMN) and anterior insula (ROI of the SN). Finally, we set one large injection in the hippocampus to evaluate the polysynaptic pathways between the amygdala, hippocampus, and ROIs in the contralateral ROIs.

Results: The amygdala had strong monosynaptic connections with all the SN and DMN ipsilateral ROIs. Injections in the lateral precuneus and anterior insula validated these connectivity patterns. Amygdala injections had scarce or absent connections with the contralateral ROIs.

All amygdala injections had strong connections with the hippocampus, and the hippocampal injection had connections with the contralateral ROIs of the DMN.

Conclusions: fMRI neurofeedback modulates large-scale networks through a combination of monosynaptic connections from the target region (amygdala) and polysynaptic connections, including areas involved in the targeted cognitive process (hippocampus and PHG during autobiographical memory recall).

Disclosure: Nothing to disclose.

Mini Panel

22. New Challenges in the Opioid Use Landscape: Translational Studies on Xylazine, Fentanyl, and Adulterants in the Drug Supply

22.1 Surveillance of Fentanyl and Newly Emergent Drugs Such as Xylazine in the United States

Joseph Palamar

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Background: The opioid crisis, driven largely by fentanyl, has continued, but most data focusing on fentanyl-related trends have focused on mortality. Little is known regarding nonfatal overdose and availability of illicit fentanyl. In addition, xylazine is now appearing to be more commonly used to adulterate illicit fentanyl, further complicating the crisis. There is a lack of national trend data focusing on availability and poisonings involving these drugs.

Methods: Trends were estimated based on three sources of data provided to the NIDA National Drug Early Warning System (NDEWS). First, quarterly trends were estimated in the number of forensic samples (primarily from medicolegal death investigations) submitted to NPS Discovery for analysis that tested positive for fentanyl and for xylazine. Next, annual trends were estimated in the number of fentanyl seizures in the US reported to High Intensity Drug Trafficking Areas (HIDTA) (with seizures serving as a proxy for availability). Trends were estimated in the number of powder seizures and pill seizures. Finally, annual trends were estimated for the number of nonfatal fentanyl poisonings reported to Poison Control in 49 states based on data obtained from RADARS.

Results: Within forensic samples, between 2018 Quarter 1 and 2023 Quarter 1, the percentage of submissions testing positive for fentanyl increased from 25% to 60% (average quarterly percent change [AQPC] = 12.6, 95% CI: 9.0-16.2) and submissions testing positive for xylazine increased from 1% to 13% (AQPC = 12.6, 95% CI: 9.0-16.2). Between 2017 and 2021, the total number of powder fentanyl seizures increased from 1,171 to 13,599 (average annual percent change [AAPC] = 64.8, 95% CI: 59.5-70.2) and the total number of pill seizures increased from 134 to 5,081 (AAPC = 105.1, 95% CI: 99.7-115.1). Finally, nonfatal fentanyl poisonings reported to Poison Control did not significantly shift between 2015 and 2018, but between 2018 and 2022, the number increased from 1,068 to 4,414 (AAPC = 49.2, 95% CI: 36.5-58.8).

Conclusions: Our monitoring efforts have been detecting increases in availability and poisonings involving fentanyl as well as an increase in exposures to xylazine. More research is needed, however, focusing on use and exposure to fentanyl and xylazine that does not result in a hospitalization or death.

Disclosure: Nothing to disclose.

22.2 Clinical Impact of Fentanyl and Novel Drug Exposure During Substance Use Treatment

Justin Strickland

Johns Hopkins University School of Medicine, Baltimore, Maryland, United States

Background: Epidemiological data document concerning trends regarding adulterants in the drug supply including the highly potent opioid agonist fentanyl and anesthetic xylazine. While these data have helped raise concerns about developing trends, the consequent impacts for treatment trajectories remain unknown. This gap is in part due to the lack of national databases that longitudinally track treatment-relevant symptoms and drug use outcomes with in-depth assessments. We will discuss treatment outcomes data related to opioid supply adulterants derived from a national treatment outcomes cohort conducted by our team.

Methods: Treatment outcomes assessments are collected from 77 substance use disorder treatment facilities across the United States including residential and intensive outpatient treatment programs. Data include assessments collected from patients at treatment intake, weekly during treatment, and monthly post discharge. Short-term treatment outcomes include standardized measures of craving (questionnaire and cue-induced), sleep, and anhedonia collected throughout a treatment episode. Long-term treatment outcomes include return to substance use and non-fatal drug overdose following treatment discharge. Patient trajectories evaluated based on fentanyl exposure in the month prior to treatment were tested using generalized linear mixed effect models for longitudinal data and generalized linear models for point comparisons.

Results: Cohort data contain information from 9,350 unique patients (31.2% women; 68.5% men; 0.2% non-binary) with 21,041 observations in the first four weeks of treatment and 4,242 patients (36.1% women; 63.5% men; 0.3% non-binary) with data in the month after treatment. Fentanyl exposure in the month prior to treatment was documented in 21% of all patients and 66% of those with primary opioid use disorder (OUD). Patients with recent fentanyl exposure reported significantly elevated craving, sleep disturbance, and anhedonia at treatment intake compared to patients without fentanyl exposure in the full cohort (d = 0.33-0.74) and specifically among patients with primary OUD (d = 0.21-0.38). These elevations were attenuated over treatment with similar symptom levels reported by fentanyl exposure after one month of treatment. Fentanyl exposure was significantly associated with a 1.98 ($p < .001$) greater odds of a return to substance use and 2.17 ($p = .03$) greater odds of experiencing a non-fatal overdose in the month following treatment discharge among patients with primary OUD. Notably, fentanyl exposure was associated with a 15.52 ($p < .001$) greater odds of a non-fatal overdose among patients without primary OUD suggestive of incidental risk in this population.

Conclusions: Exposure to emerging adulterants in the drug supply carries significant risk for poorer treatment outcomes including worsened biopsychological symptoms at substance use treatment entry and overdose risk after discharge. Within-treatment trajectories indicate the retained care may confer additional benefit for patients exposed to adulterants emphasizing the relevance of treatment retention strategies. These data emphasize the importance of recently implemented and ongoing treatment outcomes assessments evaluating other emerging trends including xylazine exposure to determine unique and interactive impacts on short- and long-term treatment outcomes.

Disclosure: Nothing to disclose.

22.3 Xylazine Co-Self-Administration Suppresses Fentanyl Consumption During Self-Administration and Induces a Unique Sex-Specific Withdrawal Syndrome That is Not Altered by Naloxone in Rats

Cassandra Gipson

University of Kentucky, Lexington, Kentucky, United States

Background: Prescription and illicit opioid use are a public health crisis, with the landscape shifting to fentanyl use. Since fentanyl is 100-fold more potent than morphine, its use is associated with a higher risk of fatal overdose that can be remediated through naloxone (Narcan) administration. However, recent reports indicate that xylazine, an anesthetic, is increasingly detected in accidental fentanyl overdose deaths. Anecdotal reports suggest that xylazine may prolong the fentanyl "high", alter the onset of fentanyl withdrawal, and increase resistance to naloxone-induced reversal of overdose. To date no preclinical studies have evaluated the impacts of xylazine on fentanyl self-administration (SA; 2.5 μg/kg/infusion) or withdrawal to our knowledge.

Methods: We established a rat model of xylazine/fentanyl co-SA and withdrawal and evaluated outcomes as a function of biological sex. 96 male and female Long Evans rats (half of each sex) underwent either xylazine injections followed by fentanyl SA, xylazine injections followed by withdrawal characterization, or intravenous xylazine adulteration of the fentanyl infusion during SA followed by naloxone challenge and withdrawal characterization across both acute and protracted timepoints. A subgroup of rats underwent a pharmacokinetics study to determine intravenous xylazine dose.

Results: When administered alone, chronic xylazine (2.5 mg/kg, IP) induced unique sex-specific withdrawal symptomatology whereby females showed delayed onset of signs and a possible enhancement of sensitivity to the motor-suppressing effects of xylazine ($p < 0.05$). Xylazine reduced fentanyl consumption both male and female rats regardless of whether it was experimenter-administered or added to the intravenous fentanyl product (0.05. 0.10, and 0.5 mg/kg/infusion) when compared to fentanyl SA alone ($p < 0.05$). Interestingly, this effect was dose-dependent when self-administered intravenously. Naloxone (0.1 mg/kg, SC) did not increase somatic signs of fentanyl withdrawal, regardless of the inclusion of xylazine in the fentanyl infusion in either sex; however, somatic signs of withdrawal were higher across timepoints in females after xylazine/fentanyl co-SA regardless of

naloxone exposure as compared to females following fentanyl SA alone ($p < 0.05$).

Conclusions: This is the first study to identify intravenous xylazine dosing for adulteration of fentanyl during SA in rats, and the first to demonstrate that this can be modeled preclinically. Together, these results indicate that xylazine/fentanyl co-SA dose-dependently suppressed fentanyl intake in both sexes, and induced a unique withdrawal syndrome in females which was not altered by acute naloxone treatment.

Disclosure: Nothing to disclose.

Panel

23. The Neuropeptide Tac2 Pathway Regulating Behavior Across Species

23.1 Abstract not included.

23.2 A Hypothalamic Node for the Control of Isolation-Altered Courtship

Moriel Zelikowsky

University of Utah School of Medicine, Salt Lake City, Utah, United States

Background: Extended deprivation of social contact produces deleterious effects on a host of adaptive behaviors. We recently identified a role for the neuropeptide tachykinin 2 (Tac2) in the control of the internal brain state produced by prolonged isolation. While we have made significant advances towards understanding the impact of social isolation to induce aggression, fear and anxiety, we nevertheless have a poor handle on how isolation negatively impacts important survival-related behaviors such as courtship.

Methods: Using a combination of in-depth behavioral analyses, machine vision, ultrasonic vocalization (USV) recordings, RNA analyses and cell-type specific in vivo calcium imaging, we interrogated the behavioral impact of social isolation on mouse courtship behavior and ultrasonic vocalizations and interrogated the role of Tac2 in the lateral preoptic nucleus (LPO) in the control of this effect. Courtship behavior, USVs, and neural activity of male C57Bl6/Ns ($n = 7$-12) was assessed in a 30 minute homecage mating assay and analyzed in our custom built behavior/machine learning/acoustic/imaging pipeline MARS/Bento. Female mouse receptivity behavior and social preference was assessed using a 3-chamber social interaction assay and pregnancy assays. Mixed-design two-way ANOVAs were used to assess between-group and within group differences and followed up with posthoc tests controlled for multiple comparisons (Bonferonni). The alpha cut-off for significance was set as $p < .05$ (two-tailed).

Results: We reveal that social isolation produces dysregulated patterns of mating behavior ($p < .01$ in comparing transitions from chasing to mating in grouped vs. isolated males) that violate Markovian principles, limits the dynamic range of courtship song ($p < .001$ for frequency range, maximum jump rate, and USV duration for grouped vs. isolated males), and alters female receptivity ($p < .05$ for preference of grouped male over isolated male). Furthermore, we identify a neural ensemble in the lateral preoptic area whose activity correlates with isolation-specific song alterations and is required for the effects of isolation on behavior and USVs.

Conclusions: Collectively, these findings provide evidence for the multi-modal disruption of mouse courtship behavior after isolation and identify a unique neural signature in the coding of this brain state.

Disclosure: Nothing to disclose.

23.3 Abstract not included.

23.4 Abstract not included.

Panel

24. Mechanism, Timing and Treatment of Cognitive Impairment in Schizophrenia

24.1 Symptom and Functional Trajectories by Cognitive Subgroups in Early Psychosis

Kathryn Lewandowski

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

Background: Cognitive symptoms are present by psychosis onset at the group level and are among the strongest predictors of community functioning and quality of life. However, considerable cognitive heterogeneity exists, and the extent to which cognitive variability in early psychosis can be characterized and examined as a predictor of illness course is unclear.

Methods: Participants included 50 men and women with a recent onset of a psychotic disorder determined by DSM-5 assessed at study entry and approximately 14 months later. Cognition was assessed using the NIH Toolbox Cognition measures; symptoms were assessed using the PANSS, CAINS, BNSS, MADRS, and YMRS; functioning was assessed using the MIRECC GAF.

Results: Using Ward's linkage followed by K-means cluster analyses, three cognitive subgroups were identified with adequate differentiation ($p < .0001$): significantly impaired, selectively impaired, and intact. All groups included participants with affective and non-affective psychosis. Groups differed anhedonia, blunted affect, and alogia at both baseline and follow-up ($p < .01$). Trajectory analysis showed different patterns of change over the follow-up: the severely impaired group showed cognitive improvement whereas the selectively impaired and intact groups showed no change. The selectively impaired group showed improved social functioning and negative symptoms.

Conclusions: People in the early course of both affective and non-affective psychosis exhibited significant cognitive impairment at the group level. However, data-driven modeling showed distinct cognitive subgroups including a subset of participants with intact cognition. Cognitive subgroups exhibited distinct patterns of symptoms and cognitive and functional trajectories over a 14-month follow-up, suggesting that these groups may reflect distinct subsets of patients.

Disclosure: Nothing to disclose.

24.2 Timing of Cognitive Impairment in Schizophrenia

Mark Weiser

Sheba Medical Center, Ramat Gan, Israel

Background: Cognitive impairments are a core feature of psychotic disorders and are a main cause of functional disability.

However, the timing of cognitive impairment in psychotic disorders remains unclear: while some patients have impaired cognitive abilities before the onset of psychosis, others seem to become cognitively impaired only after their first psychotic episode. This longitudinal study aimed to further understand the timing of cognitive impairment in psychotic disorders.

Methods: This ongoing study utilizes standardized cognitive testing administered by the Israeli Military Draft Board at age 17 on all adolescents in the country. Results are presented as a stanine score, graded 10 to 90. The study will include 50 participants aged 18-30, who had undergone cognitive testing before being diagnosed with schizophrenia, bipolar disorder or schizoaffective disorder (baseline score- T1). One to twelve years after T1 and more than six months after their first psychotic break, they retake the exact same cognitive test (T2). The test results will be compared to controls matched for sex, age and socioeconomic status, who were tested at age 17 and not later diagnosed with schizophrenia, bipolar disorder or schizoaffective disorder.

Results: To date, the study group includes 32 patients, average age of 26.5, 56.3% diagnosed with schizophrenia, 21.9% with bipolar disorder, and 21.9% with schizoaffective disorder. The control group includes 26 participants, with a mean age of 26. For the study group, the mean stanine score of the cognitive test at T1 and at T2 were 54.4 ± 19.6 and 48.1 ± 18.7 accordingly. The mean scores of the control group at T1 were 55.2 ± 16.1 and 60 ± 16.9 at T2. Hence, the mean score change for patients showed a decrease by 0.3 effect sizes, compared to controls who had a mean increase of 0.3 effect size, ($p < 0.001$). Compared to the scores before their first psychotic episode, 13.2% showed an increase in scores, 28.9% had no change in scores, whereas 44.8% showed a decrease in scores.

Conclusions: The current findings show a significant decrease in cognitive abilities following the first psychotic episode. Once completed, the study will enable examination of the course of cognitive impairment over time. Further analyses will attempt to use baseline data to predict which patient will, or will not, declines cognitively over time.

Disclosure: Nothing to disclose.

24.3 Voxel and Network-Based BrainAGE and Cognition in Schizophrenia

Sophia Fragou

University of British Columbia, Vancouver, Canada

Background: Multiple prior studies have documented the presence of widespread brain structural abnormalities in patients with schizophrenia (van Erp et al., 2016; 2018). Although some of these brain structural alterations may occur early in development, recent findings suggest that accelerated brain aging may be a possible underlying mechanism (Constantinides et al. 2023). The objective of the present study was to determine the relationship of brain aging to cognition in patients with schizophrenia with high spatial resolution.

Methods: Global, Local, and Network-Based brain-age-gap-estimates (G-brainAGE, L-brainAGE, N-brainAGE) were computed using optimised machine learning models from structural neuroimaging data from 84 patients (aged 16-35 years) with early-stage schizophrenia (illness duration < 5 years) and 1,169 healthy individuals (aged 16-37 years). Multidomain cognitive data from the patient sample were submitted to Heterogeneity through Discriminative Analysis (HYDRA) to identify cognitive clusters.

Results: HYDRA classified patients into a cognitively impaired cluster ($n = 69$) and a cognitively spared cluster ($n = 15$). Compared to healthy individuals, G-brainAGE was significantly higher in the cognitively impaired cluster (+11.08 years) who also showed widespread elevation in L-brainAGE, and N-brainAGE highest deviance was observed in the central executive and default networks. The cognitively spared cluster showed a higher L-brainAGE localized in the anterior cingulate cortex and a higher N-brainAGE of the salience network. Psychotic symptom severity in both clusters showed a positive but non-significant association with measures of brain aging.

Conclusions: Accelerated aging in schizophrenia can be detected at the early disease stages and appears more closely associated with cognitive dysfunction rather than clinical symptoms.

Disclosure: Nothing to disclose.

24.4 A Double-Blind Placebo-Controlled Study of the Effects of Combined L-Carnosine and Cognitive Training on Social Cognition in Schizophrenia

Abraham Reichenberg

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

Background: Improving cognition in individuals with schizophrenia is a major clinical target. Available pharmacological and non-pharmacological approaches have shown only modest effects in improving cognition. The goal of this study was to assess the impact of L-carnosine, a dipeptide with antioxidant and anti-glycating properties, alone and in combination with social cognitive training on improving social cognitive test performance.

Methods: 60 participants (40 males and 20 females) with chronic schizophrenia were enrolled in a double-blind, placebo-controlled, novel two-stage study design. Participants were randomized to either L-carnosine (2000mg) or placebo. To test for the effects of L-carnosine alone, in the first part of the trial, participants engaged in two weeks of L-carnosine or placebo treatment without adjunctive cognitive training. After a one-week washout period, to test for the effect of L-carnosine in combination with training, participants began the second part of the trial engaging in further two weeks of L-carnosine or placebo treatment with adjunctive cognitive training to enhance social cognition. The primary outcome measure was performance on the social cognition training task. Secondary outcomes were the MATRICS cognitive battery and clinical symptom severity (Positive and Negative Syndrome Scale (PANSS)).

Results: 70% of participants completed all study visits. Both the L-carnosine and placebo groups showed improvement on the social cognition task during the study period, suggesting potential for learning. In the first part of the trial the learning rate did not differ between groups without social cognitive training. However, when combined with social cognitive training (second part of trial), L-carnosine induced differential learning enhancement ($p = 0.042$) starting with the third of nine training sessions. Performance gains in the L-carnosine group were retained two weeks after the training cessation. Differential learning enhancement was greater among non-Black participants. There were no statistically significant group effects on any of the secondary outcomes.

Conclusions: This study demonstrated that pairing L-carnosine with social cognitive training statistically significantly enhanced performance on a social cognition task.

Disclosure: Nothing to disclose.

Mini Panel

25. Sex and Stress Regulation of Alcohol Drinking and Alcohol Use Disorder

25.1 Abstract not included.

25.2 Imaging Sex Differences in the Neuroimmune System in Alcohol Use Disorder

Yasmin Zakiniaeiz

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Background: Alcohol use is one of the leading causes of disability in the United States. Women tend to drink for stress regulation and are more vulnerable than men to the consequences of alcohol use. Alcohol initially stimulates microglia, the brain's resident immune cells, to carry out repair functions. However, excessive activation may contribute to neuronal dysfunction and alcohol-induced neurodegeneration. Neurodegeneration impairs neurocognition and precipitates drinking. Stress further disrupts microglia function and neurocognition. Women with alcohol use disorder (AUD) report higher stress and have greater neurocognitive impairments than men with AUD, which predict poorer treatment outcomes. We previously showed lower microglia marker levels in AUD vs. controls. The current study aimed to investigate sex differences in the neuroimmune system of individuals with AUD in an expanded sample. Based on prior work, we hypothesized that women with AUD would show lower microglia marker levels relative to sex-matched healthy controls. We also hypothesized that lower microglia marker levels would be related to worse cognitive performance and drinking outcomes.

Methods: To date, twenty-nine individuals with AUD (mean 42 drinks/month for 24 years; 10 women) and 28 age-, sex-, smoking status- and rs6971 single-nucleotide polymorphism genotype-matched control subjects participated in positron emission tomography (PET) scans with [11C]PBR28 to measure 18-kDa translocator protein (TSPO), a marker of microglia. The outcome measure, volume of distribution (VT), was estimated regionally in the hippocampus, frontal cortex, cerebellum, and putamen with multilinear analysis as a measure of TSPO availability. A subset of subjects completed a cognitive battery and the Alcohol Use Disorder Identification Test (AUDIT) to assess hazardous drinking.

Results: We found a main effect of diagnostic group such that individuals with AUD had significantly or trending lower VT than their control counterparts in four a priori brain regions of interest ($0.04 \leq p \geq 0.10$, effect sizes:$0.04 \leq \eta p2 \geq 0.07$). Interactions of diagnostic group and sex were significant or trending ($0.02 \leq p \leq 0.14$, $0.04 \leq \eta p2 \geq 0.09$) for all four brain regions. Women (but not men) with AUD had significantly lower VT in all four regions ($0.01 \leq p > 0.05$, effect sizes:$0.07 \leq \eta p2 \geq 0.11$) compared to sex-matched controls. Preliminary analyses revealed that the AUD group performed worse than the control group on verbal learning and memory tasks ($p \leq 0.04$, Cohen's $d \geq 2.2$) but VT values were not related to cognitive performance ($p \geq 0.59$). Preliminary analyses in the AUD group revealed that lower VT values were significantly or trending related to higher AUDIT scores in all four brain regions ($0.41 \geq R2 \geq 0.59$, $0.03 \geq p \geq 0.09$). No sex differences in these relationships were found.

Conclusions: We show evidence for sex differences in levels of a microglia marker in people with AUD vs. controls. These data extend our previous report of lower microglia marker levels in people with vs. without AUD to demonstrate greater impairment in women than men with AUD. This suggests that neuroimmune suppression may be more pronounced in women with AUD compared to sex-matched controls and this may underlie reports of greater neurodegeneration in AUD women than men.

Disclosure: Nothing to disclose.

25.3 Sex Differences in Brain Connectivity During Early Abstinence in People With an Alcohol Use Disorder

Jennifer Blackford

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Background: Rates of alcohol use disorders (AUDs) in women are increasing at alarming rates. Despite evidence of sex differences in AUDs, we know remarkably little about the underlying neurobiological mechanisms. The bed nucleus of the stria terminalis (BNST) is critically involved in stress and stress responses during early abstinence from alcohol. The BNST is also one of the most sexually dimorphic regions of the brain; therefore, the BNST may be well positioned to contribute to sex disparities in early abstinence in AUDs.

Methods: BNST network connectivity was investigated in a sample of people in early abstinence from an AUD ($n = 20$; 47% female) and controls ($n = 20$; 55% female). Structural and intrinsic functional connectivity were assessed using DTI and resting state fMRI, respectively in a BNST network (amygdala, hippocampus, insula, hypothalamus, and ventromedial prefrontal cortex [vmPFC]). Participants also completed an fMRI unpredictable threat task, based on evidence that unpredictable threat engages the BNST network. gPPI was used to estimate task-based connectivity with left and right BNST as seeds. Linear mixed models were used to test for effects of group and sex effects in structural and intrinsic connectivity across the BNST network (alpha = .05). Whole brain general linear models were used to test for group and sex effects in task connectivity during anticipation of unpredictable threat compared to predictable neutral and predictable threat cues and images ($p < .005$, cluster corrected for alpha = .05).

Results: Structural connectivity (DTI) in the BNST network was significantly stronger in abstinent women (AW) than control women (CW), with no such difference in men. The largest distinction was in BNST-anterior insula connectivity, stronger in AW compared to CW, and weaker in abstinent men (AM) than control men (CM). Intrinsic functional connectivity had significant group x sex x region interactions across the BNST network. Group x sex interactions were significant for BNST connectivity with the hypothalamus, anterior hippocampus, amygdala, and vmPFC; post-hoc tests showed group differences in men. AM showed weaker connectivity with the hypothalamus, hippocampus, and amygdala and stronger BNST-vmPFC connectivity compared to CM. In the unpredictable threat task, there were significant group x sex interactions in BNST functional connectivity. AW showed significantly lower BNST connectivity with the dorsomedial prefrontal cortex, vmPFC, caudate, and thalamus compared to CW for unpredictable vs predictable neutral anticipation. Additionally, AW had lower BNST-vmPFC, while AM had lower BNST-thalamus connectivity compared to their respective controls for unpredictable vs predictable threat anticipation.

Conclusions: Across three measures of brain connectivity we discovered significant sex differences. Group differences in men were most prominent for structural connectivity, whereas group differences in women were observed for both intrinsic and task-based functional connectivity, highlighting the importance of investigating multiple types of brain connectivity. Understanding sex differences in early abstinence has strong clinical significance given that rates of alcohol use and alcohol use disorders in

women are increasing and women have more health consequences from alcohol than men.

Disclosure: Nothing to disclose.

Panel

26. Hit Me With Your Best Shot: Personalized Targeting of Neuromodulation for Substance Use Disorders

26.1 A Disease-Informed, Network-Targeted Neuromodulation Intervention Affects Craving in Individuals With Schizophrenia and Nicotine Dependence

Heather Ward

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Background: The prevalence of tobacco use in schizophrenia (SZ) is 3-times that of the general population. Yet, treatments for nicotine dependence are significantly less effective for SZ and do not target SZ-specific pathophysiology. We sought to identify and test a neuromodulation intervention on a SZ-specific circuit of nicotine dependence.

Methods: This study consisted of 3 phases: Network Discovery, Network Validation, and Network-Targeted Intervention. In Network Discovery, we used a data-driven, multi-variate pattern analysis of whole-connectome data from 35 smokers (18 SZ, 17 controls) to identify the strongest links between daily cigarette use and functional connectivity. In Network Validation, 24 participants (12 SZ, 12 control) participated in a placebo-controlled crossover study of nicotine patch with fMRI. Based on Network Discovery results, we correlated DMN connectivity change with nicotine patch dose. In Network-Targeted Intervention, 10 people with SZ and nicotine dependence participated in a crossover study of DMN-targeted repetitive transcranial magnetic stimulation (rTMS) with fMRI and craving assessment immediately before and after each rTMS session. rTMS was targeted to the left parietal node of an individual-specific DMN map for 3 sessions: intermittent theta burst stimulation (iTBS), continuous theta burst stimulation (cTBS), sham. We compared craving change between each rTMS type using a mixed ANOVA.

Results: In Network Discovery, the strongest ($p < .001$) correlate between functional connectivity and daily cigarette use was driven by individual variation in DMN topography specific to SZ. With higher cigarette use in SZ, the DMN was pathologically expanded. In Network Validation, nicotine administration reversed DMN hyperconnectivity in SZ in a dose-dependent relationship ($R = -0.50$, $p < .05$). In Network-Targeted Intervention, we observed a treatment x time relationship ($p = .017$) where craving was increased by iTBS but not by cTBS or sham.

Conclusions: We identified a SZ-specific network of nicotine dependence, validated the effect of acute nicotine on that network, then applied a neuromodulation intervention to that network that affected craving in SZ. This is the first evidence for a circuit-based intervention for substance use in SZ that was empirically derived, unique to SZ, and affected clinical outcomes.

Disclosure: Nothing to disclose.

26.2 Individualized Dose and Target Optimization of Craving Circuits in People With Methamphetamine Use Disorder

Hamed Ekhtiari

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Background: Non-invasive brain stimulation (NIBS) techniques, including transcranial electrical/magnetic stimulation (tES/TMS), have shown promise for modulating brain plasticity in clinical trials in people with substance use disorders. However, inconsistent evidence regarding their benefits has been reported, potentially due to large within/between-subject variations that limit population-level effect sizes. To address this issue, personalized NIBS interventions are needed to suit individual situations. We assess the factors that may affect NIBS individualization at four different levels: (1) context, (2) target, (3) dose, and (4) timing.

Methods: MRI data including structural, resting-state, and task-based fMRI data were collected from 60 participants with methamphetamine use disorders (MUDs). Craving scores based on a visual analog scale were collected immediately before and after the MRI session. We analyzed inter-subject variability in the location of TMS targets and optimized dose based on the maximum task-based connectivity between the left medial amygdala (with the highest functional activity among subcortical areas during drug cue exposure) and frontopolar cortex using psychophysiological interaction (PPI) analysis and computational head modes.

Results: Left medial amygdala with the highest (mean ± SD: 0.31 ± 0.29) functional activity during drug cue exposure was selected as the subcortical seed region. Amygdala-to-whole brain PPI analysis showed a significant cluster in the prefrontal cortex (cluster size: 2462 voxels, cluster peak in MNI space: [25 39 35]) that confirms cortico-subcortical connections. The location of the voxel with the most positive amygdala-frontopolar PPI connectivity in each participant was considered as the individualized TMS target (mean ± SD of the MNI coordinates: [12.6 64.23 -0.8] ± [13.64 3.50 11.01]). Individual amygdala-frontopolar PPI connectivity in each participant showed a significant correlation with VAS scores after cue exposure ($R = 0.27$, $p = 0.03$).

Conclusions: We provide pieces of evidence on variability in targeting and dose levels in a group of people with methamphetamine use disorder and highlight gaps in knowledge regarding research strategies to optimize and tailor NIBS to enhance its therapeutic effects in people with substance use disorder.

Disclosure: Nothing to disclose.

26.3 Brain State-Dependent Responses to Therapeutic Neuromodulation in Substance Use Disorders

Tonisha Kearney-Ramos

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a promising neuromodulation approach that can selectively normalize activity in brain networks disrupted in psychiatric conditions, including substance use disorders (SUDs). However, there are individual differences in response to rTMS, with a subset of individuals showing a treatment response. These variable responses have been attributed to differences in baseline brain state. Our previously published data in cocaine users revealed that baseline cocaine cue reactivity predicted 58% of variability in treatment changes in network activity, i.e., those with high network cue reactivity at baseline had attenuated network cue reactivity after real but not sham inhibitory rTMS, while the inverse was shown for individuals with low network drug cue response at baseline.

Methods: We used these state-dependent brain findings to design an ongoing imaging-rTMS study in near-daily cannabis

users, where the influence of baseline brain state on neural and behavioral response is being tested as a predictive marker for individual differences in treatment effects. Specifically, network fMRI is used to measure brain response to cannabis cues during the Drug Stroop task in cannabis users before and after 10 days of real or sham excitatory rTMS. Preliminary feasibility and network engagement data are presented. Baseline network drug cue reactivity is regressed against change in network reactivity after stimulation to determine whether brain state predicts rTMS response; ultimately, once unblinded we will determine whether network changes are treatment-specific (active vs. sham stimulation effects).

Results: We will present preliminary feasibility and neural network engagement data from an ongoing imaging-rTMS study, and discuss how imaging can be used to inform biomarker development for therapeutic neuromodulation in SUDs. We hypothesize that baseline drug cue reactivity during the Drug Stroop task will be predictive of network changes for cannabis users in the present study.

Conclusions: These findings highlight the importance of using neuroimaging to support biomarker development for therapeutic neuromodulation techniques. While the data presented are preliminary, we also discuss research supporting the potential underlying mechanisms of state-dependent neuromodulation effects.

Disclosure: Nothing to disclose.

26.4 Circuit-Based Transcranial Magnetic Stimulation in Opioid Dependent Individuals: Do We Know Who Will Respond?

Vaughn Steele

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Background: The opioid overdose crisis could be addressed by modulating known dysregulated circuits in opioid use disorder (OUD) with repetitive transcranial magnetic stimulation (rTMS). Is reduced craving induced by rTMS related to changes within the dorsal striatum (DS) a region implicated in cue reactivity? Assessing neuroplasticity in the DS related to cue reactivity after, relative to before, an acute session of excitatory and inhibitory rTMS, targeting the left dorsolateral prefrontal cortex, would help address this question. We predict rTMS will elicit reductions in self-report craving and only inhibitory rTMS will effectively decrease DS activation.

Methods: We recruited methadone maintained participants ($N = 20$) for separate MRI/TMS days where participants completed an MRI cue reactivity task before and after an acute rTMS session. One day included intermittent theta burst stimulation (iTBS) and the other included continuous TBS (cTBS). The DS was measured before and after each rTMS session assessing whether rTMS modulates the DS. About half of our participants, although currently receiving methadone, continued to supplement their opioid use with other opioids (e.g., fentanyl). To date, 18 participants (10 who supplemented opioids) completed their iTBS day and 14 (7 who supplemented opioids) completed their cTBS day.

Results: DS activation was reduced post-iTBS in the group that did not supplement opioids, $t = -3.00$ (6), $p = .02$, cohen's $d = -2.45$ and marginally post-cTBS in the group that did supplement opioids, $t = -2.43$ (5), $p = .06$, cohen's $d = -2.17$.

Conclusions: Although these preliminary data suggest both rTMS sequences reduce cue reactivity in the DS, not all effects reached significance. Nonetheless, an important finding is the specificity of neuromodulation related to rTMS type and whether a participant supplemented opioids. Specifically, individuals in treatment who continue to supplement opioids (and thus at greatest risk of overdosing) responded favorably to cTBS and individuals not supplementing opioids responded favorably to iTBS. Together, a simple urine screen could help individualize rTMS type to maximize intervention efficacy and reduce susceptibility to overdose and death. This is an exciting development and potentially very impactful in addressing the opioid overdose crisis.

Disclosure: Nothing to disclose.

Panel

27. Dopamine, Insulin, and Nutrient Sensing in the Brain: Investigation of the Relationships to Improve Neuropsychiatric Treatments

27.1 Antipsychotics and Brain Insulin Resistance: Is it a Class Effect? Investigation of the Effects of Haloperidol, and Racloperide on CNS Insulin-Mediated Brain Glucose Uptake Using [1-14C]2-deoxy-D-glucose (2DG) Autoradiography

Sri Mahavir Agarwal

University of Toronto, Toronto, Canada

Background: Antipsychotics (APs) are associated with an increased risk of type 2 diabetes. Previous studies examining the effects of APs on insulin and glucose regulation have primarily focused on peripheral pathways. However, insulin receptors are widely distributed throughout the brain, and maybe implicated in AP-induced metabolic dysfunction. In a proof-of-concept study using [1-14C]2-deoxy-D-glucose (2DG) autoradiography, we have shown that an acute dose of olanzapine (OLA) blocks insulin action across multiple regions in the brain. However, it is not known whether other APs induce similar changes. Thus, we want to further explore whether this is a class effect by examining haloperidol (HAL) and raclopride (RAC).

Methods: 2DG autoradiography procedures were used to measure cerebral glucose uptake following an infusion of insulin or vehicle into the third ventricle. Male rats were pretreated with HAL (0.25 mg/kg) or RAC (0.3 mg/kg) or vehicle. Each dose was chosen to reflect clinically relevant D2R occupancy (> 70%). Groups included (central-peripheral) vehicle-vehicle ($n = 6$), insulin-vehicle ($n = 6$), vehicle-HAL ($n = 6$), insulin-HAL ($n = 6$), vehicle-RAC ($n = 5$), and insulin-RAC ($n = 5$). Regions of interests for analysis included the frontal cortex, hypothalamus, hippocampus, and dorsal vagal complex, based on their role in metabolism, energy homeostasis, and cognition. Regional tissue radioactivity was quantified on coded films using the MCID Elite system as an index of glucose uptake.

Results: Cerebral glucose uptake was significantly different between experimental groups across all investigated brain regions (all $p < 0.05$). Post hoc analysis using Bonferroni correction revealed that animals in the insulin-vehicle group showed increased cerebral glucose uptake in all brain regions compared to the other groups (all $p < 0.05$). The other groups did not differ amongst each other.

Conclusions: Intracerebroventricular (ICV) insulin significantly increased cerebral glucose uptake compared to ICV vehicle. This effect was abolished by peripheral HAL and RAC. Hence, acute dosing of HAL and RAC, like was seen with OLA in our pilot study, can black insulin action in multiple brain areas. Our results demonstrate that APs with varying receptor profiles may block

insulin action, suggesting a class effect mediated by D2R antagonism.

Disclosure: Nothing to disclose.

27.2 Obesogenic State, Marked by Down Regulation of Striatal Dopamine D2-Receptors, is Associated With Changes in Striatal Insulin-Related Circuitry and Inability to Adjust Consumption Relative to Metabolic State

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Background: Obesity is associated with addiction-like reward deficits and reduced dopamine D2-receptor (D2R) availability in the striatum. Traditionally, the relationships between weight gain, D2R levels, and reward processing have largely been studied using dietary manipulations to promote obesity. Here we probe these relationships through direct manipulations to the striatal dopamine circuitry.

Methods: Transgenic mice with low striatal D2R availability (iMSN-Drd2 het) were generated through a targeted single allele deletion of the Drd2 gene to indirect pathway medium spiny neurons. Body weight, metabolic and behavioral assays including feeding metabolite testing, locomotor testing, and behavioral economics were examined in these mice. Dopamine transmission was assessed ex vivo using fast-scan cyclic voltammetry (FSCV) and insulin receptor mRNA levels were measured in striatal brain regions. Mice with a deletion of the insulin receptor gene from cholinergic interneurons were generated and underwent a similar battery of testing.

Results: Male iMSN-Drd2 het mice gained more weight than littermate controls and exhibited metabolic signs consistent with obesity. Notably, these mice showed heightened expression of insulin receptor mRNA in the striatum and a stronger potentiation of dopamine transmission in the presence of insulin. These data suggest possible changes in the hedonic value of food, which we assessed using a behavioral economics task prior to the onset of obesity. In this task, male mice with low D2Rs were less motivated to work for food and consumed similar amounts under fed and unfed conditions, indicating an inability to adjust consumption relative to metabolic state. Given the identification of changes to insulin receptor circuitry in iMSN-Drd2 het mice, mice with a selective knockdown of the insulin receptor on striatal cholinergic interneurons were tested. Insulin failed to potentiate dopamine signals in the striatum of these mice, validating the loss of insulin receptors. These mice exhibited heightened D2R mRNA expression in the striatum and normal hedonic responding for food on a behavioral economics task.

Conclusions: Obesity-associated behavioral and circuitry changes are present in male mice with reduced D2Rs even prior to weight gain, and these changes may be related to alterations in striatal insulin receptors.

Disclosure: Nothing to disclose.

27.3 Antipsychotics Impair Central Lipid-Mediated Regulation of Glucose Homeostasis

Margaret Hahn

Centre for Addiction and Mental Health, Toronto, Canada

Background: Antipsychotic (AP)s are associated with adverse metabolic side effects. The AP olanzapine has been shown to impair central insulin and glucose sensing, independently of weight gain, resulting in dysregulated whole-body glucose metabolism. Central fatty acids also strongly regulate glucose homeostasis. In the current study, we examined the effects of two APs, olanzapine and haloperidol, on central sensing of the fatty acid oleic acid and subsequent regulation of peripheral glucose metabolism.

Methods: Gold-standard pancreatic euglycemic clamps and 3-3H-glucose infusions were used to assess glucose kinetics. Male rats were co-treated with a continuous central infusion of oleic acid (Ole) or vehicle (Veh) into the third ventricle and an acute injection of olanzapine (Ola) (3 mg/kg), haloperidol (Hal) (0.25 mg/kg), or vehicle. Groups included (central–peripheral) Veh–Veh ($n = 11$), Ole–Veh ($n = 9$), Ole–Ola ($n = 5$), Veh–Ola ($n = 5$), Ole–Hal ($n = 6$), and Veh–Hal ($n = 4$). The peripheral glucose infusion rate needed to maintain euglycemia during the clamp was used as a measure of whole-body insulin sensitivity.

Results: Intracerebroventricular (ICV) oleic acid caused an increase in peripheral glucose infusion rate (mg/kg/min) compared to ICV vehicle (Ole-Veh 7.82 ± 0.47 vs Veh-Veh 2.44 ± 0.52, $p < 0.001$). This was inhibited by co-treatment with olanzapine (Ole-Ola 1.99 ± 0.46 vs Veh-Veh, $p > 0.05$) or haloperidol (Ole-Hal 2.25 ± 0.58 vs Veh-Veh, $p > 0.1$). ICV oleic acid also suppressed hepatic glucose production (clamp relative to basal: Ole-Veh $79\% \pm 11.93$ vs Veh-Veh $25.23\% \pm 6.19$, $p < 0.001$) and this was prevented by co-treatment with olanzapine (Ole-Ola $28.86\% \pm 6.64$ vs Veh-Veh, $p > 0.1$) or haloperidol (Ole-Hal $22.18\% \pm 7.75$ vs Veh-Veh, $p > 0.1$). ICV oleic acid increased glucose utilization which was no longer observed in the AP co-treatment groups.

Conclusions: Olanzapine and haloperidol disrupt the ability of central oleic acid to regulate peripheral glucose kinetics, resulting in impaired whole-body insulin sensitivity. These findings are in keeping with clinical observations that APs across "classes" and agents impair glucose metabolism. Impairments in brain nutrient sensing have been observed in diabetes. Our findings suggest that disruptions in central lipid sensing represent another mechanism by which APs mediate metabolic adverse effects.

Disclosures: Alkermes: Advisory Board, Consultant (Self).

27.4 Investigating the Link Between Insulin Resistance and Impaired Emotion Processing in Major Depressive Disorder: Preliminary Results From a Human Study

Sharmili Edwin Thanarajah

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Background: Type 2 diabetes and major depressive disorder (MDD) have a high comorbidity rate with fatal outcomes. Despite the long-established association, the underlying mechanisms remain unknown. Rodent studies indicate that central insulin resistance of mesolimbic pathways may lead to a depressive phenotype. However, this interaction has not been explored in humans. We have previously shown, that the effect of intranasal insulin on basal sensory processing and mesolimbic signaling is impaired in insulin resistance. And we demonstrated that impaired reward behavior in insulin-resistant participants can be reversed by the insulin-enhancing GLP-1-analogue liraglutide. In this study, we aim to investigate the association between insulin resistance and anhedonia as well as impaired processing of emotional stimuli. These symptoms play a pivotal role in MDD and are closely linked to impairments in the mesolimbic pathways.

Methods: MDD participants ($n = 26$) and healthy controls ($n = 27$) were recruited. Blood for glucose and insulin was sampled after an overnight fast and the HOMA-IR was used to quantify insulin resistance. The participants performed a facial

emotion recognition task (FERT): They were presented 60 faces with either positive (happy, surprise), negative (sad, angry, fearful), or neutral emotions and were required to identify the emotions. Subsequently, they underwent functional magnetic resonance imaging (fMRI) after intranasal application of either insulin or placebo in a randomized, double-blind design. The study is still ongoing, we here only report the results from the FERT data. We performed linear mixed-effect models to investigate the effect of HOMA-IR on accuracy and reaction time corrected for age, gender, and valence (positive vs. negative).

Results: Insulin resistance significantly affected reaction time ($p < 0.001$). Participants with higher HOMA-IR were slower in recognizing emotional stimuli. We did not find an effect of insulin resistance on accuracy ($p = 0.59$).

Conclusions: Insulin resistance is related to impaired facial emotion recognition. While the accuracy of detecting emotions remained unaffected, the reaction speed to emotional stimuli was impaired. In the next step, we aim to investigate, whether impaired emotion processing is associated with altered insulin response of mesolimbic pathways in the fMRI data.

Disclosure: Nothing to disclose.

Study Group

28. Avolition as a Treatment Target Across Neuropsychiatric Conditions: Characteristics, Determinants, Potential Treatment Strategies, and Perspectives Based on Lived Experience

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Study Group Summary: With the announcement that the FDA has issued an IND for roluperidone, the possibility has emerged that there will be an FDA approved treatment for negative symptoms in schizophrenia. As the clinical trial data to date have suggested that the benefits of roluperidone are most salient for avolition and downstream social challenges, a detailed discussion of avolition in an ACNP study group is particularly timely. We plan to discuss the lifetime course of avolition/apathy, across various conditions defined with DSM diagnoses including schizophrenia, mood disorders, and degenerative conditions. Our topics of interest will be on the behavioral and motivational signature of avolition (including any definitional differences between avolition and apathy), the role of sad/depressed mood in determining avolition across conditions, and a variety of transdiagnostic causal and maintenance factors. We will also discuss the potential causal role of avolition for challenges in an array of everyday outcomes (Social, vocational, everyday activities) across conditions and the relationship of avolition with other elements of negative symptoms, including reduced emotional expression.

There are many potential causes of avolition, including challenges in reward sensitivity, deficits in hedonic capacity such as anticipatory anhedonia, challenges in cognitive abilities such as prospective memory, and, in some conditions, sad moods or depression. The fact that apathy is a long-appreciated feature of degenerative conditions is of considerable importance as well, because transdiagnostic treatments focusing on domains of impaired functioning are now under consideration by regulatory bodies. Understanding whether apathy in dementia and avolition in schizophrenia are closely or superficially related is very important for consideration of development of treatments.

Finally, the importance of avolition at various stages of illness may differ. Avolition at the time of the first identified episode of schizophrenia has wide-ranging functional implications when examined from a longitudinal perspective. In contrast, in individuals with chronic illness, avolition seems to be much more strongly correlated with social challenges compared to other elements of functioning. Thus, the developmental course of avolition from prodromal states to chronic illness is important, while avolition likely has a different developmental course in degenerative conditions.

To address these challenges, we will bring in data from cognitive and affective neuroscience, measurement and statistics, clinical assessment, and pharmacological intervention strategies. We also plan to provide perspectives based on lived experience with negative symptoms, considering the role of mood states, other elements of subjective motivation, and perceptions of disability associated with avolition. The study group will be broadly configured across disciplines, career stage, ACNP membership, and, of course, racial and gender characteristics.

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

Study Group

29. What is the Role of Environmental Chemicals in Neuropsychiatric Disorders and Are We Studying Them in an Effective Manner?

Amy Margolis, Hanna Stevens, Demetrio Sierra-Mercado, Tomás Guilarte, Jonathan Hollander, DuBois Bowman, Kimberly Gray, Joshua Gordon

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Study Group Summary: Neuropsychiatric disorders have complex origins in gene-environment interactions which alter the biology that matters for brain function. The chemical environment includes many components that were not developed to target human biology (e.g., air pollution, pesticides), but they have ended up as neurotoxicants, impacting a broad range of biological processes. Many other environmental factors have received greater attention than environmental chemicals for their role in neuropsychiatric disorder etiology (e.g., stress, alcohol). Reports of large effects of chemicals on neuropsychiatric health are rare, but when these have been observed, they have led to substantial policy changes (e.g., lead in gasoline, use of organophosphate pesticides such as chlorpyrifos). Are investigations of environmental chemicals that may have smaller effects sizes important for the field of neuropsychiatry to make future progress? For example, organophosphate flame retardants and replacement bisphenols may have lower toxicity than lead or chlorpyrifos. Typically, chemical surveillance occurs in adult samples; levels responsible for adult toxicity may be more deleterious to the brain at earlier stages of development due to smaller size, rapid developmental programming, distinct biological targets, and varied metabolic rates. Will better understanding of the impact of chemical exposures on neuropsychiatric outcomes improve treatment of neuropsychiatric disorders and public health measures?

The participating panelists have a wide range of expertise and represent different career stages, scientific perspectives to contribute to a fruitful study group discussion of broad interest to members of the College. Drs. Gordon, Gray, and Hollander represent NIMH and NIEHS program strategic objectives, and each

have distinct expertise in animal models or human epidemiologic studies as they relate to neuropsychiatric illness and/or chemical exposures. Dr. Guilarte, Sierra, and Stevens are actively working on model systems of chemical exposures with translational relevance to human neuropsychiatric health. Dr. Guilarte is a leading expert on lead and other heavy metal neurotoxicity, conducted seminal work showing toxicity of exposure, and can speak to the poorly understood need for ongoing work. Dr. Stevens has conducted studies of the neurodevelopmental effects of the pesticide cypermethrin and is part of a neurotoxicological PCB team in the Iowa Superfund Research Program. Dr. Sierra has independent funding to study effects of glyphosate, the active ingredient in many herbicides, on brain function. Drs. Margolis and Bowman both actively work on human epidemiologic studies in longitudinal cohorts to examine effects of prenatal exposure to pesticides and air pollutants on brain structure and function. Further, they apply advanced statistical approaches to understand profiles of mixtures of exposures or outcomes to better model the totality of the exposome. The research programs and expertise of participants not only reflect the varied locations of their institutions, but also the range of geographic diversity that matters for environmental chemicals.

Disclosure: Nothing to disclose.

Panel

30. What Can Computational Modeling Reveal About the Generality or Specificity of Neurocognitive Risk Factors for Psychopathology?

30.1 Inhibitory Performance on the Go/No-Go, and its Links With Clinical Measures, Reflect Task-General Computational Mechanisms Rather Than Specific Inhibitory Abilities

Alexander Weigard

University of Michigan Medical Center, Ann Arbor, Michigan, United States

Background: The go/no-go paradigm, in which participants respond to one category of stimuli ("go" trials) but must withhold their response to a second ("no-go" trials), is a pillar of research on the neurocognitive basis of impulsivity and associated psychiatric conditions (e.g., attention problems). Although performance on "no-go" trials is assumed to reflect inhibitory ability, applications of computational models such as the diffusion decision model (DDM) suggest it could instead be attributed to a task-general computational mechanism, efficiency of evidence accumulation (EEA).

Methods: To test the predictions of the EEA account, we fit the DDM to six go/no-go data sets: 1) the Michigan Longitudinal Study (MLS, n = 850), a longitudinal study of at-risk youth, 2) the Michigan Twin Neurogenetics Study (MTN, n = 619), longitudinal twin sample, 3) the Self-Regulation Ontology Project (n = 522), an adult MTurk sample, 4) the Adolescent Health Risk Behavior Study (n = 1413), a community sample of adolescents, 5) Brain Basics (n = 94), a sample of college students who binge drink, and 6) the NeuroMod Study (n = 122), a sample of adolescents and young adults.

Results: A meta-analysis revealed a correlation of r = .56 (CI = .46 – .66) between EEA on "no-go" and "go" trials. Multilevel models in longitudinal data suggested that trait "go" and "no-go" EEA measured across ages were strongly correlated (MLS r = .63, CI = .59 – .67; MTN r = .60, CI = .55 – .65). EEA on "go" and "no-go" trials had nearly identical relations with parent-reported ("go" r = -.15, CI = -.22 – -.08; "no-go" r = -.16, CI = -.23 – -.09) and teacher-reported ("go" r = -.23, CI = -.30 – -.15; "no-go" r = -.24, CI = -.31 – -.17) attention problems in MLS and parent-reported attention problems in MTN ("go" r = -.09, CI = -.17 – -.01; "no-go" r = -.09, CI = -.17 – -.01).

Conclusions: Computational modeling of the go/no-go across a diverse array of samples reveals a strong dependence between performance on trials that demand inhibition ("no-go") and those that do not ("go"). Further, computational measures of EEA across "go" and "no-go" trials show similar relations with clinical measures. These findings are consistent with the theory that performance across many inhibition tasks can be attributed to a broader EEA factor and highlight the importance of computational psychiatry for understanding task-general neurocognitive mechanisms.

Disclosure: Nothing to disclose.

30.2 Utility of Computational Phenotyping for Psychiatric Disorders With Low Essentiality: Empirical Findings for Attention-Deficit/Hyperactivity Disorder and Depressive Disorders

Nadja Ging-Jehli

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Background: Attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) involve heterogeneous symptom profiles (phenotypes) that determine treatment efficacy. Computational psychiatry is a nascent research field that offers process-oriented insights into behavior, accounting for individual differences and phenotypes. It underlies the premise that clinical symptoms distinctively manifest in cognitive signatures that are latent but quantifiable by computational parameters. These parameters decompose behavior from neurocognitive tests. Presenting findings from two empirical studies, I illustrate the utility of computational phenotyping for ADHD and MDD, respectively.

Methods: Study 1 included children (both sexes) with ADHD (n = 150) and without ADHD (n = 60), from a broad range of ADHD symptom severity, who performed a continuous performance test (RCT: NCT02251743). Study 2 included 50 adults (both sexes), from a broad range of depressive symptom severity, who performed an approach-avoidance conflict (AAC) task. In both studies, sequential sampling models decomposed individual differences in task performance which were then associated with clinical symptoms using multivariate regressions.

Results: Study 1 showed that lower drift rate, indexing less efficient information integration, was linked to more inattention (R = -0.34, p < 0.001) and more hyperactivity-impulsivity (R = -0.24, p < 0.001). Inattention was additionally linked to slower nondecision time, indexing slower encoding and execution time (R = 0.23, p < 0.001). Study 2 showed that higher starting point bias, indexing instrumental avoidance tendency, was associated with more depression (R = 0.34, p = 0.019) and more anhedonia (R = 0.49, p = 0.001). Depression was additionally linked to slower nondecision time (R = 0.37, p = 0.011). We also identified distinct latent cognitive signatures of different emotion states (e.g., positive affect, sadness) in both studies. Lastly, conventional performance measures (mean reaction times, response frequencies) failed to dissociate between different symptoms.

Conclusions: Computational tools can help to characterize cognitive signatures of phenotypes. This seems particularly promising for disorders with low essentiality. However, sensitive neurocognitive tests and models need to be developed and used.

Disclosure: BGBehavior: Consultant (Self).

30.3 A Preliminary Simulation Study Toward Distinguishing Working Memory vs. Reinforcement Learning Effects on Valenced Learning in Depression and Anxiety Disorders

Peter Hitchcock

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Background: We present the results of a simulation study run to create a new version of the Reinforcement Learning and Working Memory Task (RL and WM; Collins and Frank, 2012). Past work with this task showed that decrements in learning among people with schizophrenia, which had long been attributed to RL, instead arose from decreased WM (Collins et al. 2017). Separately, research has shown that depression and anxiety symptoms relate to greater punishment learning and decreased reward learning (Brown et al., 2021; Pike and Robinson, 2022), which is typically also attributed to RL.

Methods: We developed a modified task to distinguish WM vs. RL contributions to valenced learning by testing 4 task variants through simulation, each involving $N = 1000$ agents. The aim of such a simulation study is to develop task contingencies that can produce key signatures of interest in task behavior. The novel task variant for the first time pits learning to select keys that yield reward (as in the standard task) against learning to avoid keys that yield punishment.

Results: Our simulations addressed a challenge in task design, namely that there are few punishment experiences with which to assess individual differences. We introduced a task break, after which point WM contributions diminish. Simulations confirmed that performance drastically decreases after the break, leading to more punishment experiences over the next trials and thus facilitating investigation of individual differences in punishment learning. Our simulations also reveal learning curves for probability to avoid punishment stratified by set size, mirroring those for proportion correct in the classic task.

Conclusions: Our work attests to the power of simulation studies prior to running an empirical study in order to arrive at task contingencies that allow a novel question to be addressed—in this case, clarifying behavioral signatures of reinforcement learning vs. working contributions to valenced learning. Overall, our modified variant of the RLWM task may shed new light on the source of learning differences among people with elevated depression and anxiety symptoms. This has the potential to directly inform interventions that either seek to remediate subcortical reinforcement learning differences or instead target explicit negative content held in working memory.

Disclosure: Nothing to disclose.

30.4 Improving Brain-Behavior Associations by Strengthening Models of Behavior

Anthony Barrows

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Background: Improving brain-behavior associations (BBAs) may require modelling cognitive sub-processes for some constructs or generalizing to higher-level processes for others. While many efforts to improve BBAs focus on the brain data, the behavioral component receives less attention. Using data from the large ABCD study, we show how use of the racing-diffusion ex-Gaussian model for ABCD (RDEX-ABCD) to analyze Stop-Signal Task (SST) performance improves the strength of associations with brain function.

Methods: Using a Bayesian parameter estimation procedure, 11 parameter distributions related to choice responding and response inhibition were derived for ABCD study participants with SST data available from the study's baseline assessment (mean age $= 9.91 \pm 0.62$ years). We categorized these estimates into "go process" and "stop process" RDEX-ABCD parameters and used regularized regression to predict these estimates using region-of-interest (ROI) task-fMRI data. Task-fMRI regressors were SST contrasts (i.e., correct go vs. fixation; correct stop vs. correct go, incorrect stop; incorrect go vs. correct go, incorrect stop; any stop vs. correct go). We also explored associations between RDEX-ABCD parameters and NIH Toolbox cognitive measures.

Results: To assess the association strength between SST brain activation and RDEX-ABCD parameters relative to empirically derived Stop Signal Reaction time (eSSRT), model parameters were residualized for eSSRT. We found that the RDEX-ABCD model captured all variance explained by eSSRT suggesting that it is successful in decomposing SST performance into more elementary processes. In particular, "go process" parameters were more predictable than eSSRT. Importantly, some of this variance is independent of eSSRT (e.g., perceptual growth rate (PGR): model $R2 = 0.263 \pm 0.014$; PGR residualized for eSSRT: $R2 = 0.102 \pm 0.019$; $n = 4{,}706$). RDEX-ABCD parameters predicted NIH Toolbox measure Total Composite Score (TCS) better than either "stop process" components alone or eSSRT.

Conclusions: Our analysis indicates that decomposing the empirical SSRT into sub-process components increases brain-behavior associations for the SST and suggests that many components with meaningful brain-behavior associations are related to more general choice processes rather than specific to the "stop" process.

Disclosure: Nothing to disclose.

Panel

31. Neurocircuit-Informed Therapeutic Targets in OCD: Animal Models and Human Clinical Approaches

31.1 Pre-Treatment Cognitive Control Network Activity Predicts Rapid Treatment Response Induced by Ketamine in Unmedicated Adults With Obsessive-Compulsive Disorder

Xue Zhang

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Background: Obsessive-compulsive disorder (OCD) shows deficits in cognitive inhibitory control and the underlying cognitive control network (CCN). Ketamine, a fast-acting therapy for OCD, might exert its therapeutic effect via modulation of the CCN. I will talk about in OCD (1) the dysfunction of CCN, (2) ketamine's modulation effect in CCN, (3) predictors of treatment outcome in CCN, and (4) ketamine's modulation effect in CCN as a function of treatment response.

Methods: In a randomized controlled, double-blinded trial of a single infusion of ketamine (0.5 mg/kg) vs an active placebo midazolam (0.045 mg/kg), 45 unmedicated adult OCD patients (age 18-65) were randomly assigned to receive ketamine or midazolam in a 2:1 ratio. OCD severity was measured using Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at several timepoints, including baseline and Day 1 post-treatment. At both timepoints, CCN activation elicited by a Simon task was measured by functional magnetic resonance imaging.

Results: OCD (n = 30) showed significantly lower Simon task-evoked activation in the dorsal anterior cingulate cortex (dACC; F1, 47 = 4.50, p = 0.03), as compared to healthy controls (HC; n = 23). No significant modulation effect of ketamine (n = 18) within CCN was found, as compared to midazolam (n = 9), possibly due to the small sample size of midazolam arm. Among subjects with neuroimaging data, 13 (68%) and one (10%) responded to ketamine and midazolam, respectively. Responders (n = 14) showed significantly lower activation in the right precentral motor region (F1, 23 = 8.31, p = 0.008) compared to non-responders (n = 15), driven by the ketamine arm (F1, 14 = 4.64, p = 0.04). Baseline activation of the right precentral motor region was also negatively correlated with the continuous decrease of Y-BOCS at Day 1 (F1, 23 = 12.77, p = 0.002). Additionally, ketamine differently modulated the right precentral motor region in the responders as compared to non-responders (response by time interaction; F1, 34 = 11.87, p = 0.002), such that responders tended to increase its activation toward HC level but not non-responders.

Conclusions: Restoration of the dysfunctional CCN might be a neural mechanism of ketamine's therapeutic effects in OCD; baseline CCN activity might be used to determine who would respond to ketamine.

Disclosure: Nothing to disclose.

31.2 Characterization of a Novel Brain Circuit Controlling Stress Effects on Action Control: A New Treatment Target for Stress-Induced Inflexible Behaviours?

Elizabeth Manning

The University of Newcastle, Australia, Callaghan, Australia

Background: Acute stress exacerbates the symptoms of psychiatric disorders associated with inflexible behaviour, including substance use disorder, Tourette Syndrome (TS) and obsessive-compulsive disorder (OCD). Much research around the role of stress in these disorders has focused on stress hormones, specifically those involved in the hypothalamic pituitary adrenal (HPA) axis. However, stress hormone changes fail to explain many aspects of stress effects on flexible behavioural control, and therapeutics based on this hypothesis have failed in clinical trials. Recently, a novel circuit was identified linking hypothalamic stress sensitive neurons that initiate the HPA axis, and a nucleus in the indirect pathway of the basal ganglia, which is involved in suppression of actions, however the function of this circuit is unknown. We hypothesize that synaptic activity in this pathway may mediate stress-induced exacerbation of inflexible behaviour relevant to psychiatric disorders, and reflect a new treatment target.

Methods: To examine this circuit, cell-type and pathway specific optogenetic activation and inhibition was performed during baseline and stress sessions. Male and female transgenic mice expressing cre-recombinase in corticotrophin releasing hormone (CRH) neurons were used (n = 6-8/group). Optogenetics was used to examine the circuit connecting these neurons in the paraventricular nucleus (PVN) of the hypothalamus to the globus pallidus externa (GPe) in the indirect pathway, by expressing either the excitatory opsin ChR2 or inhibitory opsin eOPN3 in PVN-CRH neurons and implanting bilateral fiber optic probes above the GPe.

Results: Optogenetic activation of the PVN-CRH- > GPe pathway induces repetitive grooming, which is similar to what is observed following an acute stress. Preliminary findings suggest that inhibition of this PVN-CRH- > GPe pathway suppresses repetitive behavioural responses to stress.

Conclusions: This work adds to a growing literature demonstrating important actions of synaptic projections of PVN-CRH neurons beyond their role in the HPA axis, that have implications for how stress contributes to the pathophysiology of psychiatric disorders. Future work identifying strategies to target these pathways may help guide the development of new treatments that enhance control over symptoms when patients are stressed.

Disclosure: Nothing to disclose.

31.3 Circuit-Based Manipulation of Striatal Dopamine: A State-Dependent and Mood Stabilizing Approach

Susannah Tye

The University of Queensland, St. Lucia, Australia

Background: Deep Brain Stimulation (DBS) is a promising approach for modulating disrupted neural circuit activity in treatment-resistant psychiatric disorders. To fully harness its potential, it is crucial to understand the cellular and circuit mechanisms on which DBS acts in distinct, transdiagnostic neurobiological states. Here, we investigated the effects of ventral tegmental area (VTA) DBS on nucleus accumbens (NAc) dopamine (DA) neurotransmission and behavior within the context of hyper- and hypo-dopaminergic 'mood' states.

Methods: Male Wistar rats received 14 days of methamphetamine (m-amph) or adrenocorticotropic hormone (ACTH) injections (i.p.) to establish mania- or treatment resistant depression-like behavioral phenotypes. Control animals received saline vehicle (i.p.). A non-active VTA sham-DBS group was also included in each condition. Animals received 20 mins of VTA DBS using intermittent burst-like low frequency stimulation (LFS; 10Hz; 2 burst/sec; 300μA) or continuous high frequency stimulation (HFS; 130Hz; 200μA) (n = 10-16). Mania-like hyperlocomotor behavior or forced swim antidepressant-like active stress coping responses were quantified. We then determined effects of DBS on NAc DA dynamics using fast scan cyclic voltammetry and DA receptor/transporter expression using immunohistochemistry.

Results: Hyperlocomotor activity induced by m-amph was significantly reduced by LFS ($p < 0.01$) and HFS ($p < 0.001$) of the VTA, as were m-amph-induced increases in peak phasic NAc DA efflux and reuptake inhibition ($p < 0.05$). LFS also increased DA transporter (DAT) expression in the NAc, reversing the down-regulation induced by m-amph ($p < 0.05$). No significant effects of VTA DBS on locomotor activity or DA were observed for control saline-treated animals. Similarly, in ACTH-treated animals, active stress coping was significantly increased by LFS ($p < 0.05$) and HFS ($p < 0.05$). Within this model, sham-DBS also promoted active stress coping ($p < 0.05$), as did HFS in saline-treated animals ($p < 0.05$). Both LFS ($p < 0.01$) and HFS ($p < 0.05$) DBS conditions enhanced NAc DA release and reuptake.

Conclusions: These results demonstrate that both LFS and HFS DBS of the VTA exerted mood stabilizing effects via direct and differential modulation of phasic NAc DA dynamics, reversing the state-dependent pathophysiological activity unique to each model.

Disclosure: Nothing to disclose.

31.4 Therapeutic Connectivity Target for Deep Brain Stimulation in Obsessive-Compulsive Disorder

Martijn Figee

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Background: Deep brain stimulation of the anterior limb of the internal capsule (ALIC DBS) is an effective treatment for refractory

obsessive-compulsive disorder (OCD). However, a critical next step is to develop a refined targeting template of associated white matter (WM) pathways using high quality diffusion-weighted imaging (DWI) scans prior to surgery. Here, we determined a WM tractography map of effective ALIC DBS in OCD patients using individual 7T DWI to identify therapeutic subcortical and cortical network targets.

Methods: Patients with severe and treatment refractory OCD undergoing ALIC DBS (N = 10, 8 responders, 7 males) received pre-operative 7T MRI scans including DWI. Probabilistic tractography was performed to enable mapping of key fibers pathways and pre-surgical target selection. Following surgery and DBS parameter optimization, we built patient-specific volume of tissue activation (VTA) tractography models using postoperative CT images fused to preoperative T1 and DWI scans. First, we identified the most critical therapeutic network by averaging VTA-whole-brain connections (probtractx2, FSL) in DBS responders only (minimal 35% improvement on Yale Brown Obsessive-Compulsive Scale, YBOCS). Next, we further explored in which network nodes connectivity (tckgen, MRTrix) would be able to best explain clinical improvement across all patients, by correlating connectivity values from VTA to prefrontal and subcortical regions of interest with % YBOCS improvement (repeated measure spearman correlation FDT corrected $p < 0.05$).

Results: Patients responding to DBS shared stimulation of ALIC connections to midbrain, vlPFC, vmPFC and OFC. Connections to bilateral midbrain (lateral and medial), left vlPFC, left thalamus, and right vmPFC/OFC were positively correlated with YBOCS improvement. Early observations suggest that prospective targeting based on these high resolution tractography maps allows for faster and more predictable improvement with minimal post-surgical parameter optimization.

Conclusions: The therapeutic benefit of ALIC DBS for OCD depends on stimulation of midbrain, vlPFC and vmPFC/OFC, which can be targeted using patient-specific tractography. These circuit-response maps can be used to guide clinical targeting and programming decisions and allow for improved and more predictable outcomes of ALIC DBS for OCD.

Disclosure: Medtronic: Consultant (Self).

Panel

32. From Genes to Circuit Function: Neurodevelopmental Trajectories of Neuronal and Synaptic Proteomes

32.1 Abstract not included.

32.2 Abstract not included.

32.3 Activity-Dependent Proximity Labeling of Subcellular Proteomes

Maribel Anguiano

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Background: Recent technological advancements have revolutionized our ability to study the brain at the cellular and molecular levels. However, studying the molecular properties of functionally co-activated groups of neurons remains a challenge. There is a need to develop new methods to tag and isolate specific subpopulations of activated neurons, and then enrich the molecules that are expressed for further downstream analysis. Here we engineered a Calcium-dependent split-TurboID enzyme (CaST) that enables fast and non-invasive tagging of proteins in activated neurons.

Methods: We engineered split-TurboID to detect dynamic changes in intracellular calcium. We fused each half of split-TurboID to Calmodulin or MKII and anchored the components to the membrane or in cytosol. Upon neural activation and calcium influx, split-TurboID reconstitutes and labels proximal proteins in the presence of biotin. Biotinylated proteins can be visualized using streptavidin-AlexaFluor or pulled down using magnetic streptavidin beads. We characterized the performance of CaST in HEK293T cells (N = 332 and 283 cells), rat hippocampal neurons (N = 53 and 75 cells), and mouse prefrontal cortex (N = 218 and 220 neurons from 3 mice).

Results: In HEK293T cells, CaST biotinylated significantly more proteins in cells treated with 10 uM biotin and 5 mM CaCl2 and 1 μM ionomycin versus 10 uM biotin alone, for 30 minutes (***$P < 0.001$, Mann-Whitney U test). In cultured neurons, CaST robustly labeled KCl activated neurons with biotin in as little as 10 minutes, compared to control-treated neurons treated with biotin alone (**$P = 0.002$, Mann-Whitney U test). It could also biotinylate proteins present in neurons activated by 10 μM DOI, a 5-HT2AR agonist, in addition to KCl (***$P < 0.001$, **$P = 0.008$, Tukey's post-hoc multiple comparison's test following a 1-way ANOVA, $F3,44 = 7.373$). Finally in vivo, CaST labeled proteins in psilocybin-activated neurons in mice injected with 24 mg/kg biotin and 3 mg/kg psilocybin, compared to vehicle-injected mice (***$P = 1.6e\text{-}4$, Mann-Whitney U test).

Conclusions: These findings describe CaST as a novel technology for rapid and non-invasive protein labeling in acutely activated neurons in culture and in vivo. Future studies will utilize CaST and similar newly-developed enzymes to tag and enrich proteomes present in activated neural populations.

Disclosure: Nothing to disclose.

32.4 Neuroproteomic Signatures of Development, Neuroplasticity, and Resilience

Yevgenia Kozorovitskiy

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Background: The advent of sequencing has transformed the study of genes and RNA, yet tools for precision proteomics lag behind. We generated subcellular, genetically targeted viral and mouse reporters for proximity labeling and mass spectrometry proteomics. Early expression of APEX enzyme enabled interrogating developmental trajectory of corticostriatal axons. We identified protein dynamics across the first weeks of life, revealing clusters enriched in psychiatric disease risk genes. New studies place the data in the context of modulatory axon development, plasticity and behavior.

Methods: We use Cre-dependent APEX2 mice we developed, crossed to Rbp4- or DAT-Cre. Striatal samples (postnatal d 5-50) are extracted, reduced, enriched on streptavidin beads, TMT-labeled, fractionated, and run on Thermo Scientific Orbitrap Eclipse. To assay resilience, we use a learned helplessness task before proteomics/plasticity tests. Dendrite imaging and glutamate uncaging are done with 2-photon excitation. Glutamate is uncaged near dendrites at 2Hz to induce spine growth, with probability reported. To manipulate plasticity a new photoactivatable Rac1 is used to weaken activated synapses.

Results: We identified 5582 and quantified 2276 axon proteins without missing values across age. Most were dynamic with 1981 significantly changing in time (adjusted $p < .05$). To map expression patterns, we performed hierarchical clustering, revealing 8 trajectories with clusters 2-3 fold enriched in developmental

and psychiatric risk genes. Comparisons to dopamine axon dynamics are ongoing. Our recent unpublished work has elaborated a framework where dopamine is critical for promoting genesis of new spines and synapses. Dopamine responses to aversive stimuli vary among resilient and susceptible mice, predicting levels of plasticity reported by spinogenesis. In weak learned helplessness tests, we found correlations between failures to escape and plasticity before/after ketamine ($R2 = .76$, $p = .005$; $R2 = 0.46$, $p = .04$). Dampening plasticity with PaRac1, we demonstrate it is causal for antidepressant effects (2-way ANOVA, Sidak's $p < .0001$), and are now linking functional insights to our proteomic data.

Conclusions: These data underscore developmental neuroproteomic trajectories as a contribution to individual differences in resilience and variation in plasticity.

Disclosure: Nothing to disclose.

Panel

33. Leveraging Novel Animal Systems to Investigate Autism Risk Gene Function

33.1 Cell Type-Specific Functions of Drosophila Chd1 in Homeostatic Plasticity

Tingting Wang

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Background: Homeostatic synaptic plasticity stabilizes synapses and maintains signaling within an optimal range which is crucial for circuit performance and cognitive flexibility. Synaptic instability are common in neurodevelopmental disorders such as autism and epilepsy. Impairment of homeostatic plasticity has been hypothesized to destabilize synapses, but how synaptic homeostasis is linked to neurodevelopmental disorders at the molecular level remains to be elucidated. Chromodomain Helicase DNA-binding Protein 2 (Chd2) is a master regulatory gene implicated in autism, intellectual disability, and epilepsy. The synaptic plasticity-related function of Chd2 is virtually unknown. Here, we examined the cell type-specific roles of Chd1, tightly conserved Drosophila homologue of mammalian Chd2, in regulating homeostatic plasticity.

Methods: We performed immunohistochemistry and electrophysiological experiments to study the cell type-specific activities of Chd1 in controlling homeostatic plasticity. We used calcium and STED super-resolution imaging methods to investigate the underlying mechanisms of Chd1-dependent regulation. $N = 10$-20 cells per condition. Statistical analysis was performed using Student's t-test or One-Way ANOVA post hoc Bonferroni's test. Both male and female animals were used in the study.

Results: We show that Chd1 is required specifically in glia for the rapid induction homeostatic plasticity, but it functions in the neuron, muscle, and glia for the chronic expression of synaptic homeostasis. We found that Chd1 is required for regulating presynaptic calcium influx and the readily releasable vesicle pool during homeostatic plasticity. We conducted a genetic screen and identified downstream effector genes of Chd1 for regulating homeostatic plasticity. Student's t-test is used for comparisons of two conditions; One-Way ANOVA test is used for comparisons of more than two conditions. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, N.S. not significant.

Conclusions: We provide evidence that Chd1, an epigenetic regulator linked to autism and epilepsy, is required for homeostatic plasticity. We demonstrated that Chd1 exhibits distinct cell-type specific functions in regulating the acute and chronic forms of homeostatic plasticity, highlighting the critical role of intercellular communications in synaptic homeostasis.

Disclosure: Nothing to disclose.

33.2 Abstract not included.

33.3 Abstract not included.

33.4 Impacts of Mutations in ASD-Associated Genes on the Sensory Mechanisms Mediating Social Attachment

Devanand Manoli

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

Background: Social attachments play a central role in most, if not all, levels of human interaction. Devastating conditions such as autism spectrum disorders (ASD) and schizophrenia often manifest with a dramatic collapse of inter-personal interactions. None of the traditional genetic lab model exhibits adult social attachment behaviors. Prairie voles, in contrast, display social monogamy as adults such that mating partners form an enduring pair bond and display complex attachment behaviors. Using the prairie vole for the molecular genetic analysis of social attachment behaviors, we seek to determine the neural and genetic mechanisms that underlie social attachment behaviors, and determine how genetic risk factors for ASD alter sensory mechanisms that contribute to social bonds.

Methods: Using CRISPR-mutagenesis, we generated voles mutant for genes associated with ASD, including alleles of Shank3 and Scn2a. We used battery of behavioral assays to determine phenotypes in attachment and non-attachment behaviors that result from the mutation of ASD-associated genes ($n = 8$-11 per genotype/sex, WT vs mutant/gene, power = 0.8, alpha = 0.05). We have characterized the deficits in pair bonding and adult social attachment behaviors in animals heterozygous for Shank3 and Scn2a null alleles in both sexes. In parallel, we used fiber photometry to examine patterns of activity in brain regions implicated in the sensory processing of cues mediating social interactions in wildtype and mutant animals.

Results: We have identified deficits in social attachment behaviors that result from the heterozygous loss of Shank3 or Scn2a. The behavioral phenotypes we have identified include both sex-specific and developmentally restricted phenotypes. Furthermore, we find that the behavioral deficits we observed correlate with changes in neural activity in distinct cell populations implicated in the processing of sensory cues mediating social attachment behaviors.

Conclusions: Using parameterized behavioral characterization, molecular approaches, and in vivo imaging of neural activity, we can now begin to determine the specific deficits in attachment that result from mutations in genes implicated in autism, and the differences in activity in neuron populations implicated in the processing of social cues that influence social and attachment behaviors.

Disclosure: Nothing to disclose.

Panel

34. Targeting Stress Pathophysiology in Addiction: New Insights From Animal Models and Human Studies

34.1 A Novel Prefrontal Cortex Glucocorticoid and Endocannabinoid Mechanism Critical to the Potentiation

Effect of Mild Stress on Drug Reexposure-Induced Relapse in Rats

John Mantsch

Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Background: The contribution of stress to substance misuse and relapse is complex. While in some cases stressors directly trigger relapse, more commonly they interact with other stimuli to set the stage for drug seeking.

Methods: We have established a rat model to investigate the stage-setting effects of stress on cocaine seeking. Following self-administration under limited daily access conditions, stress does not reinstate extinguished cocaine seeking but rather potentiates reinstatement to an otherwise subthreshold cocaine priming dose, an effect observed in males and females that requires elevated corticosterone (CORT) and endocannabinoid signaling via the cannabinoid 1 receptor (CB1R) in the prelimbic prefrontal cortex (PL). Here we use PL-targeted drug infusions and ex vivo recording in layer V PL pyramidal neurons (PNs) to examine the mechanisms through which CORT promotes drug seeking.

Results: Stress-level CORT does reinstate cocaine seeking alone but potentiates reinstatement in response to cocaine priming injections, an effect also observed with PL CORT micro-infusions. CORT-potentiated cocaine seeking is prevented by PL infusions of the CB1R inverse agonist, AM-251. AM-251 prevents CORT reductions in inhibitory transmission in nucleus accumbens (NAc) core projecting PL PNs ($p < 0.05$). Potentiated cocaine seeking and reduced inhibitory transmission are also observed with PL delivery of membrane impermeable BSA-conjugated CORT ($p < 0.05$), while CORT effects are not prevented by the glucocorticoid receptor (GR) antagonist, RU486 ($n = 4$-6) or GR knockdown in a floxed rat line ($p < 0.05$), suggesting involvement of a non-canonical membrane receptor. CORT effects are prevented by inhibition of Gq signaling using a palmitoylated peptide incorporating the C terminus of Gαq/11 or by the DAG lipase inhibitor, DO-34, and are reproduced by the MAG lipase inhibitor, MJN110 ($p < 0.05$), suggesting involvement of Gq-dependent PL mobilization of the endocannabinoid, 2-AG. Finally, inhibition of core-projecting PL PNs using an intersectional hM4Di DREADD approach prevented CORT-potentiated cocaine seeking.

Conclusions: Our data suggest that during stress CORT promotes drug seeking by mobilizing PL 2-AG through GR-independent Gq signaling thereby attenuating GABA release via CB1R activation and promoting excitability of NAc-projecting PL PNs.

Disclosure: Promentis Pharmaceuticals: Stock / Equity (Self).

34.2 A Ventral Subiculum-Claustrum Circuit is Critical to Incubation of Opioid Seeking After Electric-Barrier Stress-Induced Inhibition of Opioid Self-Administration in Rats

Ida Fredriksson

IRP/NIDA/NIH, Baltimore, Maryland, United States

Background: We recently found a critical role of ventral subiculum (vSub) in incubation of oxycodone seeking after electric barrier-induced abstinence, a procedure mimicking human voluntary abstinence due to adverse consequences of drug seeking. Here, we used this model to further study the role of vSub and its afferent projections in incubation of oxycodone seeking.

Methods: We trained Sprague-Dawley rats ($n = 22$-24, 11-14 females) to self-administer oxycodone (0.1 mg/kg/infusion, 6-h/d) for 14 days. Next, we exposed the rats for 13 days to an electric barrier of increasing intensity (0.1 to 0.4 mA) near the drug-paired lever that caused voluntary abstinence. We tested the rats for relapse to oxycodone seeking without shock or drug on abstinence days 1 and 15. First, we determined projection-specific activation of vSub afferents during incubated oxycodone seeking with Fos plus the retrograde tracer cholera toxin B. Oxycodone relapse was associated with modest (anterior claustrum) and strong (posterior claustrum) Fos induction in claustrum neurons projecting to vSub. Next, we determined the causal role of posterior claustrum in incubation of oxycodone seeking by inactivating the posterior claustrum with the GABAa and GABAb receptor agonists muscimol-baclofen ($50 + 50$ ng/hemisphere).

Results: Incubation of oxycodone seeking after electric barrier-induced abstinence was associated with increased Fos expression in anterior and posterior claustrum ($F[1,20] = 19.5$, $p = 0.001$ and $F[1,20] = 52.7$, $p = 0.001$) and in anterior and posterior claustrum neurons projecting to vSub ($F[1,20] = 13.8$, $p = 0.001$ and $F[1,20] = 17.6$, $p = 0.001$). Muscimol-baclofen inactivation of the posterior claustrum decreased incubated oxycodone seeking on day 15 after electric barrier stress-induced abstinence but not non-incubated oxycodone seeking on day 1 (Muscimol-Baclofen dose x Abstinence day interaction, $F[1,19] = 5.9$, $p = 0.026$ and Muscimol-Baclofen dose x Abstinence day interaction x Lever, $F[1,19] = 24.5$, $p = 0.001$).

Conclusions: Our results indicate that the posterior claustrum is critical to incubation of opioid seeking after voluntary abstinence induced by adverse consequences of drug seeking. Our results also suggest an important role of projections from the claustrum to vSub in this incubation.

Disclosure: Nothing to disclose.

34.3 Abstract not included.

34.4 Identifying Stress Pathophysiology in Addiction and Testing Therapeutic Targets to Reverse These Effects in Humans

Rajita Sinha

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Background: Stress co-occurs frequently in patients with substance use disorder (SUD) and increases risk of addiction and of poor treatment outcomes. However, multilevel stress responses in those with and without trauma and/or SUD and their effects on drug intake are not well characterized. Also, whether drugs such as the alpha2 adrenergic agonist guanfacine (GUA) and the neurosteroid pregnenolone (PREG) may reverse such stress pathophysiology to improve drug use outcomes in patients with SUD is not known.

Methods: Study 1 enrolled 80 individuals with and without trauma (+/-) and SUD (+/-) participated in a novel stress and pain experiment with exposure to three consecutive 3-minute trials of ice cold hand/arm immersion (stress) or warm hand/arm immersion (no-stress/control) trials, presented in a randomized counterbalanced order. Study 2 enrolled women with polysubstance use disorder (PSUD, $N = 74$) and trauma who were randomized to GUA (3mg/day) or placebo (PBO) for 10 weeks to assess cocaine, opioid, cannabis and/or alcohol use outcomes. Study 3 enrolled individuals with alcohol use disorder (AUD, $N = 86$)) who were randomized to 300 mg/day, 500 mg/day or PBO for 8 weeks to assess drinking and related stress outcomes.

Results: Significant stress vs no-stress condition main effects for heart rate (HR), systolic and diastolic blood pressure (SBP/DBP), cortisol, ACTH, anxiety, pain and pain tolerance (p's < 0.01) were observed, and condition X group interactions identified specific physiologic, endocrine, behavioral and subjective dysfunction in the trauma (p's < .05), SUD alone (p's < .01), trauma+ SUD (p's < .01) vs. trauma-/SUD- groups. In study 2, trauma history moderated the positive GUA vs PBO response on number of abstinence days (p < .02) and reduction in polysubstance use per day (p < .01). In study 3, the PREG300 mg/day vs. PBO group showed greatest improvement in reduction of any or heavy drinking days (p's < .001) and in alcohol craving (p < .0001) and depression (p < .01) over the 8-week period.

Conclusions: These findings indicate multi-level specific stress dysfunction in trauma and SUD groups that significantly impact drug craving and use outcomes. Noradrenergic and neurosteroid targets need further exploration in larger scale studies to assess potential benefit in reversing the stress pathophysiology in addiction to improve SUD outcomes.

Disclosures: Embera Neurotherapeutics, Menda Health: Advisory Board (Self). CT Pharma: Grant (Self). AELIS FARMA: Contracted Research (Self). Aptinyx: Other Financial or Material Support (Self).

Panel

35. Collaborations Among Peers: Astrocyte-Neuron Interactions in Plasticity, Behavior and Brain Illness

35.1 Striatal Astrocyte-Neuron Interactions and Psychiatric Disease Phenotypes

Baljit Khakh

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Background: Astrocytes are the predominant type of glia and have coevolved with neurons over ~600 million years. Astrocytes are vital components of the brain and like neurons they display morphologies and properties that differ between brain regions. Both astrocytes and neurons are implicated extensively in brain diseases, including psychiatric disorders. However, little is known about shared or separate astrocytic and neuronal molecular mechanisms and their respective contributions within brain regions relevant to defined psychiatric diseases or their relevant phenotypes in mice.

Methods: We used transcriptomic, proteomic, behavioral, chemogenetic, and electrophysiological methods in adult mice of both sexes. The experimental design assessed how striatal astrocytes contribute to phenotypes related to repetitive and perseverative behaviors. Data from every experiment represent at least four replicates.

Results: We discovered a specific astrocyte subset in the central striatum expressing mu-crystallin (gene: Crym) and found Crym was reduced in post-mortem striatal tissue of obsessive-compulsive disorder (OCD) and Huntington's disease (HD) patients. CRISPR/Cas9-mediated reduction of mu-crystallin in striatal astrocytes in adult mice resulted in perseverative behaviors, increased medium spiny neuron fast synaptic excitation, and dysfunctional excitatory/inhibitory synaptic balance (P < 0.05). Perseveration stemmed from astrocyte-gated control of neurotransmitter release from presynaptic terminals of orbitofrontal cortex-to-striatum projections, and was remedied using presynaptic inhibitory chemogenetics that also corrected the synaptic deficits (P < 0.01). We therefore provide converging molecular, synaptic, circuit, and behavioral mechanisms by which a molecularly defined and allocated subset of striatal astrocytes gate perseveration existing in HD, OCD, and multiple other neuropsychiatric disorders.

Conclusions: We show that distinct astrocyte subsets have consequential and precise biological functions and reveal new astrocyte-neuron interaction mechanisms for potentially treating perseveration associated with diverse psychiatric diseases.

Disclosure: Nothing to disclose.

35.2 The Role of Astrocyte-Secreted Thrombospondins and Their Neuronal Receptor α2δ-1 in Goal-Directed Actions

Cagla Eroglu

Duke University Medical Center, Durham, North Carolina, United States

Background: Goal-directed actions (GDAs) rely on cortico-striatal circuits, particularly the neuronal projections from the anterior cingulate cortex (ACC) to the dorsomedial striatum (DMS). Synaptogenesis underlies the formation and remodeling of neural circuits. Astrocytes induce synaptogenesis during development by secreting thrombospondins (TSPs), which act through the neuronal receptor α2δ-1. However, whether astrocytes promote synaptogenesis in the adult brain to control GDAs is unclear.

Methods: We trained WT, α2δ-1 KO, and TSP1/2-KO mice using fixed ratio (FR) schedules and quantified excitatory synapses in the ACC L2/3 of trained and untrained mice using immunohistochemistry (4-7 mice/condition; unpaired t-tests & Two-way ANOVA with posthoc comparisons). To investigate how the loss of α2δ-1 and TSP1/2 impacts performance, we quantified the max ratio during a progressive ratio (PR) task (20-30 mice/condition, unpaired t-tests). Furthermore, we ablated α2δ-1 specifically in ACC neurons projecting to the DMS (ACC- > DMS) to determine how the circuit-specific deletion impacts excitatory synapses (3-4 mice/condition; Two-way ANOVA & posthoc comparisons) and GDA performance (12 mice/condition; unpaired t-test). All experiments used male and female mice.

Results: GDA training in adult mice induced excitatory synaptogenesis in the ACC of WT mice ($p = 0.012$). The global loss of α2δ-1 reduces this training-induced excitatory synapse formation in the ACC ($p = 0.148$) and increases effort exertion during the PR task as measured by the max ratio ($p < 0.0001$). Trained mice with ablated α2δ-1 only in ACC- > DMS neurons had reduced excitatory synapses compared to WT ($p < 0.0001$) and performed a higher max ratio during the PR task ($p = 0.003$). Surprisingly, we found that constitutive loss of TSP1/2 significantly reduced GDA performance ($p = 0.0007$) but did not impair GDA training-induced excitatory synaptogenesis in the ACC ($p = 0.0037$). Additionally, mice lacking TSP1/2 have increased inhibitory synapse density in the ACC ($p < 0.0001$), which is diminished with GDA training ($p = 0.0018$).

Conclusions: This study demonstrates that new synapses are formed in adult animals to control GDAs. Astrocyte-secreted thrombospondins 1/2 and their neuronal receptor α2δ-1 regulate developmental and adult synaptogenesis pathways to modulate effort control.

Disclosure: Nothing to disclose.

35.3 Neurons and Astrocytes Coordinate Gene Expression Related to Synapses, in Tandem Gene Expression Programs That are Suppressed in Schizophrenia

Steven McCarroll

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Background: Cells collaborate to perform key functions in the brain and other tissues, working together to construct and regulate multicellular structures such as synaptic networks. The transcriptional programs that are coordinated by cells of distinct types are, for the most part, not yet known. While single-cell transcriptomics is now routinely used to describe gene expression by diverse cell types, less is known about how gene expression arises from specific transcriptional programs, nor how such programs are coordinated at a tissue level.

Methods: We used single-nucleus RNA-seq to analyze 1.2 million nuclei from the prefrontal cortex (post mortem) of 191 persons, including 94 affected by schizophrenia and 97 controls, including males and females in both groups.

To increase the rigor and technical comparability of the data from donor to donor, we analyzed sets of 20 brain specimens (each consisting of affected and control donors) at once as a single pooled sample. In subsequent computational analysis, we used transcribed sequence variants (SNPs) to assign each nucleus to the brain donor from whom it came.

We developed novel computational methods to analyze the data. These methods are based on latent factor analysis, which infers underlying factors from many correlated measurements, such as RNA-expression levels.

Results: Cortical neurons and astrocytes exhibited a strong and surprising relationship, even among neurotypical control individuals: in brain samples in which neurons invested more transcription in synaptic components, astrocytes invested more transcription in genes with synaptic functions and in genes for synthesizing cholesterol, an astrocyte-supplied component of synaptic membranes ($p < 10\text{^-}15$).

Expression of the neuronal and astrocytic components of this gene-expression program were reduced in persons with schizophrenia ($p < 10\text{^-}7$ and $p < 10\text{^-}8$ respectively.).

Both the astrocytic and neuronal components of this gene expression program involved genes that contributed disproportionately to genetic risk for schizophrenia ($p < x\ 10\text{^-}18$ for the astrocytic and $p = 10\text{^-}4$ for the neuronal components respectively).

Conclusions: Neurons and astrocytes closely coordinate gene expression related to synapse structure and function.

Astrocytes as well as neurons provide a setting for genetic effects on vulnerability in schizophrenia.

Disclosure: Nothing to disclose.

35.4 Insights From Cellular Models of Astrocyte-Neuron Interactions

Ralda Nehme

Broad Institute of Harvard and MIT, Cambridge, Massachusetts, United States

Background: The maturation of neurons and the development of synapses rely on interactions with astrocytes and other glia. However, many gaps remain in our understanding of the specific cellular programs that mediate these processes. We are using human pluripotent stem cell (hPSC)-derived neurons and astrocytes to better understand how genes accomplish, and genetic variation affects, neuron-astrocyte interactions.

Methods: We performed RNAseq of excitatory neurons and astrocytes in monoculture or coculture and subjected to treatment with antipsychotic medications (including clozapine and haloperidol) ($n = 40$-80 male and female hPSC lines, 120 in total). To confirm the validity and reproducibility of our findings, we used both arrayed cultures (cells from each donor grown separately) and cell village systems (mixtures of cells from many donors grown and processed together). We performed differential gene expression, latent factor, gene ontology and gene set enrichment analyses to identify the impacted genes and pathways.

Results: We found that the presence of astrocytes enhanced synaptic gene-expression programs in neurons. These changes correlated with increased expression, in the cocultured astrocytes, of genes that encode synaptic cell adhesion molecules, including Nrxn1, with established roles in schizophrenia. Overall, both the neuronal and astrocyte gene expression programs were enriched for genes associated with schizophrenia risk. We further found that coculture results in the induction of genes associated with cholesterol biosynthesis in astrocytes and in the (reciprocal) downregulation of cholesterol biosynthesis genes in neurons. The most significantly induced genes in astrocytes included Apoe and Clu (ApoJ), which encode lipoproteins that shuttle cholesterol from astrocytes to neurons. Notably, this same cholesterol-biosynthesis pathway was modulated by clozapine treatment (GO:0006695; adj. $pval = 9.42 \times 10\text{-}21$ in astrocytes).

Conclusions: Our findings suggest that astrocyte expression of genes with synaptic functions is associated with stronger expression of synaptic genetic programs in neurons and suggest a potential role for astrocyte-neuron interactions in schizophrenia, along with a close connection of these programs to regulation of the cholesterol biosynthesis pathway.

Disclosure: Nothing to disclose.

Study Group

36. The Science and Ethics of Measuring and Modeling Individual and Group Behavior

Cheryl Corcoran*, Holly Moore, Elizabeth Stafford, Laura Cabrera, Justin Baker, Tingting Liu, Satrajit Ghosh, Sara Berger

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

Study Group Summary: We have the technology to monitor behavior across space and time with high resolution, across modalities, potentially capturing unique and salient experiences as individuals interact with their social and physical environment. These modalities include face expression, eye movements, spoken and written language (including social media), body kinetics, temperature, gut motility, sweat, breath, peripheral physiology and notably, simultaneous brain activity. The technologies used to measure these include advanced videography and microphones, both wearable and undetectable biosensors, smartphones and closed loop systems.

In parallel with these engineering developments, we can now design and implement computational models with the potential to create a remarkably comprehensive picture of human behavior.

The risk inherent in this, however, is that such a detailed picture can be used to identify individuals, and be potentially used in ways that can be harmful to both individuals and communities. This raises a host of ethical issues, related to informed consent and privacy, individual and community partnership in research design and ownership of data, and concerns related to equity and inclusion, especially in the context of bias in many of these computational models.

The expertise in this study group spans neuroscience, ethics, psychiatry, data science, modeling, engineering and advocacy. Panelists will lead a discussion on these and other pressing ethical

issues related to the use of rapidly evaluating technology to measure behavior. The session will be structured to assure active audience participation.

The session will start with an overview by Dr. Holly Moore of the expanding scope of biosensing and behavioral tracking technologies in research and clinical practice. This introduction is intended to bring the audience up to date on the wide array of data that can be obtained from individuals in their environments - across different levels of intrusion and time frames.

Elizabeth Stafford of NAMI is the moderator and will play an active role in fostering discussion and audience participation. Each study panelist will have a topic for which they take the lead and have a use case. These can be considered as modules. Ms. Stafford will introduce different modules as they become relevant during discussion, ensuring each module is addressed.

The study panelists include:

- Dr. Laura Cabrera, a neuroethicist at the Center for Neural Engineering at Penn State University; she will introduce a framework and lead a discussion on the potential risks and benefits associated with collecting real-time behavior and physiological data on individuals as they interact with environments that may impact privacy, freedom and self-determination.

– Dr. Justin Baker, a physician-scientist who leads the McLean Institute for Technology in Psychiatry, and its conferences; he will lead discussion on a putative ethical checklist for real-world use and on guardrails for return of individual research results
– Dr. Tingting Liu, a postdoctoral fellow in neuroscience at Penn and NIDA; she will lead discussion on bias in models
– Dr. Satrajit Ghosh, a data scientist and engineer at MIT, and lead architect of the Nipype data flow platform; he will lead discussion on data availability and transparency
– Dr. Sara E. Berger, an AI scientist and ethicist at IBM; she will discuss diversity, equity, inclusion and access in research design and data use.

Disclosure: Nothing to disclose.

Study Group

37. Informing Solutions to Challenges Related to the Replicability and Reliability of Neuroimaging Research in Psychiatric Neuroscience

Cameron Carter*, Deanna Barch, Anissa Abi-Dargham, Martin Paulus, Christoph Juchem, Lisa Monteggia, John Krystal

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

Study Group Summary: Over the past 30 years advances in PET and MRI imaging have transformed clinical research into mental and neurodevelopmental disorders. Studies examining the molecular, systems level anatomic features, and function of neural systems have led the advances in our understanding of the pathophysiology of mental illness, identified essential targets for neuromodulation-based interventions, provided biomarkers of target engagement during treatment development, provided individual level data for use in many current efforts focusing on predictive analytics and precision mental health care, and formed the basis of modern "circuit psychiatry". In parallel with the rapid emergence of these new methods this field has also been presented with many challenges. Concerns about factors confounding accurate measurement of imaging parameters, sample sizes and statistical power, the reliably of imaging measures themselves and the benefits and trade-offs of large-scale multisite studies have received repeated scrutiny in the scientific literature as well as in the popular press. This in turn has led to new efforts to establish strategies for study design, acquisition and analysis that optimize sensitivity, reliability and replicability of studies being considered for publication in the major psychiatric neuroscience journals. This study group brings together a group that includes expert practitioners in in human noninvasive neuroimaging as well as editors of major psychiatric neuroscience journals to explore the challenges of reliability and reproducibility of neuroimaging studies as well as potential solutions to these challenges. We will have brief presentations from Dr's Anissa Abi-Dargham (PET imaging), Christoph Juchem (MRS), Deanna Barch (history and challenges of reliability and reliability for clinical imaging studies), Cameron Carter (consensus efforts to enhance reliability and replicability) and Martin Paulus (case study) that will take a deep dive into these issues as well as the role of psychiatric neuroscience journals in setting and updating standards and guidelines for submissions and facilitating documentation and data sharing in order to optimize the utility of non-invasive imaging in advancing the field with group interaction and discussion led by Dr's Monteggia and Krystal.

Disclosure: Nothing to disclose.

Panel

38. A Translational Perspective on Early Risk Markers for Later Psychopathology

38.1 The Effects of Social Determinants of Health on the Development of Early Functional Connectivity

Cynthia Rogers

Washington University School of Medicine, St. Louis, Missouri, United States

Background: Burgeoning evidence supports that social determinants of health like exposure to poverty, substance use, neighborhood crime, and racial discrimination have deleterious effects on child development and psychopathology. fMRI allows investigation of the developing brain and relating this development to risk and resilience factors. Data from longitudinal studies of prenatal and postnatal exposure to social determinants and the link between infant brain development and early childhood psychopathology is reviewed.

Methods: These studies include approximately 400 caregiver-infant dyads that were predominantly Black and enriched for exposure to adversity. Participants were recruited during pregnancy with assessments of income to needs, neighborhood poverty, neighborhood crime, racial discrimination, depression, perceived stress, prenatal cannabis use, and stressful life events. Infants underwent MRI scans as neonates and again at ages 2 and 3 years. fMRI scans were analyzed for resting state functional connectivity of cortical networks and subcortical regions. Maternal inflammatory markers were also obtained. Child social-emotional development was assessed with parent-report measures, and semi-structured interviews. Social disadvantage and psychosocial stress variables were related to brain measures and developmental outcomes.

Results: Prenatal social disadvantage was related to functional connectivity of cortical networks ($R2 = 0.29$, $p < .05$) especially the frontoparietal, default-mode, and ventral attention networks. Social disadvantage and these networks were related to prenatal maternal IL-6 levels. Prenatal crime exposure was linked with altered connectivity between the default-mode network and

thalamus as well as subsequent age 2 externalizing symptoms (ps < .015). Infants with prenatal cannabis exposure had altered connectivity between cortical networks and the hippocampus, amygdala, and cerebellum (p < .05).

Conclusions: Prenatal exposure to social determinant of health factors particularly those that index social disadvantage were related to altered functional connectivity in cortical networks and between subcortical and cortical regions particularly those related to emotion regulation and processing with some data linking these alterations to externalizing symptoms in early childhood.

Disclosure: Nothing to disclose.

38.2 Development of Trait Anxiety and its Associations With Threat-Related Brain Function During Rhesus Monkeys' First Year of Life

Rachel Puralewski

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

Background: Threat-related anxiety responses are innate, trait-like, and emerge early in life. When extreme, trait anxiety is a risk factor for stress-related psychopathology. Our nonhuman primate (NHP) model of trait anxiety resembles childhood behavioral inhibition and shares similar anxiety neural circuitry with humans. Here, we longitudinally characterize trajectories of threat-related responses and associated brain function during the 1st year of life to explore the emergence of individual differences in trait anxiety as it relates to development of psychopathology.

Methods: 35 rhesus monkeys (Macaca mulatta, 24F/11M) were tested at 11, 43, 84, 168, and 365 days old. Each age, monkeys were separated from caregiver or peer, injected with 18flurodeoxyglucose (18FDG) and exposed to 30 minutes of No Eye Contact condition of the Human Intruder Paradigm (NEC). Cooing frequency and freezing duration during NEC were scored. Monkeys were then anesthetized, blood drawn for cortisol measurement, and Positron Emission Tomography (PET) performed to assess 18FDG uptake during NEC. Anatomical MRI scans were collected 1 week later.

Results: With age, cooing during NEC significantly decreased (p < 2e-16), while freezing increased (p < 2e-16). Cortisol levels also increased logarithmically (p < 8e-6). These measures' composite, Anxious Temperament (AT) also increased with age (p < 2e-16). ICC analyses suggested stability within measures: cortisol (.74, p < 1e-8), cooing (.63, p < 3e-5), freezing (.67, p < 3e-6) and AT (.44, p < 0.001). With age, threat-related metabolism in the posterior cingulate (PC) increased significantly, while metabolism in the bed nucleus of the stria terminalis (BST) decreased (p < 2e-16). AT was significantly associated with NEC-related metabolism in PC (p = 0.03), and BST (p = 0.01).

Conclusions: These data describe the early-life development of trait anxiety in NHPs. Behavioral and physiological components of anxiety are relatively stable, suggesting potential to identify individual differences of trait-like anxiety early in the 1st year of life. During maturation, AT relates to threat-related metabolism in BST and PC. This work supports the importance of conceptualizing early-life intervention strategies to reduce risk of developing stress related psychopathology, and indicates potential, early-life neural treatment targets.

Disclosure: Nothing to disclose.

38.3 The Onset of the COVID-19 Pandemic Modulated Trajectories of Infant Negative Affect: Comparisons Within a Longitudinal Sample via Bayesian Models

Koraly Perez-Edgar

Penn State University, University Park, Pennsylvania, United States

Background: The onset of the COVID-19 pandemic, and the ensuing social, economic, and health hardships, contributed to a rise in mental health concerns for individuals of all ages. However, little is known about the impact of the pandemic on infant emotional development. Available studies focus on outcomes at a single time point or use samples that lack non-COVID comparisons. In this study, we examined whether the development of infant negative affect (NA), a risk factor for internalizing disorders, differed as a function of the pandemic onset.

Methods: Data were derived from the Longitudinal Affect and Temperament Study (LAnTs), which assessed longitudinal trajectories of temperament-linked factors associated with psychopathology risk in a large (n = 357) and diverse sample of infants and their caregivers. Caregivers reported on NA at 4-, 8-, 12-, 18-, and 24-months of age via the Infant Behavior Questionnaire (IBQ) and the Toddler Behavior Assessment Questionnaire (TBAQ). Spline models were fit in a Bayesian framework, with pandemic onset (03/11/2020) as the knot point. We first examined "normative" developmental trends in NA among infants who completed data collection prior to COVID (n = 200). We then used these trends to inform our expectations for infants who provided data before and after pandemic onset (n = 157).

Results: Infant who completed the study prior to COVID onset showed a predicted increase in NA over time (Bayes Factor (BF) > 100, 95% credible interval (CI) [.04 - .10]), in line with the larger literature. However, preliminary results suggest strong evidence that for COVID-interrupted infants, NA increased before pandemic onset (BF > 100, 95%CI [.07 - .14]) but then flattened (BF = 0.32, 95%CI [-.02 - .09]) relative to priors. Follow-up analyses will examine whether NA following pandemic onset differed by caregiver anxiety.

Conclusions: Although infants are not consciously aware of the turmoil surrounding the COVID-19 pandemic, it appears that it may have none-the-less altered normative trajectories of affective development. NA is an early-appearing individual predictor for later psychopathology, particularly in the context of environmental stress or distress. These data provide the groundwork to examine how, if at all, the pandemic triggered long-term variation in socioemotional development.

Disclosure: Nothing to disclose.

38.4 Naturalistic Infant Vocalizations at 12 Months: Concurrent and Predictive Validity With Irritability and Psychopathology

Lauren Henry

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

Background: Objective, observable, early risk markers of psychopathology are key to prevention. Infant vocalizations are behavioral candidates; large volumes can be collected with low burden and high ecological validity. We share new, unpublished findings: (1) hand-annotated, naturalistic infant vocalizations (cry, whine/fuss, scream, yell); (2) validity of vocalization types to cross-sectional symptoms; (3) prediction of later psychopathology based on vocalization duration (length of time in ms) and frequency (# of events); and (4) emerging machine learning work validating an existing cry detection model in our infant vocalization data.

Methods: We recruited 356 infants enriched for psychopathology as part of the When to Worry study at Northwestern. Families

completed naturalistic, day-long audio recordings via the Language Environment Analysis system (12 mos). Trained RAs hand-annotated 4 vocalization types (cry, whine/fuss, scream, yell) in 10-min continuous audio segments from 100 infants (60% male) to reliability (70% agreement), identifying frequencies (# of events) and durations (length of time in ms) for each recording. Infant irritability was reported by parent (Multidimensional Profile of Disruptive Behavior-Infant-Toddler), and a standardized lab-based task with presses to elicit frustration was administered (Disruptive Behavior Diagnostic Observation Schedule) (12 mos). One year later, parents were interviewed about child psychopathology (Preschool Age Psychiatric Assessment, 24 mos).

Results: Hand annotation generated 2,429 events: whine/fuss (1,574, 65%), cry (664, 27%), yell (115, 5%), scream (76, 3%). Longer and more whine/fuss were associated with greater lab-based irritability (rs = .25, ps < .01). Infant vocalizations were unrelated to parent-reported irritability (rs -.06 to .01, all ns). Longer (r = .28) and more (r = .26) cry, and longer (r = .27) and more (r = .26) yell, predicted more internalizing symptoms (ps < .05). Longer (r = .26) and more (r = .25) whine/fuss predicted more externalizing symptoms (ps < .05).

Conclusions: Hand-annotated vocalizations show associations with concurrent irritability and specificity with later psychopathology. In future directions, we present a machine learning algorithm to leverage the full, longitudinal dataset (63,000+ hrs) and predict later psychopathology.

Disclosure: Nothing to disclose.

Mini Panel

39. The GLP-1 Paradox: Balancing the Scales Between Weight Loss Breakthroughs and Appetite Suppression

39.1 Hindbrain Glucagon-Like Peptide 1 (GLP-1) Neurons Modulate Behavioral State and Stress Responsiveness Through Highly Collateralized Central Axonal Projections

Linda Rinaman

Florida State University, Tallahassee, Florida, United States

Background: In rodent models, increased GLP1 receptor (R) signaling in multiple distinct brain regions consistently suppresses motivation to obtain and consume chow and/or palatable foods and addictive substances. Conversely, GLP1R signaling in distinct central regions has differential effects on stress-induced activation of the endocrine HPA axis, behavioral arousal/vigilance, and sympathetic outflow. In rodents and primates, including humans, GLP1-positive axons originate from two small clusters of glutamatergic GLP1 neurons whose cell bodies occupy the hindbrain caudal nucleus of the solitary tract (cNTS) and intermediate reticular nucleus (IRt), and whose axons target a large number of subcortical GLP1R-expressing brain regions. GLP1 neurons within the cNTS and IRt are activated/recruited by stressful stimuli in a metabolic state-dependent manner, but it is unknown whether GLP1 inputs to discrete CNS regions arise from discrete subsets of GLP1 neurons that may serve different functions. The present study sought to address this question using an anatomical approach.

Methods: We developed a knock-in rat model (Gcg--Cre) in which GLP1 neurons within the cNTS and IRt express iCre (https://doi.org/10.1016/j.molmet.2022.101631). To determine whether GLP1 axonal inputs to various CNS regions arise from distinct subsets of hindbrain GLP1 neurons, the paraventricular nucleus of the hypothalamus (PVN) and the anterior ventrolateral bed nucleus of stria terminalis (avBST) were microinjected with Cre-dependent retrograde AAVs (i.e., AAVrg-EF1a-DIO-hChR2:mCherry and AAVrg-EF1a-DIO-hChR2:EYFP; Addgene; 400 nl/injection site) that fully label the cell bodies and axon collaterals of Cre-expressing projection neurons. Heterozygous Gcg-Cre rats (N = 9; 3M, 6F) received unilateral AAVrg injections in the PVN and the ipsilateral avlBST (i.e., one fluorescent reporter per site). Rats were perfused transcardially with fixative 3-5 weeks later. Fixed brains and spinal cords were sectioned and processed to enhance EYFP and mCherry fluorescent reporters. In each experimental case, a semi-quantitative approach was taken to map the distribution of labeled GLP1 cell bodies within the cNTS and IRt and the CNS-wide distribution of their axon collaterals, and to document the relative density of axon collaterals within each CNS region (i.e., sparse +, moderate ++, or dense +++).

Results: AAVrg injections targeting the PVN or avlBST produced retrograde labeling restricted to GLP1-positive cNTS and IRt neurons. Cases with injections targeting both structures (N = 5) displayed many double-labeled cNTS and IRt neurons. In all cases, axon collaterals of PVN- and avlBST-projecting GLP1 neurons were present within not only the AAVrg injection site, but also in the spinal cord and in every brain region known to contain GLP1-positive axons.

Conclusions: The observed widespread distribution of axonal labeling achieved after PVN- and/or alBST-targeted injections of AAVrg indicates that individual GLP1 neurons have widely branching axons that target multiple CNS regions. We interpret this as evidence that GLP1 neurons broadcast signals simultaneously to all subcortical CNS targets, consistent with global GLP1R-mediated modulation of behavioral and motivational state, rather than elicitation of specific behaviors or physiological processes.

Disclosure: Nothing to disclose.

39.2 Abstract not included.

39.3 Treatment of Binge Eating Disorder With the GLP-1 Agonist Semaglutide: A Retrospective Cohort Study

Jesse Richards

University of Oklahoma Health Sciences Center, Tulsa, Oklahoma, United States

Background: Binge eating disorder (BED) is the most common eating disorder and yet there is only one FDA-approved pharmacotherapy, lisdexamfetamine, which has some potential for abuse. Topiramate is also commonly prescribed off-label for binge eating but has several medical contraindications and a delayed onset of effect. In contrast, the glucagon-like peptide-1 (GLP1) analog semaglutide has rapid and profound effects on central satiety signaling leading to reduced food intake and has been approved for the treatment of obesity. Based on its efficacy and safety profile, semaglutide would seem to be a potential candidate for the treatment of BED.

Methods: This open-label retrospective study examined the effects of semaglutide on binge eating symptomatology as measured via Binge Eating Scale (BES) scores in individuals with obesity. 98 patients (80 women, 18 men) attending an obesity medicine and bariatric surgery clinic completed the BES on intake and at follow-up. Patients were divided into three groups: those prescribed semaglutide (SEMA; n = 46), those prescribed either lisdexamphetamine or topiramate (Other anti-obesity medications, OAOM; n = 24), and those prescribed a combination of semaglutide with lisdexamphetamine or topiramate (SEMA + OAOM; n = 28). ANCOVA testing was performed with treatment group as the

independent variable and gender, initial BES score, and days between baseline and follow-up as covariates. A subgroup (n = 48; 41 women, 7 men) was identified as likely having moderate to severe BED as defined by BES score of 17 or more on intake.

Results: The ANCOVA revealed a significant effect of treatment on BES score: $F(2,92) = 10.1$, $p < 0.001$. On average, BES scores decreased by 14 points in the SEMA group, 12.9 points in the SEMA + OAOM group, and 5.9 points in the OAOM group. Tukey's HSD post hoc analysis showed a significant difference in BES change score between the SEMA group and the OAOM group ($p < .001$) as well as between the SEMA + OAOM group and the OAOM group ($p < .001$). BES changes between the SEMA group and SEMA + OAOM were not significantly different. In the moderate to severe BED subsample, the ANCOVA revealed a significant effect of treatment on BES scores ($F(2,42) = 8.02$, $p < 0.01$) with the same pattern of effect between treatment type.

Conclusions: Treatment with semaglutide resulted in a significantly greater reduction in binge eating symptomatology compared to compared to those receiving lisdexamfetamine and topiramate, two common anti-obesity medications used to treat BED. This study provides initial human evidence to suggest that GLP-1 receptor agonists may effectively reduce binge eating symptoms. Determining the mechanism by which GLP-1 receptor agonism reduces binge eating symptomatology will be important to understanding the therapeutic effects in BED.

Disclosures: Rhythm Pharmaceuticals: Advisory Board (Self). Rhythm Pharmaceuticals, Novo Nordisk: Speakers Bureau (Self).

Panel

40. Lost in Loss: Preclinical Research on Grief and Prolonged Grief Disorder

40.1 The Pull to Be Close: The Differentiating Effects of Intranasal Oxytocin and Grief Stimulus Type on Approach Behavior and Neural Correlates in Prolonged Grief

Mary-Frances O'Connor

The University of Arizona, Tucson, Arizona, United States

Background: Theoretical models of prolonged grief suggest that maladaptive motivational tendencies (e.g., perseverative proximity-seeking of the deceased; excessive avoidance of reminders) interfere with a person's ability to recover from their loved one's death. We sought to identify behavioral differences and neural correlates between complicated/prolonged grief and healthy bereaved controls based on the tendency to approach or avoid reminders of the loss and test the role of oxytocin in shaping behaviors.

Methods: Thirty-nine widowed older adults completed an approach/avoidance task in a within-subject, double-blind, randomized, counterbalanced design, with an intranasal oxytocin and placebo sessions. In a standardized Approach Avoid Task, participants viewed photos from each category: (1) deceased spouse, (2) living loved one, (3) stranger, (4) grief-related scenes (e.g., tombstone, casket) and (5) neutral scenes. Participants pushed or pulled a joystick based on photo frame color, and relative approach/avoidance bias to each stimulus category was computed using mean response time. Aims were to (1) identify differential effects of complicated grief group and stimulus type on implicit approach/avoidance bias, and (2) investigate interactive effects of complicated grief group, stimulus type, and oxytocin vs. placebo on approach/avoidance bias. (ClinicalTrials.gov Identifier: NCT04505904).

Results: Unpublished data demonstrate that oxytocin decreased avoidance bias in response to photos of the deceased spouse in complicated grief only. Repeated-measures ANOVA specified stimulus and condition (oxytocin or placebo) as within-subjects factors, group as the between-subjects factor, and response bias as the outcome. A main effect of stimulus ($F[4,148] = 8.64$, $p < .001$, partial Cohen's $f = 0.48$) was found, as well as a group x condition interaction ($F[1,37] = 7.28$, $p = .010$, partial Cohen's $f = 0.44$)). That is, oxytocin made the complicated grief group slower to push spouse photos away compared to placebo, and had no statistical impact on bereaved controls.

Conclusions: Findings support the hypothesis that oxytocin has a differential effect on motivational tendency in complicated grief vs. bereaved controls and emphasize the need to consider differences in personalized vs. generic stimuli when designing grief-relevant tasks.

Disclosure: Book royalties: Royalties (Self).

40.2 Abstract not included.

40.3 Prolonged Partner Separation Erodes Pair-Bond Enhancement of Dopamine Release

Zoe Donaldson

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Background: Yearning engages motivational systems that contribute to proximity-seeking and bond maintenance, and the intensity of yearning must subside to successfully adapt to loss. We used monogamous prairie voles to delineate the role of dopamine in pair bond motivation and ask how partner-elicited dopamine release changes as a function of long-term bond disruption.

Methods: We designed a social operant task to disentangle the appetitive and consummatory aspects of social interaction. We used pharmacological approaches to determine the necessity of dopamine D1- and D2-class receptors in partner motivation. We then coupled the fluorescent dopamine sensor, GRABDA, with fiber photometry to measure real-time, in vivo dopamine release as voles sought out and interacted with their partner or a novel vole before and after bond disruption.

Results: Blockade of dopamine D1-class receptors decreased lever pressing for access to a pair bonded partner or a novel vole (RM-ANOVA: effect of treatment $F(1, 13) = 33.5$, $p = 6.30E\text{-}05$, $\eta 2 = 0.72$, $n = 15$).

Via GRABDA, we observed greater accumbal dopamine release for partner lever pressing and door opening compared to the same events in novel trials (paired t-tests: lever press $t(10) = 2.791$, $p = 0.0191$, Cohen's $D = 0.72$; chamber open $t(10) = 2.307$, $p = 0.0438$, $D = 0.57$, $n = 11$). After entering the social chamber, voles were also more affiliative towards their pair bonded partner than a novel vole, which was associated with greater dopamine release (unpaired t-test: $t(7) = 3.268$, $p = 0.0137$, $D = 2.27$).

Finally, we observed a consistent intra-animal decrease in partner-associated dopamine release after four weeks of separation (partner paired t-tests: lever out: $t(10) = 2.88$, $p = 0.0164$, $D = 0.88$; chamber open: $t(9) = 2.403$, $p = 0.0397$, $D = 1.09$; chamber entry: $t(9) = 2.705$, $p = 0.0242$, $D = 0.975$, $n = 11$). A lack of change in dopamine release during novel trials indicates that decreased partner-associated dopamine release is not the product of technical considerations.

Conclusions: Enhanced partner-associated dopamine release and its erosion as a function of partner separation are consistent with a model of dopamine as a reward valuation signal. We believe the enhanced dopamine release when seeking a pair bonded partner provides a potential mechanism to facilitate bond

maintenance whereas the erosion of the signal may enable new bond formation.

Disclosure: Nothing to disclose.

40.4 Neuroinflammatory Processes are Involved in the Loss of Social Bonds

Erica Glasper

The Ohio State University, Columbus, Ohio, United States

Background: Perceived social isolation and loneliness are health concerns that increase risk for many conditions linked to inflammation and behavioral disorders. Understanding biological substrates that drive the negative sequelae following social bond loss is necessary for developing a framework for interventions to reduce health risks associated with loss and loneliness. Using the California mouse, we determined to what extent social bond disruption, in adulthood or early life, augments neuroinflammation and/or behavioral functioning.

Methods: In Experiment 1, we tested the hypothesis that pair bond dissolution enhances neuroinflammatory responses to a peripheral inflammatory stimulus beyond the effects of isolation without a previous bond by examining IBA1+ microglial activity in the frontal cortex and hippocampus after LPS challenge.

In Experiment 2, in mice control-reared (biparental care) or paternally-deprived (sire removed 1 day after birth), we explored the relationships among rearing, social behavior, and neuroimmune correlates stress-reactive brain regions in adulthood.

Results: Experiment 1: LPS+bond dissolution exacerbated microglial branching (i.e., Scholl analysis) in Cg1 beyond LPS +isolation alone (mixed-effects analysis: interaction between social housing and treatment, females: $F(25,40) = 2.3$, $p < 0.05$; $n = 2$-4; males: $F(3,24) = 3.5$,$p < 0.05$; $n = 2$-4).

Experiment 2: A significant relationship between neural tumor necrosis factor-alpha (TNFα) and social behavior was observed. Avoidance behavior toward a novel mouse was significantly correlated with more TNFα in the hypothalamus of paternally-deprived males ($R2 = 0.59$, $p = 0.02$), but not in control males ($R2 = 0.22$,$p = 0.25$), but more time spent with a novel mouse was positively correlated with less TNFα in frontal cortex ($R2 = 0.67$, $p = 0.01$), a relationship that dissipated in paternally-deprived males ($R2 = 0.30$, $p = 0.12$). When social vigilance behavior was observed toward a familiar, same-sex conspecific in control-reared mice, this was significantly correlated with more TNFα in the frontal cortex.

Conclusions: Our findings suggest region-specific neuroinflammatory mediators may be involved in loss that is associated with pair bond dissolution or the loss of a caregiver and reveal therapeutic targets to alleviate some of the neurobiological consequences of bond loss.

Disclosure: Nothing to disclose.

Panel

41. MDMA and Entactogens: Bridging Preclinical and Clinical Science

41.1 Neuromodulatory Basis of MDMA-Induced Structural and Functional Plasticity in Frontal Cortex

Alfred Kaye

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Background: MDMA-assisted psychotherapy recently showed efficacy in a Phase 3 clinical trial for PTSD, and enhances fear extinction in rodents. The precise mechanisms of MDMA role in altering emotional learning and expression are thus a vital question. Here, we utilized cutting edge optical dissection of neuronal activity and structure using in vivo microscopy to identify circuit and subcellular mechanisms of MDMA effects on plasticity in medial prefrontal cortex (mPFC) in the context of fear extinction learning.

Methods: Two-photon imaging of dendrites in Thy1-GFP mice was over the course of 37 days to assess frontal cortex spine density changes following MDMA (vs saline control). Miniscope calcium imaging of mPFC neurons was conducted for 3 days over the course of fear learning and extinction (day 1 - 30s tone with 1mA 1s shock Context A, day 2 - MDMA 7.8 mg/kg or saline 30 min prior to 6 tones in a Context B, day 3 - 6 tones in context B). Neural activity was assessed following non-negative matrix factorization to determine neural response to tones. In a separate cohort, we utilized fiber photometry of fluorescent neurotransmitter release in vivo (AAV-expression GRAB sensors) in response to MDMA and ($n = 8$/drug/sensor).

Results: MDMA induced dendritic spine density increases on days 1 to 7 relative to saline control ($p < 0.001$). Acute administration of MDMA led to decreased activity in medial prefrontal cortex (71% reduced vs 28% control; KS test $p < 1e\text{-}16$ $n = 520$ neurons total). MDMA and another entactogen methylone caused decreased fear expression one day later ($p < 0.05$, $n = 10$ mice per group). mPFC neurons showed increased response to fear extinction cues one day after MDMA exposure, consistent with enhanced representation of extinction memory. MDMA led to supraphysiological release of norepinephrine and serotonin in mPFC, while entactogens showed diversity in norepinephrine release ($p < 0.0001$, MDMA vs MBDB 10 mg/kg).

Conclusions: We identified structural and functional plasticity changes after MDMA administration in the medial prefrontal cortex. MDMA enhanced synaptic density, a marker of potential antidepressant response. Similarly, MDMA enhanced fear extinction learning and lead to increased representation of the extinction memory in this region, opening a critical window into the effects of this potential treatment on learning processes relevant to PTSD.

Disclosure: Transcend Therapeutics, Freedom Biosciences: Contracted Research: (Self).

41.2 Brain-Wide Activity Mapping Reveals a Required Role for the Dorsal Endopiriform Nucleus in MDMA-Evoked Prosocial Behavior

Boris Heifets

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Background: MDMA- (ecstasy) assisted psychotherapy is a potentially effective treatment for PTSD. Its long-lasting therapeutic effects may relate to enhanced feelings of social connection, empathy, and trust during therapy. However, MDMA's abuse potential warrants understanding its mechanism to develop safer, scalable treatments. We previously discovered that MDMA-driven serotonin release in the nucleus accumbens (NAc) is a prerequisite to induce prosocial effects in mice. Here we aim to uncover the broader network of brain regions required to produce MDMA's prosocial effects.

Methods: Brain-wide neuronal activity was mapped in wild-type mice of both sexes following MDMA (7.5 mg/kg ip) or saline given in social and non-social contexts. 2 hours post injection mice

were perfused, brains were labeled for cFos, made optically transparent (iDISCO+), and imaged via light sheet microscopy. We detected active cells, registered brains to standard atlas, and made voxel-wise p-value maps. We validated hotspots with an Ai14 reporter line crossed to TRAP2 mice (Targeted Recombination in Active Populations 2). Active ensembles in TRAP2 mice were chemogenetically silenced by injecting AAV8-DIO-hM4Di-mCherry or AAV8-DIO-mCherry, TRAPing the MDMA social ensemble, and silencing TRAPed regions of interest (CNO vs vehicle) before a 3-chamber sociability test with MDMA or saline.

Results: In both social and non-social contexts, MDMA evoked activity in the ventral lateral shell of the NAc and several prefrontal cortical regions (e.g., prelimbic and orbital areas). However, in the social context MDMA preferentially enhanced activity in the dorsal medial shell of the NAc and the dorsal endopiriform nucleus (dEN)/claustrum. We confirmed these findings twice (with brain slices and whole brains from TRAP2;Ai14 mice). Wide-spread chemogenetic silencing of the mPFC MDMA social ensemble preserved the prosocial effect of MDMA, whereas silencing ensembles in the dorsal medial shell of the NAc or the dEN/claustrum blocked the prosocial effect of MDMA.

Conclusions: Unbiased brain-wide activity mapping revealed focal MDMA social ensembles that are required for MDMA-elicited sociability. Future experiments will better characterize these neurons, revealing their connectivity and roles in social behavior and drug reward, which may lead to improved treatments for PTSD.

Disclosure: Nothing to disclose.

41.3 Behavioral Components of the Therapeutic Effects of MDMA: Evidence From Healthy Human Volunteers

Anya Bershad

UCLA, Los Angeles, California, United States

Background: MDMA-assisted psychotherapy is a promising new treatment for multiple psychiatric disorders. However, the way in which MDMA interacts with the psychotherapeutic process is not known. Here we assessed the effects of MDMA on multiple separate dimensions of social interaction in order to understand how MDMA may work in combination with psychotherapy to produce its beneficial effects.

Methods: Healthy adults were recruited to participate in two double-blind placebo-controlled trials using a crossover design. In Study 1 ($N = 36$), participants received MDMA (0.75mg/kg and 1.5mg/kg), methamphetamine (20mg), and placebo. In Study 2 ($N = 25$), they received MDMA (100mg), methamphetamine (20mg), and placebo. Ninety minutes after consuming the drug, they completed laboratory tasks assessing social behavior. These paradigms included ratings of social emotions, a social feedback task, an affective touch task, and a structured conversation.

Results: Both MDMA and methamphetamine increased self-report ratings of sociability and friendliness ($p < 0.05$). During the social feedback task, MDMA dose-dependently increased positive mood following social acceptance ($p < 0.05$), and similarly increased pleasantness ratings of affective touch ($p < 0.05$). Methamphetamine did not produce either of these effects. Finally, during a verbal interaction, both MDMA ($p < 0.05$) and methamphetamine ($p < 0.01$) increased ratings of closeness with a conversational partner.

Conclusions: These findings suggest behavioral mechanisms through which MDMA may facilitate the therapeutic process. Further, these results suggest that MDMA may share some prosocial effects with methamphetamine. By acting on social emotions, responses to social acceptance, affective touch, and conversation, MDMA may enhance the patient-therapist connection during dosing sessions. Future studies are needed to extend these findings to clinical populations.

Disclosure: Nothing to disclose.

41.4 Primary Findings From a Long-Term Observational Follow-Up Study on MDMA-Assisted Therapy for Treatment of PTSD: MPLONG

Jennifer Mitchell

UCSF, San Francisco, California, United States

Background: In 2017, the US Food and Drug Administration (FDA) granted 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) Breakthrough Therapy designation for the treatment of post–traumatic stress disorder (PTSD). Two phase 3 trials of MDMA-AT versus placebo have been completed and met primary and key secondary endpoints. Further data from MDMA-AT trials are important for evaluating long-outcomes. This presentation will summarize findings from an observational follow-up study (MPLONG) evaluating the long-term safety and efficacy of MDMA-assisted therapy for PTSD.

Methods: MPLONG (ClinicalTrials.gov identifier, NCT05066282) is a non-interventional long-term follow-up (LTFU) protocol for MDMA-assisted therapy clinical trials measuring persistence of effectiveness using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) as a measure of PTSD symptom severity. The primary objective is to evaluate the long-term effectiveness of MDMA-AT for treatment of PTSD as measured by the change in CAPS-5 Total Severity Score (actual or imputed) from the main study Baseline and Study Termination to LTFU.

Results: At the time of abstract submission, data collection is ongoing. Preliminary interim findings showed that participants demonstrated durable improvements in PTSD via CAPS-5 Total Severity scores at least six months after the last dosing session. Effects of treatment were maintained in participants who were followed up within a year of their last dosing session as well as those who were followed more than a year after their last dosing session. There was a low incidence of relapse following treatment response or loss of PTSD diagnosis, and an even lower incidence of relapse following remission.

Conclusions: Preliminary interim findings of MPLONG were consistent with previously published phase 2 data suggesting sustained effectiveness of MDMA-AT for the treatment of PTSD. Final data will be presented during the panel presentation.

Disclosure: Nothing to disclose.

Mini Panel

42. Beyond the Monolith: Individual and Contextual Influences on Depressive and Associated Health Outcomes Within Minoritized Ethnic and Racial Communities

42.1 Intergenerational Sequelae Following Perinatal Experiences of Discrimination: The Importance of Considering Sociocultural Context

Claudia Lugo-Candelas

Columbia University Medical Center, New York State Psychiatric Institute, New York, New York, United States

Background: Poor sleep health in pregnancy may have intergenerational sequalae, including increased risk for neurodevelopmental disorders and poor offspring sleep health. This is of concern, as the first years are critical to the development of sleep-wake patters and early sleep problems are associated to risk for psychopathology. Rodent models support this association, as offspring of sleep-deprived dams show inhibited hippocampal neurogenesis, immature sleep-wake cycles, and deficits in self-regulation. However, large ethnic and racial inequities in sleep health exist, suggesting experiencing discrimination may influence prenatal maternal sleep health, which may be key in the intergenerational transmission of the nefarious effects of discrimination. However, studies have been limited in understanding within-group variation, overlooking important sociocultural determinants of health. Further, studies have not examined mechanisms of transmission, limiting implications for prevention and intervention.

Methods: We aimed to elucidate the relationship between maternal experiences of discrimination, prenatal maternal sleep and associated inflammation, and newborn offspring hippocampal connectivity in a sample of 157 mother-offspring dyads (51.4% females) part of the ECHO-Boricua Youth Study. This intergenerational cohort is comprised by Puerto Rican families living in two sociocultural contexts: Puerto Rico (PR; where they are part of the ethnic majority) and the South Bronx (sBx; where they are a minoritized population). Pregnant participants reported on experiences of interpersonal discrimination and prenatal sleep health and provided saliva samples. A subsample of offspring underwent MRIs at 4-6 weeks of age ($n = 67$).

Results: Logistic regression models demonstrated greater maternal experiences of discrimination were associated to poorer sleep quality and greater sleep. However, there was a significant interaction with study site, such that stratified models demonstrated that discrimination-sleep associations were only significant for participants residing in the sBx, and not for participants residing in PR. For sBx participants, poorer prenatal sleep quality predicted increased prenatal c-reactive protein (CRP) levels, but only among pregnancies involving female fetuses. CRP was in turn associated to decreased resting state connectivity between the left hippocampus and the lateral left occipital cortex in infants.

Conclusions: Experiencing discrimination may be detrimental to prenatal sleep health, yet results highlight the importance of considering the contexts and mechanisms that underlie discriminatory processes to fully understand health disparities. For participants in the sBx, discriminatory experiences may set off a pro-inflammatory cascade that results in atypical fetal neurodevelopment, although analyses are exploratory due to the subsample size. Basic sensory networks develop early, with intrinsic functional connectivity of the occipital lobe having been documented in fetuses. The occipital cortex has important sensory input into the hippocampus and has been found to predict future working memory abilities, an important deficit in neurodevelopmental disorders like ADHD. Findings highlight that achieving sleep health equity may have effects beyond one generation for minoritized groups and suggest important offspring sex effects.

Disclosure: Nothing to disclose.

42.2 Physical Activity, Memory and Depression in Cognitively-Unimpaired Presenilin-1 E280A Carriers With Autosomal-Dominant Alzheimer's Disease

Edmarie Guzman-Velez

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Background: Neuropsychiatric symptoms (e.g., depression) are common in the preclinical stage of Alzheimer's disease (AD), before the onset of cognitive impairment, and significantly contribute to cognitive decline and poorer quality of life. Physical activity has been shown to help reduce depression symptoms and improve cognition in healthy older adults. Yet, less is known about whether physical activity is associated with fewer symptoms of depression and better cognition in individuals who are in the preclinical stage of AD and already have significant accumulation of pathology and evidence of neural injury. We studied carriers of the Presenilin-1 (PSEN-1) E280A mutation from a Colombian kindred with autosomal-dominant AD that causes early-onset AD and healthy non-carriers, and examined whether physical activity was associated with lower symptoms of depression and better cognitive performance in the presence of neurodegeneration.

Methods: 594 PSEN-1 E280A carriers (45% men; $\mu = 30.30$, $SD = 9.61$)) and 653 age-matched healthy non-carriers (45% men; $\mu = 34.36$, $SD = 12.18$) completed the Geriatric Depression Scale to assess symptoms of depression, a word list recall test to measure memory performance, and provided plasma to measure neurofilament light chain (NfL), a marker of neural injury. A subset of those individuals (25 mutation carriers and 36 non-carriers) wore FitBits to measure physical activity for a week. The average number of steps for 7 consecutive days was used as a measure of physical activity. All PSEN-1 E280A carriers were in the preclinical stage of AD, with high levels of pathology but no dementia or significant cognitive impairment.

Results: Compared to non-carriers, PSEN-1 E280A carriers exhibited higher NfL levels ($t(865) = -3.93$, $p < .001$, 95% [-2.20, -.73]), as well as greater symptoms of depression ($t(1223) = -2.67$, $p = .008$, 95% [-.877, -.134]) and worse memory performance ($t(804) = 2.77$, $p = .006$, 95% [.066, .389]). Greater symptoms of depression were associated with worse memory performance ($R2 = .014$, $F(1, 590) = 8.50$, $p = .004$) in mutation carriers only, and not with NfL levels or age ($p > .05$), a marker of disease progression in this population. Greater physical activity was not related to NfL levels nor memory performance ($p > .05$). However, greater physical activity was related to less symptoms of depression in mutation carriers only ($r = -.450$, $p = .024$, 95% [-.724, -.055], and less symptoms of depression were associated with better memory performance ($r = -.348$, $p = .035$, 95% [-.610, .018]).

Conclusions: Our findings indicate that individuals in the preclinical stage of AD with evidence of neurodegeneration and who will invariably develop dementia exhibit higher levels of depression compared to age-matched healthy controls, which is associated with worse memory functioning. Preliminary findings show that engaging in physical activity was associated with lower symptoms of depression, which were in turn related to better memory performance, suggesting that physical activity may be an effective way to reduce depression and aid with memory.

Disclosure: Nothing to disclose.

42.3 Innovation for Me but Not for Thee: The Role of Technology-Based Interventions in the Treatment of Depression for Racial-Ethnic Minoritized Individuals

Lorenzo Lorenzo-Luaces

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Background: The United States (U.S.) is scheduled to become a "majority minority" country in the sense of having a greater proportion of individuals who are minoritized on the basis of race-

ethnicity, underscoring the need to focus on minority mental health, a topic that has been understudied. Technology has revolutionized the treatment of depression in the sense of large knowledge gains regarding the efficacy of digital mental health interventions (DHMIs) for depression. Although reducing disparities in access to mental health care is an aim of research on DMHIs, the extent to which racial-ethnic minoritized (REM) individuals have been represented in this research is unclear.

Methods: In Study 1, we conducted a systematic review of randomized controlled trials of DMHI studies, calculating reporting and representation of different REM groups. In Study 2, a nationally representative sample of participants ($N = 423$; 31% REMs) were surveyed about their willingness to try DMHIs vs. more traditional forms of care. In addition to self-report, we also measured participants' decision to learn more about DMHIs following a behavioral paradigm at the end of the study.

Results: In Study 1, 62 DMHI trials across 17,210 participants were represented. Only 27% of the trials reported race, and only 19% reported ethnicity, although this differed by country ($p < 0.001$). Outside the U.S., reporting of REM status was almost non-existent, either as REM categories or with other identifiers (e.g., place of residence, immigration status). In the U.S., almost all studies reported REM status, but the number of Non-White participants was statistically lower than would be expected when sampling depressed individuals. In Study 2 ($N = 423$), REM participants were either equally or more likely to express willingness to try DMHIs, a finding which was confirmed in their decision to learn more about DMHIs ($p < 0.001$).

Conclusions: REM individuals have been excluded from DMHI studies but this finding does not appear accounted for by a lower willingness or interest to engage with DMHIs.

Disclosure: Syra Health: Consultant (Self)

Panel

43. How Brain Development and Cognition Can Inform Mechanistically-Driven Understanding of Psychopathology and Aid in Precision Medicine Development in Psychosis

43.1 Evidence of Critical Period Plasticity in PFC During the Transition From Normative Adolescence to Adulthood

Beatriz Luna

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Background: Schizophrenia emerges during the transition from adolescence to adulthood indicating that mechanisms supporting this developmental process, notably in late maturing prefrontal cortex (PFC), may be implicated in the disorder. To understand the neural mechanisms underlying adolescent critical period plasticity in PFC, we will use novel multimodal neuroimaging approaches measures of to assess changes in excitatory/inhibitory (E/I) balance in normative development. Methods include Magnetic Resonance Spectroscopic Imaging (MRSI) measuring glutamate (Glu) and gamma-aminobutyric acid (GABA) balance, in conjunction with Hurst analyses of fMRI data, and FOOF analyses of aperiodic EEG data to provide a comprehensive assessment of maturation of E/I balance.

Methods: MRSI, EEG, and fMRI, data were collected on 164 participants (87 assigned female at birth), between 10-32 years of age with up to 3 visits per person at approximately 18mo intervals, for a total of 286 sessions. 7T MRSI data was acquired for a slice across PFC with 24x24 voxels (1.0x0.9x0.9mm) using J-refocused spectroscopic imaging. EEG was collected with a 64-channel system during 8min resting state, allowing analysis of aperiodic activity in PFC electrodes using Fitting Oscillations and One Over f (FOOOF) python toolbox. Hurst analyses were performed on 8min of fixation resting state fMRI.

Results: As previously reported cross-sectionally, we found in longitudinal data that Glu/GABA balance increased into adulthood ($F = 11.04$, $p = 0.001$). FOOOF EEG analyses indicated that the aperiodic EEG slope ("exponent") ($F = 63.16$, $p < 0.0001$) and amplitude ("offset") ($F = 240.07$, $p < 0.0001$) significantly decreased with age across adolescence. The Glu-GABA balance increased with the EEG aperiodic exponent ($\beta = 0.15$, $t = 2.01$, $p = 0.04$) and mediated age-related changes in exponent (ACME: -0.00067, 95% CI [-0.0015, 0.00], $p = 0.032$). HURST increased with age ($\beta = 0.32$, LH $p = 0.00000116$, RH $\beta = 0.29$, $p = 0.0000106$). We will report its association with Glu-GABA balance and EEG FOOOF.

Conclusions: The association between neurotransmitter, brain function, and neural oscillation measures of E/I balance provide compelling evidence of critical period plasticity in PFC impacting hierarchical stages of brain processing, which could reflect impairments underlying the emergence of schizophrenia.

Disclosure: Nothing to disclose.

43.2 Progressive Network Dysconnectivity Related to At-Risk States for Schizophrenia: Multiplex Network and Causal Discovery Analysis of Brain Circuitry for Potential Mechanisms to Develop Treatments and Preventive Strategies

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Background: Granular elucidation of progressive changes in multimodal brain circuitry from adolescence to adulthood in persons with familial high-risk (FHR) for schizophrenia may identify circuits and mechanisms for novel treatments to reduce conversion to psychosis. We present results using locally collected and big data from UK Biobank (UKB).

Methods: We longitudinally examined multimodal MRI data for structural covariance, diffusion and working memory functional connectivity (FC) using graph theoretic methods and independence-based causal discovery analysis among 49 FHR and 38 controls over ≈15 years and supplemented with multiplex diffusion and resting FC data from UKB on persons with psychotic-like experiences (PLE) as a proxy to at-risk state.

Results: The volumes of hippocampal subregions/fields and regions connected to hippocampus showed extensive volume loss, especially in the CA3 and prefrontal regions more prominently around 14 years of age in FHR and in males. The volume loss over 15 years ranged from 150%-600% and significantly correlated with social anhedonia, negative symptoms, working memory and executive function deficits (all $p < 0.01$). Structural covariance networks of these regions showed significantly lower assortativity, clustering coefficient, modularity, betweenness centrality, path length and transitivity but higher eigenvector centrality at 15 years compared to baseline in FHR that correlated with social anhedonia and perceptual aberrations. Causal discovery analysis of working memory FC showed multiple reverberatory circuits in the prefrontal, insula, and temporal regions with high α centrality in controls while FHR had them in the auditory and parietal regions with 3-times lower α centrality. Multiplex network analysis showed longer anatomical distances for mono and polysynaptic edges underlying FC edges in PLE mainly in the prefrontal, parietal and subcortical regions that correlated with overall mental health scores.

Conclusions: Our integrated and multimodal analyses show progressive dysconnectivity of hippocampal circuitry from adolescence to young adulthood with quantifiable metrics. Self-reexciting reverberatory circuits related to working memory deficits, and longer pathways that may delay communication are testable models of neurobiology of risk to develop novel preventive strategies.

Disclosure: Nothing to disclose.

43.3 Development of a Novel Structural Neuroimaging Score to Identify Psychosis and an Assessment of Our Ability to Calculate This Score Using Low-Field MRI

Maria Jalbrzikowski

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Background: Grey matter disruptions in the brain are well-established features of psychosis, but analysis methods and the diffuse nature of the alterations have prevented application of this information in clinical settings. By leveraging methods used in psychiatric genetics (e.g., polygenic risk scores), we integrated multifactorial aspects of brain structure to create a "Psychosis Neuroscore". We tested this score's potential as a marker of disease liability, in adults with psychosis and those at clinical high-risk for developing a psychotic disorder (CHR). Then, in a community sample of young people, we examined the correspondence between Psychosis Neuroscores calculated with low-field MRI in comparison to scores calculated using 3T MRI.

Methods: We extracted measures from T1-weighted scans from multiple studies. For each participant, we created a "Psychosis Neuroscore" from multiple weighted neuroimaging features. We tested the score's ability to differentiate case-control status in adults (Psychosis $N = 618$, Healthy Control $N = 315$), the ability of the score to differentiate CHR individuals ($N = 1792$) from healthy controls ($N = 1377$), as well as conversion status. Finally, in a sample of young people ($N = 32$, 9-26 years), we examined the correlation between the Psychosis Neuroscores derived from MRI images obtained on a 3T scanner and scores calculated from scans obtained on a low-field 0.064T scanner.

Results: The Psychosis Neuroscore significantly differentiated adults with psychosis from controls ($d = 0.56$, $p = 1.3e\text{-}8$, $q = 1.0e\text{-}4$). Elevated Neuroscores were associated with greater positive symptom severity ($\beta = 0.21$, $p = 0.002$, $q = 0.004$). Compared with healthy controls, individuals at CHR exhibited higher Psychosis Neuroscores ($d = 0.40$, $p = 8.1e\text{-}4$, $q = 5.2e\text{-}3$). Higher Psychosis Neuroscores were also associated with psychosis conversion ($d = 0.31$, $p = 2.6e\text{-}8$,$q = 4.1e\text{-}6$). In the sample of young people, Psychosis Neuroscores strongly correlated across methodologies ($r = 0.730$, $p = 3.7e\text{-}5$).

Conclusions: Development of the Psychosis Neuroscore is a significant step towards leveraging the widespread nature of structural brain alterations in psychosis to identify a robust neurobiological marker of psychosis. By calculating this score with low-field MRI, we enhance the real-world applicability of this measure and increase accessibility of biomarkers.

Disclosure: Nothing to disclose.

43.4 Causal Mechanisms of Medial Prefrontal Function on the Self-Agency Network in Schizophrenia

Karuna Subramaniam

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Background: Self-agency is of cardinal importance because it underlies self-awareness in human interactions with the outside world. Patients with schizophrenia (SZ) show severe deficits in self-agency - the experience of being the agent of one's own thoughts and actions. These deficits contribute to psychotic symptoms and distort reality monitoring (distinguishing self-generated from externally-derived information). We have previously found, across fMRI and MEG studies, that the medial prefrontal cortex (mPFC) represents one critical neural substrate in the self-agency network (SAN) in healthy controls (HC). Although mPFC is hypoactive in SZ, we can effectively modulate its activity and connected SAN nodes with high-frequency rTMS. This study is the first TMS clinical trial to provide the first causal test of mPFC function on SAN in SZ.

Methods: In our ongoing RCT, we present data from SZ ($N = 15$), who were demographically-matched to HC ($N = 30$), and randomly assigned to either active 10Hz rTMS to enhance mPFC excitability or to 10Hz rTMS targeting a control rTMS site (outside SAN). Using MEG reality-monitoring tasks from pre-to-post rTMS, we tested how stimulation of mPFC modulates MEG neural activity, and the temporal propagation of neural connectivity and information flow in SAN, compared to subjects in control rTMS.

Results: Active 10Hz rTMS enhanced mPFC excitability (in beta frequencies,12-30Hz, $p < .001$), and induced significant improvements in self-agency abilities ($p < .05$) in HC and SZ, compared to control rTMS. MEG phase transfer entropy (PTE) metrics revealed that rTMS modulated excitability in the mPFC target site, and improved neural information flow to connected SAN nodes (e.g., cingulate gyrus, striatum, superior temporal gyrus) in beta frequencies in HC and SZ ($p < .001$). These rTMS-induced neural improvements generalized to improvements in working-memory, only in subjects who completed active rTMS.

Conclusions: These preliminary data provide the first evidence to suggest that mPFC plays a causal role in SAN, and can be modulated by rTMS to enhance self-agency abilities in HC and SZ. Findings suggest that mPFC activity increases within specific beta frequencies may represent the neural signaling mechanism that is fundamental for modulating self-agency abilities and may, thus, represent a novel biomarker for treatment-response to TMS.

Disclosure: Nothing to disclose.

Panel

44. A Multifaceted Framework for Addressing Heterogeneity in Autism and Related Neurodevelopmental Conditions

44.1 Connectome-Wide Mapping of Heterogeneity Within and Beyond Autism

Adriana Di Martino

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Background: The marked clinical and biological heterogeneity within autism paired with frequent overlaps with other neurodevelopmental conditions, are obstacles for biomarkers identification. This presentation will highlight critical conceptual and methodological steps required to address these barriers by reporting 1) a systematic PRISMA-informed review of studies using data from the autism brain imaging database exchange (ABIDE) repository relative to the non-ABIDE ASD literature, and 2) a connectome-wide association study of autistic traits in a pediatric transdiagnostic sample of ASD and ADHD.

Methods: 1: we conducted a systematic review of the ABIDE-based peer-reviewed studies published in the 10 years since the ABIDE data aggregation as well as of the non-ABIDE literature. Two independent reviewers completed PRISMA guided manuscripts' screening, selection and data extraction. Clustering of data extracted allowed for an unbiased summary. 2: Using low motion resting state data of 166 children with ASD and/or ADHD, an unbiased voxel-wise brain connectome multi-distance-based matrix regression examined functional connectivity association with clinician-based indices autistic traits. We then explored whether genes topographically expressed within the behaviorally-relevant connectivity maps were significantly enriched for genes known to be dysregulated in ASD and/or ADHD.

Results: 1: In the past decade 625 ABIDE and 688 non-ABIDE studies of ASD have been published in similar journals. The ABIDE literature has facilitated a greater number of publications of connectome-based studies using larger samples focusing on development of new multivariate methods. Findings suggest that a) mosaics of hyper and hypo-connections characterize autism b) neurosubtying is a promising approach to specify such mosaicisms, but c) well-characterized data across diagnoses are lacking. 2 connectome wide association analyses revealed that higher internetwork connectivity is associated with more severe autistic traits transdiagnostically. Gene expression analyses on these internetwork maps revealed significant enrichment for genes known to be shared across autism and ADHD.

Conclusions: Advancing our understanding and characterization of the autism brain connectome require large-samples, novel multivariate and transdiagnostic approaches.

Disclosure: Italian version of the social responsiveness scale distributed by organizzazioni speciali: Royalties (Self).

44.2 Abstract not included.

44.3 Abstract not included.

44.4 Etiological Decoding of Brain Functional Dysconnectivity in Autism Via Cross-Species fMRI

Alessandro Gozzi

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Background: Brain imaging studies in autistic individuals have revealed highly heterogenous patterns of atypical or disrupted functional connectivity as measured with fMRI. However, the origin and significance of these heterogeneous findings remain unclear. Leveraging the translatability of fMRI across species, here we clustered functional connectivity alterations in 19 etiologically-distinct mouse models of autism, and successfully decoded the observed dominant patterns of dysconnectivity in fMRI scans of autistic individuals. We also probed the neural bases of the observed fMRI dysconnectivity using mechanistically-relevant chemogenetic manipulations in the mouse.

Methods: The mouse fMRI database consists of 286 mutant mice and 290 control littermates. Connectivity mapping in autism was carried out on $n = 945$ autistic individuals and $n = 1044$ controls from ABIDE-1, 2 and an in-house dataset. Overexpression of DREADD receptors was carried out in neocortex of Vglut1-cre or Parvalbumin-cre mice to increase or decrease cortical excitability, respectively.

Results: Patterns of fMRI connectivity mapped in the mouse database could be clustered into two dominant hypo- and hyperconnectivity subtypes. These subtypes were functionally dissociable and associated with distinct signalling pathways involving synaptic signalling, or transcriptional and immune mechanisms, respectively. Region-specific decoding of these fMRI connectivity patterns in autistic people revealed two groups of individuals ($N = 166$ and $n = 79$, respectively) recapitulating the hyper- and hypo-connectivity patterns identified in rodents. These two subtypes were stable in cross-validation, encompassed dissociable network structure and symptom severity, and were spatially enriched for molecular pathways initially modelled in mice (hypoconnected, synaptic-signalling; hyperconnected, immune mechanisms). Corroborating a synaptic origin for the hypoconnected subtype, chemogenetics studies showed that fMRI hypoconnectivity can be the result of excitatory-inhibitory imbalance during early developmental windows.

Conclusions: Our data show that heterogenous fMRI connectivity in autism encodes for biologically-relevant information, and delineate two reproducible patterns of dysconnectivity underpinned by biologically-distinct etiological mechanisms.

Disclosure: Nothing to disclose.

Study Group

45. Is Psychiatry Ready for the Master Observational Trial?

Aristotle Voineskos*, Carolyn Rodriguez, Louise Gallagher, Stephanie Ameis, John Krystal, Dost Ongur

University of Toronto, Toronto, Canada

Study Group Summary: The Master Observational Trial (MOT) is a new master protocol that hybridizes the power of master interventional trials with the richness of real-world data. The MOT was recently conceptualized in oncology, because of challenges in interventional trials incorporating precision-based approaches, and in connecting those approaches with real world data (i.e., any data that can help advance patient care from sources other than clinical trials, e.g., electronic medical record, mobile devices, insurance claims). While most would agree that advances in therapeutic innovation have lagged in psychiatry, use of the MOT could provide a leap forward in treatment advances for the patients whom we serve, and bring us closer to the pace of innovation of our medical counterparts.

Currently, key domains of clinical psychiatric research tend to proceed in parallel. Efficacy or effectiveness trials tend to focus on a specific intervention in a specific population at a specific time, often with limited inclusion of biomarker or precision medicine data. Biomarker studies tend to attempt to identify a brain signature of disease but do not tend to integrate fully with intervention studies. Research aimed at collecting real world data is often not tied to patient populations engaged in an intervention or biomarker study. While there are now a number of longitudinal cohorts with rich phenotypic data, these cohorts are primarily from the general population, not clinical populations, limiting clinical trial opportunities. The MOT is a prospective observational trial that broadly accepts patients independent of biomarker signature and collects comprehensive data on each to integrate precision medicine/biomarkers, interventional trials and real-world data. MOTs have ten key characteristics: transparent governance, centralized trial administration, traditional interventional trial organization, IRB-approved patient consent and HIPAA privacy authorization, biomarker testing classification, standardized clinical data elements, longitudinal data collection, modular clinical trial design, seamless integration with real world data, and artificial intelligence and machine learning from multiple perspectives.

Expertise in the Study Group cuts across psychosis, addiction, anxiety/mood disorders, RDoC research, and neurodevelopment, biomarker and intervention research. Each participant will discuss the MOT concept as it relates to their expertise and experience of

moving beyond traditional research domains. Some Study Group participants are Editors of key journals, who will describe current limitations in clinical trials and biomarker studies, and how the MOT can help address those limitations. Several participants are also involved in a recently funded six-center MOT in child and youth psychiatry that aims to recruit and follow 4,000 patients receiving mental health care with modular clinical trials – its design, objectives, and the challenges and limitations that are already foreseen will be presented. Simplifying barriers to data sharing, ethics approvals, intellectual property rights, financing, and governance is needed. If done right, the MOT has the potential to build sustainable cohorts of patients that can go beyond identifying biological subtypes, serve to incorporate modular clinical trials that can track change in disease mechanisms, and include real world data meaningful for patient outcomes.

Disclosure: Nothing to disclose.

Study Group

46. Understanding Brain-Behavior Relationships Across Controlled and Natural Settings

Sarah Lisanby, Holly Moore, Karen Bales, Linda Wilbrecht, Shelly Flagel, Alik Widge, Avniel Ghuman

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

Study Group Summary: What is the best way to study brain-behavior relationships? With structured behavioral tasks and laboratory settings, we can precisely manipulate variables of interest while controlling for confounding variables; but this reductionistic approach may lack ecological validity, limiting its value in understanding brain function in the "real world". On the other hand, research conducted in natural or "naturalistic" settings can lack the rigor to determine the effects of the variables of interest. This raises the question, can we integrate the strengths of highly controlled laboratory and minimally intrusive field research to develop ethologically-informed, rigorous behavioral neuroscience that we can apply to multiple species? In this study group, this question will be considered by scientists with expertise in cognitive neuroscience, ethology and translational psychiatry, and who use multidisciplinary approaches and computational tools to move their research between controlled laboratory settings and more complex environments. Dr. Karen Bales of UC Davis will discuss studying multiple species in their natural environments and laboratory settings to understand conserved mechanisms underlying social cognition within ecological and evolutionary contexts. Dr. Linda Wilbrecht of UC Berkeley will discuss using wild mice and ethologically-informed research designs in the laboratory to study the impact of resource scarcity on brain development and decision making. Dr. Shelly Flagel of U Michigan will discuss moving the study of sign- and goal-tracking in animal models to humans from the laboratory to more complex environments in order to strengthen the translational value of the research. Dr. Alik Widge of U Minnesota will discuss using mechanistic laboratory experiments in human and animal models designed to determine effects of neurostimulation on cognitive control to inform modulation of human behavior, captured with passive metrics, as subjects navigate their "real worlds". Dr. Avniel Ghuman of University of Pittsburgh will discuss the value and challenges of building ecologic validity into laboratory research on verbal and non-verbal communication, including facial expression, and the neural basis of visual information processing in humans. He will address the value of computational modeling in establishing rigor in experiments where multiple dynamic variables are under varied degrees of experimental control. Together, the participants will illustrate the challenges and potential value of bringing ethologically-informed approaches and computational tools to translational cognitive neuroscience. Drs. SH Lisanby and Holly Moore of the NIH BRAIN Initiative's Brain Behavior Quantification and Synchronization Program will moderate an interactive discussion with the audience around leveraging and integrating diverse research designs to generate a more comprehensive, mechanistic understanding of the complexity of behavior in dynamic environments.

Disclosure: Inventor on patents and patent applications on electrical and magnetic brain stimulation therapy systems held by the NIH and Columbia University (no royalties): Patent (Self).

Panel

47. Under Pressure: Stress, Fear and the Amygdala

47.1 Cortico-Amygdala Regulation of Fear Propagation

Mihaela Iordanova

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Background: Investigations into the neurobiology of fear have exclusively focused on cues that are directly paired with an aversive event (primary fear cues). However, fear can propagate to secondary cues that are never paired with the aversive event, but are able to elicit fear through their associative links with primary fear cues. These secondary cues can be generated through retrospective (past) and prospective (future) associative links. Understanding the role of basolateral amygdala (BLA) neuronal ensembles activated by primary fear cues in generating secondary fear cues is unknown as is its interaction with the orbitofrontal cortex (OFC) in orchestrating fear propagation.

Methods: We use behavioural methods (higher-order conditioning) to create retrospective and prospective secondary fear cues alongside RNAscope, daun02 inactivation, light sheet theta microscopy and circuit-bases analyses to examine the neurobiology of fear propagation. Both male ($n = 8+$) and female ($n = 8+$) rats were used. Freezing data were analyzed using Analysis of Variance.

Results: Retrospective but not prospective fear propagation critically depends on the integrity of the primary fear cue memory in the BLA (Retrospective: $F(1, 40) = 6.560$, $p = 0.014$, effect size $= 0.141$; Prospective: $F(1, 32) = 0.508$, $p = 0.481$, effect size $= 0.016$). BLA neurons activated by retrospective and prospective fear cues project to the OFC (Retrospective: 15.52%, Prospective: 15.86%, Overlap: 8.08%) and silencing BLA-- > OFC or OFC-- > BLA pathways disrupt retrospective fear propagation (BLA-- > OFC: virus: $F(1, 37) = 4.352$, $p = 0.044$, effect size $=0.105$, group x virus interaction: $F(1, 37) = 5.502$, $p = 0.025$, effect size $= 0.130$. OFC-- > BLA: virus main effect: $F(1, 33) = 9.617$, $p = 0.003$, effect size $= 0.225$, group x virus interaction $F(1, 33) = 4.798$, $p = 0.035$, effect size $= 0.127$) whereas only the former pathway disrupts prospective fear propagation (BLA-- > OFC: virus main effect: $F(1, 31) = 6.555$, $p = 0.016$, effect size $=0.175$, group x virus interaction: $F(1, 31) = 6.834$, $p = 0.014$, effect size $=0.181$).

Conclusions: Our data show how fear propagates at the behavioural and neural level. We uncover a novel neural locus of fear regulation, the OFC and its reciprocal connection with the BLA, as well as show that retrospective and prospective fear propagation depends differentially on the original fear memory.

Disclosure: Nothing to disclose.

47.2 Amygdala-Striatal Circuitry Modulating Choice Under Risk of Punishment

Andrew Holmes

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Background: Behavior elicited by the same stimulus can result in either pleasant or unpleasant outcomes on different occasions. Brain systems that weigh the potential for varying outcomes and guide behavior accordingly are critical to optimizing some adaptive needs (e.g., foraging) while avoiding others (e.g., predation). In humans, pathological dysregulation of these systems can produce behaviors characterized by excessive risk-aversion, as seen in certain anxiety disorders, or, conversely, risk-insensitivity, as in alcohol and substance use disorder.

Methods: It remains unclear whether subpopulations of BA neurons defined by their projection targets exhibit responsivity and mixed selectively as animals learn about and respond to stimuli associated with opposing – rewarding or punishing – outcomes. Therefore, to address this question in the current study, we performed cellular-resolution and population-level in vivo Ca2+ imaging of BA and NAcS-projecting BA neurons as animals made a choice between a high-value, but potentially punished, and a low-value but safe, reward.

Results: We found that NAcS-projecting BA neurons become active as animals exhibit a learned preference for a high-value reward, over a low-value reward. This value-related bias in neuronal activity is absent when the high-value reward is associated with potential punishment. Optogenetic excitation of NAcS-projecting BA neurons caused maintenance of preference for the high-value reward, despite the risk of punishment.

Conclusions: Our data reveal a critical role for NAcS-projecting BA neurons in dynamically adjusting choice for risky rewards. These findings suggest this neural circuit could be compromised in alcohol and substance use disorder.

Disclosure: Nothing to disclose.

47.3 Stress and Threat Memory Generalization in Mice: Examining the Molecular and Circuit Microstructure Mechanisms

Sheena Josselyn

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Background: Threat memories generalize following stress. Here we examined the mechanisms by which stress generalizes threat memories from a novel angle. Neuronal ensembles (engrams) store memories. Despite many studies confirming the critical importance of engrams, little is known about how engrams supporting threat memories are impacted by stress at the level of microcircuits and molecules.

Methods: We tested mice in a threat discrimination paradigm in which one tone (Conditioned Stimulus -; CS-) is presented alone and a second tone (CS+) is presented with a footshock (unconditioned stimulus, US). During the subsequent test, precise threat memory is defined as mice showing defensive freezing when presented with the CS +, but not CS-, tone. Generalized threat memory is defined as mice freezing similarly to both the CS + and CS-. Unlike Control mice that showed a precise threat memory, mice (both male/female) restrained or administered systemic corticosterone (CORT) before training showed generalized threat memory. We investigated examined the mechanisms mediating this effect using a range of pharmacological, molecular (overexpression, CRISR), optogenetic, chemogenetic and visualization (activity tagging, immunohistochemistry, fiber photometry with GCaMP and endocannabinoid sensors and slice electrophysiological) methods.

Results: We found that stress and CORT increases the overall size of engram neurons in a lateral amygdala (LA) supporting a threat memory. In control mice inhibitory parvalbumin (PV) positive neurons constrain the size and sparsity of the LA engram. By contrast, stress increases levels of the endocannabinoid ligand anandamide (AEA), which disrupts PV function, leading to a larger LA engram. Knocking out cannabinoid type 1 (CB1) receptors in PV neurons in the LA not only restored the overall size of the LA engram supporting threat memory, but also restored threat memory precision.

Conclusions: Together, these findings show stress increases AEA signaling in the LA, which results in decreased PV output onto excitatory neurons. Consequently, more neurons get recruited or allocated into the engram supporting a threat memory, resulting in generalized threat memory expression. The results of these studies may provide a foundation for developing targeted treatments for disorders in which threat memory is generalized, such as PTSD.

Disclosure: Nothing to disclose.

47.4 Identification of a Stress-Integratory Subregion of the Basolateral Amygdala

Matthew Hill

University of Calgary, Calgary, Canada

Background: In humans and rodents, the amygdala is rapidly activated by stress and hyperactivated in conditions of pathological stress or trauma. There is, however, a paucity of information regarding the subregions and circuits of the basolateral amygdala (BLA) explicitly activated by stress, and of their role in governing HPA axis responses to stress.

Methods: In adult rats, we used fiber photometry to record temporal patterns of activation within the BLA to novel stimuli: swim, restraint, shock, bobcat odor, citral odor, and crackers. We tested if systemic administration of propranolol, a B-noradrenergic antagonist, altered temporal patterns of restraint-induced activation. In a different subset of rats, brains were collected to plot the spatial pattern of activation via labelling of FOS+ neurons following exposure to each stimulus. Using restraint as a model for stress, we then used retrograde tracing (CTb) and immunohistochemistry (cFos) to map topographical distribution and circuit-specific activation of BLA projection populations targeting 6 downstream brain regions. Finally, we employed chemogenetics and optogenetics, respectively, to inhibit or stimulate BLA projection neurons, and determine the influence on stress-induced activation of the HPA axis.

Results: While all novel stimuli were found to activate BLA projection neurons in the lateral amygdala, aversive/stressful stimuli exclusively activated BLA projection neurons in the medial basal region of the BLA (mBA). Projection neurons in the mBA exhibited unique spatial and temporal patterns of activation to different aversive stimuli. Administration of propranolol reduced stress-induced activity, as measured using fiber photometry, indicating norepinephrine contributes to this response. Exposure to restraint stress increased FOS expression in discrete BLA projection populations emanating from the mBA. Chemogenetic inhibition of projection neurons in the mBA attenuated stress-induced corticosterone secretion, while optogenetic activation of the mBA triggered HPA axis activation.

Conclusions: These data identify the mBA as an anatomically diverse subregion of the BLA that is robustly recruited by stress exposure to drive changes in HPA activity through widespread projections to multiple downstream targets.

Disclosure: Nothing to disclose.

Mini Panel

48. Maternal Immune Activation and Offspring Development: A Cross-Species Investigation to Guide Our Thinking During a Unique Moment in Time

48.1 Risk and Resilience to the Neurodevelopmental Effects of Maternal Immune Activation in Isogenic Mouse Models

Urs Meyer

University of Zurich, Zurich, Switzerland

Background: Infectious or non-infectious maternal immune activation (MIA) during pregnancy is a transdiagnostic risk factor for neurodevelopmental and psychiatric disorders in the offspring. Despite the increasing evidence for significant health consequences, the majority of MIA-exposed offspring will not develop overt pathological sequelae, suggesting that there is a substantial degree of resilience to the neurodevelopmental effects of MIA. We recently provided experimental evidence for this hypothesis using a mouse model of viral-like MIA, which revealed the existence of subgroups of adult offspring characterized by the presence or absence of behavioral, transcriptional and inflammatory anomalies even under conditions of genetic homogeneity. The present study aimed to investigate the developmental ontogeny and mechanisms underlying dissociable consequences of MIA in an isogenic mouse model of viral-like MIA.

Methods: In a first cohort, pregnant C57BL/6N mice were treated with the viral mimetic, poly(I:C) (5 mg/kg, i.v.) on gestation day 12, whereas control dams received vehicle (sterile saline solution) on the same gestational stage. Male and female offspring of MIA-exposed and control dams were subjected to a social interaction test at juvenile age (postnatal day [PND] 25) and were then left to mature into adulthood. At adult age (PND 100 onwards), the same offspring were tested in a number of behavioral tests, including open field exploration, social interaction, prepulse inhibition and working memory. A second cohort of MIA-exposed and control offspring were generated for analyses of hypothalamic oxytocin-expressing cells and plasma oxytocin levels after the social interaction test at juvenile age (PND 28). In the firsts cohort, the sample sizes were $n = 46$ (22 males and 24 females; from 8 litters) MIA offspring and $n = 30$ (14 males and 16 females; from 6 litters) control offspring in the first cohort, and $n = 16$ (8 males and 8 females; from 8 litters) MIA offspring and $n = 10$ (5 males and 5 females; from 5 litters) control offspring in the second cohort.

Results: Regardless of sex, MIA-exposed offspring could be stratified into two subgroups with low sociability ($n = 26$) and high sociability ($n = 20$) scores at juvenile age (PND21). MIA-exposed offspring with low juvenile sociability scores differed from control offspring (=30) with regards to social approach behavior at juvenile age ($p < .001$). As adults, MIA-exposed offspring with low juvenile sociability scores continued to display reduced social interaction compared to control offspring and MIA-exposed offspring with high juvenile sociability scores ($p < .001$) and also displayed significant deficits in prepulse inhibition ($p < .01$) and working memory ($p < .05$). Hypothalamic oxytocin-expressing cells and plasma oxytocin levels were reduced in MIA-exposed offspring with low juvenile sociability scores (oxytocin-expressing cells: $p < .01$, plasma oxytocin: $p < .05$), but not in MIA-exposed offspring with high juvenile sociability scores.

Conclusions: Our findings provide experimental evidence suggesting that the presence of social impairments at juvenile age is predictive of multiple behavioral dysfunctions in adulthood and associated with impaired production of the pro-social hormone, oxytocin. High social functioning at juvenile age may represent a resilience-promoting factor against long-term behavioral abnormalities after MIA.

Disclosure: Nothing to disclose.

48.2 Abstract not included.

48.3 Maternal COVID-19 During Pregnancy is Not Directly Associated With Negative Infant Neurodevelopmental Outcomes But Poorer Maternal Mental Health is Associated With Poorer Temperament and Socio-Emotional Functioning

Clare McCormack

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Background: The health of infants exposed to maternal COVID-19 during pregnancy is a priority given the number of pregnant individuals who have contracted this disease. While vertical transmission is exceedingly rare, COVID-indued maternal immune activation (MIA) is well-documented and MIA could play an indirect fetal programming role. MIA secondary to other viral infections has been linked to offspring negative neurodevelopmental outcomes and increased risk of disorders such as autism and schizophrenia. Here, we investigate whether maternal COVID-19 during pregnancy is associated with altered developmental outcomes at 6 and 12 months. Secondarily, we investigated possible effects of infection and/or pandemic environment on maternal mental health, given known association between maternal wellbeing and child outcomes.

Methods: We present data from two distinct samples of mother-infant dyads with (CV+) and without (CV-) maternal COVID during pregnancy: NYU's COPE ($n = 92$ CV+, $n = 183$ CV-) cohort representing dyads from NYC, and Columbia's COMBO ($n = 274$ CV+, $n = 519$ CV-) cohort, representing dyads from NY, UT, and AL. Our primary outcomes were parent-report scales at 6 months to measure temperament (IBQ-R) and social-emotional development at 12 months (BITSEA) in COPE, and development (ASQ-3) and socioemotional functioning (ASQ-SE) in COMBO. Maternal mental health was investigated using composite scores. In COPE, a global BSI average score was computed from three subscales (anxiety, depression, somatization). In COMBO, a z-score composite was generated from PHQ9, BSI, PCL-5, PSS and STAI. Finally, the association between maternal mental health and infant outcomes was tested.

Results: No differences between CV+ and CV- groups were observed on any developmental outcome. There were also no group differences in maternal mental health composites in either cohort. A significant association between poorer maternal mental health and poorer infant outcomes was observed on two IBQ-R subscales (effortful control: $F = 7.26$, $p = 0.009$; negative affect: $F = 8.31$, $p = 0.006$) in the CV+ but not CV- group in COPE. In COMBO, no significant association was observed between maternal mental health and any of the five ASQ-3 subscales, but poorer mental health was associated with poorer ASQ-SE scores in both CV+ ($F = 12.43$, $p = 0.0007$) and CV- groups ($F = 12.74$, $p = 0.0004$).

Conclusions: In two samples representing over 1,000 mother-infant dyads from three states, 34% of whom contracted COVID-19

during pregnancy, we show a lack of direct effect of infection on infant outcomes, which is overall reassuring to pregnant individuals. However, our data represents early timepoints. Additionally, we show maternal mental health, which is widely reported to have been worsened by the pandemic, was predictive of poorer developmental outcomes in both cohorts. Continued research is critically needed to determine the potential adverse health consequences as the COVID-19 generation ages into various risk windows. MIA has been associated with increased risk for later psychopathology; the present studies thus far have only assessed neurodevelopment at very early time points. Continued research is therefore needed to determine the potential adverse health consequences as the COVID-19 generation ages into various risk windows.

Disclosure: Nothing to disclose.

Panel

49. The Habenula and PVT Roles in Diverse Behaviors Across Ages: Data From Neuroimaging and DBS Studies in Clinical Cohorts

49.1 Anatomy and In Vivo Image Segmentation of the Human Habenula and Paraventricular Nucleus of the Thalamus

Junqian Xu

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Background: The Habenula (Hb) and paraventricular thalamic nucleus (PVT) are midbrain hubs for modulating motivated behaviors. They are located along the dorsomedial wall of the 3rd ventricle. Recently, evidence from small animal studies has implicated PVT in social behaviors and points to a concerted circuit involving the prefrontal cortex with direct connections to PVT and Hb. However, the thin and elongated shape of the human PVT is challenging for in vivo human neuroimaging studies. Existing human PVT studies have used atlas-based approach to define the PVT nuclei, which could lead to substantial partial volume contamination, and do not take into account of the large variability of the Massa intermedia (MI). Leveraging our prior experiences in Hb segmentation, we propose a heuristic segmentation approach to better delineate PVT for in vivo human neuroimaging.

Methods: Locally collected (n = 10, age 38 – 56 yrs) HCP-style structural MRI (T1w and T2w, 0.8 mm iso.) and high resolution (~ 2 mm iso.) resting-state fMRI data. For each subject, we used a heuristic PVT segmentation approach to define the PVT and other regions of interest (ROIs), such as the Hb, centromedial thalamic nucleus, and anterior thalamic nucleus. We calculated the segmented PVT volume from the T1w native space and transformed the ROIs to fMRI-resolution space using a shape-optimized method. Finally, we compared the functional correlation between different ROIs and the power spectrum of the timeseries for each ROI.

Results: Large inter-subject variability of the PVT volume was observed in both cohorts. MI was not present in one of the subjects. The PVT volume is 25.0 ± 12.2 mm3. Inter-hemispheric functional correlation (mean ± SD) is high for PVT (0.38 ± 0.19), anterior thalamic nucleus (0.40 ± 0.13), and Hb (0.24 ± 0.12) as compared to centromedial thalamic nucleus (0.11 ± 0.15). Functional correlation across the ROIs are all less than 0.15. Power spectrums reveal stronger frequency components representing neuronal signal in PVT, centromedial thalamic nucleus, and Hb than those in MI, anterior thalamic nucleus, and CSF.

Conclusions: Similar to our previously reported Hb segmentation, we developed a heuristic PVT segmentation approach that accounts for the variable size and presence of the MI, avoids CSF contamination, and mitigates partial volume effects from the anterior thalamic nucleus.

Disclosure: Nothing to disclose.

49.2 Habenula and Paraventricular Thalamus Connectivity in Healthy, Depressed, and Anxious Adolescents

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Background: Adolescence is a vulnerable period when psychiatric symptoms, including hypersensitivity to threats and pain, often emerge. Preclinical work has identified two small subcortical structures, the habenula (Hb) and paraventricular thalamus (PVT), as highly responsive to aversive stimuli and important for harm avoidance behavior. However, the role and relationship of Hb and PVT in humans remains poorly understood. Here, we jointly examined Hb and PVT resting-state functional connectivity (FC) in two adolescent cohorts.

Methods: Our study included 122 adolescents recruited locally and 300 adolescents from the public Adolescent Brain Cognitive Development (ABCD) study. Local subjects were ages 12-19 with mood and anxiety symptoms (99) or healthy controls (23). ABCD subjects were ages 11-13 (Year 2 timepoint) with symptoms of depression (100), anxiety (100), or healthy controls (100). All subjects completed diagnostic assessment and questionnaires to assess depression and anxiety severity. Resting-state functional magnetic resonance imaging (fMRI) was collected at 3T using similar protocols; local subjects also completed a pain task. Local data preprocessing followed HCP pipelines. Hb ROIs were optimized using our published methods. A PVT ROI was obtained from the Morel Thalamus Atlas. ABCD data were preprocessed by the DCAN study site using similar pipelines. FC analyses were performed in 32k CIFTI space.

Results: Adolescent Hb FC was consistent with adults, encompassing the ventral striatum, monoamine nuclei, primary sensory cortices, and salience network. PVT FC with the subcortex was largely similar; however, cortical PVT FC was dominated by the default network.

Conclusions: This is the first study of human PVT FC. The Hb and PVT both had strong FC with conserved subcortical targets known from animal studies, yet had opposite cortical FC patterns: the Hb associated with task-positive, externally oriented regions while the PVT associated with task-negative, internally oriented areas. As such, the Hb and PVT may play complimentary roles in aversion processing, enabling signals from different cognitive systems to converge on the same underlying harm avoidance circuits. Ongoing work to improve PVT definition, examine associations with clinical symptoms, and assess task-evoked aversion responses will also be presented as appropriate.

Disclosure: Nothing to disclose.

49.3 Abstract not included.

49.4 Pilot Study of Lateral Habenula Deep Brain Stimulation for Treatment Resistant Depression

Wayne Goodman

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Background: The lateral habenula (LHb) are evolutionarily well-conserved nuclei that flank the midline pineal gland in the walls of the third ventricle. Preclinical studies have shown that the LHb is activated when animal expects an aversive outcome or fails to receive an expected reward ("disappointment"). It is thought that output of LHb is inhibitory to major monoaminergic nuclei (VTA [dopamine]) and (DRN [serotonin]) that regulate neurotransmitter systems implicated in depression. It has been hypothesized that abnormally increased LHb activity may suppress reward function (induce anhedonia) and conversely that targeting the LHb by deep brain stimulation (DBS) may release inhibition of VTA and alleviate symptoms of depression. Translating this work, our aims were to test safety, feasibility and potential efficacy of applying bilateral DBS to the LHb in adults with treatment resistant depression (TRD).

Methods: Design was an open-label study followed by randomized, double-blind, graded discontinuation of DBS at 12 months. Participants were 5 adults with TRD with an active depressive episode ranging from 6-24 years (ages 26-67 y.o; 3 women). All had failed ECT treatments. DBS protocol: using myelin segmentation method, the leads were placed bilaterally close to lateral aspect of LHb at exit of fasciculus retroflexus to avoid oculomotor nuclei and minimize side effects.

Results: Of the 5 participants, 2 had response defined as at least 50% reduction in the HDRS17 relative to the baseline assessment. Side effects were tolerable and revisable. One case had an unexpected pulse generator failure that required surgical replacement. Programming related side effects problematic in first two cases in which outflow tracts (fasciculus retroflexus) was targeted. Fewer programming related side effects in third case in which input to LHb (stria medullaris) was targeted. No reproducible acute behavioral effects during programming.

Conclusions: Despite the small cohort, this study suggests feasibility and promise to targeting the LHb in TRD using DBS. Future studies should include LHb connectivity and activation as target of engagement and as an inclusionary criteria in addition to clinical manifestation of TRD. Future studies should use steerable current leads to minimize off target side effects (e.g., contralateral paresthesias and oculomotor disturbances.)

Disclosure: Biohaven: Consultant (Self). Nview: Royalties (Self).

Mini Panel

50. Neurotensin: New Takes on an Old Target

50.1 Neurotensin-Induced Synaptic Plasticity and Methamphetamine Self-Administration in Mice

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Background: Methamphetamine (METH) use disorder is chronic and progressive, and currently no therapeutic is approved by the FDA for its treatment. Dopamine neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) are necessary for learning associated with drug reinforcers. Recent work has highlighted a role for the peptide transmitter neurotensin in modulation of METH self-administration behavior and plasticity of inhibitory neurotransmission in the SNc/VTA. Neurotensin receptors in the SNc/VTA are localized not only on neurons but also on astrocytes, which can act through local circuits to affect dopamine neuron excitability and reward-related behavior. Mutant mouse strains are now coming on line that will enable the first determination of which neurotensin receptors on which cell types contribute to METH self-administration and responding to related cues.

Methods: Here we combined patch clamp electrophysiology of SNc/VTA dopamine neurons in mouse brain slices with i.v. methamphetamine self-administration in mice, making use of newly developed and validated NtsR1 and NtsR2 flox/flox lines.

Results: We observed that long-term depression (LTD) of D2 dopamine receptor-mediated inhibitory postsynaptic currents (D2-IPSCs) is dependent on neurotensin release from dopamine neurons and activation of NtsR2 receptors. Further, mice with a history of METH self-administration exhibited an increased amplitude of LTD of D2-IPSCs. As NtsR2 receptors in the SNc/VTA are mainly localized to astrocytes, we are focusing our mechanistic studies on that population. Optostimulation of VTA astrocytes produced depression of D2-IPSCs, consistent with a central role for astrocytes in neurotensinergic plasticity. We have also created and validated a NtsR2 flox/flox mouse line and demonstrate astrocyte-specific knockout of that receptor.

Conclusions: The advent of updated techniques in mice is enabling studies into the complex interactions between neurotensin, midbrain dopamine, and METH self-administration. The production and validation of NtsR1 and NtsR2 floxed mice will allow us, for the first time, to induce cell type-specific deletions of those receptors in specific cell types in the midbrain. Determining the physiological and behavioral roles of these receptors could lead to novel therapeutic strategies for addressing METH use disorder and relapse.

Disclosures: Novo Nordisk: Stock / Equity (Self). Hough Ear Institute: Contracted Research (Self).

50.2 Central Neurons Modulation of Ingestive Behavior

Gina Leinninger

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Background: Chronic pain and obesity frequently occur together and negatively impact the lives of over one-third of Americans. An ideal therapy would alleviate pain without weight gain, and most optimally, could promote weight loss. Central treatment with the neuropeptide neurotensin (Nts) reduces weight and alleviates pain, suggesting promise for the Nts signaling system to treat both obesity and obesity-induced pain. However, the lack of clarity of the endogenous source of Nts and the Nts receptors mediating these effects has hindered leveraging the Nts system therapeutically. Our team previously showed that activating lateral hypothalamic area neurons expressing Nts (LHANts neurons) suppresses feeding and promotes weight loss. Here we hypothesized that activating LHANts neurons can also alleviate pain.

Methods: To test this, we injected normal weight male and female NtsCre mice in the LHA with AAVs to cre-dependently express either mCherry (Control) or excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in LHANts neurons, permitting their activation after treatment with the DREADD ligand clozapine N-oxide (CNO, 0.3 mg/kg, i.p., $n = 6$-12 per cohort and pain test). We also prepared diet-induced obese male and female mice that express excitatory DREADDs or mCherry in the LHA to assess how activating LHANts neurons impacts obesity-pain ($n = 6$ per group). Statistical differences were assessed either by student's paired t-test or 2-way ANOVA.

Results: Activating LHANts neurons had no effect on thermal pain responses in naïve mice. By contrast, spared nerve injury-induced pain hypersensitivity was completely reversed by CNO-mediated activation of LHANts neurons compared to Vehicle treatment (VEH, control), both acutely and after chronic injury

($p < 0.001$, students' t-test comparing vehicle and CNO treatment). In mice treated with complete Freund's adjuvant (which induces inflammatory pain), activating LHANts neurons also relieved pain hypersensitivity ($p < 0.05$, 2-way ANOVA). However, pretreatment with the brain permeable Nts receptor pan-antagonist SR142948 (1mg/kg, i.p, 30 min before VEH/CNO) blocked CNO-mediated analgesia ($p < 0.0001$, 1-way ANOVA), indicating that LHANts neurons alleviate chronic pain in an Nts-dependent manner. Excitingly, activating LHANts neurons in diet-induced obese mice alleviated their baseline and CFA-induced pain, which was blocked by pre-treatment with the Nts receptor pan-antagonist ($p < 0.05$, 2-way ANOVA).

Conclusions: Taken together these data suggest that augmenting signaling via LHANts neurons may be a common actionable target for both pain and obesity. Going forward we are defining the mechanisms by which Nts signaling from LHANts neurons modulates feeding and pain, including the key Nts receptor isoform and receptor-expressing cells, to guide evidence-based design of pharmacological interventions for pain and obesity.

Disclosure: Nothing to disclose.

50.3 Modulation of NTSR1 in Alcohol Behaviors

Zoe McElligott

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Background: The neurotensin system is a target for psychiatric intervention that has been recently revisited. In particular, modulating the neurotensin system is attractive for targeting several affective disorders including, but not limited to, pain, feeding, and substance use disorders. Our recent investigations have demonstrated that neurons in the central nucleus of the amygdala (CeA) that target the parabrachial nucleus are reinforcing, and promote the consumption of alcohol and other reinforcing fluids. Additionally, recent studies investigating a biased modulator of the neurotensin 1 receptor (NTSR1), SBI-553, have demonstrated that it can attenuate addictive behaviors without deleterious side effects. Based on this and the previous literature, we hypothesized that SBI-553 may alter alcohol related behaviors.

Methods: Male and female C57BL6/J mice and Long-Evans rats were singly, or group housed based on experiment. N = 5-10/experiment. SBI-553 was administered at 12 mg/kg (mice) or 2-12 mg/kg (rats).

Mice: Drinking in the Dark (DID) paradigms: Both single bottle and 2-bottle paradigms (ethanol vs. water) were investigated. We used 20% ethanol for all ethanol bottles. 1% sucrose DID was also investigated.

Rats: Pavlovian drug discrimination was performed as in Randall et al., Addiction Biology, 2020.

2-way ANOVA was performed for all experiments, with post-hoc Sidak test where appropriate. Significance was determined if $p < 0.05$.

Results: We first investigated if SBI-553 would alter the consumption of ethanol in a DID paradigm. Singly housed male and female mice were injected with vehicle 30 minutes prior, and presented with 1 bottle of ethanol (or sucrose) 3 hours into their dark cycle for 4 days/week. On day 5 mice were injected with either vehicle or 12 mg/kg SBI-55330 minutes prior to receiving their ethanol bottle. In male and female mice, we found that SBI-553 pre-treatment reduced ethanol ($p < 0.05$), but not sucrose consumption. In a separate study using a 2-bottle DID procedure, we found that SBI-553 again reduced the consumption of ethanol ($p < 0.05$), but that this was significantly driven by a reduction in the female mice (posthoc analysis, $p < 0.05$).

To investigate if SBI-553 disrupts the interoceptive qualities of alcohol, we administered SBI-553 to rats that had been previously trained to discriminate alcohol at an oral training dose of 2 g/kg. While both male and female rats were able to discriminate between water and ethanol when vehicle was injected 30 minutes prior to their experimental session (main effect of drug both sexes $p < 0.05$, interaction in the males $p < 0.05$). Both male and female rats lost this ability when SBI-553 was administered prior to the experimental session (across all doses). While SBI-553 treatment had no significant decrease in locomotion in either sex, there was a dose dependent increase in locomotion in both water and alcohol experimental sessions in the males.

Conclusions: Our data suggest that SBI-553, or a drug of similar mechanism, may be a promising pharmacotherapeutic for alcohol use disorders. We found that pre-treatment with SBI-553 reduced both binge consumption of alcohol, altered alcohol preference, and reduced the interoceptive qualities of alcohol. We also found that there may be sex differences in the effects of SBI-553 to reduce alcohol related behaviors, which should be further investigated.

Disclosure: Epicypher: Grant (Self).

Panel

51. Auditory Perception and Misperception in Mice: Implications for Auditory Hallucinations

51.1 Nigrostriatal Dopamine Modulates the Striatal-Amygdala Pathway in Auditory Fear Conditioning

Qiaojie Xiong

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Background: The auditory striatum plays an essential role in learning and memory. In contrast to its roles and underlying mechanisms in operant conditioning, however, little is known about its contribution to classical conditioning. Here, we examined the function of the auditory striatum in auditory-conditioned fear memory.

Methods: Both male and female 2-4-month-old mice were used. We performed in vivo Ca2+ imaging, dopamine sensor imaging, optogenetic and chemogenetic manipulations in the auditory striatum and substantial nigra of behaving mice, to assess those neuron's function in auditory-conditioned fear memory acquisition and execution.

Results: We found that optogenetically inhibiting auditory striatal neurons impaired fear memory formation, which was mediated through the striatal-amygdala pathway. Using calcium imaging in behaving mice, we found that auditory striatal neuronal responses to conditioned tones were potentiated across memory acquisition and expression. Furthermore, nigrostriatal dopaminergic projections played an essential role in modulating conditioning-induced striatal potentiation.

Conclusions: Together, these findings demonstrate the existence of a nigro-striatal-amygdala circuit for auditory-conditioned fear memory formation and expression.

Disclosure: Nothing to disclose.

51.2 The Modulation of D1 Spiny-Projection Neurons Paradoxically Normalizes Dopamine-Driven Auditory Misperception and Correlates With Clinical Antipsychotic Efficacy

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Background: Antipsychotic drugs are effective for auditory hallucinations, but the neural circuitry underlying hallucinations and how it is modulated by antipsychotics are poorly understood. Our lab has developed the foremost functional readout of antipsychotic drug efficacy in mice based on imaging Ca2+ activity in D1 and D2 dopamine receptor expressing spiny-projection neurons (SPNs) in the dorsomedial striatum (DMS), a brain region with increased dopamine release in schizophrenia. Here we determined how effective versus ineffective antipsychotic drugs and drug candidates modulate D1- and D2-SPN ensemble dynamics and extrapolated our observations to characterize the possible neural substrates of auditory hallucinations using cell-type specific chemogenetic manipulations and the recently established hallucination-like auditory perception task.

Methods: We used miniature microscopes and a genetically encoded Ca2+ sensor to image D1- and D2-SPN ensemble dynamics under normal (vehicle treatment) and hyperdopaminergic (amphetamine treatment) conditions with and without antipsychotic drug/candidate treatment. Data will be presented on the effects of various mainstay and candidate treatments for psychosis, including newer D2R-independent drugs. We imaged D1- and D2-SPNs in both male and female D1-Cre and A2A-Cre mice, respectively, and used chemogenetics to manipulate neural activity in the DMS during open field locomotion, sensorimotor gating, and hallucination-like auditory perception. The size of each experimental group ranged from 7–18 mice.

Results: Despite the strong correlation between antipsychotic drug potency and D2 dopamine receptor antagonism, the clinically efficacy of these drugs is paradoxically associated with the selective attenuation of D1-SPN hyperactivity under hyperdopaminergic conditions. Accordingly, inhibiting D1-SPNs in the DMS is sufficient to suppress dopamine-driven hallucination-like auditory misperception.

Conclusions: Our results suggest that the modulation of D1- rather than D2-SPNs is important for the therapeutic benefits of antipsychotics. In agreement, inhibiting D1-SPNs in the DMS reversed dopamine-driven auditory misperception. Studies are underway to compare the roles of the DMS and tail of the dorsal striatum, which has previously been implicated in auditory misperception.

Disclosure: Nothing to disclose.

51.3 Striatal Neuromodulators in Hallucination-Like Perception

Katharina Schmack

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Background: Auditory hallucinations are a hallmark of psychosis, a condition linked to excessive dopamine signaling. However, recent clinical trial results suggest that acetylcholine might also play a key role in psychosis but the exact relation between acetylcholine, dopamine, and auditory hallucinations remains unclear, mainly because auditory hallucinations have been challenging to study in mouse models. Here, we aimed to elucidate the role of acetylcholine and its interactions with dopamine in hallucination-like perception in mice. We focused on the striatum, a major site of cholinergic and dopamine signaling.

Methods: Mice were trained to perform our recently established task to measure hallucination-like perception. Using optogenetics and dual-color fiber photometry, we related striatal acetylcholine release to hallucination-like perception and striatal dopamine release.

Results: We found that optogenetic inhibition of striatal acetylcholine release increased hallucination-like perception ($T = 4.6$, $p = 0.02$). Moreover, acetylcholine release peaked before hallucination-like perception and was inversely related to dopamine release.

Conclusions: These results suggest that reduced striatal cholinergic transmission might give rise to psychotic experiences, and that this is accompanied by increased dopamine release. Ongoing work is aimed at understanding the causal relationship between dopamine and acetylcholine during hallucination-like perception.

Disclosure: Nothing to disclose.

51.4 Reward Driven Associative Learning and Auditory Perception in a Mouse Model of 22q11 Syndrome

Arturo Torres Herraez

Columbia University/RFMH, New York, New York, United States

Background: Heterozygous deletion of the 22q11 region in humans increases the risk for schizophrenia by 25 to 30 fold. Patients show a variety of cognitive, negative and positive symptoms including associative learning and auditory hallucinations. Auditory hallucinations have been linked to alterations in the dopamine system and 22q11 carriers show increased dopamine precursor uptake in the striatum. Here, we used mice carrying a deletion of the syntenic region of 22q11 in mice (Df(16)A+/- mice) to determine how the deletion affects in vivo striatal dopamine release, associative learning and auditory perception.

Methods: We used adult heterozygous male and female Df(16)A+/- mice (Het, $n = 7$) and littermate controls (Wt, $n = 6$) in combination with fiberphotometry imaging of the genetically encoded dopamine sensor, dLight1.2, in the nucleus accumbens. Mice were tested first in an instrumental conditioned reinforcement task followed by a progressing fixed interval training and Pavlovian discrimination task. An independent cohort of mice was tested in an auditory signal detection task (Het = 4, Wt = 4).

Results: Het mice showed a delay in acquiring the conditioned reinforcement task. Moreover, while overall dopamine release was not compromised in Het, Wt adapted their dopamine release in response to increasing time rules in the fixed interval task while this was not observed in Het mice (RM 2-way ANOVA genotype x session interaction, aligned to lever extension: $p < 0.005$; aligned to reward presentation: $p < 0.05$). Consistent with a deficit in reward driven associative learning, during Pavlovian discrimination, differences in time invested in the dipper port during CS+ and CS- were only observed in Wt (RM 2-way ANOVA CS type, $p < 0.05$) and differences from initial values appeared sooner in Wt than in Het ($p < 0.05$ from session 6 and 8, respectively). Preliminary data further suggest that Df(16)A+/- mice are able to acquire the signal detection task, but they are prone to more false alarms (unpaired t-test, $p = 0.06$).

Conclusions: There is no general deficit in meso-accumbens dopamine release in Df(16)A+/- mice, yet dopamine release does not adapt when task conditions change. Learning is delayed in instrumental and Pavlovian reward-driven tasks. Df(16)A+/- mice may also show a propensity to false alarms in a signal detection task consistent with hallucination like percepts.

Disclosure: Nothing to disclose.

Panel

52. Exploring Mechanisms of the Persisting Effects of Psilocybin

52.1 The Role of Ventral Hippocampal Parvalbumin Interneurons in Gating the Anxiolytic Effects of the Serotonergic Psychedelic, DOI, in Rodents

Vidita Vaidya

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Background: Clinical and preclinical studies indicate that serotonergic psychedelics can ameliorate anxiety-like behavior. Evidence from rodent models suggests an anxiolytic action of serotonergic psychedelics in ethologically relevant behavioral tasks, like the elevated plus maze (EPM). Here, we evaluated the specific brain region, neuronal cell type, and receptor involved in the anxiolytic actions of the serotonergic psychedelic DOI.

Methods: Male and Female Sprague-Dawley rats or C57BL/6 mice received acute systemic treatment with vehicle/DOI (1 mg/kg) prior to behavioral analysis on the EPM. Animals bilaterally received vehicle or DOI (1μg/μl) through cannulas into the prelimbic (PL) or infralimbic (IL) medial prefrontal cortex subdivisions; dorsal or ventral hippocampus (dHPC/vHPC), or basal amygdala (BA) prior to behavioral analysis. Pharmacological experiments with 5-HT2A receptor antagonists or 5-HT2A receptor knockout mice with cell-type specific restoration of receptor expression were used to delineate the brain region and cell type involved in the anxiolytic actions of DOI. Neuropixel 1.0 probes were used for electrophysiological analysis in the vHPC. Statistical analyses involved two-tailed, unpaired Student's t-tests or two-way analysis of variance (ANOVA). All experiments had an $n = 7$-10 per treatment group.

Results: Male and female rats or mice, exhibited anxiolytic responses on the EPM following acute systemic administration of DOI. DOI infusion in the vHpc CA1/sub region, in male or female rats, evoked significant decreases in anxiety-like behavior (Open Arm time: Male rats: $p = 0.004$, Female rats: $p = 0.005$). Integrating anatomical, pharmacological, electrophysiological and genetic approaches, we find that DOI enhances the firing rate of hippocampal fast-spiking cells, and that 5-HT2A receptors in the vHpc CA1/sub region mediate the anxiolytic action of DOI. Restoration of 5-HT2A receptors in parvalbumin (PV)-positive interneurons in a loss-of-function background reinstated anxiolytic responses evoked by DOI in the vHpc CA1/sub region.

Conclusions: Collectively, our results indicate that PV-positive fast spiking interneurons in the vHPC CA/subiculum region contribute to the anxiolytic actions of the serotonergic psychedelic DOI in rodent models.

Disclosure: Nothing to disclose.

52.2 Cell-Type Specificity in the Neural Plasticity Evoked by Psilocybin

Alex Kwan

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Background: Psychedelics are known for their ability to alter perception and therapeutic potential for mental illnesses. The neural basis underlying the behavioral benefits is unknown, although structural neural plasticity is likely involved. In a recent study, my lab showed that a single dose of psilocybin leads to an increase in dendritic spine density for at least a month. However, pyramidal neurons are heterogeneous, comprising of non-overlapping cell types including pyramidal tract (PT) and intratelencephalic (IT) subpopulations. The goal of this study is to determine the sensitivity of PT and IT neurons to psilocybin and their relatively importance for mediating the drug's behavioral effects.

Methods: We targeted PT and IT subpopulations of pyramidal neurons using retrogradely transported adeno-associated viruses or mutant Fezf2-CreER and PlexinD1-CreER mouse strains. For each cell type, we used two-photon microscopy to measure effects of psilocybin (1 mg/kg, i.p.) on dendritic spine turnover and dendritic calcium signaling. Using chemogenetics, we tested if suppressing the activity of PT or IT neurons during drug administration will abolish the ability of psilocybin to alleviate stress-related behavioral deficit.

Results: Psilocybin selectively enhances the dendritic spine size in the PT subpopulation. This cell-type-specific synaptic potentiation is preceded by an acute elevation of dendritic calcium signaling in PT neurons. Finally, silencing PT neurons in medial frontal cortex was sufficient to render psilocybin ineffective in two stress-related behavioral assays. Collectively, these data indicate PT neurons as the primary pyramidal cell type targeted by psilocybin for mediating its long-term behavioral consequences.

Conclusions: The results reveal how PT and IT subpopulations exhibit differential plasticity-related changes to psilocybin and pinpoint the pyramidal neuron subtype that mediates the behavioral effects of psilocybin. Because PT and IT neurons differ sharply in their long-range axonal projections and represent the two major output pathways of the frontal cortex, the study provides insights into the neural circuitry involved in mediating psilocybin's behavioral effects.

Disclosures: Empyrean Neuroscience, Freedom Bioscience: Advisory Board (Self). Psylo, Biohaven: Consultant (Self).

52.3 Investigating the Role of Serotonin 1B Receptors in the Behavioral Effects and Mechanisms of Actions of Psilocybin

Kate Nautiyal

Dartmouth College, Hanover, New Hampshire, United States

Background: While the mechanisms of the behavioral effects of psilocybin are most commonly attributed to serotonin 2A receptor (5-HT2A R) binding, psilocin, the active metabolite of psilocybin, binds many serotonin receptor subtypes. Some recent studies in rodents have suggested that some effects could be independent of 5-HT2AR activation. Our work addresses the hypothesis that psilocybin modulates depressive- and anxiety-like behaviors in mice in part via activation of the serotonin 1B receptor (5-HT1BR).

Methods: We used a chronic (4 weeks) corticosterone treatment to test the effects of high dose psilocybin (5mg/kg) on behavior 2-5 days following treatment in a lickometer assay to measure anhedonia and elevated plus maze and novelty suppressed feeding tests to measure anxiety-like behavior. We investigated the role of the 5-HT1BR in the response to psilocybin by comparing the behavioral response in 5-HT1BR transgenic loss-of-function mice and littermate controls. Ongoing work is also comparing the neural activity related to 5-HT1BR following psilocybin administration.

Results: Psilocybin reduces anxiety-like behaviors and increases reward motivation in mice following chronic corticosterone treatment, an effect largely driven by female mice in our study. Specifically, psilocybin increased reward motivation in a 6 bottle choice sucrose lickometer assay ($p = 0.030$) and reduced latency

to eat in the novelty suppressed feeding test ($p = 0.040$) in females. Mice lacking 5-HT1BR throughout the brain in adulthood showed no effect of psilocybin in the sucrose lickometer assay ($p = 0.787$) or novelty suppressed feeding test ($p = 0.153$). Although control mice showed an increase in head twitches in the first 15 minutes following psilocybin administration compared to saline ($p < 0.0001$), as expected there was no significant differences in head twitch response in mice lacking 5-HT1BR compared to control mice ($p = 0.942$).

Conclusions: Overall, our work shows that psilocybin induces post-acute behavioral changes in female mice following high dose psilocybin administration following chronic corticosterone. Interestingly the data illustrate that the effects on anxiety and depressive-like behavior are modulated by 5-HT1BR expression, suggesting a non-5-HT2A mechanism of action for persisting behavioral effects of psilocybin in mice.

Disclosure: Nothing to disclose.

52.4 The Role of Cognitive Control and the Human Claustrum in the Acute and Enduring Effects of Psilocybin

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Background: Adaptive responses to the environment rely on a balance and trade-off of opponent states of cognitive control, namely flexibility and stability. Meta-control refers to our capacity to monitor and regulate this tradeoff (Eppinger et al., 2021). The development and maintenance of mood and substance use disorders may rely on disruption of meta-control and the over-learned value of stability (e.g., being stuck in rumination or drug seeking behaviors) to the exclusion of flexibility (Morris and Mansell, 2018). The claustrum may support instantiation of cortical brain networks to subserve cognitive control (Madden et al., 2022). The current analyses will investigate whether administration of psilocybin can bias the meta-control state of study participants towards a state of flexibility (Sayali and Barrett, 2023) by modulating cortical connectivity of the human claustrum (Madden et al. 2022).

Methods: Thirty healthy participants (15M, 15F) are completing a clinical trial (NCT05301608) comparing the acute effects of placebo and 10 mg/70 kg oral psilocybin on cognitive control behavior and blood-oxygenation level-dependent (BOLD) signal measured while performing the Multi-Source Interference Task (Bush et al., 2003), in addition to other measures not reported here. In a separate trial (NCT04620759), a subset of 90 patients with major depressive disorder and co-occurring alcohol use disorder (MDD/AUD) are completing a task-switching paradigm (Sayali and Badre, 2019) during MRI measurement of BOLD signal before and 1 week after administration of either placebo or 25 mg psilocybin under supportive conditions.

Results: Acute effects of psilocybin on MSIT task performance (accuracy and the difference in log response time to difficult vs easy blocks of trials) as well as brain function (static and dynamic functional connectivity of the claustrum with default mode network [DMN] and fronto-parietal network [FPN]) will be compared to placebo using general linear modeling techniques in the healthy participant study. Enduring effects of psilocybin on task-switching performance and brain function will also be compared to placebo in our study of MDD/AUD.

Conclusions: A positive finding of both acute and enduring effects of psilocybin on performance and brain function will support a hypothesis of meta-control as a potential transdiagnostic target of psilocybin.

Disclosure: WavePaths, Ltd, MindState Design Labs, Inc.: Advisory Board (Self). Gilgamesh Pharmaceuticals, Inc.: Consultant (Self).

Study Group

53. How Will Novel Antipsychotic Drugs Update Schizophrenia Management?

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Study Group Summary: The discovery of the antipsychotic activity of dopamine receptor antagonists in the 1950s emptied out mental hospitals around the world and provided tremendous advantage to people with psychosis. Now, we see that many with people with psychosis are non-responders to current antipsychotics; most are only partial responders. Dopamine antagonists do not cure psychotic disorders, nor even moderate all parts of the disorder, like negative or cognitive dysfunctions. So, pharmacologists have been speculating about what treatments with novel mechanisms of action will provide for people with psychosis, especially for the most severe psychoses in schizophrenia. Do all mechanisms funnel through dopamine, so advantages will be small? Will there be characteristic therapeutic advantages to each new mechanism which will be additive? Will each new drug treat an additional facet of psychosis so that we will see many extensive recoveries with multiple drugs? Will we find clues to pathophysiology? Will we be able to articulate indications for each antipsychotic drug?

We have a unique opportunity now to preview the place of these new compounds with answers to these critical questions. We have drawn together an expert group in this field who will pull from their research, their experience, and speculations on the answers to these questions. The question is of great interest now, because of the promise of antipsychotic drugs, with novel mechanisms of actions. It is KarXT which is likely to be first in line and a drug which takes advantage of the muscarinic actions of M1/M4 of xanomeline to reduce psychosis. Then, we are likely to see Ulorant results with its TAAR-1 agonism and examine its spectrum of outcomes. Meanwhile, drug development directed toward cognitive enhancement is active, with at least one drug moving forward, although with more difficulty in this area than anticipated. How will regulatory agencies respond to these drugs: what will they want to see done to consider them for unique labeling and what to consider them as treatment advances? How will the actions of these drug treatments affect the way we treat psychotic disorders to achieve maximal clinical efficacy?

Disclosures: Merck Pharmaceutical: Board Member (Self). Sunovion: Consultant (Self). Karuna: Stock / Equity (Self) KyNexis: Founder (Self).

Study Group

54. What is the Impact of the Restricted Abortion Access on the Neuropsychiatric Health of Pregnant Individuals and Their Offspring?

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Study Group Summary: Before the Dobbs v. Jackson Women's Health Organization ruling, one in four people capable of pregnancy had one or more abortions. In fourteen states (with more to come), these individuals no longer control the most personal aspect of their bodies and lives. In these states, mental illness as a reason to allow abortion is either specifically eliminated, or implicitly excluded by requiring a physical health or "organ damage" standard. These states maintain the myth that disorders of the brain are separate from the remainder of diseases in the corpus. How do we counter this recurrent falsehood and advance the scientific understanding of neuropsychiatric disease in this context?

Individuals with few resources and limited access to health care constitute the majority of abortion seekers. Compelling a person to continue an unwanted pregnancy creates major challenges that increase the need for mental health care from an already overwhelmed system. The burden extends beyond pregnant individuals and their families to healthcare practitioners, medical organizations and sociopolitical systems. With expertise in the natural history of neuropsychiatric diseases, perinatal mental health, the impact of maternal distress and mental illness on pregnancy and offspring outcomes, ethics, law, and policy, the ACNP is the ideal organization to host this discussion.

The often-contentious debate about abortion will continue as the mental health needs of pregnant individuals escalate. We recognize that a variety of views about abortion exist; however, this study group is focused on the mental health of the childbearing individuals, their offspring and families, as well their clinicians, rather than the disputed morality of abortion.

What neuropsychiatric disorders will emerge from this crisis in access to reproductive health services? Destabilization of existing mental disorders and the emergence of major depressive and post-traumatic stress disorders are likely. What preventive and intervention approaches are available and suitable for implementation? Is there a role of digital mental health innovations? Exposure to prenatal maternal psychological distress has enduring adverse consequences for offspring neurodevelopment with evidence of specific brain structural, cognitive and socioemotional impacts. What strategies (psychotherapeutic, nutritional, socio-environmental) are available to mitigate this risk? What is the impact on prescribing treatment during pregnancy for individuals who need medication for psychiatric stability when it increases the risk for fetal malformations or offspring neurodevelopmental disorders? How will maternal self-harm attempts be managed in this context? For individuals whose pregnancies result in serious mental health problems or offspring with developmental support needs, how will care for the family be arranged? Can mental health professionals assist patients in ban states with travel to states where the reproductive healthcare they need is legal?

Clinicians are faced with risk for moral injury that can negatively impact their own health. For example, practitioners who do not agree with abortion bans but are practicing in states that have them must cope with the awareness that they are facilitating adaptation to a policy they oppose. For clinicians who agree with the law, how do they maintain a neutral therapeutic approach to the patient who strongly opposes it?

Disclosure: Nothing to disclose.

Panel

55. Dopamine Function in the Amygdala: Insights Into the Role of Dopamine Outside of the Striatum

55.1 Basolateral Amygdala Dopamine Signals Track Emotionally Salient State Transitions

Benjamin Saunders

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Background: Ventral tegmental area (VTA) dopamine neurons are critical for cue-based learning and motivation in adaptive decision-making situations, as well as for behavioral dysfunction in diseases like addiction. The basolateral amygdala (BLA) is a central locus of emotional learning in the brain, receiving dense dopamine projections from the VTA. The details of BLA dopamine signaling dynamics during behavior, and their functions in the context of cue-based learning and drug-related actions, remain unknown.

Methods: We used a combination of dLight fiber photometry and optogenetics in transgenic rats to record dopamine dynamics and manipulate BLA neurons during a valence discrimination Pavlovian learning task ($n = 10$) and an intermittent access cocaine self administration task ($n = 6$-8 per recording group, $n = 6$ per optogenetics group).

Results: We found that BLA dopamine signals respond to both positively and negatively-valence outcomes, such as food and footshock. Through Pavlovian learning, BLA dopamine signals emerged in response to conditioned stimuli, regardless of valence. Under conditions of valence discrimination, BLA dopamine signals were largest to threat predictive cues and cues signaling safety from threat.

During intermittent access cocaine self-administration, we found that behavior came under the control of state-level cues signaling drug availability. These state transitions triggered enduring (~10-15sec) BLA dopamine signals, compared to sharp (1-2sec) phasic GCaMP signals recorded from BLA D1-receptor containing neurons in D1-cre rats. Additionally, brief optogenetic activation of BLA neurons at the transition to drug availability sped up subsequent drug seeking responses.

Conclusions: These data indicate that BLA dopamine signals dynamically report the presence of emotionally salient events, including unconditioned stimuli, as well as learned states, in both Pavlovian and instrumental conditioning. In the context of drug seeking, BLA dopamine and BLA D1 neuron activity tracks the receipt of cocaine, and the emergence of state-level control of drug seeking motivation. Together, these studies point to a complex role for non-striatal, amygdalar dopamine systems in sensory-guided learning.

Disclosure: Nothing to disclose.

55.2 Dopamine Projections to the Basolateral Amygdala Drive the Encoding of Identity-Specific Reward Memories

Kate Wassum

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Background: To make adaptive decisions, we build an internal model of associative relationships in the environment and use it to predict specific forthcoming outcomes. Detailed stimulus-outcome memories are a core feature of such cognitive maps, yet little is known of the neuronal systems that support their encoding.

Although there is little known of how we form stimulus-outcome memories, recent evidence suggests dopamine might actually contribute. New data have challenged the value-centric dogma of dopamine function, indicating it plays a much broader role in learning than originally thought. How dopamine contributes to identity-specific stimulus-outcome learning is unknown, yet critical for understanding dopamine's emerging multifaceted function in learning.

Methods: We used fiber photometry, cell-type and pathway-specific optogenetic manipulation, Pavlovian cue-reward conditioning, and a decision-making test in male and female rats (N = 8-16/group), to reveal that ventral tegmental area dopamine (VTADA) projections to the basolateral amygdala (BLA) drive the encoding of stimulus-outcome memories.

Results: We found that the BLA is active, and dopamine is released into the BLA at the time of stimulus-outcome pairing, when subjects have the opportunity to link the features of a rewarding outcome to a predictive cue. Correspondingly, VTADA- > BLA projection activity at stimulus-outcome pairing is necessary to encode identity-specific stimulus-outcome memories as assessed using Pavlovian-to-instrumental transfer, but not to develop a goal-approach response or cache value to the cues to support general motivation. VTADA- > BLA pathway activation is sufficient to rescue the encoding of identity-specific stimulus-outcome memories in a Pavlovian blocking task but is neither reinforcing itself nor sufficient to enhance reinforcement of a Pavlovian goal-approach response.

Conclusions: These data reveal the VTADA- > BLA pathway as a critical contributor to the formation of detailed stimulus-outcome memories, fundamental components of the internal model of environmental relationships, aka cognitive map, that supports flexible decision making. They also demonstrate a dopaminergic pathway for the learning that supports adaptive decision making and help understand how VTADA neurons achieve their emerging multifaceted role in learning.

Disclosure: Nothing to disclose.

55.3 VTA Dopamine Projections to the Lateral Amygdala Provide a Learning Signal Necessary for Acquisition of Cocaine Self-Administration

Mary Torregrossa

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Background: Dopamine signaling in the amygdala, particularly the basolateral amygdala (BLA), is known to be important for associative learning. However, the dynamics of dopamine release in the BLA during different phases of cue-reward learning has not been well-established. Moreover, the precise role that ventral tegmental area (VTA) dopamine neuron projections to the BLA play in modulating cocaine-cue learning during self-administration and reinstatement of cocaine seeking has not been established.

Methods: We used a combination of fiber photometry recordings of dopamine release using the dLight1.2 sensor in the BLA and projection specific DREADD-based inhibition of VTA to BLA projections in male and female Sprague-Dawley or TH-Cre rats. The first experiment measured the pattern and timing of DA release in the BLA as rats acquired Pavlovian conditioned approach, instrumental learning and Pavlovian to instrumental transfer for a sucrose reward. The second experiment determined the effect of inhibiting VTA neurons that project to the BLA on acquisition of cocaine self-administration, reinstatement of cocaine seeking, and cocaine conditioned place preference.

Results: Fiber photometry recordings revealed that dopamine release in the BLA peaked in response to a cue predictive of reward availability only when the individual animal acquired the cue-reward association (i.e., met acquisition criteria). Rats that failed to increase dopamine release in response to predictive cues never learned the task. These results were specific for Pavlovian conditioning and not other forms of learning. Inhibition of the BLA projecting dopamine neurons also led to a failure to acquire cocaine-self-administration, while inhibiting the projection had no effect on cue-induced reinstatement after the cocaine-cue association was learned. There was also no effect of VTA-BLA inhibition on the formation of a cocaine conditioned place preference. No sex differences were observed in any of the outcome measures.

Conclusions: Our results suggest that dopamine projections to the BLA are critical for initial learning of discrete cue-reward associations for both sucrose and cocaine, but are not required for instrumental or contextual learning and do not modulate the response to the reward itself.

Disclosure: Nothing to disclose.

55.4 A Mesoamygdala Circuit Mechanism for Enhancing Threat Stimulus Discrimination During Periods of Uncertainty

Larry Zweifel

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Background: Stimulus discrimination is the ability to distinguish between discrete sensory cues that are predictive, or non-predictive, of a positive or negative outcome. Stress caused by uncertainty, and vice versa, can impair discriminatory learning resulting in maladaptive generalization. We have found that the neurotransmitter dopamine, in particular dopamine release in the central nucleus of the amygdala (CeA) from neurons of the ventral tegmental area (VTA) plays a key role in facilitating stimulus discrimination during threat conditioning. Based on these observations, we hypothesized that increased dopamine release in the CeA in response to a positive affective stimulus may be an important neural substrate underlying the ability of positive emotional stimulus to suppress threat generalization.

Methods: We utilized DAT-Cre mice with an AAV to conditionally express stimulatory opsins, inhibitory opsins, or the dopamine sensor dLight1.3b. Mice were conditioned Pavlovian reward conditioning paradigm with a predictive CS (Rew-CS+) or non-predictive CS (Rew-CS-). Following reward conditioning mice were conditioning in a probabilistic fear conditioning paradigm to induce generalization followed by re-conditioning with co-presentation of the rew-CS+ or rew-CS- at the onset of the higher probability threat CS (CSh). Dopamine neurons and dopamine neuron terminals were optogenetically manipulated and dopamine signals were recorded in the central amygdala. All groups utilized 10-12 mice (male and female) per group.

Results: We show that a Rew-CS+ can prevent, or reverse impaired stimulus discrimination associated with a high-intensity or uncertain threat (foot shock). Positive recall can also facilitate the extinction of a conditioned threat response. Mechanistically, we demonstrate that the impact of positive recall on stimulus discrimination is mediated by the midbrain dopamine system. Enhanced dopamine release in the central nucleus of the amygdala facilitates discriminatory coding between a threat conditioned stimulus (Thr-CS+) and non-conditioned stimulus (Thr-CS-) that promotes behavioral discrimination.

Conclusions: Our data help to resolve how positive and negative stimuli interact in the brain and how recall of a positive experience can be an effective means to suppress threat generalization.

Disclosure: Nothing to disclose.

Panel

56. Avoidance Learning: Fundamental Mechanisms, Individual Differences, and Implications for Psychiatry

56.1 Individual Differences in Human Avoidance of Social Threat are Explained by Utilization of Sophisticated Social Inference Mechanisms

Toby Wise

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Background: Human avoidance decisions often involve a social element, for example navigating an unfamiliar town at night or managing difficult work relationships. Social avoidance processes are implicated across mental health problems (e.g., social anxiety) and neurodevelopmental disorders (e.g., autism and ADHD). However, the mechanisms that enable us to avoid complex social threats remain unknown, and it is unclear how these mechanisms relate to mental health problems. We answered these questions using computational modeling of behavior in a gamified social avoidance task.

Methods: We designed a social avoidance task in which participants navigated a character around a 2D grid seeking reward tokens while avoiding a computer controlled predator. The predator behaved in a goal-directed way, and successful avoidance depended on participants inferring its goal (e.g., trees) and predicting its trajectory. We used computational models to determine whether participants relied on knowledge of the predator's goal-directed behavior (goal inference) versus using simpler heuristics. Human participants ($N = 631$) completed the task, also completing self-report measures of mental health symptoms and neurodevelopmental traits.

Results: GDA training in adult mice induced excitatory synaptogenesis in the ACC of WT mice ($p = 0.012$). The global loss of α2δ-1 reduces this training-induced excitatory synapse formation in the ACC ($p = 0.148$) and increases effort exertion during the PR task as measured by the max ratio ($p < 0.0001$). Trained mice with ablated α2δ-1 only in ACC- > DMS neurons had reduced excitatory synapses compared to WT ($p < 0.0001$) and performed a higher max ratio during the PR task ($p = 0.003$). Surprisingly, we found that constitutive loss of TSP1/2 significantly reduced GDA performance ($p = 0.0007$) but did not impair GDA training-induced excitatory synaptogenesis in the ACC ($p = 0.0037$). Additionally, mice lacking TSP1/2 have increased inhibitory synapse density in the ACC ($p < 0.0001$), which is diminished with GDA training ($p = 0.0018$).

Conclusions: Our results show that individual differences in social avoidance can be explained by the use of sophisticated goal inference strategies. Surprisingly, we found no links with anxiety. However, our results suggest that challenges experienced in difficult social situations across neurodevelopmental disorders may be linked to altered use of social avoidance strategies coupled to reduced confidence in avoidance abilities.

Disclosure: Nothing to disclose.

56.2 Medial Orbitofrontal Cortex (mOFC) Recruitment During Active Avoidance Learning

Brittany Chamberlain

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Background: Negative reinforcement-based theories of OCD suggest compulsions are driven by temporary relief from obsession-related anxiety, but underlying mechanisms are largely unknown. Medial orbitofrontal cortex (mOFC) has been implicated in excessive avoidance in OCD, with our recent clinical study (Panny et al., in review) showing increased mOFC activity when OCD patients remove compulsion-related images. To dissect mechanisms underlying active avoidance learning, we measure mOFC activity via single-photon Ca2+ imaging in WT mice during a novel negative reinforcement task.

Methods: C57Bl6/J mice ($n = 10$; 7M, 3F) were trained to avoid shocks predicted by a cue light by pressing a lever in the 20sec cue period. Prior to training, mOFC was injected with AAV5-CaMKII-GCaMP6f and implanted with GRIN lenses to visualize activity using miniature microscopes (Inscopix). Single-cell Ca2+ fluorescence was extracted (CNMFe) and time-locked to task-relevant events (cue onset, avoid response, shock onset). Individual neurons were tracked across sessions (CellReg).

Results: Mice learned to avoid foot shocks (90% acquisition rate) over 7 days (Day 3: 8/10 met acquisition criterion). % task-modulated mOFC neurons increased over learning [neurons positively modulated by shock-predicting CS+: Day 1 = 10% (56/539); Day 7 = 15% (81/832); $p = 0.013$]. Proportion of avoid-responsive neurons also increased over learning: Day 1 = 21% (114/539); Day 7 = 28% (160/581); $p = 0.019$. Of 95 neurons responding to initial punishment receipt (Day 1), 60% (57/95) evolved a task-relevant response on Day 2 (modulation to punishment-predictive cues / avoidance). When we investigated well-learned avoidance, only 28% of Day 1 avoid-responsive neurons (25/89) were avoid-responsive on Day 7. However, when we tracked responses from Day 4 (when avoidance was well-established) to Day 7, we found 42% (43/103) maintained their avoid-responsive identity from Day 4-7. This suggests single-cell representation of avoidance in mOFC becomes increasingly stable as behavioral performance stabilizes.

Conclusions: We developed a negative reinforcement task that leads to rapid acquisition of active avoidance in mice. We observed an increase in CS+ responsive and avoid-responsive neurons as avoidance is learned and increased stability of neural responses following behavioral acquisition.

Disclosure: Nothing to disclose.

56.3 Mesoaccumbal Core Circuit Dynamics in Avoidance Learning

Gabriela Lopez

Feinberg School of Medicine, Northwestern University, Chicago, Chicago, Illinois, United States

Background: To avoid danger, animals must learn about cues in their environment that predict danger and act in response. Previous work investigating dopamine release in the nucleus accumbens core (cNAc) implicates the mesoaccumbal circuit in avoidance learning, but interpretations are limited by several factors. First, although several studies record cNAc dopamine responses to unavoidable aversive stimuli, the contribution of these responses to shaping avoidance behavior is unclear. Second, reports of dopamine responses to unavoidable aversive stimuli have found inconsistent results, which we hypothesize are due to dopamine neuron heterogeneity. Third, it has been unclear how cNAc dopamine influences downstream cNAc circuit dynamics. Our studies address these issues, recording cNAc dopamine and downstream neuronal activity simultaneously.

Methods: To record dopamine release and activity of dopamine D1 receptor (D1R)- or D2 receptor (D2R)-expressing striatal projection neurons (SPNs), respectively, D1-Cre and A2A-Cre mice were injected with AAVs to express a fluorescent dopamine sensor (pAAV9-CAV-dLight1.3b) and a cre-dependent, fluorescent calcium sensor (pAAV1-CAG-FLEX-NES-jRCaMP1b) in the cNAc. Mice were trained on an active avoidance task, in which a 5s cue predicted a footshock. Mice learned to move between compartments to avoid or escape shocks over 7 days of testing (30 trials/

day). At the end of active avoidance, mice received one day of Pavlovian conditioning, during which a 5s cue predicted an unavoidable 5s footshock (10 trials).

Results: All mice learned to avoid ≥80% of shocks within 7 days of active avoidance training, with individual variability in the speed of learning. cNAc dopamine decreased in response to shocks and shock-predicting cues. D1- and D2-SPN activity increased in response to shocks and shock-predicting cues, with activity in response to the shock-predicting cue increasing across days and as mice avoided more shocks. Response dynamics were unique to instrumental behavior as signals during the Pavlovian conditioning session differed in magnitude and duration.

Conclusions: Mesoaccumbal core circuit dynamics evolve over the course of active avoidance learning. We hypothesize that these circuit dynamics shape individual differences in the speed of avoidance learning and will explore causality relationships.

Disclosure: Nothing to disclose.

56.4 Midbrain Dopamine Neurons Mobilize 2-AG to Encode Predictive Warning Signals During Active Avoidance Learning

Miguel Angel Lujan Perez

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Background: Proactive behavioral control over threat-predictive stimuli allows individuals to avoid aversive events by diminishing generic threat responses. This learning process depends on mesolimbic phasic dopamine signals encoding the association between threat-predictive stimuli and aversive outcomes. In this study, we investigate how certain molecular components of the eCB system modulate in vivo dopamine signaling and active avoidance learning in mice.

Methods: Here, we exploit a novel viral-genetic approach to selectively delete the enzyme diacylglycerol lipase alpha (DGLa) in VTA TH-positive neurons (C57Bl6/J WT and DGLaf/f mice; $n = 24$; 14M, 10F). We also use fiber photometry to measure phasic dopamine release (GrabDA) in the NAc ($n = 12$) and eCB release (GrabeCB2.0) in the VTA of WT mice ($n = 5$). Then, we delete cannabinoid receptors type 1 (CB1R) from ventral pallidum (VP) terminals projecting to the VTA (C57Bl6/J WT and CB1f/f mice; $n = 15$; 7M, 8F). For all experiments, mice were trained to avoid predictable foot-shocks (0.08-0.16 mA) by pressing a lever cued by a 2s-long warning signal.

Results: Our results indicate that WT and DGLaf/f sham mice learned to respond to a short predictive warning signal (2s) in order to avoid foot-shocks. Distinct patterns of NAc dopamine release characterized avoidance and escape responses. Unsupervised random forest classification revealed that avoidance strategy selection could be recovered by phasic features of the NAc GrabDA signal during cue presentation (OOB accuracy = 0.844; 238 trials). Active avoidance behavior ($p < .0001$) and its characteristic dopamine features (OOB accuracy = 0.57; 215 trials) were severely impaired in DGLaKO mice. Furthermore, VTA GrabeCB2.0 recordings during active avoidance learning revealed a downward deflection of eCB release during shock presentation (bootstrapped CI 95% < 0). Finally, we show that deletion of CB1R expressed in VTA-projecting VP terminals also resulted in decreased responding to outcome-predictive cues ($p < .001$).

Conclusions: These results reveal a novel VTATH → VPCB1R 2-AG message sculpting NAc dopamine encoding events responsible for active avoidance learning. Further characterization of the eCB foundation of avoidance behavior could inform future pharmacotherapies enhancing proactive coping strategies in anxiety-related disorders.

Disclosure: Nothing to disclose.

Panel

57. Markers and Mediators of Brain Maturation and Psychiatric Risk in Adolescence: A Cross-Species Perspective

57.1 Dopaminergic Modulation of Prefrontal GABA/Glutamate Balance Suggests Critical Period Plasticity During Adolescence

Ashley Parr

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Background: Changes in prefrontal cortex (PFC) excitatory (glutamatergic, Glu) and inhibitory (GABAergic) balance (E/I) have been identified in human adolescence, potentially reflecting critical period plasticity supporting maturation of PFC-dependent cognition. Adolescent increases in dopamine (DA) may be a trigger for critical period plasticity, and animal models implicate DA in regulating developmental changes in E/I. We assessed the role of striatal tissue iron indices of DA availability in the development of PFC GABA/Glu balance during adolescence.

Methods: Longitudinal 7T Magnetic Resonance Spectroscopic Imaging (MRSI) indices of GABA/Glu and T2*-based indices of tissue iron were obtained in 166 participants (86 female, ages 10-32 years-old, 1-3 visits, 267 visits total). PFC GABA/Glu was acquired via an oblique MRSI slice of 24x24 voxels (1.0x0.9x0.9mm) using a J-refocused spectroscopic imaging sequence. Striatal tissue iron was assessed by time-averaged and normalized T2*-weighted imaging (nT2*w) during 8-min of resting-state.

Results: As in prior studies, striatal tissue iron ($F = 8.03$, $p = 3.87e\text{-}05$) and DLPFC GABA/Glu balance ($F = 10.76$, $p = 9.88e\text{-}07$) increased during adolescence. Trajectories did not differ by sex (DA: $F = 2.11$, $p = .10$; GABA/Glu: $F = .87$, $p = .46$). Critically, we observed a significant age by DA interaction on DLPFC GABA/Glu ($F = 3.01$, $p = .03$). Post-hoc tests revealed that higher DA was associated with greater GABA/Glu imbalance in early adolescence (age 10–15), and subsequently, steeper age-related increases in balance (i.e., decreases in imbalance; $F = 12.44$, $p = 2.49e\text{-}07$) relative to low DA ($F = .90$, $p = .44$). Exploratory tests revealed that higher DA was associated with higher DLPFC Glu in early adolescence, followed by moderate age-related decreases ($F = 2.45$, $p = .06$) relative to low DA ($F = .44$, $p = .73$).

Conclusions: Increased DA is associated with greater GABA/Glu imbalance early in adolescence, potentially driven by DAergic enhancement of excitatory inputs to the PFC, creating a shift out of balance towards greater excitation. As DA stabilizes, Glu may be downregulated, potentially via synaptic pruning, facilitating developmental increases in GABA/Glu balance. These results support a model of critical period plasticity whereby increases in DA are involved in fine-tuning GABA/Glu, and thus E/I balance, in adolescence.

Disclosure: Nothing to disclose.

57.2 Influence of Gonadal Hormones at Puberty on Motivated Behaviors and Mesolimbic Dopamine Circuits

Kristen Delevich

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Background: Adolescence is associated with the maturation of reward-related processing and motivated behaviors. While

puberty coincides with adolescence, the causal relationship between puberty and the maturation of mesolimbic dopamine circuits remains poorly understood. Here, we test whether that prepubertal gonadectomy decreases motivated responding for food by altering mesolimbic dopamine circuit function.

Methods: Male C57Bl/6 mice underwent sham or GDX surgery at postnatal day 25 (P25) or P90 (n = 9-14 mice/group). After 35 days, mice were trained to nosepoke for 20 mg grain pellets from FED3.1 devices, under no cost or escalating cost conditions (progressive ratio closed economy). Mice were tested on the closed economy task after systemic saline or the D2R antagonist haloperidol (0.5 mg/kg) injection to determine the effects of surgery, age at surgery, and drug on foraging strategy. Mice were also assessed for sucrose preference. In a separate group of D1-tdtomato mice, the intrinsic excitability of nucelus accumbens core D1R+ and D1R- spiny projection neurons were compared following prepubertal GDX vs. sham surgery at P60 (n = 8-11 cells/4 mice/group).

Results: No difference was observed in daily pellet consumption under no-cost conditions ($p > 0.05$). However, there were baseline differences in sucrose preference, with P25 GDX exhibiting lower sucrose preference compared to P25 sham and P90 GDX mice ($p < 0.05$). Under escalating cost conditions, P25 sham males tested at ~P70 exhibited higher max breakpoints on saline compared to P25 GDX males ($p < 0.0001$) and P90 sham males ($p < 0.01$) and were the only group in which haloperidol reduced max breakpoints ($p < 0.01$). Haloperidol significantly decreased pellet consumption in sham but not GDX mice ($p < 0.01$). Finally, P25 GDX mice exhibiting reduced excitability of D1R+ SPNs and increased intrinsic excitability of D1R- SPNs compared to age-matched sham mice.

Conclusions: We find that prepubertal but not postpubertal GDX blunts sucrose preference in adulthood. Sham males at ~P70 exhibit a unique peak in breakpoint responding for food that is blocked by prepubertal GDX. GDX before or after puberty decreases the effects of haloperidol on effort allocation. Finally, ephys results suggest that prepubertal GDX reduces the relative excitability of direct pathway D1R+ SPNs in nucleus accumbens core.

Disclosure: Nothing to disclose.

57.3 Abstract not included.

57.4 Gains and Losses: Resilience to Social Stress in Adolescence

Cecilia Flores

McGill University, Montreal, Canada

Background: Adolescence is a unique period of psychosocial growth when social adversity can negatively influence mental health trajectories. Understanding how adolescent social stress impacts males and females differently and why some individuals are particularly affected is becoming increasingly urgent. Social defeat stress models for adolescent male mice have been effective in reproducing physical and psychological aspects experienced by bullied teenagers. However, designing a model suitable for females has proven challenging.

Methods: We report a new version of the adolescent male accelerated social defeat stress (AcSD) paradigm adapted for females. Early adolescent C57BL/6J female mice (n = 107) were exposed to our modified AcSD procedure twice a day, for 4 days, and categorized as "resilient"/"susceptible" based on a social interaction test performed 24 h later. Mice were then assessed for changes in Netrin-1/DCC guidance cue expression in dopamine systems, for inhibitory control capacity in adulthood in the Go/No-Go task, or for alterations in dopamine connectivity organization in the matured prefrontal cortex.

Results: Most adolescent females show protection against stress-induced social avoidance, but in adulthood, these "resilient" females develop inhibitory control deficits and diminution of prefrontal cortex presynaptic dopamine sites. Conversely, female mice classified as "susceptible are protected against cognitive impairment and dopaminergic alterations. AcSD does not alter Netrin-1/DCC expression in adolescent females, contrary to previous findings in males.

Conclusions: Preserving prosocial behavior in adolescent females may be important for survival advantage but seems to come at the price of developing persistent cognitive and dopamine deficiencies. The female AcSD paradigm produced findings comparable to those gathered in adolescent males, allowing investigation of mechanistic underpinnings in either sex.

Disclosure: Nothing to disclose.

Panel

58. Mechanisms and Mitigation of Cognitive Impairment After Cancer and Cancer Therapy

58.1 Using a Mouse Model to Understand Cognitive and Executive Function Deficits in Survivors of Childhood Leukemia and Chemotherapy

Teresa Reyes

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Background: Nearly 95% of children diagnosed with acute lymphocytic leukemia (ALL), the most common form of childhood cancer, achieve long term survival, due in large part to highly effective chemotherapeutic protocols. However, children that survive leukemia are at an increased risk for long-term executive function deficits. A better understanding of the neurobiological effects of early life leukemia and chemotherapy is an essential step in improving the quality of life for leukemia survivors.

Methods: We developed a translationally-relevant mouse model consisting of leukemic cell line (L1210) injection into postnatal day (P)19 mice followed by four cycles of chemotherapy with methotrexate, vincristine, and folinic acid. Beginning one week after the end of chemotherapy, the following behavioral tasks were completed: social behavior (3 chambered social preference and recognition), recognition memory (novel object task) and executive function (using the 5 choice serial reaction time task (5CSRTT)). Prefrontal cortex (PFC) and hippocampus (HPC) were collected at the conclusion of behavioral assays and used for targeted and genome-wide transcriptional analyses. (n = 9-12/group)

Results: Both male and female mice exposed to early life leukemia and chemotherapy showed decreased social and object recognition (main effect for treatment in both tasks, $p < .05$). Exposed mice were slower to progress through increasingly difficult stages of the 5CSRTT ($p < .05$) and showed an increase in premature errors ($p < .05$), indicating impulsive action. Expression of genes related to DNA methylation and microglial function were altered in PFC and HPC ($p < .05$). An exploratory analysis identified a cluster of microglial-related genes in the PFC that were associated with performance in the 5CSRTT and acquisition of the operant response ($p < .005$). RNAseq completed on isolated microglia and astrocytes identified sex-dependent transcriptional

responses, with significantly more genes altered in astrocytes vs microglia, and females more than males.

Conclusions: This work identifies gene expression changes in PFC and HPC that may underlie cognitive deficits in survivors of early life exposure to leukemia and chemotherapy, and suggests the involvement of prefrontal cortical microglia in long term cognitive deficits.

Disclosure: Nothing to disclose.

58.2 Mechanisms and Treatment of Cognitive Impairment After Androgen Deprivation and Docetaxel to Model Prostate Cancer Treatment in Healthy Rats and Rats With Syngeneic Prostate Tumors

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Background: Androgen deprivation (ADT) is a mainstay treatment of prostate cancer, with 5-yr survival > 98%. Cognitive impairment compromises quality of life after ADT. Adding chemotherapy with docetaxel improves survival in advanced cases, but also impairs cognition. Preclinical studies are needed to identify neural mechanisms for these impairments and to develop treatments to improve quality of life. We previously showed ADT impaired set-shifting and mPFC function in young healthy rats. Vortioxetine, a SSRI with unique pharmacology, reversed the deficits. Here, we extend our findings to visuospatial cognition and circuit function in hippocampus (Hipp). We include middle-aged rats, relevant to age of prostate cancer onset, and show preliminary data with a syngeneic rat model to study cognitive impairment after docetaxel and ADT in rats with prostate tumors.

Methods: Young (3 mo) and old (12-14 mo) SD rats were castrated surgically or with degarelix. Vortioxetine was given in the diet (24 mg/kg/day) for 21 d until testing. Behavioral tests include set-shifting (AST; old rats only, to extend prior results) and novel object location (NOL). Hipp circuit function was assessed by afferent-evoked field potentials. Gene expression in dHipp of young rats was assessed by microarray. To introduce prostate cancer, Copenhagen rats were implanted s.c. with syngeneic Dunning R3327G rat prostate tumor fragments, treated with degarelix or docetaxel (3×4.5 mg/kg) and tested on NOL and AST.

Results: As in young rats, ADT impaired set-shifting in old rats. ADT impaired visuospatial cognition and afferent-evoked responses in CA1 of dHipp. Vortioxetine reversed these effects. ADT altered gene expression in dHipp, in pathways related to synaptic plasticity. Vortioxetine had little effect on gene expression. In COP rats, degarelix and docetaxel both attenuated tumor growth. Both tumor and docetaxel impaired visuospatial cognition, but a floor effect prevented detection of combined impact. Early results in ongoing studies suggest tumor + degarelix impairs set-shifting but with too few observations at this point for definitive conclusions; these results remain exploratory for now.

Conclusions: Both cancer and cancer therapy induce cognitive impairments in a rat model now being used to study mechanisms and to test novel therapeutics to improve quality of life for survivors.

Disclosure: Nothing to disclose.

58.3 The Challenge of Measuring Cancer-Related Cognitive Impairment: New Opportunities Using Cognitive Neuroscience in a Sample of Breast Cancer Survivors

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Background: There remains no standard for assessing cancer-related cognitive impairment (CRCI) for several reasons. Historically, studies have incorporated patient-reported cognitive measures as well as objective neuropsychological assessment. However, these approaches often fail to agree about the nature and severity of CRCI, raising debate about best practices. Cognitive neuroscience approaches have emerged as potentially more sensitive to patient-reported symptoms than neuropsychological measures. Cognitive neuroscience paradigms eliciting the Foreperiod Effect measure the temporal preparedness of attentional mechanisms. Protracted Foreperiod Effects (i.e., longer response rates at short intervals, suggesting less efficient preparedness to respond) are observed in normal aging and dementia, but have never been investigated in CRCI. Since CRCI could represent advanced cognitive aging, this preliminary study examines the relationship between the Foreperiod Effect and self-reported cognition in a sample of breast cancer survivors.

Methods: Breast cancer survivors diagnosed 1.5-5 years prior and currently taking endocrine therapy were screened for dementia and then completed online questionnaires that included the Functional Assessment of Cancer Therapy – Cognition, Perceived Cognitive Impairment (PCI) and clinical/demographic information. Participants then underwent a remote cognitive neuroscience battery on the Bruin Health platform that included a reaction time task capturing the Foreperiod Effect with five varied interstimulus intervals (ISIs).

Results: We recruited 44 women age 38-66 ($\bar{x} = 53.7$, $SD = 7.6$) with 17 ± 1.5 years of education. Participants were grouped based on PCI scores < 54 into Impaired ($n = 19$) and Non-Impaired ($n = 25$); there were no group differences on age, education, or IQ. Repeated measures ANOVA within group main effect of ISI demonstrated the Foreperiod Effect ($F(2.439, 102.437) = 55.8, p < .01$), and a Group x ISI interaction ($F(2.439, 102.437) = 4.08, p < .01, p = .01$) suggested that the Impaired group exhibited a more pronounced Foreperiod Effect compared to the Non-Impaired group.

Conclusions: Cognitive neuroscience paradigms measuring temporal preparedness in attentional mechanisms could be sensitive to self-reported cognitive decline in breast cancer survivors taking endocrine therapy.

Disclosure: Nothing to disclose.

58.4 Abstract not included.