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ABSTRACTS COLLECTION

ACNP 58th Annual Meeting: Panels, Mini-Panels and Study Groups

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Panel

1. Leveraging Brain Initiative Technology to Advance Neuropsychopharmacology

1.1 Single Cell Approaches for Studying the Mechanism of Opioid Response

Abstract not included.

1.2 Imaging Opioid-Mediated Intracellular Signaling Events With Cellular and Subcellular Resolution in Living Tissue

Tianyi Mao

Oregon Health & Sciences University, Portland, Oregon, United States

Background: Opioids affect both sensory-discriminative and affective-motivational pains. Opioids also affect Opioids affect both sensory-discriminative and affective-motivational pains. Opioids also affect sensory perception, motor output, decision making, and motivation. The striatum and its two primary excitatory inputs, the cortex and the thalamus, play critical roles in governing brain functions that are sensitive to opioids. However, the precise action sites and the underlying cellular mechanisms of opioid modulation in the thalamo-cortico-striatal circuit are not fully understood. Based on our whole brain mesoscopic connectomic information and novel imaging modality established using BRAIN Initiative funding, we investigated the effects of different opioid receptor family agonists on specific synapses and different neuronal types in the thalamo-cortico-striatal circuit. One much less explored aspect of how opioids affect the circuit is the spatiotemporal dynamics of the intracellular signaling events triggered by distinct opioid agonists in living tissue, particular in living animals. This is mainly due to the lack of robust readout with high spatiotemporal resolution for imaging intracellular signaling events downstream of opioid receptors. The cAMP/PKA pathway is a major mediator for all receptor types, which are generally coupled to the Gi protein to decrease intracellular cAMP levels. We will present the work that allows direct imaging of the opioid-mediated PKA responses in living tissue and behaving animals.

Methods: We will present our work in the development of genetically encoded indicators for monitoring intracellular events downstream of opioids, and implementing in vivo imaging of these indicators in combination with slice physiology and two-photon fluorescent lifetime imaging microscopy (2pFLIM) in vivo.

Results: We first screened from the previously published PKA sensors using hippocampal organotypic slice culture preparations with 2pFLIM technique. We then further improved the sensor performance and developed a variant (named tAKARα) with 3 times increased sensitivity and a broadened dynamic range. tAKARα allows the detection of PKA activation at physiologically-relevant concentrations and kinetics. We then examined the PKA responses to agonist-induced changes in the cortex, thalamus, and striatum in multiple cell types and interaction of the signal with dopamine and norepinephrine. We also used physiology recordings and immunostaining to confirm the agonist specificity and synaptic modification effects.

All experiments include at least 10 cells from 3-5 animals. All experiments involving multiple conditions (baseline, agonist, antagonist) were first tested with a Skillings-Mack test for significant changes in any of the conditions. Only when a significant change was reported, three Wilcoxon signed-rank tests between combination of conditions was performed. There is so far no evidence of differences between male and female mice under our experimental conditions. Therefore, mice of both sexes have been used and sex information was tracked for post hoc analysis to uncover any potential differences.

Conclusions: Our data suggest that tAKARα, combined with 2pFLIM enables the interrogation of opioid-induced PKA signaling in behaving animals. And cell type-specific and subcellular-specific PKA signaling, including soma, dendrite and axonal were identified.

Disclosure: Nothing to disclose.

1.3 An All-Optical Toolkit for Probing Dynorphin Dynamics in the Brain

Matthew Banghart

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Background: Like other neuromodulators, neuropeptides support the brain's ability to remain flexible in dynamic environment. Most neurons synthesize and release neuropeptides in addition to fast transmitters such as glutamate and GABA, yet our understanding of neuropeptide signaling is cursory and many fundamental questions about NP transmission remain: In what behavioral contexts does neuropeptide release occur? What activity patterns and molecular mechanisms govern release? What is the extent of volume transmission, and how long do peptidergic signals last? To address these questions, we are developing all-optical toolkits that

directly and precisely measure and manipulate neuropeptide signaling in behaving animals. Recent progress has been made on probes to study interactions between the opioid neuropeptide dynorphin and the kappa opioid receptor, which are implicated in the negative aversive states associated with pain, drug addiction, stress, and depression.

Methods: Photoactivatable or "caged" dynorphin derivatives were synthesized and evaluated at heterologously expressed receptors using a functional secreted alkaline phosphatase assay in HEK293 cells and at endogenous opioid receptors using brain slice electrophysiology. In parallel, two analogues were assayed in brain slices using genetically-encoded optical sensors for dynorphin developed by Lin Tian's lab at UC Davis. The kinetics of dynorphin signal activation, duration and spread were characterized in striatum using a combination of photorelease, sensor imaging and electrophysiology.

Results: Caged dynorphin variants exhibited up nearly 5,000-fold reductions in EC50 at the kappa, mu and delta opioid receptors depending on peptide length and caging site (e.g. at KOR: Dyn-8 = 7 nM, CYD8 = 16 μM, N-MNVOC-D8 = 33 μM, DynA-17 = 4 nM, CYD17 = 152 nM). Both caged Dyn-8 variants yielded robust photoactivation of GIRK currents in brain slices (tau-on: CYD8 = 241 ms, nMNVOC-D8 = 437 ms at 32 °C). Bulk fluorescence imaging of Dyn-8 photorelease using KOR-light sensors revealed large, graded fluorescence changes that lasted for several minutes (ΔFmax = 23%, tau-off = 185 sec).

Conclusions: The combination of photoactivatable neuropeptides and genetically-encoded optical neuropeptide sensors enable experiments into the spatiotemporal dynamics of neuropeptidergic signaling in the brain. Current caged dynorphin-8 variants exhibit sufficient inactivity to achieve robust, rapid and spatially-resolved receptor activation with light and are compatible with concomitant fluorescence imaging. Efforts toward in vivo application of both technologies are ongoing.

Disclosure: Nothing to disclose.

1.4 DART: A New Way to Study Brain Dynamics, Drugs, and Disease

Abstract not included.

Mini Panel

2. Novel Exosomal Mechanisms of Brain Plasticity for Personalized Interventions in Mood and Cognitive Disorders

2.1 Effects of Early Life Adversity on Central and Systemic Metabolic Dysfunction in Mood Disorders

Abstract not included.

2.2 The Influence of Periphery-To-Brain Communication in Alzheimer's Disease

Abstract not included.

2.3 Exosomal Biomarkers of In-Vivo Brain Insulin Dysfunction in Depression

Carla Nasca

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Background: Previous studies showed an association between peripheral inflammation and mood disorders. However, unlike the role peripheral inflammation in mood disorders, molecular mechanisms of central inflammation in the pathophysiology of mood disorders remain to be fully elucidated. Exosomes are emerging as viable strategies to study in-vivo molecular mechanisms of central inflammation (e.g. aberrant insulin function) otherwise inaccessible in humans. Exosomes are extracellular nanovesicles secreted by most cell types (including CNS cells) that carry proteins, such as the insulin receptor substrate (IRS), important for synaptic plasticity. Exosomes are released in the peripheral blood, thus allowing to their isolation from the plasma of patients.

Methods: 98 subjects suffering from major depressive disorder (MDD) and 45 age- and sex- matched controls participated in this in-vivo study of molecular mechanisms of central insulin function. The psychiatric examination included the Structured Clinical Interview for DSM-IV (SCID) and the psychiatric scale HDRS-17. All patients with MDD were in an acute episode during study participation. Total and CNS-specific exosomes were isolated, and their molecular fingerprint was characterized by using previously described protocols. In brief, brain-enriched exosomes were immunoprecipitated by using magnetic beads conjugated with the antibody for the cell adhesion molecule (LCAM). Enzyme-linked immunosorbent assays were used to measure expression of insulin receptor substrate-1 (IRS1). Finally, we used two machine-learning algorithms to test whether integrated measures of central and systemic insulin function aided depression diagnosis and/or individualized predictions of severity of depressive symptoms.

Results: Our new data showed an aberrant secretion of LCAM+ exosomes in subjects suffering from MDD as compared to controls ($p = 0.03$, effect size = 0.62). LCAM+ circulating exosomes were enriched for the IRS1 marker in patients suffering from MDD ($p = 0.0004$). Within the group of subjects suffering from MDD, no association was found between central and systemic measures of insulin function. By using machine learning, we found that integrated molecular measures of LCAM+ exosomes, CNS-IR together with systemic measures of IR distinguished patients with MDD from healthy controls (sensitivity = 85%), and predicted individual severity of symptoms ($r = 0.5$).

Conclusions: Our new findings suggest a previously unrecognizable condition of insulin resistance in the CNS in subjects suffering from MDD that were previously characterized with a deficiency in the epigenetic modulator of glutamaergic function acetyl-L-carnitine (LAC). The new findings also suggest a role for IRS1 expression in CNS-enriched exosomes as a possible novel determinant of the pathophysiology of MDD. Moreover, the computational approach showed that multidimensional measures of both central and systemic metabolic measures can aid depression diagnosis with higher precision than a single biomarker.

Disclosure: Alfasigma, Advisory Board.

Panel

3. Improving Outcome in Early Phase Psychosis: From Early Intervention Services to Guaranteed Medication and its Effects on Brain Morphology

3.1 Long Term Effects of Early Intervention Services for First Episode Psychosis: Outcomes Over Five Years From the Recovery After a 1st Episode of Schizophrenia-Early Treatment Program (RAISE-ETP)

Nina Schooler

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Background: Early intervention services (EIS) for first episode psychosis (FEP) are now implemented worldwide and these integrated and team-based treatment programs improve FEP outcomes while patients are participating. EIS models provide care for limited periods followed by return to standard services. Cross sectional follow-up studies conducted after EIS participation ends have not found advantages compared with standard care. The RAISE-ETP study was the first US-based, multi-center randomized clinical trial to compare an EIS, called NAVIGATE, to usual clinical care. Those who received NAVIGATE experienced significant improvement in symptoms and functioning compared to those who received usual care during the initial two-year treatment period. We now report clinical outcomes covering five years, a time frame that includes care after EIS participation ended.

Methods: RAISE-ETP was a cluster randomized clinical trial conducted at 34 US sites; 17 sites provided NAVIGATE to 223 participants and 17 sites provided usual clinical care to 181 participants. NAVIGATE was available until the last randomized subject had the opportunity for two years of services. Participants were assessed every six months by masked, centralized assessors utilizing live two-way video and using the Heinrichs-Carpenter Quality of Life Scale (QLS) and the Positive and Negative Syndrome Scale (PANSS).

Results: Participants had a mean age of 23 years and the majority were male; (78% in NAVIGATE and 66% in usual care). The mean opportunity for NAVIGATE treatment was 33.8 (SD = 5.1) months; the longest 44.4 months. Analysis of missing data patterns suggested using a not missing at random (NMAR) approach instead of the more commonly used missing at random (MAR) statistical approach. A NMAR shared parameter analysis of QLS total scores revealed a significant overall treatment by time interaction ($p < 0.001$) with a 13.14 unit difference favoring NAVIGATE over the full five-year study. A similar analysis of the PANSS total score also revealed a significant overall treatment by time interaction ($p < 0.002$) with a 7.73 unit difference favoring NAVIGATE over the 5-year study.

Conclusions: The RAISE-ETP study provides compelling evidence of a substantial benefit in quality of life and in symptom outcomes of the NAVIGATE EIS compared with usual care for FEP over 5 years, a period with EIS and non-EIS treatment. Our ability to detect these advantages in contrast to earlier EIS follow-up studies may be due to our longitudinal assessment model that provided periodic assessment over the full five-year study as well as differences in the statistical approaches of the studies.

Disclosures: Alkermes, Advisory Board; Allergan, Consultant; Intra-Cellular Therapies, Advisory Board; Lundbeck, Advisory Board; GW/Greenwich Biosciences, Advisory Board; Otsuka, Grant.

3.2 Preventing Hospitalization as a Treatment Target for Schizophrenia Interventions

Abstract not included.

3.3 The Prevention of Relapse and Hospitalization in First Episode and Early Phase Schizophrenia: Results From the Prelapse Trial

John Kane

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Background: As emphasized in the 2nd presentation, despite treatment advances in other domains, hospitalization rates in early phase psychosis remain high. Even with early intervention services, a third or more of first-episode patients are hospitalized over the first 2 yrs. of treatment. Non-adherence is a major factor in increasing risk of hospitalization. Long-acting injectable antipsychotics (LAI's) have shown effectiveness in addressing this concern in mirror image and cohort studies. However, randomized controlled trials (RCT's) have reported mixed results. RCT's can change the ecology of care and do not reflect "real world" conditions, particularly when adherence is a focus of study. The large simple trial (LST) is a design intended to address such concerns.

Methods: The PRELAPSE trial was a LST involving cluster randomization of 39 clinics. 19 sites were randomized to provide LAI treatment-the Aripiprazole Once Monthly (AOM) condition and 20 sites to treatment as usual-Clinician's Choice (CC). The primary hypothesis was that the opportunity for treatment with AOM would significantly delay time to first hospitalization. Inclusion criteria were: 1) schizophrenia diagnosis confirmed by a Structured Clinical Interview for DSM-5, Research Version (SCID-5); 2) <5 years lifetime antipsychotics, 3) age 18 – 35 yrs; 4) informed consent. Consistent with a LST, rating scale assessments were done (by centralized raters using live, two-way video) only at baseline, 12 and 24 months. Participants were interviewed via phone every other month for data on hospitalizations/ER visits.

A key challenge in conducting this study was facilitating the acceptance of LAI's among early phase patients at the experimental sites. AOM-specific training included information on the role of non-adherence in relapse/hospitalization, the effectiveness of LAIs in this context, the rationale for LAI use and selection of aripiprazole; shared decision-making principles; discussing LAIs with patients/ families; discussion of transition to LAI's and prescribing guidelines consistent with the package insert for AOM. Training included providing suggested "scripts", frequently asked questions, role-playing and overcoming logistical barriers to the use of LAIs across different healthcare settings.

Results: The 489 participating subjects had a mean age of 25, 75% were male, 44% African American and 35% Caucasian. 46.0% had <=1 year lifetime antipsychotic exposure. As a result of the staff training at AOM sites only 14% of potential subjects declined participation because of the LAI treatment, and 91% of eligible subjects received at least one LAI treatment within the first three months of study.

There were 489 subjects (234 AOM and 255 CC). A total of 52 AOM subjects had at least one hospitalization (22.2%) and 90 CC subjects had a least one (35.3%). For time to first hospitalization, under the proportional hazards assumption, the hazard ratio was HR = 0.56 (95% CI = 0.34, 0.92), p = 0.02.The estimated survival probabilities and 95% CI's from the Cox model were 0.73 (0.65, 0.83) for AOM subjects and 0.58 (0.50, 0.67) for CC subjects. This translates to a number needed to treat (NNT) for prevention of one additional hospitalization for every 6.67 subjects treated with AOM relative to CC.

Conclusions: This study demonstrates the feasibility of engaging the overwhelming majority of early phase patients in the use of LAI's if clinical staff are well trained. The use of LAI's in this population produced a significant delay in time to hospitalization and a NNT of 7 for the prevention of hospitalization.

Disclosures: Alkermes, Allergan, Genentech, Lundbeck, Intracellular Therapies, Janssen, Johnson & Johnson, Merck, Forum, Neurocrine, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, Takeda, Teva, Consultant; Vanguard Research Group, LB Pharmaceuticals, Stock/Equity; Alkermes, Intracellular Therapies, Lundbeck, Neurocrine, Otsuka, Pierre Fabre, Roche, Sunovion, Takeda, Teva, Reviva, Advisory Board

3.4 Changes in White Matter Diffusivity in Early Psychosis: Comparison of Treatment With Long-Acting Injectable Antipsychotic Versus Usual Care

Stephan Taylor

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Background: The effects of antipsychotic treatment vs. effects of psychosis on brain structure remain unclear. Early work by Bartzokis and colleagues suggested an effect of long-acting injectable (LAI) antipsychotic medication, specifically biweekly risperidone, on intracortical myelination. Such effects could potentially be due to the medication itself, or more specifically the consistent administration of the medication achieved through LAI's, rather than oral administration where non-adherence is a major problem. The present study aimed to compare the effects of aripiprazole once monthly (AOM) vs. clinician's choice oral medication (CC) in patients with early psychosis on white matter measures using diffusion tensor imaging (DTI).

Methods: Analyses of structural and diffusion data at baseline and 24 months from AOM-treated individuals ($n = 18$) and individuals in the CC arm ($n = 24$) across 10 sites. Age range was 18-34 yrs, with mean (SD) 24.5 (4.11) One client in the AOM arm completed only sMRI at 24mo. White matter volume was calculated from the structural (T1w) scans using Freesurfer (v6.0.0, longitudinal stream). The diffusion images were preprocessed and fit with a tensor model with FSL (DTIFIT) and registered to the ENIGMA skeleton template, then whole skeleton values of Fractional Anisotropy (FA), Mean Diffusivity (MD), Radial Diffusivity (RD) and Axial Diffusivity (AD) were calculated. The change from baseline to 24-month timepoints was calculated for each measure and input as the dependent variable in a linear model investigating the effects of treatment arm (AOM vs CC), age and treatment arm x age interaction with gender as a covariate. Bonferroni correction was used to account for the 5 models tested.

Results: A significant age by treatment arm interaction was observed for whole skeleton MD ($t[36] = -3.34$, $p < 0.01$, corrected) and RD ($t[36] = -3.41$, $p < 0.01$, corrected). Specifically, both measures of white matter microstructure (diffusivity) decreased during the trial for younger participants in the CC Arm, but increased for younger individuals in the AOM arm. A similar trend was observed for AD ($t[36] = -2.63$, $p = 0.012$, uncorrected). A weaker trend towards a similar age by treatment arm interaction was observed for cerebral white matter volume ($t[37] = 1.83$, $p = 0.07$, uncorrected).

Conclusions: We found preliminary evidence for differential effects of LAI's vs. oral medication by age in people with early psychosis. Specifically, younger individuals showed decreases in MD and RD (plus a trend for AD), depending upon treatment arm. The early interpretation of these results may be that LAI vs. oral administration of antipsychotic medication may exert effects on white matter brain health in late adolescence or early adulthood while the brain is still highly plastic, and final peaks of myelination are still active.

Disclosures: Otsuka, Grant; Boehringer-Ingelheim, Grant.

Study Group

4. ABCD Data Use: Challenges and Opportunities for Prospective and Current ABCD Data Users

Steven Grant*, Muhammad Parvaz, Hugh Garavan, Angela Laird, Wesley Thompson, Giorgia Michelini

Study Group Summary: The ABCD study is a landmark study on brain development and child health. The goal is to advance our understanding of environmental, social, genetic, and other biological factors that affect brain and cognitive development. The study has recently released around 100 terabytes of data acquired data from over 11,000 youth and their families. Imaginably, providing and maintaining access to data of such scale, as well as accessing and analyzing these data, requires education, training but more importantly an open dialogue between the ABCD data providers [the Data Analytics and Informatics Center (DAIC)] and the end users.

While there are several platforms (such as ACNP) available for ABCD users to present their findings, a similar platform for an open dialogue and discussion regarding users' experiences, challenges they have faced and opportunities they have identified while accessing and analyzing these data and perspectives from data providers is missing. Such an initiative is critical especially, since the study has only released Baseline data to date, and plans to periodically release more data over the next decade. Therefore, we propose a Study Group to provide a stage for these important discussions, with representation from NIDA (Dr. Steve Grant), ABCD DAIC (Dr. Wesley Thompson), ABCD investigators and data users (Drs. Angela Laird and Hugh Garavan) and junior investigators using ABCD data (Drs. Muhammad Parvaz and Giorgia Michelini).

Dr. Grant will present the overview and outline the importance of this Study Group in initiating this much-needed dialogue and developing a knowledge base. Dr. Thompson will speak about the Data Exploration and Analysis Portal (DEAP) tool that is available to facilitate analysis of ABCD Study data, providing appropriate statistical models and tools that take advantage of the study design. Dr. Laird will share her group's experience in developing novel methods to navigate this large dataset to identify and download data of interest as well as in leveraging existing computational resources to perform high volume image analyses. Dr. Garavan, will contribute to the discussion by highlighting methodological details about data quality control, statistical modeling (i.e., a nested random effects model is required as the sample contains many siblings scanned across multiple scanners) of the fMRI data, and deriving activation measures most sensitive to individual differences. Dr. Parvaz will discuss how his lab is using the miNDAR, an RDS database in the cloud, to setup data for analyzing the impact of prenatal exposure to illicit substances on brain function in youth. He will also highlight the use of high performance computing resources for image preprocessing and data analysis. Dr. Michelini, will share insights from working on the 2018 and 2019 data releases, and will focus on aspects of the data download, identification of relevant participants (twins/siblings/multiples), and validation of dimensions of child and parent psychopathology based on factor analysis.

The anticipated outcomes of this Study Group are (i) initiation of a common knowledge base around the ABCD data, and (ii) development of a critical mass of interested data users, both of which will continue to grow and can be an invaluable resource for all stake-holders for years to come. Indeed, ACNP, by virtue of its notable attendees, is uniquely positioned to provide this initiative the platform that it truly deserves.

Disclosure: Nothing to disclose.

Study Group

5. Bridging the Gap From Your Research Discovery to a Bonafide Neurotherapeutic: The Role of the NIH Blueprint Neurotherapeutics Network (BPN)

Courtney Miller*, Enrique Michelotti, Charles Cywin, Sharon Rosenzweig-Lipson, Susan Slaugenhaupt, Michael Detke, Amir Tamiz, Lorenzo Refolo, Elena Koustova,

Study Group Summary: Academic researchers are making groundbreaking discoveries in our understanding of neuropsychiatric disorders, regularly identifying new potential therapeutic targets. However, the majority of academic researchers are not trained in the drug discovery and development process, hindering advancement of their discoveries. In the past, pharmaceutical companies could be relied on to continue the process. However, despite the large societal cost of mental and neurological disorders, the majority of large pharmaceutical companies have stopped or significantly reduced their neuroscience efforts. Because academic institutions do not have the significant drug discovery and development expertise or financial resources needed to bring novel neurotherapeutic chemical leads to clinical development, an enormous gap has been created in the development of therapeutics for brain disorders. To directly address this need, the NIH established the Blueprint Neurotherapeutics Network (BPN). The goal of the BPN is to de-risk potential novel small molecule neurotherapeutics to the point that private industry will invest in them. The BPN provides neuroscience researchers from academic institutes and small companies with funding and access to a full range of industry-style drug development services and expertise, via consultants with experience in every stage of drug discovery and development, to Phase I clinical testing. Further, the BPN serves as an excellent training tool for academic researchers in the drug development process.

The goals of this Study Group are the following: 1) Foster discussions around challenges to advancing early stage academic neurotherapeutics to clinical development, 2) Educate attendees on how to translate a promising basic research discovery and partner with biotech/pharma, as well as NIH, 3) Provide guidance on how to utilize BPN support to de-risk novel approaches to brain-related drug discovery and development projects.

To facilitate discussions with attendees, the Study Group will consist of representatives from academia, industry, and the NIH. A concise overview of the BPN's design and intent will be provided by BPN Director, Dr. Charles Cywin (NINDS). This will be followed by short presentations by current and "graduated" grantees. Drs. Courtney Miller (Scripps Research), Sharon Rosenzweig-Lipson (AgeneBio) and Susan Slaugenhaupt (Massachusetts General Hospital) will share their experiences in chaperoning their projects from early stages through to licensing and clinical development with BPN support. Additional members of the BPN will participate in the discussion, providing insight from the program and consulting perspectives. These include Drs. Michael Detke (Chief Medical Officer, Cortexyme), Amir Tamiz (Director of Translational Research, NINDS), Elena Koustova (Director, Office of Translational Initiatives and SBIR Coordinator, NIDA), Lorenzo Refolo (Program Officer, NIA), and Enrique Michelotti (Molecular Pharmacology Program Chief, NIMH).

Disclosure: Nothing to disclose.

Panel

6. The Transition From Acute to Chronic Pain: From Circuits to Molecules

6.1 Sexually Dimorphic Influence of the Chemokine, Colony Stimulating Factor 1, on Spinal Cord Microglia and Neuropathic Pain Processing

Abstract not included.

6.2 Regulators of G Protein Signaling as Targets for the Treatment of Chronic Pain

Venetia Zachariou

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Background: Regulator of G protein signaling 4 (RGS4) is a potent modulator of G protein-coupled receptor (GPCR) signal transduction, which is expressed at various levels of the nociceptive pathway as well as in circuits controlling stress and motivation. RGS4 binds to activated G alpha subunits of heterotrimeric G proteins to promote their transition to inactive states, while it may also dynamically control the direction of signaling by acting as effector antagonist for G alpha subunits. Here, we use genetic mouse models and a several paradigms of peripheral inflammation and peripheral nerve injury to demonstrate a role of RGS4 in the maintenance of chronic pain states.

Methods: The role of RGS4 in the induction, intensity and maintenance of chronic pain related symptoms is investigated using constitutive and conditional knockout models. We used the Complete Freund's Adjuvant, formalin, spared nerve injury and chemotherapy-induced neuropathy paradigms understand the role of RGS4 in chronic pain-induced behaviors. We applied Von frey, Hargeaves, Cold plate, adhesive paper and rough floor avoidance assays to monitor sensory hypersensitivity, and running wheel, social interaction, novelty suppressed feeding to monitor affective components of chronic pain. For all behavioral assays we applied 8–12 mice per group, and data were analyzed using ANOVA for repeated measures followed by Bonferroni test. We also used RNA Sequencing to assess differential gene expression between genotypes, and Ingenuity Pathway analysis to predict pathways affected by chronic pain and pain recovery. Findings were validated using qPCR and western blot analysis ($n = 8$–10 per group, t-test or two way ANOVA for statistical comparisons).

Results: Using models of peripheral inflammation, peripheral nerve injury and chemotherapy-induced neuropathy we demonstrate that prevention of RGS4 action leads to recovery from chronic pain states. While knockout of RGS4 does not affect the onset or the intensity of chronic pain, it leads to recovery from sensory hypersensitivity behaviors and restores running wheel activity and deficits in social interaction, sucrose consumption or novelty-suppressed feeding. This phenotype was observed in both male and female mice. Conditional downregulation of RGS4 in the ventroposteriolateral thalamus is sufficient to promote recovery from sensory hypersensitivity, whereas down regulation of RGS4 in the nucleus acumens prefrontal cortex or in the dorsal root ganglia did not significantly affect the trajectory of pain symptoms. Our RNA Sequencing and bioinformatic analysis reveals that prevention of RGS4 action restores pain-induced gene expression adaptations in the thalamus and promotes the expression of metabotripic glutamate receptor2.

Conclusions: Our findings support the notion that distinct intracellular mechanisms promote sensory hypersensitivity at early versus later time points after nerve injury or peripheral inflammation. The intracellular modulator RGS4, expressed in throughout the pain matrix plays a prominent role in pain chronicity in male and in female mice. Disruption of RGS4 activity may provide an efficient avenue for the management of chronic pain conditions.

Disclosure: Nothing to disclose.

6.3 Why!? Why Was I Programmed to Feel Pain? Neural Circuits Encoding the Unpleasantness of Nociception

Gregory Corder

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Background: Pain is fundamental to our conscious experiences and evolutionary survival, and the ancestral neural circuits for pain are likely conserved from rodents to humans. Pain acts as an instructive signal that directs our attention to prioritize threats from the world or within our own bodies. So then why does pain "hurt"? Like all subjective experiences, pain is constructed on a moment-by-moment basis from a complex integration of information from across the brain. However, unlike almost every other sense (e.g. vision, touch, audition, etc.), pain is both a sensation and an innate emotion with strong motivational significance. Decisions and behaviors exhibited by humans and animals are conditional upon the transformation of rapid sensory stimuli (e.g., noxious stimuli, such as a pin prick) into lasting internal states, commonly referred to as affect or emotion (e.g., pain unpleasantness). The negative affective dimension of pain underlies the suffering of chronic pain patients. Thus, the discovery of specific neural circuits responsible for the unpleasant quality of pain perception must be the first step in developing novel, efficacious pain treatments.

Methods: To discover other circuit elements of the BLA pain affect pathway, we are identifying the brain-wide, input-out neural architecture using a mouse driver line to genetically target pain-active neurons in combination with activity-dependent viruses. To assess the functional influence of computations between these circuit elements toward acute and chronic pain perception, we leverage implantable miniature integrated fluorescence microscopes, with built-in optogenetic capabilities, for simultaneously imaging the activity of hundreds of deep brain neurons in freely behaving mice while also optogenetically inhibiting BLA pain-affect projections into different circuit elements of the pain-affect pathway.

Results: We find that amygdalar nociceptive neurons send long-range projections that preferentially innervate the posterior nucleus accumbens (NAc) core and shell subnuclei, and encircle neurons co-expressing dopamine receptor 2 and the endogenous opioid enkephalin. Preliminary in vivo calcium imaging illustrates that nociceptive neural activity is localized to the caudal NAc core/shell. This suggests pain valence information transmitted from the BLA to NAc could influence motivational and hedonic behavior, e.g., depression co-morbid with chronic-pain.

Conclusions: We recently identified a critical cell population within the brain's pain pathway that specifically encodes the affective, rather than sensory, component of chronic pain. This nociceptive-specific cluster of amygdalar neurons does not directly encode rewarding or other aversive experiences. Pain-affect information from the BLA is then transmitted to several cortical and subcortical regions important for motivation and decision-making. This suggests that novel treatments disrupting the processing of pain in this pathway may meet the long-sought criteria of high analgesic efficacy without addictive liability.

Disclosure: Nothing to disclose.

6.4 Pain and the Infant Brain

Rebeccah Slater

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Background: Pain perception in adults is influenced by our experiences, leading to differences in pain vulnerability between individuals. Neuroimaging studies reveal that these differences are related to individual differences in structural and functional organisation of the brain. Infants also exhibit substantial variability in terms of their behavioural, autonomic, and neurophysiological responses to acute noxious events. The study aim was to investigate whether resting-state brain activity recorded in the first few days of life in newborn infants can be used to predict individual infants pain-related changes in brain activity following acute noxious stimulation.

Methods: 18 healthy term infants (10 males; 8 females) with mean gestational age (GA) 38.7 weeks and mean birth weight 3,408 g, were recruited to take part in this study within the first postnatal week (mean postnatal age: 2.3 days). Resting-state brain activity and stimulus-evoked blood oxygen dependent (BOLD) responses to noxious stimulation were recorded when the infants were naturally still in the Magnetic Resonance Imaging (MRI) Scanner. Resting-state networks were identified using probabilistic functional mode analysis, and amplitudes of these networks at rest were used to predict noxious-evoked activity. The nine resting state networks included in our model included somatomotor, visual, auditory, dorsal attention, default mode and executive control networks. Our model was a support vector regression model, predictions being generated using leave-one-out cross-validation. In a 215-subject sample of dHCP data, we explored the relationship between predicted response magnitudes and white matter structure - mean diffusivity (MD) and fractional anisotropy (FA) - using tract-based spatial statistics (TBSS). Main TBSS analysis included multiple testing corrections for modalities (MD and FA tissue properties) and contrasts (positive and negative relationships).

Results: Nine resting-state networks were robustly identified and replicated in two independent datasets. The amplitude of the resting-state network activity in each infant is highly predictive of the magnitude of the infant's stimulus-response following noxious stimulation. A significant correlation (not driven by potential confounds including gestational age, total brain volume, subject motion and temporal signal to noise ratio) was observed between the predicted stimulus-response scores and observed scores (mean squared error $= 0.91$ ($p = 0.001$); R Spearman correlation coefficient $= 0.75$ ($p = 0.0002$); R2 Prediction [coefficient of determination] $= 0.66$). Using the dHCP dataset, predicted stimulus-response magnitudes had a statistically significant negative relationship with MD in the anterior limb of the internal capsule. Post-hoc analysis identified this relationship to be bilateral and widespread, with relationships identified in other internal capsule regions, corpus callosum, and somatosensory and motor fibre bundles in the centrum semiovale. All maps were thresholded using TFCE with default parameters and FWER correction of $\alpha = 0.05$.

Conclusions: Noxious-evoked changes in brain activity recorded in individual newborn infants can be predicted from their resting-state activity. Resting-state activity recorded in infants contains information that is relevant to pain processing, demonstrating the central importance of an infant's neural functional architecture in processing noxious events. These approaches lead to the possibility of using stimulus-free resting-state fMRI to predict infant' pain sensitivity.

Disclosure: Nothing to disclose.

Panel

7. Novel Extensions of Computational Psychiatry to Decode Treatment Targets in Depression and Anxiety

7.1 Heterogeneous Neural Substrates and Computational Modeling of Attention Bias in Transdiagnostic Anxiety

Rebecca Price

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Background: Biased patterns of attention are implicated as key mechanisms across many forms of psychopathology, including clinical anxiety, and have given rise to automated mechanistic interventions designed to modify such attentional preferences. However, progress is substantially hindered by limitations in widely-used methods to quantify attention bias and its neural substrates, leading to imprecision of measurement. Furthermore, substantial heterogeneity within clinical, neural, and attentional features of anxiety is overlooked in typical group-level comparisons.

Methods: In a transdiagnostic clinically anxious sample (n = 70), we used a previously validated method for data-driven parsing of neural connectivity, applicable for use in smaller samples, to reveal connectivity-based subgroups among the anxious patients. These neural connectivity-based subgroups were externally compared on the attentional patterns derived from behavioral measures. In a novel analytic approach to the behavioral attention bias task data, we applied a well-established form of computational modeling (Drift-Diffusion Model; DDM) to trial-level reaction time data from a two-choice "dot-probe task" in order to model distinct components of task performance. The computational modeling-based attentional bias indices, relative to conventional attention bias indices, yielded substantially improved split-half reliability and modestly improved test-retest reliability. Both DDM-based and conventional (eyetracking, reaction time) measures of attentional bias were used to test whether the neural connectivity-based subgroups generalized to predict unique attentional patterns in behavior.

Results: Two functional connectivity-based subgroups were identified within our heterogenous sample. Subgroup A (68% of patients) showed stronger executive network influences on sensory processing regions. Subgroup B was defined by a larger number of limbic influences on sensory regions. These neural connectivity-based subgroups predicted complex, differential patterns of performance across multiple external indices of attentional bias (p's < 0.05 for unpaired t-tests across multiple indices), including those derived through computational (DDM) modeling ($F(1,58) = 7.75$, $p = 0.007$).

Conclusions: Neural connectivity-based categorization was used to parse heterogeneity among clinically anxious adults, and revealed an atypical, limbic-driven pattern of connectivity in a subset of anxious patients, which generalized to atypical patterns of attentional bias according to external task-based performance measures. Data-driven parsing of connectivity patterns suggests heterogeneous neural substrates of anxiety, with possible implications for personalized, mechanistic treatments targeting attention. When combined with computational modeling of behavioral task-based data, this approach may represent a new way forward to improve precision and specificity in understanding the cognitive neuroscience underpinnings of anxiety.

Disclosure: Nothing to disclose.

7.2 Neurocomputational Mechanisms of Antidepressant Placebo Effects

Marta Pecina

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Background: Reinforcement learning (RL) theories of placebo effects – informed predominantly by placebo analgesia experiments – posit that an individual's expectation of improvement is updated with the arrival of new sensory evidence (e.g., pain), by incorporating a reward prediction error (RPE), which signals the mismatch between the expected (expected value) and perceived improvement. Consistent with this framework, neuroimaging studies of placebo analgesia, have demonstrated increased blood-oxygen-level dependent (BOLD) responses in regions tracking expected values [e.g., ventromedial prefrontal cortex (vmPFC)] and RPEs [e.g., ventral striatum (VS)]. Despite promising leads, the investigation of antidepressant placebo effects has been impeded by the lack of experimental approaches informed by conceptual theories that bridge the psychological, neural, and molecular aspects of the placebo effect phenomenon.

Methods: We will present data in forty patients with Major Depressive Disorder (MDD, 75% women) who completed the Antidepressant Placebo fMRI task, developed by our group to examine how placebo-induced expectations of mood improvement and their reinforcement by sham neurofeedback contribute to the formation of placebo effects. Antidepressant placebo expectancies were fitted to a model of RL using the Variational Bayes Approach (VBA) toolbox implemented in MATLAB. Estimated learning signals (expected values and RPEs) generated from the RL model were mapped to neural activity and analyze according to standard procedures.

Results: Patients reported greater expectations of mood improvement following the "antidepressant" infusions (vs. "calibrations"), especially when reinforced by positive neurofeedback, as reflected in a positive two-way interaction (Estimate = 0.96, S.E. = 0.12, p = <10-9). Participants also reported greater mood improvement after receiving positive (vs. baseline) sham neurofeedback, which was enhanced by the "antidepressant" infusions (Estimate = 0.4, S.E. = 0.17, p = 0.02). The RL model ¬was significantly better at predicting the patient's evolving expectancies of improvement than the null model – which assumed no learning – (Bayesian Omnibus Risk = <10-6). Reward learning signals resulting from the RL model predicted greater placebo-induced mood improvement (Expected value: Estimate = 0.17, S.E. = 0.07, p = 0.01; RPEs: Estimate=1.71, S.E. = 0.09, p = 10-15). Furthermore, the "antidepressant" infusions (vs. "calibrations" resulted in a significant greater effect of both, learned expected values (Estimate = 0.44, S.E. = 0.10, p = <10-6) and RPEs (Estimate = 0.22, S.E. = 0.10, p = 0.005) on mood. This model was a better predictor of placebo-induced mood improvement that the model with the task conditions alone (RL model's AIC: 2485, Task conditions model's AIC: 2630, p < 10-16). At a neural level, the whole-brain analysis of the RL model-derived revealed increased BOLD responses in the ventrolateral and ventromedial prefrontal cortex, subcortical areas (ventral striatum and thalamus) and visual processing areas, whereas the RPE map revealed isolated areas of activation in the VS, thalamus and visual processing areas.

Conclusions: Reinforcement learning models explain evolving expectancies of improvement in patients with depression. Reward learning signals resulting from the RL model predicting antidepressant expectancies were mapped onto cortico-striato-thalamic networks and modulated the effect of the placebo cues on mood responses. These results provide a neurocomputational framework for the prediction of antidepressant placebo effects.

Disclosure: Nothing to disclose.

7.3 Clusters of Canonical Neural Circuit Dysfunction are Distinguished by Symptom and Treatment Profiles

Leanne Williams

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Background: Computational approaches applied in functional neuroimaging measures of resting state functional connectivity

show promise for identifying neural circuit-based subtypes for mood and anxiety disorders. However, these approaches have not yet been applied in the investigation of functional neuroimaging measures of task-evoked activation and functional connectivity. Here, we deployed cluster analysis and machine learning convolutional neural network approaches to determine if there are coherent and clinically interpretable subtypes defined by distinct disruptions in functional activation connectivity across tasks designed to probe systems of emotion valence and cognition.

Methods: A multidiagnostic sample of 174 adults with mood and anxiety disorders (18 to 60 years) and a depression combined with anxiety sample of 102 adults (18 to 60 years) took part. These samples comprised 60% females and 40% males on average. Participants were scanned using 3T GE functional neuroimaging during facial emotion viewing (conscious, nonconscious), Go-NoGo inhibition and n-back working memory tasks and completed comprehensive batteries of symptom questionnaires and computerized neurocognitive tests. Regions of interest were anchored in preregistered circuit definitions and operationalized using the neurosynth.org database. Functional activation of all regions was derived using contrasts of interest and functional connectivity between region pairs was quantified with generalized psychophysiological interaction analysis. Machine-learning approaches were used to identify coherent subtypes based on both activation and functional connectivity data. We then tested if subtypes were distinguished by symptom-behavior profiles.

Results: We identified four subgroups with distinct activation and functional connectivity profiles across circuits of interest. Although Solmogorov-Smirov tests comparing mean clinical symptom distributions between the training and test patients revealed no significant differences for any of the groups (all $Ds > 0.2$, $ps > 0.758$), circuit-derived subgroups were distinguished by their symptom profiles. For example, Subgroup 1 was distinguished by low levels of worry and a higher propensity to keep emotions to themselves while subgroup 2 was distinguished by high levels of worry and poor quality of life.

Conclusions: This study demonstrates a novel application of machine-learning methodologies to task-evoked functional activation and connectivity to identify circuit-based subtypes of mood and anxiety that correspond to clinical profiles and which may be useful for advancing precision psychiatry.

Disclosure: Blackthorn Therapeutics, Consultant; Psyberguide, Advisory Board; Laureate Institute for Brain Research, Advisory Board.

7.4 Approach-Avoidance Conflict in Major Depression: Clues From Human and Non-Human Primate Investigations

Diego Pizzagalli

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Background: Major depressive Disorder (MDD) is characterized by abnormal approach-avoidance behaviors, which have been linked to worse disease trajectory. Despite their clinical prominence, systems-level dysfunctions associated with these abnormalities remain insufficiently understood. A contributor to such modest progress is the use of different tasks across species, which limits integration.

Methods: To fill this gap, we adapted an approach-avoidance conflict task previously utilized in non-human primates (NHPs) (Amemori & Graybiel, 2012) for use in humans with fMRI. Using fMRI (in 42 humans, including 18 unmedicated individuals with MDD) and electrophysiological recordings (in 2 NHPs) in conjunction with functionally analogous tasks, we investigated the neural correlates of approach-avoidance conflict across species. Hierarchical Bayesian parameter estimation of the drift diffusion model (HDDM) was used to quantify the impact of neural variation on dynamic decision parameters.

Results: Relative to controls, the MDD group showed reduced sensitivity to reward and bias toward approach (HDDM: $p < 0.05$). In both species, shared neural correlates of approach-avoidance conflict and aversiveness emerged in the anterior cingulate cortex (humans: GLM: $p < 0.05$, whole-brain corrected; NHPs: stepwise regression: $p < 0.05$), particularly the pregenual anterior cingulate cortex. Abnormal task-related activation in MDD emerged also in the prefrontal cortex and striatum (unpaired $t = 3.54$, $p < 0.001$), and such abnormalities correlated with current symptoms and perceived stress and predicted perceived stress 6 months later (Pearson r: −0.57 to -0.65, $p < 0.03$).

Conclusions: Using functionally analogous tasks, we identify shared cross-species mechanisms of approach-avoidance conflict, which highlight promising candidates for translational and computational biomarkers.

Disclosure: BlackThorn Therapeutics, Consultant; Boehringer Ingelheim, Consultant; Compass Pathways, Consultant; Takeda, Consultant; BlackThorn Therapeutics, Stock/Equity.

Panel

8. Experience-Dependent Modification of Fear Memories and Implications for Mechanisms Underlying Post-Traumatic Stress Disorder

8.1 Circuit Dynamics of Linking and Separating Aversive Memories

Denise Cai

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

Background: Post-traumatic stress disorder (PTSD) is a debilitating condition characterized by persistent and intrusive memories of a traumatic event. Here, we investigated a novel mechanism that may contribute to fear generalization in PTSD: temporal memory-linking. We recently found that two neutral memories learned within a day share an overlapping neural ensemble in the hippocampus linking the temporally related memories so that recall of one memory triggers recall of the other. Although these findings demonstrate a mechanism for temporal linking of neutral memories, pathological experiences leading to PTSD are far from neutral. It is critical, therefore, to understand how negative valence (e.g. fear) impacts memory-linking and contributes to the transfer of fear. Here, we show how negative valence extends the temporal window for memory-linking and increases the spread of fear from aversive to safe (neutral) contexts.

Methods: Experiment 1: Mice ($n = 8–10$ per group) learned a neutral context and 5h, 1d, 2d, 7d later, learned a different context paired with a footshock (aversive context). Two days later, mice were placed back in the neutral context to assess if fear from the aversive context transferred retrospectively to the neutral context previously learned. Experiment 2: Mice ($n = 4–7$ per group) were injected with AAV-GCaMP6f and implanted with GRIN lenses in dorsal CA1 to visualize hippocampal calcium activity during learning and retrieval of the two context memories (similar to Experiment 1 but only with 2d interval). Experiment 3: Mice ($n = 6$ per group) were injected with either hM4Di-GFP or GFP virus in dorsal CA1 and underwent context learning (similar to Experiment 2). After learning the second aversive context, mice were injected (i.p.) with CNO to decrease hippocampal activity in CA1 during the

offline memory consolidation phase. Two days later mice were returned to the neutral context to assess if inhibiting hippocampal activity during the consolidation phase decreased the transfer of fear from the aversive context to the neutral context. (Male mice were used in these studies.)

Results: Negative valence (i.e., footshock) during encoding of a context extends the window of memory-linking retrospectively up to two days and this behavioral transfer of fear is mediated by sharing an overlapping neural ensemble between the aversive and neutral context representations. Experiment 1: Transfer of fear to the neutral context as measured by freezing during retrieval was higher in the 5h, 1d and 2d groups compared to the 7d group (One-way ANOVA, $p = 0.02$, posthoc, Fisher's LSD, $p = 0.02$, $p = 0.03$, 0.04, respectively). Experiment 2: There was a higher level of neural overlap between the aversive and neutral context representations compared to the representations of two neutral contexts (unpaired t-test, $p = 0.01$). Experiment 3: In the GFP control group, fear from the aversive context transferred to the previously learned neutral context but not to a novel context (unpaired t-test, $p = 0.03$). However, in the hM4Di group, fear was not transferred to the neutral context as the freezing in the neutral context was not different from the novel context (unpaired t-test, $p = 0.83$).

Conclusions: Combining our contextual learning paradigm with in vivo miniature microscopes, we demonstrate that adding negative valence may extend the temporal window in which memories can be linked across time. This transfer of fear may be mediated by an overlapping neural representation in hippocampus that emerges during an offline consolidation phase. Furthermore, the linking can be abolished by decreasing hippocampal neural activity during the consolidation phase.

Disclosure: Nothing to disclose.

8.2 Distinct Hippocampal Ensembles Control Extinction and Relapse of Learned Fear

Michael Drew

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Background: Extinction-based treatments, such as exposure therapy, are used to reduce maladaptive fear and anxiety, but these treatments do not permanently abolish fear. The relapse of fear after extinction is believed to occur because extinction fails to abolish the original fear and, instead, creates a new memory suppresses fear. Previous research demonstrates that the hippocampal dentate gyrus (DG) generates a contextual fear memory trace, which is a neuronal ensemble whose activity is necessary and sufficient for expression of learned fear. Using activity-dependent neural tagging in mice, we investigated whether DG also generates an extinction memory trace.

Methods: Experiment 1 addresses whether extinction training suppresses reactivation of DG fear acquisition neurons. We used male and female ArcCreERT2 transgenic mice to tag neurons active during fear acquisition ($n = 15$) or fear extinction training ($n = 16$). Mice were euthanized after a context test session 5d ($n = 16$) or 28d ($n = 15$) after extinction. Using Arc immunohistochemistry, we assessed reactivation of fear acquisition-tagged and extinction-tagged neurons. Experiment 2 addresses whether the fear-tagged and extinction-tagged neurons are necessary for expression of extinction or spontaneous recovery of fear. ArcCreERT2 x Halo-eYFPflx mice were used to express eNpHR3.0 in acquisition-tagged ($n = 9$ Cre+, 9 Cre-) or extinction-tagged neurons ($n = 8$ Cre+, 7 Cre-). Light was delivered into DG to silence these ensembles during context fear test sessions. Experiment 3 addresses whether fear expression and extinction expression recruit different ventral hippocampal projection pathways. rAAV-retro was injected into prelimbic (PL) or infralimbic (IL) prefrontal cortex or basolateral amydgala (BLA) of male and female mice. cFos Immunohistochemistry was used to assess activation of ventral hippocampal projections to these regions during fear, extinction, and spontaneous recovery.

Results: In Experiment 1, fear extinction-tagged neurons in DG were more strongly reactivated than acquisition-tagged neurons during the context test 5d after extinction, when fear was low. During the test session 28d after extinction, fear was elevated due to spontaneous recovery and acquisition-tagged neurons were more strongly reactivated than extinction-tagged neurons [RM-ANOVA Session X Tagging interaction, $F(1,27) = 41.47$, $P < 0.0001$]. In Experiment 2, silencing extinction-tagged neurons in an extinction retrieval test increased freezing [RM-ANOVA Genotype × Light interaction, $F(1,16) = 10.24$, $P = 0.006$]. Silencing fear acquisition tagged neurons had no effect during the extinction retrieval test but reduced spontaneous recovery of fear [RM-ANOVA interaction $F(1,13) = 10.68$, $P = 0.006$]. In Experiment 3, injections of AAV-retro into PL, IL, and BLA labeled distinct neuronal subpopulations in ventral hippocampus. Experiments in progress assess activation of these subpopulations during recall of fear, recall of extinction, and spontaneous recovery.

Conclusions: Our results demonstrate that expression of extinction is associated with suppression of the DG fear memory ensemble and activation of a distinct extinction representation in DG. During fear relapse, the fear ensemble is reactivated and the extinction ensemble is suppressed. Optogenetic silencing demonstrate that these ensemble dynamics play a causal role in fear regulation. Our data demonstrate that suppression of fear and spontaneous recovery are controlled by competition between distinct fear and extinction representations in the hippocampus.

Disclosure: Nothing to disclose.

8.3 Propranolol Decreases Fear Expression by Modulating Memory Traces in the Dorsal Dentate Gyrus

Christine Ann Denny

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Background: Posttraumatic stress disorder (PTSD) is triggered by a traumatic event, resulting in heightened fear, anxiety, flashbacks, and intrusive thoughts. Although approximately 8% of the United States general population is affected by PTSD, only two drugs have been approved by FDA, both with limited efficacy. Propranolol, a non-selective β antagonist, has shown efficacy in decreasing fear expression and there has been recent, renewed interest in using it for fear disorders. Here, we sought to determine the mechanisms by which propranolol decreases fear expression by utilizing an activity-dependent tagging line, the ArcCreERT2 x enhanced yellow fluorescent protein (eYFP) mice, to identify individual fear memory traces.

Methods: 129S6/SvEv mice were administered a 4-shock contextual fear conditioning (CFC) paradigm followed by immediate or delayed context exposures ($n = 4$ cohorts; $n = 9$–10 mice per group). A single injection of saline or propranolol was administered either prior to or following the first context re-exposure. In a second set of experiments, to control for whether acute propranolol administration altered anxiety, mice previously exposed to a 4-shock CFC paradigm received either propranolol or saline immediately before being place in an elevated plus maze (EPM) or in an open field (OF) ($n = 9$ mice per group). In a third set of experiments, we sought to determine if the propranolol-induced decrease in fear expression was due to a central or peripheral β-adrenergic blockade. A 4-shock CFC paradigm was administered and saline or sotalol, a peripheral β-adrenergic blocker, was administered prior to a delayed context exposure ($n = 9$–10 mice

per group). Finally, ArcCreERT2 mice were administered 4-shock CFC and a delayed context exposure with either a saline or propranolol injection prior to the first context exposure (n = 9 mice per group). eYFP+, c-fos+, and eYFP+/c-fos+ (e.g., memory traces/engrams) were visualized and quantified throughout the dorsal-ventral axis of the hippocampus.

Results: Propranolol was effective at decreasing fear expression only when administered prior to a delayed context exposure ($p < 0.0001$). Propranolol's effects on fear expression did not extend past the first context exposure ($p > 0.05$). Propranolol administration did not change any measure of anxiety ($p > 0.05$). Sotalol was ineffective in attenuating learned fear ($p > 0.05$). Finally, propranolol was also effective at decreasing fear expression in the ArcCreERT2 mice. This behavioral effect was correlated with altered memory traces in the hippocampus. Specifically, the percentage of eYFP+/c-fos+ cells (e.g., reactivated fear memory traces) was decreased in the dorsal dentate gyrus (DG) ($p < 0.0125$) of ArcCreERT2 mice that received propranolol prior to re-exposure, but not in the ventral DG (vDG), dorsal CA3, or ventral CA3 (p's > 0.05).

Conclusions: These data indicate that propranolol decreases fear expression by modulating fear memory traces in the dorsal DG, but not in the ventral DG or CA3, by potentially weakening the reactivation of the initial traumatic memory that was encoded. Ongoing work is to further elucidate the mechanisms by which propranolol alters reactivation of fear memory traces outside of the hippocampus. In summary, this work adds support to the resurgence of interest in noradrenergic drugs as assistance to therapies for PTSD patients.

Disclosure: Nothing to disclose.

8.4 Population and Projection-Specific Segregation of Hippocampal Fear and Reward Engrams

Steve Ramirez

Boston University, Boston, Massachusetts, United States

Background: The hippocampus is involved in a variety of mnemonic computations and in modulating emotional behaviors. While much attention has been given to its role in processing spatial-temporal dimensions of an experience, much less known about whether or not the hippocampus contains circuit elements processing discrete emotional experiences. Here, we combine transgenic and all-virus based activity-dependent tagging strategies, as well as RNA sequencing strategies, and provide evidence that the hippocampus recruits two partially segregated populations in response to rewarding or aversive stimuli.

Methods: FosCreER (Jax stock: #021882) and Wildtype male C57BL/6 mice (2-3 months of age; Charles River Labs) were injected with a virus cocktail consisting of cFos-tTA and TRE-ChR2-EYFP, as well as DIO-Breaches-tdTomato, to confer activity dependent labeling of cells during either a positive or negative experience in a within-subject manner (n = 8–12 mice per group; n = 4 cohorts). A positive experience consisted pairing male and female mice for an hour or administering condensed milk to each subject; a negative experience consisted of a 4-shock contextual fear conditioning paradigm or a 2-hour immobilization stress procedure. All subjects were raised on Doxycycline, which binds to tTA to inhibit activity-dependent labeling, thus raising the possibility of opening or closing windows for tagging active cells with this strategy. Subjects were first pulsed with 4-OHT to label active cells during a positive (n = 8) or negative experience (n = 8) via the FosCreER system, followed by removal of Doxycycline to open a second window for tagging active brain cells in a counterbalanced manner. Next, all subjects underwent optogenetic manipulation of each ensemble and tested under an optoplace preference / aversion assay. Moreover, three separate groups (n = 8 per group) received optogenetic stimulation of hippocampus outputs to the nucleus accumbens, basolateral amygdala, or medial prefrontal cortex. Finally, all subjects underwent immunohistochemical procedures to stain for EYFP and tdTomato-positive cells.

Results: While optogenetic manipulation of tagged cell bodies in hippocampus is not sufficient to drive behavior ($p = 0.45$), tagged hippocampus terminals projecting to the amygdala ($p < 0.001$) and nucleus accumbens ($p < 0.05$), but not the prefrontal cortex ($p = 0.31$), have the ability to drive preference and aversion. Moreover, histological analyses indicated that cells active during a fearful experience and thereby labeled with tdTomato, are statistically segregated from cells active during a rewarding experience, and thereby labeled with EYFP. Finally, using an RNA Sequencing approach, we find that the hippocampus contains fear and reward cells that upregulate genes associated with Alzheimer's Disease and neuroprotection, respectively (n = 3 triplicates).

Conclusions: Here we show that the hippocampus processes fear and reward in populations of cells that are partially distinct at the molecular and anatomic levels, as well as in their capacity to drive behaviors through functionally plastic projection-specific terminals. Additionally, by combining activity-dependent tagging transgenic strategies with all-virus-based expression of light-sensitive effectors, our design permits the monitoring and manipulation of multiple ensembles in a within-subject manner. These approaches enable the tagging, manipulation, and molecular documentation of cells processing fear and reward, which opens the possibility of cataloguing topographical similarities and differences between the two in a brain-wide manner.

Disclosure: Nothing to disclose.

Mini Panel

9. Looking Beyond Replacement Therapies for Pharmacological Strategies to Treat Drug Addiction

9.1 Cell Adhesion Systems in the Orbitofrontal Cortex Confer Resilience to Cocaine

Shannon Gourley

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Background: Prefrontal cortical development during adolescence involves the pruning of some dendritic spines and the stabilization of others. This dynamic process may create a window of vulnerability during which drugs of abuse can have durable consequences that ultimately contribute to long-term susceptibilities to drug addiction and related deficits in decision making. Of interest then, are molecular factors that promote dendritic spine stability. β1-integrins, subunits of the heterodimeric integrin cell adhesion receptor, are necessary for dendritic spine stabilization in adolescence and for optimal decision-making in tasks in which mice must prospectively evaluate the consequences of their actions.

Methods: We use site-selective gene silencing in the orbitofrontal cortex (OFC), projection-specific inactivation techniques, pharmacological strategies, and food- and cocaine-reinforced behavioral tasks to reveal how β1-integrins confer resilience to cocaine.

Results: We present new, unpublished evidence that β1-integrins confer resilience to cue-induced reinstatement of cocaine self-administration, and that β1-integrins support action-outcome (as opposed to habitual) decision-making via the

substrates Abl2/Arg kinase and Rho-kinase. Finally, we find that β1-integrins in the OFC act by sustaining connections with the basolateral amygdala, which support action-outcome decision-making in a "bottom-up" fashion.

Conclusions: Connections between the OFC and basolateral amygdala are necessary for updating learned action-outcome associations to then optimize future behavior. This process is disrupted by cocaine, but stimulating β1-integrin signaling pathways confers resilience to the drug.

Disclosure: Nothing to disclose.

9.2 Cell Selective Targeting of Integrins to Limit Cocaine Relapse and Plasticity

Abstract not included.

9.3 Disruption of A2AR-D2R Heteroreceptor Complexes After A2AR Transmembrane 5peptide Administration Enhances Cocaine Self-Administration in Rats

Abstract not included.

Panel

10. NPPR Panel: Sleep and Neuropsychiatric Illness

10.1 Neurochemical Mechanisms for Memory Processing During Sleep – Basic Findings in Humans and Neuropsychiatric Implications

Gordon Feld

Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany

Background: Sleep has been shown to benefit memory through the repeated reactivation of memory traces encoded during prior wakefulness. Active Systems Consolidation suggests that, while information is stored in a transient labile store during wakefulness, reactivation during sleep transfers it to a more permanent stabile store. In the declarative domain transient and permanent stores are within the medial temporal lobe and the neocortex, respectively. The complementary synaptic homeostasis theory suggests that during sleep synaptic weights are also renormalized. This process is thought to erase unneeded synapse but spare relevant ones. Together these mechanisms allow for an effective management of memory in the brain. I will present research from human neuropharmacological experiments that try to identify the neurochemical processes underlying these mechanisms.

Methods: In this research, we have generally relied on placebo-controlled, balanced, crossover designs with group sizes between 11 and 30 participants. Participants usually arrive at the lab in the evening and learn declarative and/or procedural memory tasks. Afterwards they receive the drug, such as glutamatergic, dopaminergic and GABAergic antagonists or agonists, timed to achieve plasma maximum during the first half of the night. After sleep, memory retrieval is measured and the difference between retrieval and learning, the retention performance, is used to indicate consolidation. Depending on drug characteristics, the timeline can be adapted.

Results: Generally, we find some evidence for glutamatergic involvement in cortical consolidation during sleep that is not as strong in the declarative domain. Here, we have so far failed to identify the mechanisms, which are driving consolidation in humans, but have now some promising data from using gap junction blockers. Regarding GABAergic processes we find that the effect of agonists heavily depends on their primary effects on the cardinal oscillations during slow wave sleep, the sleep slow oscillation and sleep spindles. In the dopaminergic system we have received mixed results after enhancing and blocking d2-like receptor activation, which may be hinting towards a more complex interaction of reactivation and memory relevance than previously thought.

Conclusions: Overall, we are making some progress disentangling the neurochemical mechanisms of sleep-dependent memory consolidation. However, stricter regulations and high costs seem to limit the number of labs willing to run neuropharmacological studies in humans. Although, a lot of highly relevant work is also being done in animal models, they must be reproduced in humans as far as possible. Without additional effort in this field from other labs it will remain extremely hard to translate our basic scientific into effective neuropsychiatric applications. Nevertheless, I will give some examples of promising targets for such sleep-related interventions.

Disclosure: Nothing to disclose.

10.2 Alcohol Use Disorder and Sleep Disturbances: A Feed-Forward Allostatic Framework

George Koob

National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, United States

Background: Alcohol use disorder (AUD) is a devastating chronic disease that has a major negative impact on the lives of patients and their families. The pathway to the development of AUD involves binge drinking to high levels of intoxication that leads to a compulsion to consume it, the loss of control in limiting consumption, and finally the expression of a negative emotional state when alcohol is removed. Sleep disturbances, alterations of sleep architecture, and the development of insomnia are ubiquitous in AUD.

Methods: This cascade of events that occurs over an extended period of time has been framed as a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation ("craving"). These three stages map onto the dysregulation of functional domains of incentive salience/habits, negative emotional states, and executive function, mediated by neurocircuitry of the basal ganglia, extended amygdala, and frontal cortex, respectively. Sleep disturbances are mapped onto these three types stages in the present review.

Results: During the binge/intoxication stage, alcohol intoxication leads to a faster onset of sleep, but the quality of subsequent sleep is poor relative to nights when no alcohol is consumed, with a substantial increase in wakefulness during the sleep period, especially later in the night. The reduction of sleep onset latency and increase in wakefulness later in the night may be related to the acute effects of alcohol on γ-aminobutyric acid (GABA)ergic systems that are associated with sleep regulation and the effects on brain incentive salience systems, such as dopamine. During the withdrawal/negative affect stage, there is a decrease in slow-wave sleep and some limited recovery in rapid-eye-movement sleep when individuals with AUD stop drinking. However, there appears to be limited recovery in sleep disturbances that are seen in AUD within the first 30 days of abstinence. The effects of withdrawal on sleep variables may also be related to the loss of alcohol as a positive allosteric modulator of GABAA receptors, a decrease in dopamine function, and the overactivation of stress neuromodulators, including hypocretin/orexin peptides, norepinephrine, corticotropin-releasing factor, and cytokines. During the preoccupation/anticipation stage in individuals with AUD who are

abstinent long-term, there are persistent sleep issues, including a longer latency to fall asleep, more time awake during the night, a decrease in slow-wave sleep, decreases in delta electroencephalogram power and evoked delta activity, and an elevation of rapid-eye-movement sleep. The dysregulation of glutamatergic systems that is observed in AUD is a likely substrate for some of the observed protracted and persistent sleep disturbances.

Conclusions: Sleep pathology clearly contributes to AUD pathology; conversely, AUD pathology contributes to sleep pathology, possibly as a feed-forward drive to an unrecognized allostatic load that drives the addiction process.

Disclosure: Nothing to disclose.

10.3 Integrating Sleep, Neuroimaging, and Computational Approaches for Precision Psychiatry

Leanne Williams

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Background: Precision psychiatry draws on advances in imaging technology and computation. These advances may be directed to refining diagnostic subtypes and personalized tailoring of interventions for sleep impairment in mood and anxiety disorders. Current diagnostic criteria for mood and anxiety tend to lump different forms of sleep disturbance together. Parsing the biological features of sleep impairment and brain circuit dysfunction is one approach to identifying subtypes within these disorders that are mechanistically coherent and offer targets for intervention.

Methods: To illustrate such an approach, this presentation focuses on large-scale neural circuits implicated in sleep impairment and in mood and anxiety disorders: the default mode network and negative affective network. A testable framework is posed for understanding how hyper- versus hypo-engagement of these networks may underlie distinct features of mood and sleep impairment, and offer mechanistic, personalized targets for interventions.

Results: Alterations of the default mode are implicated in insomnia, as a specific feature of depression and in depression defined as a diagnosis relative to healthy controls. There is also a striking overlap in negative affective network dysfunction, observed in sleep disturbance and in both depression and anxiety. At least for some individuals, default mode and negative affective network dysfunction may be an intermediate step between sleep disruption and mood and anxiety features. Such dysfunction may be a modifiable target to regulate sleep problems and accompanying symptoms of emotional distress.

Conclusions: Current knowledge offers a framework for parsing specific features of sleep disturbance that traditionally have been lumped together in classifying mood and anxiety disorders, and to develop precision markers for guiding intervention studies that target disrupted sleep mechanisms in these disorders. Future directions of this approach include the potential for deploying machine learning in the discovery of additional circuit-defined subtypes, and the connection of these subtypes to more distal features derived from digital phenotyping and wearable technologies.

Disclosure: Blackthorn Therapeutics, Consultant; Psyberguide, Advisory Board; Laureate Institute for Brain Research, Advisory Board.

10.4 Sleep Therapeutics and Neuropsychiatric Illness

Abstract not included.

Panel

11. Brain-Based Biotyping of Trauma Responses

11.1 Digital Markers of Behavioral and Physiological Functioning as Predictors of Post-Traumatic Stress Response

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Background: Direct behavioral and physiological features such as facial expression of emotion, body and eye movement, acoustic elements and content of speech may represent indices of clinical functioning that more closely represent underlying central nervous system functioning when compared to existing psychiatric nosology and associated paper and pencil measures. Mental health assessment has traditionally relied on self-report or clinician assessment of psychiatric symptoms. We present a machine learning based model to detect clinical risk based on automated measurement and integration of face, voice, and speech features, captured during unstructured speech as predictors of PTSD severity trajectories (chronic, recovery, resilient) from 1 month to 12 months following admission to the emergency room following a life threatening traumatic event.

Methods: We utilized computer vision, and voice/speech-based feature of 1) emotions and their intensity; 2) movement; 3) speech prosody; 4) natural language content; 5)movement in $n = 90$ individuals who completed a qualitative interview about their experience 1 month after admission to the emergency room (ER) following a significant accident or injury. Neural networks were utilized to build classification and forecasting models of PTSD at 1 month and across 12 months using audio and video features.

Results: Audio and video features correctly classified clinical trajectories (PTSD AUC = 0.87) and predicted the chronic trajectory at the highest accuracy (Chronic PTSD AUC = 0.90). Facial features of emotion, voice prosody, speech content, and movement all contributed to the model.

Conclusions: Machine learning based detection of behavioral and physiological markers in unstructured data can accurately identify clinical functioning and predict clinical course.

Disclosure: AiCure, Employee.

11.2 Neuroimaging Prediction of Future Symptom Change in the Acute Post-Trauma Period: Preliminary AURORA Study Findings

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Background: Exposure to environmental stressors can be a catalyst for new or increased symptoms among most forms of psychopathology. Events involving traumatic injuries can be highly stress-inducing and affect the majority individuals in the United States at some point in their lifetimes. However, only a minority of injury survivors have persistent and impairing mental health symptoms over the long term. Biomarkers that predict risk for chronic symptoms, and the type of symptoms likely to occur, would be of very high value to the field. However, few biomarkers have reached standards of validity and reproducibility to allow for wide clinical usage. The AURORA Study investigates a number of potential biomarkers of future symptoms among Emergency Department (ED) patients, with structured longitudinal sampling of different psycho-somatic domains following an R-DoC framework. Generalizability of predictive biomarkers will be tested with

data collected across over 30 different EDs, and 5 magnetic resonance imaging (MRI) neuroimaging centers.

Methods: Patients in the Emergency Department (ED) of 30 hospitals across the US were enrolled, with data collection ongoing. Neuroimaging data were collected 2 weeks post-trauma from a subset of participants enrolled near to the location of a neuroimaging center. The first freeze of neuroimaging data included N = 102 motor vehicle crash survivors. Quality control and acquisition parameters were standardized across sites. Scans included a high-resolution T1w structural image, diffusion-weighted images, resting state and task-based functional MRI (fMRI), including a fearful faces task. Publicly available pipelines were used to centrally analyze the data, including fMRIprep (https://fmriprep.readthedocs.io). Participants also completed app-based surveys assessing symptom change for at least 4 timepoints over the first 8 weeks following the index trauma.

Results: N = 72 participants were included in the analyses – those who met quality thresholds for MRI data and had complete survey data. Linear growth models estimated symptom change over the first 8 weeks post-trauma, using survey items within 10 RDoC-based dimensions: Sleep, Pain, Anxiety, Hyperarousal, Avoidance, Reexperiencing, Thinking difficulties, Somatic symptoms, Loss, and Nightmares. FWE-corrected voxel-wise analysis of the Fearful Faces task covaried for age, sex, and site, and investigated associations with the linear slope and intercept for each RDoC dimension. A greater ventral visual response to fearful>neutral faces appeared protective: activation was negatively associated with the slope of future Anxiety, pFWE < 0.05. In contrast, greater activation of somatomotor regions (paracentral lobule, and bilateral clusters in pre/postcentral gyri) was positively associated with the slope of future Reexperiencing, pFWE < 0.05. With additional data collection, within-study replication of these findings will be assessed.

Conclusions: The AURORA Study represents a repository of data with a high sampling rate and a wide variety of phenotypes and biomarkers in the weeks and months after an ED trauma. Initial fMRI analyses indicated that the ventral visual response to social threat cues (fearful faces) predicted a future decrease in anxiety symptoms over the first 8 weeks post-trauma, whereas a somatomotor response to threat cues predicted a future increase in re-experiencing symptoms. Independent replication will be critical. A major goal will be to develop profiles of neuroimaging features across fMRI and structural scans, to assess risk for different post-trauma symptoms profiles.

Disclosure: Nothing to disclose.

11.3 DNA Methylation Based Predictor of Lifespan: Associations With PTSD and Cortical Atrophy

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Background: Posttraumatic stress disorder (PTSD) is a debilitating disorder that can develop following a trauma exposure. Previous studies reported that trauma exposure and PTSD may accelerate cellular aging. Recently developed predictor of lifespan based on DNA methylation (DNAm) data, referred to as DNAm GrimAge, correlates with mortality risk, health measurements and lifestyle factors. This study evaluated the effect of trauma exposure and posttraumatic stress disorder (PTSD) diagnosis on accelerated DNAm GrimAge in a traumatized civilian cohort. We also examined the association between cortical atrophy and DNAm GrimAge acceleration.

Methods: 1097 male and female subjects from the Grady Trauma Project (GTP) were included in the study. Lifetime trauma burden was assessed using the Traumatic Events Inventory (TEI). PTSD diagnosis was assessed by the Clinician-Administered Post-traumatic Stress Disorder Scale (CAPS) and modified PTSD symptomatic scale (mPSS). We defined 243 current PTSD cases and 481 trauma exposed non-PTSD controls. DNA was extracted from whole blood and interrogated using the Methylation EPIC or HumanMethylation450 BeadChip. DNAm GrimAge estimates were calculated from beta values after quality control procedures, using the validated methylation age calculator. For analyses purposes, the age-adjusted version of DNAm GrimAge (GrimAge acceleration) was used. Structural MRI data available for a subset of 105 participants was evaluated by FreeSurfer Software to assess cortical measures. Associations between trauma exposure, PTSD, cortical thickness and DNAm GrimAge acceleration was tested with multiple regression models that controlled for cell composition and methylation array.

Results: Trauma burden associated with GrimAge acceleration (effect size = 0.16, p = 1.99e-4), such that more lifetime trauma exposure associated with a shorter predicted lifespan. Current PTSD was also a significant predictor of GrimAge acceleration (effect size = 0.74, p = 0.040). We next tested the relevance of this peripheral indicator of lifespan to brain regions relevant to PTSD and identified multiple brain regions that are thinner in those with more GrimAge acceleration (lower predicted lifespan): right posterior cingulate (p = 0.004), right insula (p = 0.009), right superior temporal cortex (p = 0.022) and left temporal pole (p = 0.045). Interestingly many of these regions have previously been associated with PTSD.

Conclusions: Finding of this study shows the association between trauma burden, PTSD and accelerated DNAm GrimAge and indicate that trauma exposure and PTSD negatively impacts lifespan. Our results also link PTSD relevant cerebral cortex regions to accelerated DNAm GrimAge and suggest a plausible relation between reduced cerebral cortex thickness and mortality risk.

Disclosure: Nothing to disclose.

11.4 Dissecting Phenotypic Variation in PTSD Using Genetically-Regulated Transcriptional Variation

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Background: PTSD occurs in some trauma-exposed individuals, but its molecular basis remains uncharacterized. Previously, we have associated genetically regulated gene expression (GReX) across tissues with PTSD revealing the importance of RNA splicing in the prefrontal cortex for PTSD biological mechanisms (Huckins et al. Under review 2019). We additionally, established that brain GReX is more closely associated with brain biomarkers (i.e., neuroimaging), while blood GReX is closer to blood biomarkers (i.e., observed blood gene expression and peripheral cytokines) (Chatzinakos et al. In Preparation 2019). Here, we study the relationship between genetically-regulated transcriptional variation, and phenotypic variation in PTSD, in a cohort of 9400 inner-city, low-socioeconomic-status, primarily-African-American patients of the Grady Memorial Hospital.

Methods: Each individual was ascertained phenotypically using interview-based assessments, self-reports and lab tests. In addition, we imputed gene expression across 48 tissues using GTEx project's eQTL maps. To study the comorbidity patterns of transcriptomic and phenotypic information across individuals, we used MixEHR, a Bayesian unsupervised learning method (Li & Kellis, 2018).

Results: We identified 3 latent disease topics predictive of PTSD diagnosis (absolute LASSO coeffiecient > 5). Based on symptom

severity and trauma exposure, 2 of the topics were related to vulnerability (one with high childhood trauma and depression) and one related to resilience. We found enrichments for genes and tissues in the disease topics across multiple tissues. Top brain tissues with the highest PTSD associations are dorsolateral prefrontal cortex and anterior cingulate cortex, which have been associated with cognition, emotion/stress regulation and PTSD. We also constructed a ranked list of PTSD genes across multiple disease topics. The top genes were: adipose and cardiovascular GXYLT1, a glucoside xylosyltrasnferase, blood SLC35A4, a glucose transporter, and brain genes related to post-transcriptional and post-translational modifications.

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

Disclosure: Nothing to disclose.

Panel

12. Glutamate System in Suicidality: Genes, Biomarkers and Treatment

12.1 The Suicidal Brain: Biological Insight From Postmortem Human Tissue

Giovanna Punzi

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Background: Suicide is the 10th leading cause of death for all age group combined and is on the rise across the U.S., according to the Centers for Disease Control and Prevention (CDC). Transition from suicide ideation to action may represent a distinct phenotype of short-term risk related, among others, to features of impulsive aggression. In this regard, in completed suicides, the biology underling the choice of a violent method may offer a target to detect genetic signatures for the behavior at large. In a prior study focused on suicide method, we have found that differences in dorso-later prefrontal cortex (DLPFC) expression of a human-specific non-coding RNA (lincRNA) may influence emotional regulation, aggressive behavior and suicide by violent means.

Methods: In the present study, RNA sequencing (RNA-seq) data from postmortem human DLPFC (n = 226 [n = 127 suicides] Caucasian patients with psychiatric disorders, mixed diagnosis; adults) were examined to detect gene expression signatures associated with suicide by violent means. The sample size had the appropriate power (>80%) to detect genes differentially expressed with a log2 fold change of 0.3. Attribution of suicidal method was determined blind to the postmortem RNA-seq data. Cause and manner of death and contributory causes or medical conditions related to death were obtained from medical examiner documents. Cases where manner of death was pending or not determined at the time of the curation, and suicidal samples with ambiguous means of suicide, in regard to the level of violence employed, were excluded. The resulting suicides were assigned to the violent (n = 77) or non-violent (n = 50) category through in-depth behavioral assessment, based on narrative summaries obtained from all sources of historical information, including interviews with next of kin. The differential expression analysis was conducted on all features, including genes, exons, junctions, transcripts and expressed regions data, correcting for diagnosis, sex, age, and qSVs, a measure of RNA integrity.

Results: At pFDR-corr. < 0.05, minimal to null signal arose when comparing non-suicide with suicide (all kinds of method); however, comparison between non-suicides and suicides specifically by violent means produced a remarkably greater list of features (i.e. 537 genes). The top-list differentially expressed genes suggest, in suicide by violent means, the engagement of pathways modulating glutamatergic transmission in stress-linked neuropathology.

Conclusions: These results confirm that classifying suicide by method is key in revealing the underlying different biology, and indicate novel genes with a potential role in the etiopathogenesis of completed suicide.

Disclosure: Nothing to disclose.

12.2 mGluR5 as a Biomarker for Suicidal Behavior in Trauma Related Disorders: Evidence From in Vivo Pet Imaging Studies

Abstract not included.

12.3 Brain Imaging Correlates of Immediate Response to Chronotherapeutics: Effects on Glutamate, White Matter Microstructure, and Functional Connectivity

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Background: One-third of patients with bipolar disorder (BD) attempt suicide. Depression in BD associates with drug-resistance, hence the urgent need of new rapid treatment options. Total sleep deprivation (SD) and light therapy (LT) prompt a rapid and stable antidepressant response in BD, and can provide hints about new therapeutic targets. Our previous MRI studies associated BD and suicidal ideation with disrupted white matter (WM) microstructure, reduced grey matter (GM) volumes, and abnormal functional cortico-limbic connectivity during emotional processing.

Methods: We studied 204 (121 females, 83 M) depressed inpatients with BD, treated with repeated SD+LT (3 cycles in one week), and assessed with Hamilton Depression Rating Scale.

A subsample of 50 patients was studied with multimodal MRI imaging before/after treatment: diffusion tensor imaging (DTI) for white matter (WM) microstructure, voxel-based morphometry (VBM) and cortical thickness for grey matter (GM) structure, BOLD neural activation and functional connectivity parameters changes in response to a cortico-limbic activating task, and single-proton magnetic resonance spectroscopy (1H-MRS) in the anterior cingulate cortex (ACC).

Data were analyzed with software packages: for DTI, FMRIB Software Library (FSL) to perform Tract-Based Spatial Statistics (TBSS), and the ENIGMA-DTI protocol to study 43 tract-wise regions of interest, derived from the Johns Hopkins University white matter parcellation atlas; for 1H-MRS, automatic quantification of spectra with LCModel; for GM structure, the CAT12 toolbox of SPM; for BOLD fMRI, SPM and the CONN toolbox. Statistical threshold was always whole-brain $p < 0.05$ FDR corrected for multiple comparisons.

Results: After treatment 137 patients (67.2%) achieved response (HDRS score <8). All patients showed an immediate decrease of suicidal ideation, soon after the first SD cycle and irrespective of final response. This effect was significant in non-responders, too.

Multimodal imaging detected several correlates of treatment effects. 1H-MRS showed that in ACC both, Glutamate and the composite measure of Glutamate+Glutamine (Glx) significantly decreased after treatment, while glutathione increased, irrespective of final response. For DTI, TBSS showed an increase of

fractional anisotropy (FA) and a decrease of mean diffusivity (MD), spread in the WM skeleton, which was proportional to clinical response (Delta HDRS). The ENIGMA-DTI protocol showed peak effects of treatment in corpus callosum, hippocampal part of the cingulate gyrus, uncinatus, fornix, sagittal striatum, internal capsule. For BOLD fMRI, significant interactions between task and response to chronotherapeutics were found for connectivity between left amygdala and several structures, including hippocampus, insula, supramarginal gyrus, and occipital cortex. Finally, VBM showed increased GM volumes after treatment in BA 39–40 and right caudate, with no significant changes in cortical thickness.

Conclusions: Irrespective of final response, treatment caused an immediate decrease of suicidal ideation, and of brain glutamate content in the ACC. Treatment caused spread changes of DTI measures of WM microstructure (increased FA. decreased MD), which associated with final clinical response to treatment, as measured on HDRS. These effects were paralleled by changes in functional cortico-limbic connectivity.

Disclosure: Nothing to disclose.

12.4 Suicide Ideation Response in the Context of a Glutamatergic Modulator

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Background: Ketamine, a glutamatergic modulator, has been linked with rapid reductions in suicidal ideation (SI), which has potential implications for the relationship of SI to the glutamatergic system. However, beyond these initial efficacy results, there are a number of remaining questions to be answered about the nature of the relationship of SI and glutamate in the context of ketamine. First, are reductions in SI due to ketamine's antidepressant effects or is there a direct impact of ketamine on SI? Second, are specific biomarkers of glutamatergic activity linked with SI response to ketamine?

Methods: The results will address two areas: 1.) clinical results using rating scales which address whether ketamine has a direct impact on SI, independent of its antidepressant effects and; 2.) initial biomarker work evaluating whether changes in SI can be linked to neurobiological changes within the glutamate system. Potential biomarkers include glutamate levels as measured by proton magnetic resonance spectroscopy (1H-MRS) at 7T fMRI, plasma markers implicated in the glutamatergic system including quinolinic and kynurenic acid, and markers of glutamatergic signaling using dynamic causal modeling (DCM) of magnetoencephalography (MEG).

Results: Clinically, ketamine appears to have direct effects on SI, independent of depressant response ($n = 128$, $F(6,324) = 2.32$, $p = 0.03$). Furthermore, this relationship may differ by responder group, in that a subgroup of individuals do not have a SI response to ketamine, but still have an antidepressant response. Analyses using MRS (administered 24 hours post-ketamine) did not show a relationship between glutamate and SI ($n = 20$, $p > 0.05$). Plasma markers of quinolinic and kynurenic acid (collected one day post-ketamine) were also not associated with SI response to ketamine ($n = 128$, $p > 0.05$). Lastly, DCM modeling of MEG (administered 6-9 hours post-ketamine) showed that AMPA-mediated connectivity in the insula-anterior-cingulate cortex was associated with depression ($n = 29$, $r = -0.29$, $p = 0.04$), but not SI.

Conclusions: A multimodal approach is required to evaluate the relationship of SI to the glutamatergic system in the context of ketamine administration. While it appears that ketamine may have a direct effect on SI, independent of antidepressant effects, initial biomarker analyses have not yet linked SI response to glutamate markers. This work may be limited due to the length of time between ketamine administration and biomarker assessment. Future studies which assess potential markers during and just after ketamine administration may provide insights into the relationship between SI and glutamate.

Disclosure: Nothing to disclose.

Panel

13. Unraveling the Biological Basis of the Perceived Stress of Racism and Its Impact on Mental Health

13.1 Biomarkers of Neuropsychiatric Disease: Modeling the Perceived Stress of Racism as Preconception Female Stress in Mice

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Background: African-Americans (AA) are at a 20% greater risk to suffer from serious mental health problems. Further, AA women are twice as likely to present with pre- or postpartum depression, and an AA woman with an advanced degree is still 4X more likely to suffer morbidity and mortality in pregnancy and postpartum than a Caucasian woman with an 8th grade education. Infants born to AA mothers are also more likely to be delivered preterm or low birth weight, further increasing the risks for the next generation. Racial discrimination evokes a physiological stress response, and exposure to the perceived stress of racism (PSR) precipitates a chronic stress state and increased allostatic load. Despite the substantial epidemiological and clinical data, the biological mechanisms by which this chronic and persistent stress experience of PSR increases disease risk are unknown. In order to elucidate programming mechanisms related to PSR that may be unmasked during pregnancy and postpartum, we have developed a mouse model of female preconception stress.

Methods: To model PSR as preconception stress, female mice were exposed to chronic stress for 6 weeks from PN28 to PN70, a time period when the juvenile brain would become aware of discrimination (preconception stress). Females were then mated with naïve males and a copulation plug confirmed for pregnancy. To examine biomarkers of increased stress reactivity, dams were killed either mid-gestation or postpartum, and plasma, maternal brain, placenta and fetal tissues collected. Plasma biomarkers of an altered stress state (predictive of increased allostatic load) including cell-free mitochondrial DNA (cfmtDNA) and extracellular vesicles were examined. Brain and placental transcriptomics were also determined. Outcomes were compared to those obtained from human subject studies for validation of translational potential.

Results: Maternal plasma biomarker analyses have examined changes in EV proteomics and small noncoding RNA transcriptomics altered by preconception stress. Significant increases were also found in circulating cfmtDNA levels that correlated with changes in proinflammatory cytokines. In the offspring of preconception stressed dams, we found that female, but not male, brain transcriptomic changes corresponded to enrichment in genes critical for synaptic development and mitochondrial energetics. Similarly, pathway analyses in the placenta identified sex-specific changes supportive of altered transplacental signals that likely impact neurodevelopment. Phenotypically, female, but not male, offspring also showed a significant increase in their HPA stress reactivity as adults.

Conclusions: Similar to our translational studies in female human subjects, we have been able to model the chronic preconception stress aspect predictive of changes to allostatic load in pregnant females. Our elevated cfmtDNA changes in mice mimic those found in women reported experiencing high levels of racial discrimination. Many of the biomarker changes we have detected fit with a model in which stress, and a corresponding shift in the allostatic load, are intersecting with the host immune system, during a critical period of high physiological demand of pregnancy. Validation of this mouse model will allow us to probe further the mechanistic and causal biology by which the PSR programs lasting systemic changes and increases disease risk. Our studies support potential useful biomarkers as predictive in identifying a vulnerable population, especially for mental health disorders in AA women pre- and postpartum, a high-risk population.

Disclosure: Nothing to disclose.

13.2 Racism and Experiences of Discrimination Increase Autonomic Arousal in Women With Trauma Exposure

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Background: Racism and discrimination causes significant distress in minority populations. Along with structural racism, that impacts many socioeconomic variables, such as housing, education, employment, as well as access to healthcare, race-related stress directly impacts the health of an individual. Race-related stress is associated with increased allostatic load, or "weathering" in African American women (Geronimus et al. 2006), as well as accelerated biological aging independent of poverty (Gerominus et al. 2010). In a sample of African American children, we found that accelerated biological aging was associated with increased heart rate (Jovanovic et al. 2017), which may be a potential mediator of the effects of race on health disparities. Further, we found intergenerational effects on heart rate variability in children (Jovanovic et al. 2011). In the current study of African American women, we examined the association between self-reported racial discrimination and measures of autonomic nervous system function, which we have previously found to be associated with Posttraumatic Stress Disorder (PTSD) in women (Kamkwalala et al., 2012). In addition, we examined the intergenerational impact of discrimination on autonomic function in their school-age children.

Methods: The study participants were $N = 75$ African American women recruited from a publicly funded urban hospital in Atlanta, GA, and their male ($N = 47$) and female ($N = 44$) children (ages 6-13). Self-report measures included Experiences of Discrimination Questionnaire (EDQ), trauma history and demographic data. Autonomic function was assessed by measuring electrocardiogram (ECG) data during an acoustic startle task. ECG data were collected using a Biopac MP150 system at a sampling rate of 1000 Hz, and heart rate (HR) high frequency heart rate variability (HF HRV) a measure of parasympathetic activity, and LF to HF HRV ratio, a measure of sympathovagal balance, were calculated using HRV guidelines.

Results: Experienced discrimination was negatively associated with HF HRV ($r = -0.24$, $p < 0.05$) and positively associated with LF/HF HRV ($r = 0.27$, $p < 0.05$). These associations remained significant after covarying for income and trauma exposure. Maternal experiences of discrimination were negatively correlated with HF HRV in their daughters ($r = -0.32$, $p < 0.05$), but not their sons ($p > 0.1$). These associations also remained significant after controlling for household income and age of child.

Conclusions: These results suggest that experienced racial discrimination has observable impacts on autonomic function in AA women and their daughters. Specifically, discrimination was associated with decreased parasympathetic and relatively increased sympathetic activity during a mildly stressful startle task. Given the association of HRV with future cardiovascular disease (Monk et al 2001) and PTSD (Kamkwalala et al. 2012), these measures provide potential mechanism by which racism may impact health disparities across generations independent of socioeconomic measures such as low income.

Disclosure: Nothing to disclose.

13.3 Examining the Biomarkers of Perceived Racial Discrimination and its Relation to PTSD Among Low-Income African American Women

Sierra Carter

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Background: Previous studies have shown that experiences of racism/discrimination may lead to severe trauma symptoms that resemble PTSD, adjustment disorder, and acute stress disorder. Furthermore, recent research has begun to find a relationship between racial discrimination and PTSD symptoms showing that individuals who experienced racial discrimination were significantly more likely to screen positive for PTSD. Although studies have examined the link between perceived racial discrimination, and negative psychological outcomes, there continues to be a paucity of research examining how experiences of racial discrimination and trauma could be interwoven or uniquely distinct.

A growing body of literature indicates that racial discrimination is a particularly important facet of the set of social stressors that exert acute and chronic effects on health outcomes, particularly for African American (AA) adults. Research has shown that chronic stress from perceived racial discrimination can evoke physiological changes within body systems leading to increases in proinflammatory cytokines, premature illness and mortality. As health outcomes linked to racial discrimination have been characterized as a reaction to chronic stress linked to increased allostatic load, it is essential to consider the social stressor of perceived racial discrimination as an influential factor in sustained racial health disparities for African Americans. This presentation will discuss study findings that examined how the multilevel construct of perceived racial discrimination interacts with PTSD symptomatology, biomarkers, and health/well-being for low-income AA women.

Methods: Data was collected from approximately 120 African American women who were recruited as part of the Grady Trauma Project. Participants were recruited from a public hospital and interviews included demographic characteristics and self-report of functional impairments/wellbeing and health status and biomarkers/cell-free mitochondrial DNA were extracted from blood collected during a separate interview. Further assessments of variables of interest were completed utilizing the Traumatic Events Inventory, Modified PTSD Symptom Scale, the Clinician-Administered PTSD Scale, and the Experiences of Discrimination Scale.

Results: Results revealed that PTSD symptoms were associated with more experiences of perceived racial discrimination ($\beta = 0.25$, SE, 0.25, $p < 0.01$), and more experiences of perceived racial discrimination were associated with greater functional impairments ($\beta = 0.02$, SE, 0.01, $p < 0.01$). Further results also revealed that perceived racial discrimination was positively correlated with higher levels of circulating cell-free mitochondrial DNA, consistent

with increased allostatic load, and independent of trauma exposure.

Conclusions: This data highlights the importance of research examining how culturally-relevant factors such as perceived racial discrimination influences PTSD symptoms and markers of chronic stress/health decline among underserved population. Clinical implications will be highlighted during this presentation.

Disclosure: Nothing to disclose.

13.4 Childhood Violence Exposure, Social Deprivation and Adolescent Amygdala-Orbitofrontal Cortex White Matter Tract Development: A Longitudinal Study of the Sequelae of Structural Racism

Christopher Monk

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Background: Low-income families and African Americans often live in communities that are the result of chronic structural racism. Consequently, children from these communities are at increased risk for experiencing adversity, such as violence exposure and social deprivation. Adverse experiences are heterogeneous with potentially distinct dimensions of violence exposure vs. deprivation that may differentially shape the neural circuitry underlying emotion processing. Using a pre-registered approach with diffusion MRI, we examined how childhood exposure to violence and social deprivation related to adolescent white matter (WM) connectivity between the amygdala and emotion-relevant prefrontal cortex (PFC) regions.

Methods: 177 teens (age 15-17; 98 females) from a longitudinal study (Fragile Families and Child Wellbeing Study) participated. 70% was African American and almost half were living in poverty. Composite variables for safety-violence and social support-deprivation were constructed from data collected at ages 3, 5, 9. Violence indexed abuse, exposure to intimate partner violence, and neighborhood violence. Social deprivation indexed child neglect, intimate partner support for caregiver, and neighborhood cohesion. Probabilistic tractography, from diffusion MRI, assessed WM connectivity between the amygdala and specified PFC regions (BA47 & BA11 [orbitofrontal], BA10 [dorsomedial]). These regions were based on our prior work with this sample where we found that decreased amygdala-BA47 white matter connectivity is associated with heightened amygdala reactivity to threat (Goetschius et al, 2019), potentially reflecting decreased amygdala regulation. Multivariate linear regression assessed the association of childhood exposure to violence and social deprivation and amygdala-PFC WM connectivity. We pre-registered hypotheses, measures and analytics (https://osf.io/spguw).

Results: Probabilistic tractography revealed that violence exposure and social deprivation interacted to predict the likelihood of amygdala-BA47 white matter connectivity, $F(5, 170) = 2.88$, $p = 0.016$, $R2$ of 0.08. Specifically, high violence exposure with high social deprivation in childhood prospectively predicted less amygdala-BA47 white matter connectivity in adolescence, $B = -0.08$, $p = 0.026$. In contrast, violence exposure was not associated with adolescent white matter connectivity when social deprivation was at mean or low levels (i.e., when children were in relatively socially supportive contexts).

Conclusions: The interaction of violence exposure and social deprivation in childhood prospectively predicted the degree of amygdala-BA47 white matter connectivity in adolescence. The combination of more violence exposure and more social deprivation in childhood predicted less amygdala-BA47 white matter connectivity in adolescence; however, violence exposure was not associated with white matter connectivity when children were in more socially supportive contexts. Thus, social deprivation may exacerbate the effects of childhood violence exposure on the development of white matter connections whereas social support may act as a buffer. Importantly, the work was conducted in a well-sampled cohort of adolescents with high rates of poverty and a large proportion of African Americans, groups that experience high levels of structural racism.

Disclosure: Nothing to disclose.

Study Group

14. Harnessing Biomarker Identification to Optimize Opioid Use Disorder Treatment

Martin Paulus*, Shelley Su, Carlos Blanco, Sarah Yip, Shuyan Liu, Anna Konova, Alex Ramsey, Vanessa Troiani

Study Group Summary: Biomarker identification and utilization in the cancer field has resulted in significant improvements in determining cancer risk, treatment decision making, and patient outcomes. While we do not have a biomarker for treating opioid use disorder (OUD), clinical research has provided several targets of opportunity that need to be evaluated for their ability to function as biomarkers that can be use prognostically, therapeutically, or for guiding treatment selection. Yet, a number of significant questions remain unanswered, which may limit a health provider's decision to integrate biomarker assessment into routine OUD treatment. For example, replication of biomarker findings and limited sample sizes impedes scientific consensus amongst the research community. Furthermore, cost and ease of assessments and the relative performance of the biomarker against traditional clinical measures present unique challenges to clinical adoption. This delayed translation of knowledge from bench to practice hinders a health care provider's ability to improve treatment decision making for their patients and may adversely impact patient outcomes.

The purpose of this study group panel is to discuss the issues that delay biomarker identification in clinical research and hinder biomarker utilization in treatment. The outcome of the study group session would be to create recommendations and strategies to addresses these challenges. To this end, we have convened a panel of experts to provide a current review of the leading OUD biomarkers in computational neuroscience, inflammation, genetics, neuroimaging, and behavior. A unique feature of our study group panel is the inclusion of implementation science and clinicians as important stakeholders to foster an interactive dialogue between research and clinical practice. Our panel of experts will summarize the evidence for their assigned biomarkers for treating OUD. In the event that the evidence for a particular biomarker is limited for OUD, the panel expert would have latitude to discuss 'lessons learned' from other SUDs that would be applied to shaping the future of OUD research. To guide a discussion with the ACNP audience, panel experts will also address three knowledge gaps that may impact the speed with which biomarker assessment may appear in OUD treatment care: (1) Pragmatic aspects of biomarkers (relative performance of your biomarker against traditional clinical assessments, ease and frequency of assessment); (2) Target outcomes for biomarker predictions (stratified relapse risk, time to relapse, personalized response to MOUDs, adverse consequences during recovery); (3) Operational aspects of biomarker research (study design, populations, prospective biomarker studies, and individualized outcomes). Our goal for the study group is to lead an engaging discussion with the audience on recommendations to the field for generating the data needed in order to achieve faster integration of biomarker assessments into routine care.

Disclosure: UpToDate, Honoraria; SpringHealth, Board Member.

Study Group

15. Making Brain Science a Household Topic: Science Outreach & Advocacy

Robert Swift*, Victoria Heimer-McGinn, Heather McKellar, Christian Bravo-Rivera, Wade Berrettini

Study Group Summary: As scientists, we understand that our work, whether basic or clinical, is invaluable to society. A significant segment of society, however, questions the relevance of science. Common disputes relate to the authority and credibility of scientific findings ("scientist keep changing their minds about [x]"), the ethics of scientific methods (i.e. use of stem cells and animal models), and the overall relevance of research ("did they really spend my tax dollar on that?"). These impressions work to diminish the importance of brain research in the public eye and ultimately have the power to influence the policies that govern federal funding. In response, it is our responsibility as scientists to engage in outreach and advocacy work so that we can increase the perceived value of neuroscience among policy makers and their constituents alike.

In addition, a growing body of misinformation about brain diseases and their treatments makes it difficult for the public to disentangle fact from myth and ultimately diminishes our ability to influence health policies and recommendations based on our science. For instance, although many people understand that major neuropsychiatric diseases are biological disorders of the brain, there is still a lingering idea that the brain is somehow different from the "mind". With this comes the belief that medications and other forms of medical intervention are not the way to cure these diseases. Now more than ever, it's important that we communicate our work in an accessible and accurate way, not only among ourselves, but also to the public. Finally, it is vital that we promote neuroscience education among underrepresented groups and diversify the neuroscience workforce. This is vital considering that cultural context influences our work, from the research questions we ask to the methods we use to explore those questions. Diversifying our workforce will lead to a more comprehensive understanding of brain disorders and a wider-ranging set of treatments.

In this study group, we discuss successful grass root and large-scale approaches to outreach and advocacy. Our presenters will be Victoria Heimer-McGinn, Ph.D., co-founder and chair of Brain Week Rhode Island, Heather McKellar, Ph.D., founder of BraiNY and Assistant Director of Education and Outreach at NYU School of Medicine, Christian Bravo-Rivera, Ph.D., President of NeuroBoricuas, and Wade Berrettini, current chair of the ACNP Advocacy Committee and lead for the American Brain Coalition Congressional Neuroscience Caucus briefing. We hope to inspire more scientists to engage in outreach and advocacy and to discuss innovative and efficient approaches to sustaining our research careers, educating at the K-12 and adult levels, and diversifying the research fields.

Disclosure: Nothing to disclose.

Panel

16. Maintaining a Fine Balance Between Synaptic Protein Synthesis and Degradation in ASDs

16.1 Identification of Autism-Associated Mutations in Genes Encoding eIF2alpha Kinases

Eric Klann

New York University, New York, New York, United States

Background: Autism spectrum disorder (ASD) is heritable and is likely due to multiple gene mutations, resulting in a wide, albeit poorly understood, molecular and clinical spectrum. Recent whole-genome sequencing studies (WGS) resulted in the discovery of many genetic risk factors such as de novo mutations and copy number variants (CNV - both de novo and inherited) linked to ASD. However, de novo mutations and CNVs are rare and account for only 15–20% of all ASD cases. Rather, single nucleotide variants (SNVs) occur with a much higher frequency in ASD, which begs the question: how do ultra-rare SNVs contribute to ASD pathology? It is clear that a complex genetic landscape underlies the remaining ASDs, with a predicted 400-1000 unidentified genetic risk variants together contribute to the remaining idiopathic ASD cases (Geschwind and State, 2015). Due to the heterogeneous nature of ASD, it is predicted that a heterogeneous molecular spectrum underlies the disorder. A lack of understanding of the molecular spectrum and conditions co-occurring with ASD has lead to inadequate treatment options and decreased patient quality of life. Therefore, discovery of novel risk genes contributing to ASD and its co-morbidities is imperative. Although here have been multi-level investigations of mutations in genes classified as ASD high-risk genes, we sought to identify SNVs in genes encoding components of the translation initiation signaling network which has not been previously characterized in the context of autism risk

Methods: We searched the Simons Simplex Collection (SSC) whole-exome sequencing (WES) database for mutations in the four eIF2α kinase genes: EIF2AK1 (HRI), EIF2AK2 (PKR), EIF2AK3 (PERK), and EIF2AK4 (GCN2) (Iossifov et al. 2014). Of the 794 mutations we identified, we focused on 44 SNVs that were categorized as ultra-rare inherited (occurring in only one SSC family) missense, nonsense and frameshift and de novo non-synonymous mutations SNVs for our subsequent analyses. We found 4 missense ultra-rare inherited mutations and 1 de novo nonsense mutation in EIF2AK2, 10 missense ultra-rare inherited mutations and 1 de novo missense mutation in EIF2AK3. In EIF2AK4, we found 20 missense, 4 frameshift, and 4 nonsense ultra-rare inherited mutations. Using bioinformatic approaches and in silico evaluation via Polymorphism Phenotyping v2 (PolyPhen-2) of each SNV, we determined that nearly all of these mutations are highly likely to be disruptive to protein structure and function and all are within well-characterized and evolutionarily conserved functional domains of PKR, PERK, and GCN2.

Results: Using bioinformatic analysis of the Simons Simplex Collection (SSC) to identify ultra-rare heritable and de novo autism-associated single nucleotide variants (SNVs), we screened >40 ASD-associated SNVs in cell-based assays and found several Loss-of-Function (LoF) mutations in EIF2AK4, EIF2AK3, and EIF2AK2 that result in dysregulated global protein synthesis and eIF2alpha phosphorylation. Analysis of clinical data from the SSC families revealed several phenotypes associated with the LoF mutations in EIF2AK4, EIF2AK3, and EIF2AK2, including stereotypic behavior, which were recapitulated in Eif2ak, Eif2ak3, and Eif2ak2 haploinsufficient mice.

Conclusions: Our findings suggest that heritable and de novo LoF ASD-associated SNVs in the eIF2 signaling network disrupt protein synthesis and give rise to phenotypes consistent with ASD, implicating aberrant eIF2 regulation in abnormal neurodevelopment.

Disclosure: Nothing to disclose.

16.2 Shared Molecular Mechanisms Underlying Brain Wiring and Behaviour in Autism and Schizophrenia

Abstract not included.

16.3 Activation of the Autophagy/Lysosomal Degradation Pathway Rescues Cognitive and Sensory Deficits in Fragile X Mice

Abstract not included.

16.4 Distinct Regulation of Local and Long-Range Neocortical Synaptic Development by Postsynaptic MEF2C and FMRP

Kimberly Huber

University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, United States

Background: Structural and functional imaging studies in humans with autism spectrum disorder (ASD) find imbalances between local connectivity, within a cortical region, and long-range connectivity, between cortical areas. If or how ASD-relevant genes differentially regulate development and strength of local and long-range cortical connectivity is unknown.

Methods: Using optogenetic and laser-guided circuit mapping methods in acute neocortical rodent brain slices, we study how activity-dependent transcription and translational control factors and ASD genes, MEF2C and FMRP, respectively, differentially regulate development of local and long-range neocortical circuits in response to sensory experience.

Results: I will present new data related to the functional interactions of MEF2C with FMRP in regulation of local and long range synaptic connectivity in cortical circuits. We also find roles for postsynaptic Fmr1 on development of local and long-range inputs. Deleting Fmr1 in either L2/3 or L5 neurons reveals that postsynaptic Fmr1 is not necessary for L4-L2/3 synaptic input development, but promotes development of callosal inputs onto L2/3 and L5 neurons.

Conclusions: Mef2c and Fmr1 have distinct effects on development of callosal inputs and function in independent molecular pathways. These results indicate that ASD genes differentially regulate development and function of local and long-range neocortical circuits

Disclosure: Nothing to disclose.

Panel

17. Novel Molecular, Cellular, Circuit, and Behavioral Mechanisms for Treating Drug Relapse

17.1 Synaptic and Circuit Mechanisms Underlying the Vulnerability for Drug Abuse

Veronica Alvarez

NIAAA, Bethesda, Maryland, United States

Background: Dr. Veronica Alvarez will present new findings revealing a likely mechanism by which low expression of striatal D2 receptors generates vulnerability for drug abuse and relapse. The presentation will detail novel experimental evidence for drastic changes to basal ganglia circuitry that define a vulnerable brain circuitry primed for drug-induced plasticity that drives compulsive-like drug taking.

Methods: ex-vivo slice electrophysiology, biochemistry, behavioral analysis, drug self-administration

Results: For example, for alcohol abuse: our work reveals a mechanism underlying abuse vulnerability. it demonstrates a causal link between high sensitivity to alcohol stimulation and low expression of striatal dopamine D2 receptors (D2Rs). In transgenic mice, selective loss of D2Rs on striatal projection neurons, but not other cell-types, enhances sensitivity to ethanol stimulation and resilience to sedation. These mice display higher preference and escalation of ethanol drinking, which continues despite aversive outcomes. We found that striatal D1R activation is required for ethanol stimulation and this signaling is enhanced in mice with low striatal D2Rs.

Conclusions: These data offer a mechanism in which low D2Rs triggers D1R hypersensitivity, leading to heightened ethanol-induced stimulation, escalation of intake and compulsive-like alcohol drinking patterns.

Disclosure: Nothing to disclose.

17.2 Developing a Nonmuscle Myosin II Inhibitor to Target Addiction Relapse

Courtney Miller

The Scripps Research Institute, Jupiter, Florida, United States

Background: The rate of relapse among stimulant abusers is extremely high and there are no pharmacotherapies available. Memories associated with drug use can trigger motivation for the drug, leading to relapse. Most troubling, these memories are long-lasting, representing a lifelong relapse risk. Therefore, a major goal in the field of substance use disorder (SUD) research is focused on selectively disrupting drug-associated memories. Using genetic and pharmacologic approaches, we discovered that inhibiting the actin-targeting protein NMII produces an immediate, selective and retrieval-independent disruption of methamphetamine (METH) and amphetamine-associated memory storage. Single, systemic administration of the NMII inhibitor, Blebbistatin (Blebb), is sufficient to disrupt memory-induced METH seeking for at least a month. The selectivity is striking, as fear, food reward, nicotine, morphine, cocaine and mephedrone memories are impervious. While identifying the mechanism behind this specificity is a major focus, my talk will be centered on two specific topics: (1) Determining the therapeutic potential of NMII inhibition in the context of polydrug use. This is important, as the majority of individuals with SUD use multiple substances. This polydrug use could interfere with the susceptibility of METH-associated memories to NMII inhibition. Alternatively, METH could render previously impervious memories susceptible to Blebb. (2) Developing a clinical safe Blebb derivative.

Methods: For polydrug experiments, mice were administered nicotine or morphine, paired with METH and the same conditioned place preference (CPP) context. This was followed by systemic vehicle or Blebb administration prior to testing. Medicinal chemistry efforts have been directed at modifying aspects of Blebb for clinical safety and efficacy, with a particular focus on cardiac safety through selectivity for NMII over cardiac muscle myosin II (CMMII). This effort is being made while working to maintain desirable pharmacokinetic characteristics, specifically rapid clearance in order to limit unwanted central and peripheral effects and high brain penetrance.

Results: When combined with METH administration, nicotine and morphine, but not fear associations, were rendered susceptible to disruption by Blebb. Heroin is also currently being investigated. To date, we have made approximately 500 Blebb analogs and determined their NMII and CMMII potencies, solubility, stability, and in vitro ADME profile (e.g. hERG, plasma protein binding). For particularly promising compounds, in vivo PK properties, impact on human iPS cardiomyocyte function, in vivo cardiac contractility, in vivo efficacy using self-administration models and selectivity have also been determined. The resulting SAR has informed our understanding of what produces strong selectivity for NMII or CMMII. One of several compounds will be selected in the near future to serve as the clinical candidate for upcoming IND-enabling studies.

Conclusions: Due to the high lethality of opioids, the US is in the midst of a crisis. Adding to this is a resurgence of METH abuse, particularly in the western and southern regions of the country.

Interestingly, many users are turning to opioids to dampen the high produced by the ultra-pure METH available today. Further, Adderall (amphetamine) abuse is at an all-time high among students. Together, this all highlights the need for novel therapeutics for the treatment of SUD that take into account polydrug use.

Disclosure: Nothing to disclose.

17.3 Refraining From or Seeking Heroin Produces Dynamic Changes in Astroglial Morphology and the Extracellular Matrix

Peter Kalivas

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

Background: Rodent models of heroin relapse reveal the induction of transient synaptic plasticity in the nucleus accumbens during extinction-induced refraining from heroin seeking and during cued heroin seeking. This plasticity is characterized by changes in dendritic spine morphology and AMPA and NMDA currents, and is largely confined to D1 receptor expressing medium spiny neurons (D1-MSNs). In rodent models of cued heroin seeking, transient synaptic plasticity requires catalytic signaling in the extracellular matrix (ECM). Here we present unpublished research using a heroin relapse model that ECM signaling occurs during heroin seeking selectively around D1-MSNs and around D2-MSNs in heroin-extinguished rats. We also show marked plasticity in perisynaptic astroglial processes during heroin cue presentation that reduces the amplitude of seeking.

Methods: Male Sprague-Dawley or male and female D1- and D2-Cre Long Evans transgenic rats were trained to self-administer heroin, after which rats were withdrawn with extinction training, and then reinstated by heroin-conditioned cues. Tissue slices were made after extinction training or 15 min after initiating cued heroin seeking and compared to tissue slices from rats trained as yoked saline controls. To quantify astroglia, rats were micro-injected with a virus expressing membrane-targeted mCherry under control of the glial-specific GFAP promoter. Relative proximity of astroglial processes to synapses was quantified as co-localization with the presynaptic marker Synapsin I, and in some astroglia, the surface localization of the astroglial-specific glutamate transporter, GLT-1, was also quantified. In one experiment, the glial specific actin binding protein, ezrin, was down-regulated using a morpholino antisense strategy. To quantify catalytic activity in the ECM, Cre rats were transfected with a membrane targeted reporter to label either D1- or D2-MSNs. After heroin self-administration, 15 min prior to obtaining tissue slices Cre-rats were microinjected into the accumbens core (NAcore) with a FITC-quenched gelatin substrate that produces fluorescence when catabolized by activated gelatinase matrix metalloprotease-2,9 (MMP-2,9). Quantification was conducted with confocal microscopy and digital rendering of labeled astroglia or FITC puncta around D1- or D2-MSNs.

Results: After extinction from heroin self-administration astroglial processes disassociated from NAcore synapses, but presenting a heroin-paired cue caused atroglia-synapse reassociation. GLT-1 was down-regulated after heroin extinction and surface expression increased during cued reinstatement. Ezrin knockdown prevented the glia-synapse reassociation and potentiated reinstated heroin seeking. MMP activity following extinction was selectively increased around D2-MSNs and during cue heroin seeking was selectively elevate around D1-MSNs.

Conclusions: These data show dramatic morphological changes in astroglia-synapse association produced by heroin-paired cues that induce heroin seeking, and demonstrate that the cue-induced reassociation of astroglia with synapses reduces heroin seeking. Additionally, we show that MMP-2,9 activity is increased around D2-MSNs following extinction, but around D1-MSNs during cued heroin seeking. The dramatic effects of both extinction and heroin seeking on astroglial morphology and ECM signaling offer a number of novel targets for possible intervention in restraining opioid relapse.

Disclosure: Nothing to disclose.

17.4 Role of Ventral Subiculum in Incubation of Oxycodone Craving After Electric Barrier-Induced Voluntary Abstinence

Ida Fredriksson

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

Background: In humans, abstinence is often self-imposed, and relapse typically involves a conflict situation where addicts choose between the desire to experience the drug's rewarding effects and adverse consequences of drug seeking. To mimic this human condition, we developed a novel rat model of incubation of opioid craving after electric barrier-induced voluntary abstinence and studied the role of ventral subiculum (vSub), a brain region previously implicated in relapse to drug seeking, in this new form of incubation.

Methods: We trained male and female rats to self-administer oxycodone (0.1 mg/kg/infusion, 6-h/d) for 14 days. We then introduced an electric barrier of increasing intensity (0.1 to 0.4 mA) near the drug-paired lever that caused cessation of oxycodone self-administration. In Exp. 1 ($n = 56$ males/48 females), we compared incubation of oxycodone craving (the time-dependent increase in drug seeking after cessation of drug self-administration) after electric barrier-induced voluntary abstinence versus homecage forced abstinence (the classical incubation model). In Exp. 2, we examined the role of vSub in incubation of oxycodone seeking after electric barrier-induced abstinence, using the activity marker Fos ($n = 6$–7/group) and local muscimol+baclofen (GABA A+B receptor agonists, $n = 10$–12/group) inactivation.

Results: In Exp. 1 we found that, independent of sex, incubation of oxycodone craving (non-reinforced lever presses on abstinence days 15 and 30 was higher than on day 1) was more pronounced after voluntary abstinence than after forced abstinence (main effect of Abstinence Condition for day 15 and day 30, $F(1,48) = 14.7$, $p < 0.001$ and $F(1,48) = 5.6$, $p = 0.022$, respectively; Sex or Abstinence Condition x Sex, p values > 0.1). In Exp. 2 we found that "incubated" drug seeking on abstinence day 15 was associated with increased Fos expression in vSub ($F(1,11) = 32.3$, $p < 0.001$ for relapse test versus no-test group comparison) and that local inactivation of vSub decreased incubated oxycodone seeking ($F(1,19) = 5.9$, $p = 0.025$ for vehicle versus muscimol+baclofen comparison).

Conclusions: Together, these data demonstrate that voluntary abstinence induced by adverse consequences can potentiate opioid seeking and craving over time and demonstrate a role of vSub in this phenomenon.

Disclosure: Nothing to disclose.

Panel

18. Using Stem Cell Models to Explore Polygenic Risk for Psychiatric Disease

18.1 Exploring Synergistic Effects of Schizophrenia Risk Variants Using Stem Cells

Kristen Brennand

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

Background: Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. Whereas highly penetrant variants have proven well-suited to human induced pluripotent stem cell (hiPSC)-based models, the power of hiPSC-based studies to resolve the much smaller effects of common variants within the size of cohorts that can be realistically assembled remains uncertain.

Methods: We applied a genetics-driven human induced pluripotent stem cell (hiPSC)-based isogenic approach to evaluate the effects of schizophrenia (SZ)-associated common variant single nucleotide polymorphisms (SNPs) predicted to function as brain expression quantitative trait loci (eQTLs). To facilitate isogenic analyses of the impact and penetrance of risk variants across genetic backgrounds, we integrated CRISPR-mediated gene editing, activation and repression technologies with our hiPSC-based neural platform, testing the effect of manipulating the growing number of SZ-associated variants and genes in neuronal, glial and 3D organoid models.

Results: By integrating CRISPR-mediated gene editing, activation and repression technologies to study one putative causal SZ SNP (FURIN rs4702) and four top-ranked SZ-eQTL genes (FURIN, SNAP91, TSNARE1, CLCN3), our hiPSC-based neuronal platform resolved specific pre- and post-synaptic neuronal deficits, recapitulated genotype-dependent gene expression differences in post-mortem brains, and revealed convergence downstream of SZ-eQTL gene perturbations. We demonstrated strategies to interpret and evaluate the growing number of SZ-associated variants and genes across donor backgrounds, highlighting the cell-type-specific nature of common variant effects. Our observations uncovered an unexpected synergistic effect between SZ-eQTL genes that converged on synaptic function and linked the rare and common variant genes implicated in psychiatric disease risk, one which may represent a generalizable phenomenon occurring more widely in complex genetic disorders. Ongoing work is now comparing the impact of CRISPR-perturbations across donors with very high and low polygenic risk for SZ, in order to further resolve potential additive and/or epistatic interactions underlying polygenic risk for psychiatric disease.

Conclusions: We predict a growing convergence between hiPSC and post-mortem studies as both approaches expand to larger cohort sizes. We demonstrate a systematic and scalable strategy to interpret and evaluate the growing number of SZ-associated variants and genes across neural cell types and genetic backgrounds. Altogether, our objective is to dissect the genetic origins of SZ while developing a precision medicine approach to

Disclosure: Alkermes, Consultant

18.2 Schizophrenia: From Genetic Association to Disease Biology

Dimitri Avramopoulos

The Johns Hopkins University, Baltimore, Maryland, United States

Background: Our laboratory focuses on exploring the biology behind genetic associations with schizophrenia (SZ). We start by using an array of tools to identify which of the many variants at each locus is functional, a necessary step in order to proceed with confidence to editing these variant regions into iPS cells and differentiating them into neurons for further study. We then use the transcriptome as a readout reflecting changes in cellular homeostasis, which our previous work has shown to be powerful in revealing the consequences of even variants of small effect. We report on our work on characterizing SZ variants identified by GWAS as well as one variant showing Mendelian inheritance in a multiply affected family.

Methods: To identify functional variation we use chromatin conformation capture (4CSeq) on human neuroblastoma cells (SH-SY5Y). After crosslinking, primary digestion, reversal, and secondary digestion, we circularize and amplify from the viewpoint to capture interacting DNA fragments and sequence to ~10 million reads. Enrichment of junctions within 1 Mb is calculated after correcting for confounders, obtaining Z-scores and identifying outliers. Positive results are tested by the reverse test. We generate deletions to test functionality by CRISPR/Cas9 editing of SH-SY5Y and iPS cells from healthy individuals using a dual gRNA approach. We test single gene expression by real time RT-PCR on cDNA from 10 edited and unedited clones. The SZ family we report was characterized by interview reports of two psychiatrists and arbitration of a third. Genome sequencing and primary data analysis was performed by the Baylor Hopkins Center for Mendelian Genomics.

Results: To identify the genes responsible for GWAS signals near SDCCAG8 and CKAP5 we used 4CSeq from their promoters. CKAP5 showed no interactions with the GWAS variants. SDCCAG8, interacted with the lead associated SNP, confirmed by reverse analysis. Deletion of the variant sequence resulted in reduction of the gene's expression in SH-SY5Y ($p < 0.01$) validating its functionality. The same deletion in hiPSCs did not change expression suggesting neuronal specificity. Analysis of induced neurons is pending.

In a published search around the CACNA1C gene, 4CSeq did not have the resolution to identify a single variant. A protein array analysis however suggested that combinatorial effects of variants might be involved. We have now completed a massively parallel reporter assay (MPRA) screen, supporting this may be a common phenomenon in larger haplotype blocks. This observation is important for accurately recapitulating the biological effects of variants by genome editing.

Finally, in our search for high penetrance SZ variants we analyzed a large pedigree from Greece, including 6 affected and 9 unaffected individuals with apparent autosomal dominant inheritance. Exome sequencing of four members identified two brain-expressed genes with rare non-synonymous variants. Sanger sequencing showed that one is predicted highly damaging, perfectly segregates with disease and is in a functional interactor of NRX1, an established schizophrenia gene. We are characterizing this variant by genome editing.

Conclusions: Identifying the functional variant among many in LD may be challenging but tools such 4CSeq can succeed. Genome editing can then be used to confirm the functionality and study how such variants change cellular homeostasis. Doing so across multiple schizophrenia variants will help understand its phenotypic diversity and improve treatments through precision medicine.

Disclosure: Nothing to disclose.

18.3 Modeling Schizophrenia and Its Polygenic Risk Using Induced Pluripotent Stem Cell-Derived Neurons

Brady Maher

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

Background: Progress towards a better understanding of etiology and the development of novel treatments for schizophrenia (SZ) has been hindered by a lack of animal models with face validity for the disorder. Moreover, current animal models cannot effectively model polygenic risk contributing to schizophrenia. The advent of

induced pluripotent stem cell (iPSC) provides a unique opportunity to study human cells that retain the personal genetic architecture of schizophrenia risk, thus opening the door to developing in vitro models that can improve our ability to detect cellular and circuit abnormalities and develop novel treatment strategies.

Methods: We have established a systematic and quantitative iPSC platform to model common risk variation associated with SZ. To model genomic risk from common variants, we generated iPSCs from 14 SZ patients with high polygenic risk scores (PRS) and 16 neurotypical individuals with low PRS. To identify and control for technical variability, iPSCs underwent four independent rounds of directed differentiation into cortical neurons, a process that was monitored at each stage using a variety of quality control assays, including qPCR and immunocytochemistry followed by high-content imaging. To identify phenotypes differing between high PRS SZ cases and low PRS controls, a battery of assays was performed on neural progenitor cells (NPCs) and cortical neurons in a double-blind manner. These assays include immunocytochemistry, electrophysiology, Ca2+ imaging, metabolomics, qPCR, and RNA sequencing.

Results: Statistical analysis of both quality control and phenotypic discovery assays is currently underway as all experiments are now complete. Given the double-blind design of the study, both positive and negative results will be valuable to the research community.

Conclusions: These varied approaches for measuring functional and dynamic properties associated with neuronal development will assist in the identification of pathological differences between SZ cases and controls. Overall, we have established a robust in vitro platform to study the effects of polygenic risk for schizophrenia, and we anticipate this model system will advance our ability to identify therapeutic targets for drug development.

Disclosure: Nothing to disclose.

18.4 Single Cell Transcriptomes in Cortical Organoids From Patients With Autism Spectrum Disorder

Flora Vaccarino

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

Background: Autism spectrum disorder (ASD) is a complex genetic disorder where both rare and common variants are thought to play significant roles. To identify convergent mechanisms of disease downstream from genetic heterogeneity, we investigated the developmental neurobiology of ASD using patient-derived induced pluripotent stem cells (iPSC).

Methods: We generated iPSC lines from 15 probands with ASD, with or without macrocephaly, and unaffected controls. We then differentiated iPSC into cortical organoids, which recapitulate embryonic/early fetal cortical development in vitro. Single cell RNA sequencing (scRNA-seq) was used to compare gene expression and cellular phenotypes between probands and their unaffected first-degree family members. In parallel, enhancer regulatory regions were mapped via Chromatin immunoprecipitation and sequencing (ChIP-seq) and their activity (H3K27ac signal, ATAC-seq) compared in patients vs controls.

Results: The scRNAseq data analyzed using the Seurat pipeline revealed 29 cell clusters. Cell distribution among clusters differed among time points as expected and were similar across individuals. For each cluster, we identified 300~1,200 markers, i.e. genes that are differentially expressed between cells in one cluster and all other cells outside the cluster. The average expression of organoid's cluster markers matched with one or a few cluster markers from published scRNA-seq dataset from human fetal brains. Cell distribution across clusters was generally similar across individuals, with patients exhibiting higher proportion of cells in medial ganglionic eminence, interneurons and radial glia clusters. In addition, there were differentially expressed genes between patients and controls within several clusters.

Conclusions: Comparisons between our dataset and scRNA-seq dataset from human fetal brains suggested that our organoid culture largely recaptulate the cellular components of early cortical development in humans. The organoid system promises to unravel genes and regulatory elements driving the onset of neurodevelopmental disorders.

Disclosure: Nothing to disclose.

Panel

19. Continuous Telemetry in Psychiatry and Neuroscience: Transitioning From Snapshots to Film

19.1 Benchmarking Behavior Through Neuropharmacology for Neuropharmacology

Sandeep Datta

Harvard Medical School, Boston, Massachusetts, United States

Background: The past several years has seen a revolution in the development of methods for the measurement and analysis of behavior. However, we still lack a common framework for comparing different approaches and methods in behavioral analysis. For example, our laboratory has developed an ethologically-inspired approach to mouse behavior called Motion Sequencing (MoSeq), which merges 3D machine vision and unsupervised machine learning techniques to identify key behavioral modules (which we refer to as behavioral "syllables") and their interconnections over time (behavioral "grammar"). Is describing mouse behavior as being composed of syllables and grammar more informative than more traditional or alternative methods for describing behavior? To address this question, we treated more than 500 mice with one of 15 different commonly used neuro- or psycho-active drugs at one of 2-6 different doses. We then characterized the behavior of each mouse in this reference dataset using a variety of different methods — including MoSeq, a clustering-based approach called MotionMapper, and more traditional scalar metric-based approaches — and asked which method was best able to predict the drug and dose each mouse received. We also asked how these methods characterized the behavioral phenotype of the CNTNAP2 mouse model of autism, and the ability of Risperdal to revert this phenotype.

Methods: Mice were injected with one of 15 different drugs belonging to 5 main classes (anti-psychotic, SSRI, SNRI, psychostimulant, anxiolytic) at one of 2-6 doses via IP injection before imaging in the circular open field (using a 3D camera) for 30 minutes. Data were then extracted and subjected to analysis using published protocols to generate either MoSeq, MotionMapper or scalar-based "fingerprints" for each mouse describing its behavior. CNTNAP2 mice (Jackson labs) were imaged identically, but a subset of mice was pre-treated with Risperidone following a protocol from the Geshwind lab demonstrated to revert the CNTNAP2 hyperactivity phenotype. Prediction of drug and dose based upon behavior was performed using simple linear classifiers or logistic regression.

Results: This framework reveals that MoSeq quantitatively outperforms alternative methods (including traditional scalar descriptions of behavior and MotionMapper) both at classifying behavioral drug effects ($p < 0.05$) and at preserving information about pharmacological and therapeutic relationships amongst

drugs ($p < 0.05$). MoSeq revealed that neuro- and psychopharmacological agents elicit changes in small collections of characteristic behavioral syllables. We took advantage of this phenomenon to identify specific on-target and off-target syllables modulated by the clinically-used drug risperidone in the CNTNAP2 mouse model of autism.

Conclusions: This work describes a generalizable strategy for comparing the performance of behavioral representations, and establishes a reference database that can be used to compare current and future analysis methods. This benchmarking approach reveals the power of modular, time-series descriptions of behavior, demonstrates that MoSeq can effectively encapsulate complex behavioral phenotypes in behavioral data at scale, and suggests that behavioral syllables may represent a new and useful category of therapeutic target for future drug development.

Disclosure: Syllable Life Sciences, Stock/Equity; Abelian Therapeutics, Stock/Equity; Optogenix, Stock/Equity.

19.2 Neuropsychiatric Features of Perinatal Immune Activation in Mice: Interactions With Daily Rhythms

Galen Missig

Harvard Medical School, Belmont, Massachusetts, United States

Background: Accumulating evidence supports a role for immune signaling in psychiatric conditions. There is growing support for an epidemiological association between various forms of inflammation during pregnancy, including infections and autoimmune disorders, and a predisposition for the offspring to develop a psychiatric condition. Modeling this risk factor in mice has demonstrated that perinatal immune activation can result in a phenotype that reproduces some of the core features of autism spectrum disorder (ASD) and schizophrenia. Here, we use a comprehensive battery of tests, including those involving continuous telemetry, to extend these findings demonstrating that 1) different forms of immune activation may result in divergent phenotypes and 2) that these models exhibit neurophysiological alterations resembling humans with psychiatric conditions.

Methods: In a "two hit" model, pregnant mice are injected with poly I:C (20 mg/kg) on prenatal embryonic day 12.5 and a subset receives a second hit of LPS (10mg/kg) on postnatal day 9. Preliminary data from this model indicated heightened levels of multiple inflammatory markers in the brain and microglia hyperproliferation in adulthood. In a second model, prenatal TLR7 activation, a TLR7 agonist (Imiquimod 5mg/kg) is given on emybronic days 12.5, 14.5, and 16.5. Both paradigms of mice were tested on a battery of behavioral tests including those related to social interaction, repetitive behavior, anxiety-like behavior, and communication-related behavior. Additionally, we used wireless (untethered) electroencephalogram (EEG) telemetry to assess multiple physiological measures continuously over a span of numerous days.

Results: The two hit model produced a complex behavioral phenotype with features that are characteristic of ASD and schizophrenia, including alterations in pup and adult ultrasonic vocalizations ($p < 0.01$), decreased social interaction ($p < 0.01$), and increased anxiety-like behavior ($p < 0.05$). Continuous EEG telemetry revealed alterations in sleep ($p < 0.05$), a form of epileptiform activity ($p < 0.01$), and a shift in EEG spectral power ($p < 0.01$). In contrast, prenatal TLR7 activation induced a markedly different phenotype with opposing changes in communication-related behavior ($p < 0.05$), an increased but fragmented social behavior ($p < 0.05$), and decreased anxiety-like behavior ($p < 0.05$). Further, on multiple tests these mice exhibited a "conditional hyperactivity" in response to both external (environmental) and internal (hormonal) stimuli. For example, in female mice there was a robust increase (>3 fold) in locomotor activity specifically during a night of estrus. Paralleling these changes in both models there were differential changes in microglia and immune responses within the brain.

Conclusions: These studies further support a potential link between perinatal inflammation and a predisposition towards psychiatric conditions. Using continuous EEG telemetry, we find that these models exhibit neurophysiological alterations that resemble psychiatric conditions. Additionally, we find that different types of perinatal immune activation can result in highly divergent phenotypes offering a potential explanation for the broad association between inflammation and psychiatric conditions.

Disclosure: Nothing to disclose.

19.3 Wireless, Battery-Free, Implantable Neural Recording and Stimulation Devices for Studying Brain Disorders

Cameron Good

US Army Research Laboratory, Aberdeen Proving Ground, Maryland, United States

Background: Most commonly used in vivo methods for recording electroencephalography (EEG) or optogenetic stimulation require physically tethering the animals to external recording hardware and light sources during discrete experimental windows. These connections can constrain and alter natural animal mobility, prevent social interactions and impede motion, particularly in complex, three-dimensional environments. Recent years have seen growth in wireless recording and stimulation technologies for obvious reasons – eliminating tethers allows animals to exhibit more naturalistic behavior. However, existing wireless technologies mostly still require some external hardware (transmitters) or large implanted batteries whose lifespans are limited to weeks, and whose weight/bulk are still disruptive to animals' behavior, physiology, and overall health. To overcome these limitations, we developed fully-implantable wireless, battery-free EEG and optogenetic devices that allow researchers to perform long-term, continuous experiments in freely moving animals in a more natural state.

Methods: We designed, prototyped and tested an EEG signal conditioning and filter circuit that can harvest energy and stream EEG/EMG data wirelessly. A Bluetooth Low Energy transmission circuit and implantable optogenetic μLED probes are wirelessly powered by a 13.56 MHz, near field communication standard. To validate the EEG circuit, we implanted 9 male Sprague-Dawley rats with standard EEG screws mated to a Plastics One connector that was surgically affixed to the animal's heads. We then built a bifurcating connector that allowed simultaneous neural recording from the tethered and wireless systems using shared EEG screws. Following ten minutes of baseline recording, baclofen (10 mg/kg, i.p.) or pilocarpine (400 mg/kg, i.p.) was administered to test the wireless circuits' ability to track dynamic changes in EEG parameters. An additional 5 male rats were implanted with wireless EEG/optogenetic devices and recorded. In separate mobility experiments, 3 groups of C57/B6J male mice ($n = 5$-7 per group) were injected with adeno-associated virus and either implanted with fiber optic or wireless optogenetic probes, or no probes for surgical controls. For testing, animals were placed in the center of a circular arena (34 cm diameter) and allowed to roam freely for 1 hr. Movement was video-recorded and motion analysis was performed posthoc using Ethovision 11.

Results: EEG signal comparisons between the wireless and tethered systems showed near-identical statistical power/frequencies from baseline through drug effect (Pearson correlation, 0.995

to 0.999). Implanted wireless devices demonstrated an ability to continuously track EEG for extended durations. In the open field test, mice connected to fiber optic tethers showed a statistical reduction in distance traveled throughout the first 30 minutes, compared to both surgical control and wireless subjects ($p < 0.01$, ANOVA).

Conclusions: Wireless implants allow animals to move more freely, compared to fiber optic, by removing the behavioral effects of torque applied to the head. The EEG technology is ideally suited for long-term sleep and seizure experiments that benefit from continuous data streams. Ultimately this technology could be applied to humans, and might enable a more effective use of rodents to predict health and safety-related outcomes under a variety of environmental conditions.

Disclosure: Nothing to disclose.

19.4 Intensive Longitudinal Monitoring: Taking Addiction Research Beyond the Snapshot

Kenzie Preston

National Institute on Drug Abuse, Baltimore, Maryland, United States

Background: Our addiction-research clinic has incorporated ambulatory assessment of behavior, mood, and environment (using smartphones and GPS) into natural-history studies with intensive longitudinal monitoring. We are using field data to study the relationships among stress, craving, cue exposure, and drug use across extended observation periods, with the goal of developing empirically grounded future-predicting mobile interventions. We have shown that participants' real-time ratings of stress and craving are associated with objective ratings of the physical and social environmental disorder they encountered during the 5 hours before making randomly prompted (RP) ecological momentary assessment (EMA) entries. We are now using machine-learning models to predict when patients are at risk for craving 90 minutes into the future to order to time treatment intervention delivery.

Methods: EMA and GPS data were collected for up to 16 weeks in 189 patients in treatment for OUD. Participants rated heroin craving 3 times/day (RP). Property tax values at GPS points along participants' travel paths were the environmental measure of socioeconomic conditions. We calculated predictions of heroin craving 90 min prior to each EMA entry using random forest machine learning with tax-value data (6.5 to 1.5 hrs before each entry) as a time-varying predictor and sex, race, and other demographic and drug use history data at intake as person-level variables. To cross-validate predictions, we compared each participant's actual to predicted craving in a "leave-one-out" analysis approach using a training database of the other 188 participants. We calculated model performance per person per week, aggregated across all participants, then by sex and race and conducted a latent class cluster analysis to derive person-level trajectory clusters based on weekly prevalence.

Results: Overall prevalence of heroin craving in RPs was mean (SD) 15.2% (0.01). Mean per person diagnostic accuracy and mean negative predictive value (NPV) were similar: 80% at week 1, increasing to about 93% at 16 weeks. Mean positive predictive value (PPV) was lower: .01% at week1 and fluctuating around 60% in weeks 2-16. There were no differences between model performance in men and women. Diagnostic accuracy differed for African Americans (AA) (91%) compared to non-AA (84%). The cluster analysis showed a 4 cluster solution: low craving (87% of participants); moderate, decreasing (9%); moderate/high, increasing (9%); high, increasing (6%). Accuracy varied systematically by cluster with the highest NPV in the low cravers (97%) and highest PPV in the high cravers (91%). In a regression analysis, cluster retained almost all its predictive value when race was controlled for, and race lost almost all its predictive value when cluster was controlled for [Race: $F(1,174) = 1.45$, $p = 0.23$; Cluster: $F(3,174) = 132.09$, $p < 0.0001$; Race x Cluster: $F(3,174) = 0.39$, $p = 0.76$].

Conclusions: We have demonstrated that heroin craving can be predicted reasonably accurately (over 90% accuracy) 90 minutes into the future. However, there is substantial individual variability in the prevalence of craving that affects our ability to predict. Overall accuracy is an unhelpful statistic for prediction of rare outcomes, whereas positive predictive value is more directly related to the target event.

Disclosure: Nothing to disclose.

Mini Panel

20. Pharmacogenetics in Psychiatry: The Truth, the Whole Truth, and Nothing but the Truth

20.1 Impact of CYP2C19 and CYP2D6 Genotype on Escitalopram, Risperidone, and Aripiprazole Treatment

Marin Jukic

The Karolinska Institutet, Stockholm, Sweden

Background: Most psychotropic drugs are metabolized by the CYP2C19 and CYP2D6 enzymes. The genes coding these enzymes are polymorphic and CYP2C19/D6 genotype determines the enzymatic capacity. Consequently, genotype may also affect the exposure to and treatment outcome of drugs such as escitalopram, risperidone, and aripiprazole. However, it is not yet clear whether preemptive CYP2C19/D6 genotyping can be utilized for dose personalization in treatment with these drugs.

Methods: A total of 2,087 CYP2C19 genotyped patients treated with escitalopram, 1288 CYP2D6 genotyped patients treated with risperidone, and 1334 CYP2D6 genotyped patients treated with aripiprazole were included in this analysis. Patient data were retrospectively obtained from a routine therapeutic drug monitoring database at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. Based on CYP2C19/D6 genotype, patients were classified into four subgroups: (1) Poor metabolizers carrying two defect alleles - these patients have no enzymatic activity, (2) Intermediate metabolizers are characterized by genotypes which are substantially reducing enzymatic capacity, but do not abolish it completely, (3) Normal metabolizers carry fully functional alleles and exhibit extensive CYP2C19/D6 metabolism, and (4) Ultrarapid metabolizers are patients with higher predicted enzymatic capacity, which can be caused by specific alleles or whole gene duplications. Drug exposure was calculated as the active moiety serum concentration divided by dose and compared between metabolizer subgroups. A follow-up systematic review and meta-analysis was performed on 60 studies in which escitalopram, risperidone, and aripiprazole exposure were analyzed in relation to CYP2C19/D6 metabolizer status to calculate the changes in drug exposure between different metabolizer phenotypes. Treatment failure was defined as an event in which a patient continued antidepressant/antipsychotic therapy and escitalopram/risperidone or aripiprazole was omitted from the treatment during the one year follow-up period, and treatment failure rates were compared between subgroups.

Results: CYP2C19 poor metabolizers exhibit 2.22-fold (95% CI: 2.03-2.41) increased exposure to escitalopram, while CYP2D6 poor metabolizers exhibit 1.40-fold (95% CI: 1.31-1.49) increased risperidone and 1.55 (95% CI: 1.40-1.70) increased aripiprazole exposure. CYP2C19 intermediate metabolizers exhibit 1.28-fold (95% CI: 1.21-1.36) increased exposure to escitalopram, while

CYP2D6 poor metabolizers exhibit 1.37-fold (95% CI: 1.21-1.53) increased risperidone and 1.44 (95% CI: 1.36-1.51) increased aripiprazole exposure. Escitalopram treatment failure was 3.3 times more frequent among CYP2C19 poor and 1.4 times more frequent among ultrarapid metabolizers compared with normal metabolizers. Risperidone treatment failure was 1.9 times more frequent among CYP2D6 poor and 2.9 times more frequent among ultrarapid metabolizers compared with normal metabolizers. The effect of CYP2D6 metabolizer status on aripiprazole treatment failure rate was not statistically significant.

Conclusions: CYP2C19 and CYP2D6 metabolizer status is a clinically relevant feature in psychiatry and patients treated with risperidone, aripiprazole, and escitalopram would likely benefit from preemptive CYP2C19/D6 genotyping

Disclosure: Nothing to disclose.

20.2 Antidepressants, CYP2D6 and CYP2C19: Toward Better Clinical Associations With Functional Diplotype

Abstract not included.

20.3 Commercial Pharmacogenetic Testing: Taking a Look Under the Hood

Abstract not included.

Panel

21. New Approaches to Dissecting Treatment Response in Psychosis

21.1 Easy to Claim but not so Easy to Show: Individual Differences in Treatment Response

Philipp Homan

University Hospital of Psychiatry/University of Zurich, Zurich, Switzerland

Background: It is a widely held belief that patients with schizophrenia vary considerably in their response to antipsychotics in randomized controlled trials. Yet, although there is obviously variation in the observed treatment responses, it is crucial to distinguish between observed and true treatment response, and to recognize that the estimation of treatment response benefits from statistical modeling.

Methods: We will illustrate the different components of variation in clinical trials and show that it is crucial to recognize the treatment-by-patient interaction (which reflects individual treatment response) as the component of interest. We will then test for the presence of such treatment-by-patient interaction in empirical data from antipsychotic drug trials and compare the overall variability in the treatment group to the overall variability in the control group, using data from 30 years of placebo-controlled, antipsychotic RCTs in schizophrenia. We hypothesized that the often-highlighted heterogeneity in patients with schizophrenia would be reflected by a clinically relevant increase in overall variance of treatment compared to control, compatible with a personal element of response that deviates from the estimated average treatment effects.

Results: In over 15,000 patients, we found an overall lower variability in treatment compared to control (Variability Ratio = 0.97, 95% CI: 0.95, 0.99; P = 0.01) which indicates that the overall variability across treatment groups was 3% lower compared to the control groups. We also compared the variances with regard to individual antipsychotics and found the same pattern with lower variability across treatment compared to control (Variability Ratio = 0.97, 95% CI: 0.95, 1.00, P = 0.02).

Conclusions: Even though it is widely believed that patients differ substantially in their antipsychotic treatment response, it is more complex than often appreciated to provide evidence for this belief. A likely explanation for this belief is that we are tempted to take observed treatment response as true treatment response, thereby ignoring the components of variation that we are most likely to encounter random variation within patients and differences between patients. The empirical evidence for such individual differences is weaker than we expected and suggests that we need to make use of repeated measures and complex statistical modeling to capture individual differences in treatment response.

Disclosure: Nothing to disclose.

21.2 Polygenic Approaches to Pharmacogenetics

Abstract not included.

21.3 Functional and Structural Brain Connectivity as Markers of Antipsychotic Treatment Response

Nina Kraguljac

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Background: Schizophrenia is now widely regarded as a disorder of brain dysconnectivity. To develop biomarkers of treatment response to antipsychotic drugs that capture dysconnectivity, we evaluated functional and structural connectivity in two cohorts of patients with a schizophrenia spectrum disorder (unmedicated patients and medication-naïve first episode patients) prior to a six-week trial of antipsychotic treatment. Baseline patterns of connectivity were tested for their ability to predict subsequent response to treatment in each cohort.

Methods: Here, we obtained connectivity metrics in two cohorts of unmedicated/ antipsychotic-naïve patients who participated in a six-week trial of risperidone treatment and healthy controls matched on key demographic variables (total n = 180). Response to antipsychotic treatment was operationally defined as follows: ([BPRS baseline – BPRS week 6]/ BPRS baseline*-100). The first cohort consisted of 42 unmedicated patients with schizophrenia and 42 controls who were scanned on a Siemens Allegra scanner. The second cohort consisted of 55 antipsychotic-naïve first episode psychosis patients and 41 controls who were scanned on a Siemens Prisma scanner. To assess functional connectivity, we obtained resting state fMRI scans and used a seed based approach to assess left hippocampal connectivity. To assess structural connectivity, we obtained Diffusion Weighted Imaging and used Neurite Orientation Dispersion and Density Imaging (NODDI), a biophysical diffusion model to compute extracellular free water and orientation dispersion index (ODI) maps. We used regression and correlation analyses to assess the relationship between functional/ structural connectivity patterns at baseline and treatment response after six weeks.

Results: We found that functional connectivity of the hippocampus to the visual cortex was predictive of treatment response in both cohorts (pFDR < 0.05), where more intact functional connectivity at baseline was associated with better antipsychotic treatment response. In the first cohort, we further report a negative correlation between baseline ODI and treatment response both in the whole sample (r = −0.38; p = 0.049), and when only medication-naïve subjects were taken into consideration (r = −0.52 p = 0.027), suggesting that more intact baseline

structural connectivity is associated with better antipsychotic treatment response.

Conclusions: Here, we demonstrated in two different cohorts of medication-free/ antipsychotic-naïve schizophrenia spectrum patients that baseline connectivity predicts subsequent response to antipsychotic treatment. Our data support the hypothesis connectivity signatures could be leveraged as clinically relevant biomarkers, where more intact brain connectivity patterns predict favorable response to antipsychotic treatment.

Disclosure: Nothing to disclose.

21.4 The Dopaminergic Sub-Type Hypothesis of Psychosis and Treatment Response: New in Vivo Evidence

Oliver Howes

King's College London, Institute of Psychiatry, London, United Kingdom

Background: There is considerable variability in response to antipsychotic treatment, and psychosis is resistant to antipsychotic treatment in about one third of patients. It has been hypothesised that there is a dopaminergic sub-type of psychosis that responds well to antipsychotic treatment, and a non-dopaminergic sub-type characterised by more marked glutamatergic dysfunction that is treatment resistant. However, this has not been tested early in the course of illness or in a longitudinal study before.

Methods: Drug naïve/free patients ($n = 32$) presenting with first episode psychosis and matched controls ($n = 20$) received [18F]-DOPA PET scans to index striatal dopamine synthesis capacity and 1H-MRS imaging to measure glutamatergic function in the anterior cingulate cortex. Patients then received antipsychotic treatment and longitudinal follow-up to determine clinical response and adherence was checked. PET and MRS imaging was repeated in patients to determine if treatment was associated with alterations in dopaminergic and glutamatergic measures.

A second cohort of eighty-two patients were recruited from first episode services on the basis of response to antipsychotic treatment over six months and received 1H-MRS imaging.

Results: Baseline dopaminergic, but not glutamatergic, function was elevated in patients who subsequently responded to antipsychotic treatment relative to patients who were subsequently found to be treatment non-responders (cohen's $d > 1.2$; $p = 0.01$), and controls (cohen's $d > 1.2$; $p < 0.05$). Psychotic symptoms were positively associated with dopaminergic function ($r = 0.37$; $p < 0.05$) but were negatively associated with glutamatergic function ($r = -0.40$; $p < 0.05$). Consistent with these symptom relationships, glutamatergic function was negatively associated with dopaminergic function at baseline ($r = -0.4$, $p < 0.05$), in contrast to the relationship seen in controls. However, following antipsychotic treatment, the relationship between dopaminergic and glutamatergic function was significantly changed ($p < 0.05$), and no longer significantly different from that in controls.

In the second cohort of patients, glutamate levels were significantly elevated in treatment non-responders relative to treatment responders ($p < 0.05$).

Conclusions: These data indicate that dopaminergic function determines initial response to antipsychotic treatment, but that subsequent treatment resistance is associated with glutamatergic dysfunction, and that the relationship between striatal dopaminergic and cortical glutamatergic function alters with antipsychotic treatment.

Disclosure: Angellini, Astra-Zeneca, Autifony, Biogen, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand, Recordati, and Roche, Grant.

Panel

22. The Contribution of Abnormal Sleep to Neurodevelopmental Disorders

22.1 Using Fruit Flies to Study Sleep Regulation and Function During Development

Matthew Kayser

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Background: Developmental sleep abnormalities are highly prevalent across neuropsychiatric disorders, and early life sleep may be a modifiable risk factor for these illnesses. However, the basic mechanisms underlying developmental changes to sleep ("sleep ontogeny") remain unknown. Moreover, examination of a function for sleep in even earlier phases of brain development, when neurons are first being born, has been limited by lack of tractable experimental systems. Research in the fruit fly, Drosophila melanogaster, has yielded seminal insights into the regulation of sleep and circadian rhythms, and is poised for the study of sleep during development. Sleep in Drosophila shares most features with mammalian sleep, including developmental changes. We used this powerful model system to determine molecular mechanisms controlling sleep maturation, and to investigate sleep regulation and function during nascent neurodevelopmental periods.

Methods: To identify sleep ontogeny-specific genes, we conducted a screen of adult Drosophila sleep with panneuronal RNAi-driven knockdown of ~1000 neurally-expressed genes. "Hits" were defined as lines lacking sleep ontogenetic change from young adulthood to maturity. A variety of genetic, behavioral, and imaging approaches were used to determine how loss of gene function translates into disrupted sleep ontogeny. To study sleep during earlier developmental periods, we developed a machine vision platform to define and study sleep in Drosophila larvae, coupled with genetic tools to interrogate circuit-specific sleep functions.

Results: Screening approaches converged on the transcription factor pdm3 as a novel genetic regulator of sleep ontogeny. Loss of pdm3 abolishes sleep ontogeny, and leads to sleep fragmentation. Temporal mapping indicates that pdm3 acts specifically during early development to control later sleep maturation from young to mature adulthood. Sleep ontogenetic change derives from developmentally-regulated activity changes in the dorsal fan shaped body, part of the Drosophila central complex. We find that loss of pdm3 alters dopaminergic innervation and intrinsic architecture of the central complex, suggesting pdm3 acts during development to pattern sleep circuits. Studies of sleep during even earlier development reveal that genetic and cellular control of sleep during this time is distinct from that in adulthood. We have identified 2 neurons per brain hemisphere (out of ~10,000 neurons in the larval nervous system) that control sleep. In addition, sleep loss during this critical period attenuates proliferation of neural progenitors, suggesting early developmental sleep loss has long-lasting consequences on brain and behavioral maturation.

Conclusions: We have identified pdm3 as the first known genetic regulator of sleep ontogeny. In contrast to many previously described sleep genes, pdm3 acts during early development to regulate young adult sleep behavior, and controls

formation of ontogeny-relevant sleep circuits. Our findings from the fly larval platform underscore that the genetic and cellular regulation of sleep depends on the developmental period being studied. Dissecting the mechanistic control of early developmental sleep and sleep maturation will yield new insights into sleep function during this period, and provide a platform for investigating behavioral sequelae of developmental sleep abnormalities.

Disclosure: Nothing to disclose.

22.2 Determinants of Early Sleep Patterns That Influence Risk for Psychopathology

Ruth Benca

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Background: Sleep disturbances in childhood are associated with increased risk for psychiatric disorders later in life. Sleep problems during pregnancy have been associated both with postpartum depression as well as later sleep disturbance in both mothers and infants. Furthermore, sleep problems in infants lead to increased risk of sleep disturbance in childhood, and persistent sleep problems in children are predictive of increased risk for psychiatric disorders later in life, although all of these relationships have not been assessed within the same cohort. This presentation will review prior work in this area and present new data on 1) effects of sleep disturbance during pregnancy on postpartum depression, a risk factor for child psychopathology, and (2) the relationship of maternal sleep during pregnancy/postpartum and maternal depression on sleep patterns in infants and children.

Methods: Women ($n = 211$; age 29.91 ± 5.33 yrs at delivery) were enrolled during the first trimester of pregnancy. Sleep and mood of mothers was assessed with self-report questionnaires [Pittsburgh Sleep Quality Index (PSQI), Center for Epidemiologic Studies Depression Scale Short Form (CES-D-SF), Edinburgh Postnatal Depression Scale (EPDS)] and structured interviews during 5 prenatal/2 postnatal visits. Offspring were followed for 8+ yrs. Infants were assessed with the Child Sleep Interview (CSI) and Child Sleep Questionnaire (CSQ). The Children's Sleep Habits Questionnaire - Parent Report (CSHQ), the Child and Adolescent Sleep Perception - Child Report (CASP-C), the Children's Behavior Questionnaire (CBQ), the Child Behavior Checklist (CBCL), and the K-SADS interview were collected on older children. Mixed model repeated measure analyses were used to examine differences in sleep and mood across time in mothers. Logistic regression controlling for age, years of education, and baseline depression was performed to estimate the association between poor sleep quality during pregnancy and presence of postpartum sleep and depressive symptomatology. Offspring analyses are ongoing.

Results: At 15 weeks pregnancy, 42.1% of participants had a PSQI score indicative of poor sleep quality, and sleep quality deteriorated significantly during second and third trimesters, followed by improvement over postpartum period (all $p < 0.001$). The prevalence rate of postpartum depression was 8.5% and 8.9% at 3 and 6 months after delivery, respectively. PSQI scores at 25 weeks and 36 weeks pregnancy were associated with increased odds of (1) having persistent poor sleep postpartum (OR 1.64, 95% CI = 1.07–2.51; and OR 1.91, 95% CI = 1.04–3.50, respectively), and (2) having postpartum depressive symptoms at 3 months (OR 1.37, 95% CI = 1.03–1.83; and OR = 1.35; 95% CI = 1.06–1.73, respectively). Effect of maternal pregnancy/postpartum sleep disturbance and postpartum depression on sleep patterns in infants will be reported, as well as the relationship of infant and childhood sleep problems with psychiatric symptoms in children.

Conclusions: Women experienced marked sleep disturbances across pregnancy and postpartum. Poorer subjective sleep quality during pregnancy contributed to development and extent of clinical postpartum depression. Maternal sleep concerns during pregnancy may be an important premorbid clinical indicator of postpartum mood disorders and may impact sleep patterns and psychiatric symptomatology in their offspring. Our findings suggest that screening for sleep problems during pregnancy may be of clinical significance for psychiatric risk in both mothers and their infants.

Disclosure: Merck, Consultant; Eisai, Consultant; Jazz, Consultant; Genomind, Consultant; Madefor, Consultant.

22.3 Sleep Spindles and Slow Waves Abnormalities in First Episode Psychosis and Prodromal Patients

Fabio Ferrarelli

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Sleep spindles and slow waves are the two main oscillatory rhythms occurring during NREM sleep. Spindles are waxing and waning, 12–16 Hz oscillations, which are generated within the thalamus and then relayed to, and amplified in the cortex, whereas slow waves are 0.8–1.2 Hz, large amplitude oscillations that are initiated and propagated primarily within the cortex. Marked deficits in sleep spindles have been reported by our and other research groups in patients with schizophrenia (SCZ) compared to both healthy individuals and psychiatric non-schizophrenia patients. However, it remains to be established when these deficits first occur, and if they are restricted to spindles, or rather extend to slow waves. Here I will present data from ongoing longitudinal studies performing sleep EEG recordings in first episode psychosis (FEP) patients as well as in individuals at clinical high risk for psychosis (i.e., prodromal patients) relative to healthy controls (HC).

Methods: Whole night sleep high density (hd)-EEG recordings were performed in FEP ($N = 27$), prodromal ($N = 11$) and HC groups ($N = 23$ and $N = 11$ respectively). Follow-up sleep hd-EEG recordings at six-month (for FEP) and one year (for prodromal) are also being collected. NREM sleep power spectra, power topography, and several parameters of sleep spindles -amplitude, duration, density- and slow waves -density, amplitude, up- and down-slope- were calculated and compared across groups. Differences between groups were assessed with Statistical non-Parametric Mapping (SnPM), a statistical approach which allows correction for multiple comparisons.

Results: FEP patients had significant reduction in spindle duration ($p = 0.01$, SnPM), spindle density ($p = 0.008$, SnPM), and slow wave density ($p = 0.007$, SnPM), in a frontal area compared to HC both at baseline and at six-month follow-up assessments. Furthermore, these sleep parameters showed similar, though not yet significant reductions in prodromal patients relative to HC.

Conclusions: Altogether, these findings: 1) indicate that sleep spindles and slow wave deficits are present and can be reliably detected in FEP patients; 2) suggest that sleep impairments may precede the appearance of full-blown psychosis; and 3) point to a critical involvement of frontal thalamo-cortical circuit dysfunctions in the development and manifestation of SCZ and related psychotic disorders.

Disclosure: Nothing to disclose.

22.4 Abnormal Sleep Spindles in Neurodevelopmental Disorders: Treatable Endophenotypes That Link Risk Genes to Impaired Cognition?

Dara Manoach

Massachusetts General Hospital, Charlestown, Massachusetts, United States

Background: Although neurodevelopmental disorders are defined by waking phenomena, abnormal sleep is a pervasive feature that may contribute to their manifestations. Patients with schizophrenia and their unaffected relatives have a specific deficit in sleep spindles, a defining oscillation of Stage 2 non-rapid eye movement sleep that, in coordination with cortical slow oscillations and hippocampal ripples, mediate memory consolidation. In schizophrenia, the spindle deficit correlates with impaired sleep-dependent memory consolidation, positive symptoms and abnormally increased functional connectivity of the thalamus with sensory and motor cortex. These relations point to dysfunction of the thalamic reticular nucleus (TRN), which generates spindles, gates the relay of sensory information from the thalamus to the cortex and modulates thalamocortical communication. Genetic studies provide clues to possible neurodevelopmental origins of TRN-mediated thalamocortical circuit dysfunction in both schizophrenia and autism spectrum disorder (ASD). I will present unpublished findings from completed and ongoing studies of sleep spindles in ASD, their relations to other TRN-related phenotypes and a new approach to treatment. The aim of this work is to determine whether spindle activity and other TRN-mediated phenotypes are abnormal ASD, identify the functional consequences of these abnormalities and to develop an effective treatment.

Methods: In Study 1 ASD (n = 24) and typically developing (n = 18) boys completed an overnight home sleep study with memory testing. Study 2 is an ongoing study of ASD adults of both sexes (n = 12 to date) that uses simultaneously-acquired MEG and EEG recordings during daytime naps and functional connectivity MRI and event-related potentials during wake to fully characterize spindles and their relations to thalamocortical connectivity, sensory gating and sleep-dependent memory consolidation. In Study 3 we are testing closed-loop auditory stimulation during sleep in healthy people as a potential therapy for spindle and sleep-dependent memory deficits in ASD and schizophrenia.

Results: In Study 1, ASD participants showed normal spindle density and morphology, but spindles occurred later in the upstate of cortical slow oscillations and were less consistent in this timing. Study 2 confirmed these results and also found reduced sensory gating in ASD. Preliminary data from Study 3 shows that short bursts of pink noise during the upstate of slow oscillations increased spindles time-locked to slow oscillations.

Conclusions: Findings of abnormal spindle-slow oscillation timing and reduced sensory gating in ASD are consistent with recent genetic work implicating the TRN in neurodevelopmental disorders. Spindle-like TRN stimulation gives rise to cortical slow oscillations, which together with hippocampal ripples underlie memory. Reduced TRN inhibition results in increased relay of sensory information from the thalamus to the cortex (i.e., reduced gating). Importantly, pharmacological and brain stimulation studies of typically developing individuals show that enhancing spindles in coordination with slow oscillations can improve memory. Collectively, this body of work identifies abnormal sleep spindles as a potentially treatable mechanism of cognitive dysfunction and symptoms in neurodevelopmental disorders.

Disclosure: Nothing to disclose.

Panel

23. Clinical and Pre-Clinical Implications for Ion Channels in Psychiatric Disorders

23.1 Role of KCNQ Potassium Channels in Behaviors Associated With Heroin Addiction

Susan Ferguson

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Background: Opioid addiction is characterized by cycles of compulsive drug-taking and drug-seeking and high rates of relapse. Susceptibility to addiction is unpredictable and overdose deaths have reached epidemic proportions. Unraveling the complex neurobiological changes that regulate pathological opioid use and contribute to respiratory depression in vulnerable individuals is therefore critical for curtailing this national crisis. The striatum has been identified as a key relay site within the cortico-basal ganglia-thalamic circuitry that drives the development of addiction, and relapse. However, the primary output neurons of the striatum (i.e., GABAergic medium spiny projection neurons (MSNs)), guide behavioral output through two divergent, and opposing, pathways (the direct and the indirect). KCNQ channels, which are low-threshold voltage-gated potassium channels that modulate neuronal excitability as well as opioid-induced respiratory depression, are found on both direct and indirect pathway MSNs. Although studies have found that KCNQ channel modulators can regulate cocaine and alcohol behaviors, no studies have examined the role of these channels in behaviors related to opioid addiction.

Methods: To begin to address this, we used pharmacological approaches to examine the role of KCNQ channels on heroin-induced locomotor sensitization and motivation to take heroin following self-administration in male Sprague Dawley rats. In addition, we developed a Cre-recombinase dependent CRISPR-Cas9 viral vector for targeted knockdown of KCNQ3 channels. We will use this vector, along with a Cre-recombinase dependent HSV viral vector for targeted overexpression of KCNQ3 channels, to selectively modulate KCNQ3 channels in direct and indirect pathway MSNs in the nucleus accumbens.

Results: We found that systemic administration of the KCNQ channel opener retigabine had no effect on the development or expression of locomotor sensitization to heroin. However, systemic administration of the KCNQ channel blocker XE-991 significantly decreased the motivation to take heroin under a progressive ratio schedule of reinforcement. Given the non-specific nature of systemic administration, we are currently using CRISPR-Cas9 knock-down and HSV viral over-expression to examine how altering expression of KCNQ3 channels specifically in direct and indirect pathway MSNs effects heroin-taking and heroin-seeking behaviors. We expect that overexpression of KCNQ3 channels on direct pathway MSNs or knockdown of KCNQ3 channels on indirect pathway neurons will decrease the motivation to self-administer heroin as well as decrease cue-induced reinstatement of drug-seeking. In contrast, we expect that knockdown of KCNQ3 channels on direct pathway neurons or overexpression of KCNQ3 channels on indirect pathway MSNs will have the opposite effect.

Conclusions: These studies use pharmacological approaches to begin to isolate the contributions of KCNQ channels in behaviors related to heroin addiction. Notably, pharmacological blockade of KCNQ channels is sufficient to reduce motivation for heroin. Given that this treatment also reverses opioid-induced respiratory depression, these findings suggest that KCNQ channel modulators may represent a new, viable treatment for heroin addiction. Ongoing studies using cell-specific targeting and novel molecular tools will probe potential mechanisms of action by determining if KCNQ3 channels on direct and indirect pathway striatal neurons

can bi-directionally, and opposingly, modulate drug-taking and drug-seeking behaviors.

Disclosure: Nothing to disclose.

23.2 Estrogen Fluctuations Modulate Ion Channel Function in Ventral Tegmental Area Altering Event Salience

Allyson Friedman

Hunter College, New York, New York, United States

Background: Estrogens have been shown to rapidly alter the activity of neurons through the modulation of potassium (K+) channels via changes in transcription of channel subunits and post-translational modification. In addition to gonadal release of estrogen, brain-synthesized estrogens, mediated by the enzyme aromatase, are the source of rapid estrogen effects in both males and females. Modulation by rapid estrogenic signaling can also be achieved by activation of specific signaling cascades, fine-tuning the neuronal circuits through regulation of voltage-gated ion channels. In female mice, in vivo ventral tegmental area (VTA) dopamine (DA) neuron bursting activity, which encodes event salience, is affected by naturally cycling estradiol levels. Translational studies have linked changes in DA firing activity to disruptions in social behaviors. We explored the physiological role of estrous cycle on DA regulation, as well as dysregulation following social stress. We find intrinsic changes in K+ channels in the VTA influences the female social stress response and that estrogen signaling modulates the level of activity of K+ channels, potentially altering the efficacy of therapeutics targeting ion channels.

Methods: We utilized electrophysiological cell-attached and whole-cell recording of VTA neurons from freely cycling female C57BL/6J mice We used a series of voltage-clamp protocols, in combination with pharmacological agents, to isolate A-type (fast) and M-type (slow) K+ channel function which influence DA neuron bursting profiles. We used vaginal cytology and estradiol 17β ELISA measurements hormone levels. In in vivo pharmacological experiments we performed local infusions to the VTA of bio-available estradiol, ICI 182,780 (estrogen receptor antagonist) and aromatase inhibitors prior to social stress and behaviorally test 24hrs post-stress.

Results: We found estrogen signaling modulates the underlying level of activity of K+ channels in the VTA. Using whole cell slice electrophysiology, we performed pharmacological characterization of estrogen signaling and withdrawal in DA neurons. We found that estrogen, both serum levels measured through ELISA or in vitro bath application is a critical modulator of both A-type and M-type K+ currents. We found that during estrogen withdrawal there is a significant reduction in K+ currents, which leads to an increase in neuronal excitability. We found that reducing estrogen signaling in the VTA of both males and female mice during stress acquisition through direct inhibition of estrogen receptors via ICI 182,780 leads to reduction in social interaction. In addition, we demonstrate that disruption of local estrogen synthesis with an aromatase inhibitor during stress acquisition leads to a reduction in social behaviors.

Conclusions: Our findings demonstrate that estradiol modulates VTA neuron physiology through regulation of unique potassium subunits. This may contribute to sexual dimorphism in social stress vulnerability, as well as the need for consideration of hormonal state during pre-clinical development of K+ channel modulators as therapeutics.

Disclosure: Nothing to disclose.

23.3 Determining the Role Potassium Channels Play in Dopamine Physiology and Behavior

Barbara Juarez

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Background: The midbrain dopamine system is comprised of dopamine neurons originating from the ventral tegmental area projecting to a number of downstream neural substrates that are involved in a number of behavioral domains such as reward, learning and executive function. These neurons fire in highly coordinated tonic and phasic patterns of action potentials. It is increasingly believed that loss of precise dopamine signaling is an underlying mechanism for a number of neurological and neuropsychiatric disorders. Thus, understanding the regulators of tonic-phasic balance could lead to new insight into the underlying basis of healthy and pathological behaviors. Voltage-gated potassium channels are known to be important regulators of neuron excitability, firing and signaling. Here, we sought to elucidate how two voltage-gated potassium channel subunits thought to regulate tonic (Kv4.3) and phasic firing (KCa1.1) exert their regulatory action on the midbrain dopamine activity to modulate distinct behavioral domains.

Methods: We targeted viral-based CRISPR-Cas9 mutagenesis to the coding regions of two potassium channel subunits: Kv4.3 (Kcnd3) and KCa1.1(Kcnma1) of midbrain dopamine neurons in adult DATiCre male and female mice to create loss-of-function mutations. Next, we performed patch-clamp electrophysiology to determine alterations to action potential shape, firing activity and firing pattern. We then conducted a detailed phenotypic analysis in mice with these channel knockouts to profile the behavioral domains affected by loss of function of each channel in dopamine neurons.

Results: Using patch clamp electrophysiology, we found that loss-of-function mutations in Kv4.3 and KCa1.1 impart distinct neurophysiological characteristics on midbrain dopamine neurons of adult mice. While knocking out each subunit increased dopamine neuron firing ($P < 0.01$), only loss of KCa1.1 induced an increase in firing irregularity ($P < 0.01$), a characteristic thought to suggest increased phasic activity. We also found that these two potassium channels regulate specific behavioral domains known to be regulated by midbrain dopamine neurons. Loss of Kv4.3 in midbrain dopamine neurons increased locomotor activity and social preference behaviors ($P < 0.05$), yet loss of KCa1.1 reduced anxiety like behaviors ($P < 0.05$). We also observed distinct effects on reward-associate behaviors between these two channel knockouts.

Conclusions: Here, we profiled how two voltage-gated potassium channel subunits, Kv4.3 and KCa1.1, contribute to dopamine firing and behavioral regulation. Kv4.3 and KCa1.1 knockouts create two animal models of hyper-tonic and hyper-phasic dopamine firing. These models have elucidated how dopamine neuron tonic-phasic balance contribute to healthy behavioral function in mice.

Disclosure: Nothing to disclose.

23.4 Targeting KCNQ Channels for the Treatment of Depression

Abstract not included.

Study Group

24. Innovative Approaches to Studying Behavior in Rodents for Understanding Neuropsychiatric Disease

Matthew Hill*, Rosemary Bagot, Tim Bussey, Rebecca Shansky, Nicola Grissom, Adam Kepecs, Jaideep Bains, Alon Chen

Study Group Summary: Over the past decade, the field of neuropsychiatric research has benefitted from rapidly evolving technologies to observe and manipulate the brain from molecules to cells and circuits, yet the full potential of this revolution has been stifled by an over-reliance on rudimentary behavioral models. Gaining meaningful insight into the brain requires investment and innovation in probing the brains primary output: behavior. It is widely recognized that many preclinical findings have failed to support translation to humans, a direct consequence of the lack of emphasis placed on elaboration of behavioral models. To move beyond this failure it is essential that, as a field, we reassess the foundations upon which we are building by developing and adopting rigorous and thoughtful approaches to studying disease-relevant behavior in non-human animals. Indeed, recent years have seen important and varied innovation in the study of behavior yet these developments are yet to be widely embraced by the field. This study group will focus on novel approaches to behavioral analysis to shine a spotlight on the critical importance of innovation in behavioral methods as an essential, yet often overlooked, foundation for the study of neuropsychiatric disease mechanism. This panel brings together a diversity of expertise to represent the richness of novel, cutting-edge behavioral methodologies. Our assembled panel of experts are employing distinct, novel approaches to analyzing behavior, incorporating: deep behavioral phenotyping in naturalistic settings (Chen); unbiased, temporal analysis of spontaneous behavior (Bains); translational cognitive phenotyping (Saksida); computational modeling as an inter-species translational bridge (Kepecs); sex-specific behavioral strategies (Shansky); and the consideration of structured organization of behavioral sequencing in decision making (Grissom). The breadth of approaches represented will frame a lively discussion around key issues including the relative merits of controlled versus naturalistic behavioral assessment, the potential contribution of computational modeling in defining links between behavior and neural computation and the utility as a translational tool, how to meaningful incorporate male and female animals to understand sex-differences in disease mechanism, and the potential for non-traditional behavioralists to bring novel analysis perspectives adapted from other biological and physical disciplines. Importantly, beyond the pronounced diversity of theoretical perspectives, our study group's diversity in gender, career-stage, and geography will fuel an exciting discussion, that will engage a broad audience in our field in a discussion of wide relevance.

Disclosure: Shoppers Drug Mart, Advisory Board.

Panel

25. Recent Advances in the Role of Social Factors in Drug Addiction: Preclinical and Clinical Studies

25.1 Central Amygdala PKCδ-Expressing Neurons are Critical to Inhibition of Incubation of Methamphetamine Craving After Social Choice-Induced Voluntary Abstinence

Marco Venniro

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Background: We recently reported that social choice-induced voluntary abstinence prevents incubation of methamphetamine craving. This protective effect was associated with activation of PKCδ-expressing neurons in central amygdala lateral (CeL) and inhibition of Fos expression in central amygdala medial (CeM). Here we used short-hairpin RNA against PKCδ mRNA (shPKCδ) and immunohistochemistry to determine the causal role of CeL PKCδ in inhibition of incubation of methamphetamine craving after voluntary abstinence.

Methods: In Exp. 1, we first used immunohistochemistry to validate the AAV virus expressing shPKCδ by injecting it ($n = 6$) (or shScram control, $n = 6$) into CeL (0.75 µl) either 2 or 4 weeks before novel context exposure to induce Fos. We then performed whole cell current clamp recordings in CeL and examined the effect of the shScram and shPKC viruses on intrinsic excitability ($n = 5$ rats/group, $n = 7$-9 cells/group). In Exp. 2, we trained two groups of rats ($n = 11$-12/group) injected with either shPKCδ or shScram into CeL to lever press for social interaction (60-s, 15 trials/d, 6 d) and then for methamphetamine infusions (6-h/d, 12 d, 0.1 mg/kg/infusion). We then assessed relapse to methamphetamine seeking after 1 and 15 abstinence days. Between tests, the rats underwent social-choice-induced voluntary abstinence (15 trials/d). After day 15 testing, we assessed Fos, PKCδ and Fos +PKCδ double-labeled expression in CeL.

Results: In Exp. 1, we found that shPKCδ decreased CeL PKCδ [Virus type: $F(1,5) = 39.7$, $p < 0.001$], Fos [Virus type: $F(1,5) = 37.5$, $p = 0.02$], and Fos+PKCδ double-labeled [Virus type: $F(1,5) = 62.9$, $p < 0.001$] expression. Additionally, shPKCδ decreased the number of spikes evoked per unit of injected current in CeL PKCδ-expressing neurons [Current x Virus type: $F(19,247) = 4.4$, $p < 0.001$] but not resting membrane potential of these neurons [$p > 0.05$]. In Exp. 2, we found that shPKCδ but not shScram restored incubation of methamphetamine craving after voluntary abstinence [Abstinence day x Lever (active, inactive) x Virus type: $F(1,21) = 5.5$, $p = 0.03$]. This effect was associated with decreased PKCδ [Virus type x Central amygdala subregion (CeL, CeM) interaction: $F(1,21) = 39.8$, $p < 0.001$], Fos [Virus type x subregion: $F(1,21) = 44.3$, $p < 0.001$], and Fos+PKCδ double-labeled [Virus type x subregion: $F(1,21) = 22.6$, $p < 0.0001$] expression in CeL.

Conclusions: Results demonstrate a critical role of CeL PKCδ in inhibition of incubation of methamphetamine craving after social choice-induced voluntary abstinence.

Disclosure: Nothing to disclose.

25.2 Brain-Based Classification and Negative Social Bias in Adolescents With Nonsuicidal Self-Injury During Simulated Social Interaction

Irene Perini

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Background: Nonsuicidal self-injury (NSSI) is defined as the direct, deliberate destruction of one's own body tissue without suicidal intent, typically including behaviors such as cutting, burning, or hitting oneself. The risk of engaging in NSSI is particularly high during adolescence, with prevalence rates around 17% in community samples and between 40-80% in clinical samples. Prevalence of early onset of alcohol use (EAU) is higher in NSSI compared to non-NSSI adolescents making this population at higher risk of developing alcohol problems. Interpersonal stress,

perceived criticism, and social rejection are common triggers of NSSI. Here, we examined behavioral and neural correlates of social interaction in NSSI adolescents.

Methods: We developed a novel task addressing the behavioral and neural correlates of social interaction in a simulated online environment in the magnetic resonance imaging (MRI) scanner. Twenty-seven adolescent individuals with non-suicidal self-injury (NSSI) and twenty-seven controls engaged in the paradigm. Participants indicated whether they liked or disliked pictures of other players during a functional magnetic resonance imaging (fMRI) scan. Participants also viewed positive and negative feedback directed toward them by others. The task also assessed the subjective effects of the social interaction, using post-task questions. Analysis of brain data was performed using general linear model and multi-voxel-pattern-analysis approaches (per-voxel $p = 0.002$, family-wise-error corrected at alpha 0.05).

Results: The NSSI group showed a negative bias in reading the social interaction although the overall quality of the social judgment was kept neutral. Patients felt rejected significantly more often than controls ($U = 172$, $p = 0.009$, $\eta 2 = 0.14$) and were more sensitive to being rejected by other players ($F0{,}47 = 11.5$, $p = 0.001$, $\eta 2p = 0.19$). The whole-brain, grey-matter, multivariate analysis rendered statistically-significant classification of subjects during anticipation of social judgment in default network nodes and subgenual anterior cingulate cortex (accuracy = 68%, sensitivity = 0.74, specificity = 0.59; permutation $p = 0.031$). Classification scores derived from the multivariate analysis, controlled for borderline personality disorder traits, significantly correlated with rejection sensitivity scores in the patients but not in controls (patients $r = 0.42$, $P = 0.04$, controls $r = 0.30$, $p = 0.18$).

Conclusions: Multivoxel pattern analysis of neural-response data yielded robust classification of nonsuicidal self-injury subjects and classification indices correlated selectively in individuals with nonsuicidal self-injury with elevated sensitivity to negative social feedback.

Disclosure: Nothing to disclose.

25.3 Neurocircuitry of Simulated Social Interactions in Cocaine Addiction: Implications for Real-World Social Competence

Keren Bachi

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Background: Social interactions profoundly impact the initiation, severity, and recovery from drug addiction. The neural basis of altered social interactions in individuals with cocaine use disorder (iCUD) is unknown, but may include regions of the social processing network: the prefrontal cortex, superior temporal sulcus, temporoparietal junction (TPJ), and temporal pole.

Methods: We compared the neural correlates of social interaction between 9 iCUD and 15 healthy controls (HC; analysis in additional participants ongoing) not differing on age, gender, race, or IQ. Using the Social Navigation neuroimaging task, not yet examined in addiction or any patient-population, participants simulated interactions with different characters for the purpose of gaining access to employment and housing. For analysis, a 'social space' was plotted by dimensions of power (hierarchy) and affiliation (intimacy). A vector was defined from the participant's point-of-view to the character, giving angle and length information, which were compared between groups in addition to differences in area, spread, and response time. Unbiased whole-brain analyses for models of vector angle and length used cluster-wise significance at a height threshold of punc < 0.005 with 20 contiguous voxels. Non-task variables examined were drug use and social competence: self-esteem as a social resource, trait social closeness, and number of close friends, which were standardized and averaged to form a social composite score.

Results: iCUD had significantly reduced self-esteem ($p < 0.005$), social closeness ($p < 0.005$), and number of close friends ($p = 0.05$) compared with HC. Behaviorally, iCUD had a larger spread, indicating a different social space structure than HC ($p < 0.05$). Neurally in iCUD, tracking the vector angles (the balance between power and affiliation of the character relative to the participant) produced greater activity in the bilateral TPJ inclusive of the L supramarginal gyrus [$x = -50$, $y = -47$, $z = 35$, Brodmann Area (BA) = 39; $Z = 3.79$, pcor < 0.005, $k = 480$] and the R angular gyrus ($x = 47$, $y = -34$, $z = 35$, BA = 40; $Z = 3.67$, pcor = 0.005, $k = 408$) relative to HC (no activation survived correction for multiple comparisons for iCUD < HC). In iCUD, TPJ activation correlated positively with current cocaine craving (BA 40: $r = 0.677$, $p < 0.05$) and severity of dependence (BA 39: $r = 0.639$, $p = 0.064$). Across groups, TPJ activation in BA 39 correlated negatively with the social composite score ($r = -0.368$, $p = 0.077$).

Conclusions: iCUD had abnormalities in social navigation. In the normalized function of power modulated by affiliation, iCUD showed greater engagement of the TPJ (BA 39), a cross-modal integrative hub implicated in attention and judgment making on contextual associations; and BA 40, involved in social perception and processing of emotions and self-reflections during decision making. In iCUD, social interactions and associated TPJ circuitry impairments may exacerbate illness severity, promote relapse and impact treatment outcome. If current results are maintained with more participants, then social-centered addiction treatments may help normalize the neural underpinnings of social interactions to improve outcomes.

Disclosure: Nothing to disclose.

25.4 Perceived Interpersonal Support Effects on Brain Responses to Stress and Alcohol Cues in Alcohol Use Disorder

Rajita Sinha

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Background: Social and interpersonal factors are known to buffer stress and can affect drinking and drug use motives as well as addiction recovery. Binge and chronic drug use exacerbate stress responses and increases drug craving, but whether there are binge and chronic drug effects on social and interpersonal processing circuits that may serve to buffer stress and drug motivation have not been well studied.

Methods: Light, moderate and binge/heavy socially drinking men and women (SD) ($N = 115$) and treatment entering individuals with Alcohol Use Disorder (AUD) ($N = 71$) were studied using structured clinical interviews and self-report assessments, including the Alcohol Use Disorder Identification Test (AUDIT) and Interpersonal Support Evaluation List (ISEL) and current drinking data using the TimeLine Follow Back assessment and Smartphone daily data collection approaches. Subjects also participated in a multimodal neuroimaging session using functional magnetic resonance imaging (fMRI) utilizing a novel brief sustained stress, alcohol cue and neutral relaxing provocation procedure using standardized visual stimuli presented in a block design. Subjective rating of perceived stress, arousal and alcohol craving were assessed during the fMRI scan.

Results: Overall, total interpersonal support (ISEL) scores were lower in AUD patients relative to social drinkers ($t(125) = 4.43$, $p < 0.0001$), including for the subscales of appraisal support ($p < 0.003$), belonging ($p < 0.0004$), Tangible support ($p < 0.0001$) and self-esteem support ($p < 0.0007$), but as expected higher overall levels of perceived stress ($p < 0.02$) and AUDIT ($p < 0.0001$) scores in AUD versus SD individuals. Furthermore, greater total ISEL

scores were associated with less alcohol use and alcohol-related problems (AUDIT) in non-dependent social drinkers ($R2 = 0.06$, $p < 0.008$) and in AUD patients ($R2 = 0.15$, $p < 0.002$). Using whole brain voxel based analyses, ISEL scores were significantly associated with brain responses to stress and alcohol cues across groups across prefrontal cortical (PFC) regions (VM: ventro-medial, dorsal and rostral anterior cingulate-ACC), limbic regions (R amygdala, hippocampus, periaqueductal gray-PAG, insula) and striatal (L caudate, putamen) regions (whole brain threshold: $P < 0.001$, cluster corr: $p < 0.05$). However, lower ISEL scores were associated with greater limbic-striatal sensitivity to stress in SD but more blunted limbic striatal responses to stress sin AUD patients. On the other hand, lower SELF was associated with greater amygdala and hippocampal responses to alcohol cues in AUD patients but lower limbic striatal responses in SD individuals.

Conclusions: These findings show specific effects of low interpersonal social support in AUD patients and in socially drinking controls on brain responses to stress and alcohol cues, suggesting differential neural limbic-striatal patterns associated with ISEL influence social support related alcohol use vulnerability in non-dependent and dependent individuals.

Disclosure: Embera Neurotherapeutics, Advisory Board.

Mini Panel

26. Understanding Brain Development and Aging: Novel Data From the ENIGMA (Enhancing Neuroimaging Genetics Through Meta Analysis) Consortium

26.1 Enigma-Origins (The Organization for Imaging Genomics in Infancy): Big Data Meets Little Brains

Abstract not included.

26.2 Genetic Variance for Human Brain Plasticity

Hilleke Hulshoff Pol

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Background: Longitudinal trajectories of brain development and aging have been found to associate with psychiatric disease and healthy aging. Individual differences in how much the brain changes over time are driven by genes, as has been recently shown in longitudinal twin cohorts from throughout the world (Brouwer et al., HBM 2017). However, it is not known which genes are involved in the brain changes over time. For this purpose the ENIGMA plasticity working group is performing a GWAS on longitudinal brain changes, investigating the genetic architecture of longitudinal changes in eight global (total brain, cerebral and cerebellar gray and white matter, lateral ventricles, cortical thickness and surface area) and seven subcortical structures (thalamus, caudate, putamen, pallidum, hippocampus, amygdala and accumbens).

Methods: Our discovery sample consisted of 6052 subjects from 29 cohorts throughout the lifespan (age range 6-97). In an initial meta-analysis, assuming the genetic effects to be the same across age, we found one study-wide significant locus for genetic variants influencing surface area change in our discovery sample ($N = 6052$).

Results: Substantial heterogeneity was observed, suggesting the existence of genetic variants that exert their effects depending on age. To distinguish between genetic variants that influence development from those that influence ageing, we performed a meta-regression that included linear and quadratic effects of age. Results from the GWAS are still being generated and will be presented during the meeting.

Conclusions: This meta-regression accounting for age is currently ongoing, and we are running a replication in an independent sample ($N \sim 4000$). Eventually, identifying the genes involved in longitudinal brain changes may aid in a better understanding of brain development and ageing, both in health and disease.

Disclosure: Nothing to disclose.

26.3 Brain Age: Applications of a Biomarker of Brain Ageing to Neurological and Psychiatric Disorders

Francesca Biondo

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Background: Ageing is associated with brain structural and functional changes, alongside cognitive and functional decline. Machine learning applied to neuroimaging data from a healthy ageing sample can be used to model these changes resulting in a biomarker of the brain ageing process – so-called 'brain age'. This allows for the calculation of 'brain-predicted age difference (brain-PAD)' which has been previously associated with neurological and psychiatric disorders, and can predict future health outcomes and mortality.

This promising line of research has led to the creation of the ENIGMA Brain Age working group, part of the broader ENIGMA network, an international collaboration of imaging genomics. ENIGMA Brain Age aims to optimise the brain age measure, generate and share brain age scores and use brain age to investigate genetic, environmental and disease influences on brain ageing.

In this talk, I will present results from the application of the brain age paradigm to Major Depressive Disorder (MDD), as well as describe ongoing work in bipolar disorder, schizophrenia and after stroke.

Methods: The ENIGMA MDD working group sample involved 2493 MDD patients and 2533 control subjects. The analysis involved three main phases. First, Freesurfer thickness and volumes were extracted from structural T1-weighted MRI (Magnetic Resonance Imaging) scans for each participant. Data from control participants were then used to train a machine learning model (support vector regression) to predict the chronological age from cortical thickness and subcortical volumes. Separate models were generated for females and males. Second, the appropriate brain age model was applied to each male or female patient's MRI and brain-PAD was calculated for all participants. Third, a regression analysis was used to calculate group differences in brain-PAD.

Results: Performance of the brain age model in predicting chronological age from neuroimaging features was Mean Absolute Error (MAE) = 6.86 (SD 5.32) years for males and 6.91 (5.34) for females. The brain-PAD regression analysis indicated that on average the depressed patients had brains which were +0.9 years older (SE 0.21, $p < 0.0001$, Cohen's $d = 0.12$, 95% CI 0.06-0.17) than controls. The strongest effects of higher brain-PAD were found in depressed patients with late age of onset (+1.7 years), currently depressed (+1.2 y), and first episode (+1.2 y), compared to controls. Furthermore, brain-PAD was positively correlated with self-reported depressive symptoms ($b = 0.05$, $p = 0.004$).

Conclusions: Structural brain ageing is detectable in patients with MDD, though is moderate in magnitude compared to degenerative disorders such as multiple sclerosis or Alzheimer's. This suggests that to an extent, the atrophy associated with MDD spatially overlaps with age-related atrophy, potentially due to some common underlying neurobiological factors. This work illustrates the value of using brain age as an accessible and

practical biomarker that can be used to facilitate research in neurological and psychiatric disorders across consortia. Future ENIGMA Brain Age work aims at optimising the brain age model further and make software widely available to the scientific community.

Disclosure: Nothing to disclose.

Panel

27. Toward Precision Psychiatry in Eating Disorders - Computational Modeling of Brain Response and Behavior for Diagnostic Classification, Disease Model Development, and Outcome Prediction

27.1 Prediction of Longitudinal Clinical Outcomes in Adolescent Anorexia Nervosa Using Resting-State Brain Connectivity and Machine Learning

Jamie Feusner

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Background: Anorexia Nervosa (AN) is often difficult to treat and relapse rates are high: 35-41% after 18 months. Currently, there are no accurate ways of predicting longitudinal clinical outcomes in AN. Worsening eating disorder symptoms and return to abnormally low BMI after intensive treatment are both potentially negative long-term outcomes with high clinical significance. To date, although multiple neuroimaging studies have provided mechanistic insights into AN, there is limited literature on how neural signatures at a given time might relate to, or predict, clinical outcomes at a future point. In this study, we used resting-state fMRI connectivity features measured after intensive treatment to predict changes in BMI 4 months later.

Methods: We have enrolled and analyzed data from 19 weight-restored and partially weight-restored adolescent females with AN (ages 13-18) who were evaluated and underwent resting-state fMRI at the end of an intensive treatment program, and 17 healthy controls (HC). BMI was measured on the day of the scan and 4 months after. Functional connectivity was computed between all pairs of time series from a 390-region whole-brain atlas using Pearson's correlations. Additionally, we computed graph network measures of clustering coefficient, measuring functional segregation, and shortest path length, measuring functional integration. To identify functional connectivity features for the prediction analysis, we utilized a recursive feature elimination-based support vector machine classifier to classify AN individuals from HCs. Next, we performed partial least squares (PLS) regression to explore the aggregate associative relationship between imaging features that distinguished AN from HC, and BMI changes. Finally, we performed support vector regression to predict BMI changes.

Results: From the PLS analysis, functional connectivity explained 47.7% of the variance in BMI changes ($P = 0.001$), graph measures explained 63.5% variance ($P = 4 \times 10\text{-}5$), while the combination of functional connectivity and graph theory measures explained 68.8% variance ($P = 10\text{-}5$). Top predictive features were associated with the fronto-parietal task control and salience networks, along with connections from the ventral visual stream and orbitofrontal cortex. Functional integration between DLPFC and anterior insula, and fronto-parietal functional connectivity explained the maximum share of this variance. The machine learning prediction analysis revealed that functional connectivity was predictive of BMI changes ($R2 = 0.28 \pm 0.09$, $P = 0.02 \pm 0.01$), as were the graph measures ($R2 = 0.20 \pm 0.07$, $P = 0.07 \pm 0.03$). The best prediction of BMI change was obtained using a combined feature set of functional connectivity plus graph measures ($R2 = 0.58 \pm 0.07$, $P = 0.0017 \pm 0.0053$).

Conclusions: Neuroimaging features from a short resting-state fMRI scan at the end of intensive treatment for AN could strongly predict longitudinal changes in BMI values. Resting-state fMRI displays promise as a tool to predict clinical outcomes in AN. If replicated in a larger population, such an approach could help identify those who are at higher risk for relapse and thereby help create more individualized treatment plans for AN patients in order to reduce relapse rates.

Disclosure: NOCD, Inc., Consultant; Pfizer, Honoraria

27.2 Computational and Neural Systems Underpinning Maladaptive Behavior in Anorexia Nervosa

Joanna Steinglass

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Background: Anorexia nervosa (AN) is characterized by rigid pursuit of a low-fat, low-calorie diet that results in extreme undernourishment. One puzzle in this severe disorder is the way in which patients have elements of focused goal-pursuit, and yet simultaneously are unable to alter behavior, suggesting habitual control. The habitual nature of maladaptive behavior in AN has also been established and a habit reversal intervention successfully mitigated habit strength and eating disorder behavior. The involvement of dorsal frontostriatal circuits in dietary restriction in AN is consistent with this habit-centered model. To better understand the seeming paradoxes inherent in self-starvation, we have applied computational neuroscience techniques to more carefully parse the components behavior. In this study, we specifically addressed the extent to which individuals with AN engage model-based versus model-free learning when the outcomes are either monetary or food-related.

Methods: Women with AN or subthreshold AN were compared with healthy comparison women (HC) in food-based decision making, with fMRI (Total $n = 135$). Individuals with AN participated during acute illness and after weight restoration; HC participated at two time points. To test the contribution of model-based and model-free learning, which are thought to underlie goal-directed vs. habitual behavior, respectively, we also administered a Two-Step decision task ($n = 41$ AN, 53 HC). There were two separate task versions, with monetary or food outcomes.

Results: Food choice task and fMRI findings replicated and extended our initial study. AN and subthreshold AN chose fewer high-fat foods than HC ($p < 0.0001$), including dieting HC. AN engaged dorsal striatum more than HC ($p < 0.005$, uncorrected). Acute weight restoration did not change food choices ($p = 0.30$) or neural substrates ($p < 0.05$, uncorrected). AN and HC did not differ significantly in their model-free learning (Estimate: 0.09, $SE = 0.06$, $z = 1.36$, $p = 0.17$). In contrast, model-based learning was significantly worse in AN relative to HC (Estimate: 0.15, $SE = 0.06$, $z = 2.27$, $p = 0.023$). This pattern was invariant to whether food or monetary outcomes were used (Estimate: -0.08, $SE = 0.07$, $z = -1.11$, $p = 0.27$) and to whether AN were acutely ill or weight restored (Estimate: 0.02, $SE = 0.08$, $z = 0.27$, $p = 0.79$).

Conclusions: Maladaptive dietary restriction becomes relatively outcome-independent and thereby is resistant to change in persistent AN. The engagement of the dorsal striatum during food choice was specific to individuals with AN, regardless of weight status. Behavioral and fMRI results suggested variability across individuals, which may have implications mechanism and treatment. Computational models indicate that AN show a deficit in goal-directed learning across domains and illness state. Computational modeling approaches to maladaptive behavior may help

clarify some of the individual variability and how and why patients with AN have difficulty changing behavior in response to treatment.

Disclosure: Nothing to disclose.

27.3 Neural Computations of Inhibitory Control After Remission From Bulimia Nervosa

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Background: Bulimia nervosa (BN) is associated with decision-making deficits and altered activation in inhibitory control circuitry. However, most individuals with BN engage in out-of-control binge-eating and purging behaviors that alternate with prolonged periods of dietary restriction. It is unclear whether inhibitory control and decision-making deficits are exaggerated after fasting, potentially increasing vulnerability to binge eating initiation, or after eating has started, potentially contributing to difficulty stopping eating and subsequent out-of-control purging behaviors, like self-induced vomiting. Model-based functional magnetic resonance imaging (fMRI) after acute periods of fasting and eating could help to identify the dynamic neurocognitive processes that underlie these BN symptoms.

Methods: Women remitted from BN (RBN; $n = 22$) and control women (CW; $n = 21$) performed a parametric Stop Signal Task during fMRI on two counterbalanced visits—once after a 16-hour fast and once after a standard meal. A Bayesian dynamic belief model was used to estimate trial-by-trial expectations of the need to inhibit responding, or p(stop). A whole-brain Group x Visit x Trial Type (go versus stop) linear mixed effects model examined group differences in the influence of fasting and eating on how p (stop) modulates neural signals for go and stop trials (voxelwise $p < 0.001$, clusterwise alpha $= 0.05$). Average neural activation for Bayesian unsigned prediction errors (UPE; the absolute difference between the actual and expected need to stop on each trial) was extracted from significant clusters from this 3-way interaction. Poissonian regressions examined associations of UPE signal with past bulimic symptoms.

Results: The neural signal associated with UPE in the right pre-supplementary motor area (SMA) was abnormally modulated by state in the RBN group compared with CW, such that RBN women showed stronger UPE-dependent activation in the fed state (Cohen's $d = 0.58$). This UPE-dependent activation in the fed state was associated with more frequent past binge eating ($z = -3.2$, $p < 0.002$) and self-induced vomiting ($z = -8.0$, $p < 0.001$).

Conclusions: Findings suggest that after eating, women with a history of BN show an exaggerated signal for surprising inhibitory-control-related outcomes that is linked to past symptom severity. This altered signal was detected in a brain area classically implicated in stopping ongoing actions, and it could contribute to difficulty stopping eating once one has started and resisting urges to induce vomiting after eating. Replication in a currently symptomatic sample is needed; however, these initial results indicate a potential neural mechanism underlying dysregulated bulimic behaviors.

Disclosure: Nothing to disclose.

27.4 Using the RDoC Framework, Computational Modeling and Prediction Error to Characterize Eating Disorders Subtypes and Psychopathology

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Background: Eating disorders (EDs) are severe psychiatric disorders of uncertain etiology. We found previously elevated brain response in anorexia nervosa (AN), but reduced brain activation in bulimia nervosa (BN) and obesity, during prediction error (PE) paradigms that are known to trigger dopamine neuronal response. Here we tested whether PE response is primarily body mass index (BMI) dependent or BMI independently associated with ED subgroups and eating behavior. In addition, we tested whether we could classify ED subtypes based on behavioral or brain imaging data.

Methods: We conducted a study adhering to NIMH Research Domain Criteria (RDoC) guidelines and recruited individuals across all ED types (ages 16–35 years). In addition, we recruited healthy controls. During a sucrose taste classical conditioning paradigm, violations of learned associations between conditioned visual and unconditioned taste stimuli evoked the dopamine-related PE. We conducted factor analyses to identify relevant behavioral and regional brain response data. Multinomial logistic regression was used to correlate nominal and continuous data and calculate classification accuracy. Non-parametric regression and partial regression analysis were used for ordinal and continuous data.

Results: We recruited to date 286 individuals: AN restricting type ($n = 68$), AN purging type ($n = 4$), AN binge eating-purging type ($n = 14$), other specified eating and feeding disorder (OSFED) AN type ($n = 18$), OSFED purging disorder type ($n = 7$), BN ($n = 47$) binge eating disorder (BED, $n = 12$), and controls ($n = 116$). Multinomial logistic regression indicated that BMI, and the ED Inventory-3 (EDI-3) derived drive for thinness, body dissatisfaction and bulimic symptoms, predicted 98% of controls, 99% of restricting type AN, 0% of AN purging type, 64% of AN binge eating-purging type, 78% of OSFED AN, 29% of OSFED purging, 87% of BN, and 58% of BED. The addition of PE brain response did not add to model accuracy.

Spearman regression analysis in ED participants showed negative correlation between ED subtype ordered from highest to least restricting, and PE brain response in nucleus accumbens left ($rho = -0.262$, $p < 0.001$, CI95% -0.387 to -0.110) and right ($rho = -0.225$, $p < 0.003$, CI95% -0.364 to -0.081) and orbitofrontal cortex left ($rho = -0.190$, $p < 0.012$, CI95% -0.334 to -0.038) and right ($rho = -0.272$, $p < 0.001$, CI95% -0.396 to -0.136). BMI was also negatively correlated with regional PE response in nucleus accumbens left ($rho = -0.274$, $p < 0.001$, CI95% -0.405 to -0.131) and right ($rho = -0.245$, $p < 0.002$, CI95% -0.372 to -0.103) and orbitofrontal cortex left ($rho = -0.220$, $p < 0.003$, CI95% -0.367 to -0.069) and right ($rho = -0.287$, $p < 0.001$, CI95% -0.418 to -0.147). Partial correlation analysis controlling for BMI showed that negative correlations between ED subtype and PE brain response persisted in nucleus accumbens left ($r = -0.207$, $p < 0.006$, CI95% -0.338 to -0.034) and orbitofrontal cortex right ($r = -0.209$, $p < 0.006$, CI95% -0.345 to -0.049).

Conclusions: This ongoing study shows that BMI and EDI-3 scales can separate controls from individuals with EDs with high classification accuracy especially for threshold or subthreshold AN restricting behaviors. We are currently exploring other behaviors that may further increase accuracy. The correlation between PE brain response and ED subgroups even after controlling for BMI suggests a specific dopamine-related psychopathology in EDs that is related to the level of food restriction.

Disclosure: Nothing to disclose.

Panel

28. Non-Neuronal Cells in the Mechanisms of Reward and Substance Use Disorders

28.1 Unique Cell Phenotypes of Mesolimbic Microglia: Impact on Development and Function of Reward Circuitry

Lindsay De Biase

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Background: Microglia influence circuit development through multiple mechanisms and shape mature neuronal function by supporting tissue homeostasis and modulating synapses. In previous work, we discovered that microglia display distinct phenotypes in different regions of the basal ganglia and mesolimbic dopamine system. Whether this regional heterogeneity includes variation in microglia regulation of circuit maturation and mature synaptic function remains unexplored.

Methods: We used a combination of immunohistochemistry, high resolution imaging, and electrophysiology to examine microglial maturation and interactions with synapses in two key regions of the mesolimbic circuitry, the nucleus accumbens (NAc) and ventral tegmental area (VTA). Both male and female CX3CR1-EGFP mice were used and significance was assessed using ANOVA followed by posthoc t-test comparisons with Bonferroni correction.

Results: We found that during postnatal development, microglia within the mesolimbic circuitry are overproduced and refined to adult levels through programmed cell death. This overproduction was particularly pronounced in the NAc compared to the VTA (Two-way ANOVA main effect of age $P < 0.00001$, main effect of brain region $P < 0.00001$, interaction $P = 0.0006$), with NAc microglial density at postnatal day 12 reaching more than twice the levels found in 2 month old mice. Ongoing studies are testing whether this period of elevated microglial density in the NAc coincides with enhanced synaptic refinement in this brain region. In the mature mesolimbic system, we found that branching of microglia in the VTA but not the NAc correlates with local density of glutamatergic synapses ($R^2 = 0.35$, $P = 0.007$) and preliminary findings indicate that elimination of microglia from the CNS prolongs duration of synaptic potentiation on dopamine neurons.

Conclusions: These findings indicate that NAc and VTA microglia show distinct patterns of maturation during postnatal development and highlight a developmental window during which the NAc may be more susceptible to inflammatory insults due to high microglial density. These data also suggest that regional variation in microglial phenotype extends to key differences in microglial regulation of synaptic function.

Disclosure: Nothing to disclose.

28.2 Beyond the Neuron: How Glia Regulate Addiction-Like Behaviors

David Dietz

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Background: Drug addiction is a chronically recurrent and debilitating disease that engenders significant financial and societal burden on a global scale. Substance abuse, including opioid and cocaine use disorder, is often mediated by a multitude of neuroadaptations involving both neuronal and non-neuronal cell types in brain regions governing reward processing. The majority of addiction studies have largely focused on cellular and molecular plasticity in the neuronal populations, leaving a significant gap in understanding how non-neuronal cell types, such as glial cells, mediate drug-induced neuroadaptations.

Our previous work has demonstrated an essential role for TGF-beta, a secreted protein that performs many cellular functions in mediating drug-induced behaviors. Further, recent evidence suggests that these secreted proteins may serve as a cellular bridge between glial and neuronal signaling.

Methods: Male rats (n = 10-12/group) were trained in a long-access self-administration paradigm in which either cocaine, heroin, or saline was available. Discrete brain regions (i.e., PFC, NAc, hippocampus) were microdissected following periods of drug abstinence (i.e., AD1, AD14, and AD30). Tissues were utilized in molecular assessments of TGF-beta signaling within glial cell populations. Further, because drugs of abuse affect brain regions involved in integrating emotional and sensory stimuli, we investigated how interaction between painful stimuli and drugs of abuse modulate cellular and molecular events in the glial cells. Male rats (n = 10-12/group) exposed to opiates received pain or no pain stimuli followed by unbiased RNA seq, which we are currently characterizing to examine glial-specific gene regulation.

Results: Our preliminary data suggest that exposures to cocaine and opiates results in dysregulation of microglial activation and expression in a brain region and drug-specific manner. We find that this imbalance is accompanied by activation of specific TGF-beta pathways and epigenetic events. Additionally, our preliminary data also suggest that opiates used as analgesics appear to reverse gene expression associated with inflammatory pain, whereas exposure to opiates in a non-painful state results in a non-overlapping expression pattern.

Conclusions: Taken together, these data suggest that drugs of abuse, in particular cocaine and heroin, mediate glial cellular plasticity through a TGF Beta dependent mechanisms. Further, these cellular adaptations mediate addiction like behaviors and serve as a novel point of therapeutic development for substance abuse disorders

Disclosure: Nothing to disclose.

28.3 Astroglial Adaptations Associated With the Incubation of Cocaine Craving

Kathryn Reissner

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Background: While investigation of the cellular consequences of illicit drug use have yielded considerable information regarding neuronal mechanisms of relapse, comparatively little insight is available into roles for astrocytes in preclinical self-administration (SA) models. Because astrocytes play critical roles in the modulation of neuronal and synaptic function, integration of this cell type into the cellular model of relapse is essential. Previously we have shown that cocaine SA (2h/day) and extinction training leads to decreased surface area and volume of accumbens astrocytes, as well as decreased colocalization of astrocyte membranes with both pre- and postsynaptic markers (Scofield et al., 2016; Testen et al., 2018). The goal of the current study is to investigate responsiveness of astrocytes in another preclinical model of addiction, the incubation of cocaine craving.

Methods: Male (N = 10/group) and female (N = 12/group) SD rats were trained in cocaine or saline SA (6h/day) for 10 days, followed by 45 days of forced abstinence. AAV5 expressing a membrane-tagged Lck-GFP under the control of an astrocyte-specific promoter was used to assess physical properties of fluorescent astrocytes. For filament analysis, astrocytes were

reconstructed in 3D and their processes were traced in order to construct a high-fidelity wire model using a fast-marching algorithm (Sethian, 1996). Individual wire models were then analyzed by a custom-made MATLAB script. Data analysis was performed using nested ANOVA for multiple measurements within each animal.

Results: Consistent with previous results, we observed significantly decreased surface area, volume, and synaptic colocalization in accumbens astrocytes from cocaine-administering rats. However, the magnitude of effect (~40%) was significantly greater than that observed in our previous studies (~15%), and affected a larger proportion of processes. Moreover, decreased branching complexity of individual astrocytes was associated with prolonged abstinence following cocaine SA. No effect of cocaine history was observed in astrocytes from female mice. Scholl analysis indicated a distinct difference in intersection patterns produced by both SA protocols, with a significantly greater magnitude of effect observed in the incubation model as compared to the short-access/extinction model. Interestingly, the length of individual branch segments (from node to node) remain unaffected by cocaine in either paradigm.

Conclusions: Findings presented herein indicate that accumbens astrocytes exist in a significantly retracted state following prolonged abstinence from cocaine use, and the magnitude of effect is more pronounced than that observed following the short-access/extinction model. Moreover, filament analysis indicates that the retracted phenotype of accumbal astrocytes following cocaine SA is likely not due to simple shrinkage of existing astrocytic processes, but is characterized by remodeling of branching complexity. Ongoing studies are designed to investigate the mechanisms of this effect and to assess the consequences of these changes in the development of the incubation of cocaine craving, as well as the physiological basis for observed sex differences.

Disclosure: Nothing to disclose.

28.4 Impacts of Heroin on Cortical Astrocyte Morphometrics and Astrocyte-Synaptic Interaction

Michael Scofield

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Background: Rodent models of relapse demonstrate that cued drug seeking is mediated, in large part, by alterations in synaptic plasticity within the corticostriatal circuit. Several cellular adaptations, directly linked to relapse vulnerability, occur specifically in astrocytes. As an example, in the nucleus accumbens core (NAcore), decreased expression of the astroglial glutamate transporter and withdrawal of astrocytic processes from synapses are required for cocaine- and heroin-paired stimuli to precipitate drug seeking behavior. However, the effects of heroin on the structural properties of cortical astrocytes, and their interactions with synapses, remains to be elucidated. Further, cued relapse to heroin-seeking is suppressed by the antioxidant, N- acetylcysteine (NAC), which inhibits relapse by repairing the astroglial homeostatic regulation of glutamate in the NAcore. While the mechanisms underlying the actions of NAC in the NAcore have been well-studied after heroin SA, the effects of NAC in the cortex have not been investigated.

Methods: Animals were trained to self-administer heroin in 3-hour sessions using a descending dose paradigm followed by extinction training, with a subset of animals yoked as saline controls. Cortical astrocytes were visualized with GFAP antibodies or virally with AAV5-GFAP-LCK-GFP. Super-resolution confocal microscopy was used to collect data sets, which were digitally rendered and analyzed with Imaris. Astrocyte-synaptic interaction was assessed with viral labeling of the astrocyte plasma membrane and concomitant synaptic marker IHC. Synaptic contact was assessed using Imaris to map coregistry of the astrocyte signal with a synaptic marker puncta. In a subset of animals, NAC was administered at 100mg/kg for the last 10 days of extinction training.

Results: Our data demonstrate that heroin self-administration increased GFAP arbor complexity as measured by total 3D Sholl intersections, which was prevented by NAC (Browne-Forsythe ANOVA for unequal variance between groups; main effect between groups $p = 0.0089$, Dunnett's T3 multiple comparison test: $p < 0.01$ comparing saline ($n = 22$ data sets, 5 animals) to heroin ($n = 14$ data sets, 5 animals), $p < 0.05$ comparing heroin to heroin + NAC ($n = 19$ data sets, 5 animals). Heroin exposure produced enhanced association of astrocytic processes with the synaptic marker Synapsin (Ordinary one-way ANOVA; main effect between groups $p = 0.01$, Tukey's multiple comparison tests: $p = 0.01$ comparing saline ($n = 9$ animals) to heroin ($n = 7$ animals), $p = 0.03$ comparing heroin to heroin + NAC ($n = 8$ animals). Our data indicates that the same is true for astrocyte contact with another synaptic marker GluA2 (Ordinary one-way ANOVA; main effect between groups $p = 0.07$, Tukey's multiple comparison tests: $p = 0.10$ comparing saline ($n = 5$ animals) to heroin ($n = 5$ animals), $p = 0.12$ comparing heroin to heroin +NAC ($n = 5$ animals).

Conclusions: Heroin exposure increases cortical astrocyte complexity at the level of the GFAP filament protein arbor and also increases the extent of astrocyte interaction with synapses. NAC, a drug known to facilitate extinction of heroin seeking and prevent cued heroin relapse, prevented these changes in astrocyte structure and synaptic interaction.

Disclosure: Nothing to disclose.

Panel

29. Neuroimmune Signaling in Mental and Physical Health: Mechanisms and Interventions

29.1 The Role of Beta-Adrenergic Signaling in Stress-Induced Activation of Inflammation and Negative Emotion: A Randomized Controlled-Trial of Propranolol

Keely Muscatell

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Background: Psychological stress is a well-established risk factor for the development, exacerbation, and maintenance of a number of psychiatric disorders. Recent work has focused on elucidating the neurobiological mechanisms by which stress is capable of inducing negative mental health outcomes. A body of literature now shows that systemic inflammation is upregulated in the face of stress and associated with the development of negative symptoms, including anhedonia, threat-sensitivity, and social withdrawal. However, little research in humans has addressed the molecular mechanisms by which stress leads to increased inflammation, despite pre-clinical work suggesting that beta-adrenergic pathways may be involved.

Methods: To address this gap in our knowledge, we conducted a randomized, double-blind, placebo-controlled trial in which 90 healthy young adults (45% female) took either a one-time 40 mg dose of propranolol, a beta-adrenergic receptor blocker, or a placebo. Subjects then completed the Trier Social Stress Test (TSST: Kirshbaum et al., 1993), an acute psychosocial stress

induction. Blood samples taken before and after the stressor were assayed for levels of inflammatory markers (i.e., interleukin-6) and immune cell gene expression in the Conserved Transcriptional Response to Adversity (CTRA) 53-gene set. Multi-level modeling analyses including both sexes examined the effect of acute stress and pre-treatment with propranolol on IL-6, CTRA gene expression, and negative affect.

Results: Analyses of change in gene expression from baseline to follow-up showed increased expression of both inflammation and antiviral/antibody-related genes in response to the TSST (inflammatory: mean change $= +0.33 \pm$ SE 0.13 log2 mRNA abundance, $p = 0.018$; antiviral/antibody: $+0.29 \pm 0.14$, $p = 0.039$), and these effects were blocked by pre-treatment with propranolol (inflammatory: -0.42 ± 0.18, $p = 0.033$; antiviral/antibody: -0.43 ± 0.19, $p = 0.035$). Bioinformatics analyses implicated CREB family transcription factors in mediating these effects and identified NK cells and dendritic cells (DCs) as the primary cellular context for transcriptional up-regulation and monocytes as the primary cellular carrier of genes down-regulated by the TSST. Levels of IL-6 also increased in response to the TSST ($b = 0.46$, S.E. $= 0.096$, $p < 0.0001$), but this stress-induced increase in IL-6 was not blocked by propranolol ($b = 0.03$, S.E. $= 0.139$, $p = 0.85$). Finally, subjects who had taken propranolol showed less of an increase in negative emotions compared to those on placebo ($b = -0.22$, S.E. $= 0.099$, $p = 0.026$).

Conclusions: These findings are some of the first evidence in humans that propranolol can decrease inflammatory gene expression during acute social stress. The data suggest that acute stress induces an "acute defensive" molecular phenotype that is mediated by beta-adrenergic signaling and involves acute mobilization of NK cells and DCs at the expense of monocytes. Further, propranolol effectively blunted negative affective reactivity to the stressor, despite no change in levels of IL-6. Together, results from this study shed light on the molecular mechanisms by which stress may induce changes in inflammation and negative mood and thus confer risk for psychiatric disorder.

Disclosure: Nothing to disclose.

29.2 Relationship Between Resting State Functional Connectivity and Inflammatory Signaling in Mental and Physical Health

Abstract not included.

29.3 Neuroimmunological Correlates of Reward Function in Youth Across Psychiatric Conditions

Vilma Gabbay

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Background: Peripheral inflammation has been associated with psychopathology. Findings suggest that inflammatory state may not be specific to one diagnostic category, but rather related to overlap of symptoms and shared etiology across disorders. We have examined peripheral inflammatory processes and neurochemical inflammatory consequences (striatal glutathione, cortical GABA) in relation to clinical symptoms and brain functions in youth. Our focus has been on reward functions in light the known effects of inflammation on the reward circuitry, and the importance of reward function during adolescence a sensitive developmental period during which many psychiatric conditions first emerge.

Methods: Participants are youth ages 12-20, with diverse psychiatric symptoms, medically healthy and psychotropic-medication free at baseline. Anhedonia, fatigue, depression severity, suicidality, sleep, and anxiety are assessed quantitatively. Peripheral inflammation is indexed by kynurenines, cellular signature profiling, and a wide panel of 41 cytokine levels at baseline and post stimulation with lipopolysaccharide. Neurometabolic immune consequences are indexed by anterior cingulate cortex GABA and striatal glutathione (GSH, antioxidant). Reward circuitry is measured by resting-state and task-based fMRI that examines brain function during reward expectancy and attainment. A subset of subjects have been followed for 2 years. Statistics include data-driven methods of cluster analyses and corrected for multiple comparisons.

Results: These studies are ongoing. To date, we have enrolled 137 youth. In a recent in press publication analyzing a subset of the sample, we found that 19 cytokines were associated with our clinical measure of anhedonia but no other clinical measures. Further, whole-brain principal component analyses showed that factor 3 (12 cytokines) was negatively correlated with precuneus/posterior cingulate cortex activity during anticipation. Factor 2 (11 cytokines) was negatively correlated with angular gyrus activity during attainment. ROI analyses additionally showed that multiple cytokines were related to activity in the basal ganglia (EGF, FGF-2, Flt-3L, IL-2, IL-13, IL-15, IL-1R, MCP-3) and ACC/MCC (Flt-3L) during attainment. Importantly, the same cytokines were correlated with anhedonia and with brain function during the reward task. At present, all analyses are repeated with the larger sample and non-published data will be presented. In follow-up analyses, both GABA and reward brain activation predicted outcome in two years. We will also present data on relationships between peripheral inflammatory markers with GSH and GABA, as well as immunological correlates of outcome at 2-year follow-up.

Conclusions: Our work suggests that complex inflammatory processes are specifically related to reward dysfunction in youth exhibited as clinical presentation of anhedonia and in relation to the reward circuitry function. We will present data of the specific mechanisms involving GABAergic neurotransmission and oxidative stress.

Disclosure: Clicks Therapeutics, Consultant

29.4 Effects of Inflammation on Corticostriatal Networks for Effort Based Decision-Making

Michael Treadway

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Background: Effort-based decision-making (EBDM) represents a powerful translational model for the study of motivational deficits in psychopathology. To date, however, understanding of the precise neural mechanisms that support EBDM remains controversial, and the pathophysiology of motivational deficits is unclear. Previously, we have suggested that impairments in motivation in clinical populations could result from an overestimation of costs (effort discounting), blunted responses to prospective reward (reward discounting) and their integration (choice difficulty). In animal models, prior studies have heavily implicated ventral striatal (VS) dopamine and dorsal anterior cingulate (dACC) as critical for intact effort-related behavior. Further, prior animal and human studies have suggested that inflammatory cytokines may precipitate motivational impairments.

Methods: This presentation will summarize data from three studies. The first two studies are fMRI studies in healthy controls isolating the precise computational roles for dACC and VS during EBDM. The third study reports interim results from an ongoing placebo-controlled clinical trial investigating the effects of inflammation on EBDM in depressed patients before and after treatment with the potent anti-inflammatory infliximab. In studies 1 and 2, ($n = 20$) and ($n = 30$) healthy participants, respectively,

completed two novel fMRI tasks designed to isolate the roles of the dACC and VS related to effort discounting, initiation of effort and choice difficult. In study 3, we examined the association between baseline CRP activity in a sample of depressed patients ($n = 36$) recruited to ensure a wide range of inflammation during EBDM, as well as post-treatment changes in reported motivational impairment. Motivational impairments were assessed using the Multi-dimensional fatigue inventory.

Results: Study 1 revealed that dACC activity is largely driven by choice difficulty, consistent with a domain general role for dACC in encoding choice difficulty rather than foraging ($pFWE < 0.005$). Study 2 found a clear role for VS in both effort discounting and effort activation ($pFWE < 0.005$), but not encoding subjective value during EBDM. Finally, in study 3, we find that higher CRP levels in MDD patients predicted attenuated dACC activity to effort information during EBDM ($r = -0.41$, $p = 0.018$). Reported symptoms of low motivation was additionally associated with both CRP ($r = 0.41$, $p = 0.021$) and dACC activity ($r = -0.417$, $p = 0.019$). Moreover, in a subset of patients receiving a second fMRI scan following treatment with placebo or the potent TNFalpha antagonist infliximab, individuals showing increases in activity in this region reported greater declines in symptoms related to motivational impairment.

Conclusions: These data highlight functions of the EBDM network as assessed by fMRI, and highlight the utility of this model for understanding the role of inflammation in the pathophysiology of inflammatory deficits and the potential for anti-inflammatory therapies.

Disclosure: BlackThorn Therapeutics, Consultant, Royalties

Study Group

30. Mentoring Researchers From Underrepresented Minorities Locally and Globally: An Update on Best Practices

Javier Escobar*, Victoria Arango, Maria Oquendo, Juan Gallego, Wilson Compton, Javier Escobar

Study Group Summary: US underrepresented populations continue to face health and mental health disparities and increasing the number of minority researchers may help expand research focusing on these populations. While NIH has made investments to enhance the research workforce, this has not yet changed existing disparities according to a brief inspection of NIH applicants (Haggeness et al, Academic Medicine 2016). Reasons for this underrepresentation are complex and multifaceted and may differ for US-born compared to foreign-born minority investigators. Some research-stimulating programs did appear to work well such as NIMH-supported "Critical Research Issues in Latino Mental Health (CRILMH) initiative focusing on Latinos and CDC's "MARI" program focusing on African Americans. The CRILMH initiative that went for more than a decade, was effective in building a network of mentors, paired with young investigators, leading to positive outcomes related to publications, grant applications and awards (Interian A. and Escobar JI, Academic Medicine, 2009). The MARI program also led to successful outcomes in publications and research awards (Sutton MY et al, American Journal of Public Health, 2013). A new program that is showing positive results is the NIDA Diversity Scholars Network. These programs may serve as models to reduce disparities in research areas in which underrepresented communities are disproportionately affected by providing individualized mentoring and support. As research collaborations (e.g., genetic studies) become more globalized, developing/mentoring global researchers become important goals as these may help elucidate the contribution of genomics to health disparities in the US and abroad (McGlone West K et al, JAMA, 2017). Developing domestic and global collaborations is time consuming, requires team building, the "buy in" by local communities, countries and practitioners, and needs to bring clear benefits to underrepresented communities or host countries. For these initiatives, language, cultural competence and "connectors" are essential elements. Given population trends in the US and the global perspective on science and research, we believe that these initiatives have become highly relevant for professional organizations (ACNP), as well as funding agencies (NIMH, NIDA). The panel will provide current personal, institutional and organizational perspectives on research mentoring across several institutions (NIMH, NIDA, ACNP) as well as academic institutions (University of Pennsylvania, Rutgers University, Zucker School of Medicine at Hofstra/Northwell), with a focus on underrepresented ethnic groups. We will provide examples of successful global collaborations contributing to building sustainable research capacity for collaborative work in psychiatric genetics in South America that provide access to unique local resources. All members of this study group are academic leaders with expertise in this area. Several of them serve as members of the ACNP minority task force (Arango, Escobar, Gallego) and another (Oquendo) is the President Elect of ACNP. Also, some of them represent NIH institutes (Arango, Compton). The discussion will highlight "best practices" in this area and recommendations will be made with the goal of enhancing the cadre of underrepresented researchers and their potential contribution to the areas of health and mental health disparities nationally and globally.

Disclosure: Nothing to disclose.

Panel

31. Towards a Computational Phenotyping for Alcohol and Drug Addiction

31.1 A Double Dissociation Between Learning Signals in Sign- and Goal-Trackers

Quentin Huys

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Background: Individuals differ in what and how they learn from experience. In Pavlovian conditioning paradigms, where cues predict reinforcer delivery at a different goal location, some animals - so-called sign-trackers - come to approach the cue, whereas others, called `goal-trackers', approach the goal when the cue comes on. Sign-trackers are at higher risk of developing addictive phenotypes in a number of paradigms, suggesting that a tendency towards sign-tracking might be a risk factors for addiction in humans. However, the neural basis of learning in human sign- and goal-trackers is not yet known.

Methods: 129 healthy subjects underwent a Pavlovian-To-Instrumental task while undergoing functional MRI and simultaneous eye-tracking. Computational modelling was used to analyse gaze, pupil dilation and fMRI data.

Results: Individuals were divided into sign- and goal-trackers based on their gaze patterns. This groping revealed a matched double dissociation in pupillometry and fMRI. Sign-trackers exhibited a greater neural reward prediction error signal in the ventral striatum and associated brain regions than goal-trackers (all $p < 0.05$). Gaze and pupil dilation in this group was better captured by model-free learning ($p < 0.01$). Goal-trackers, on the other hand exhibited a stronger model-based neural state prediction error signal ($p = 0.02$). Gaze and pupil dilation in

this group was instead better captured by model-based learning ($p < 0.01$).

Conclusions: Individuals differ in what they learn from experiences. Sign-trackers tend to use a possibly model-free reward prediction error for learning. The resulting model-free valuation of stimuli renders stimuli `wanted' in their own right for them. `Goal-trackers', on the contrary, tend not to rely on dopamine for learning and instead tend towards building a model of the structure of the world and infer values in this model.

Disclosure: Nothing to disclose.

31.2 Computational Approaches for Dissociating Substance-Specific Markers for Addiction

Jasmin Vassileva

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Background: Data-driven and theory-driven computational approaches provide powerful tools to address the heterogeneity of addiction phenotypes, improve the precision of neuroclinical assessment, and identify novel targets for treatment. This talk will present novel data using these approaches with a unique sample of mono-dependent opiate and stimulant users in Bulgaria.

Methods: Data-driven machine learning analyses included 595 participants, enrolled in a larger study on impulsivity among substance users in Sofia, Bulgaria. We used the elastic net and 10-fold cross validation to predict opiate dependence (OD) and stimulant dependence (SD), based on demographic, psychiatric, personality, and neurocognitive indices. Psychiatric measures included conduct disorder, ADHD, antisocial personality disorder, psychopathy, and depression. Personality measures included trait impulsivity, sensation seeking, aggression, trait anxiety, state anxiety, and anxiety sensitivity. Neurocognitive measures included impulsive choice tasks of decision-making, delay discounting, and risk taking; and impulsive action tasks of response inhibition.

Theory-driven hierarchical Bayesian computational modeling analyses were additionally performed with a subset of participants. Novel cognitive models were developed and tested for the Cambridge Gambling Task (CGT; $N = 419$), the Monetary Choice Questionnaire of delay discounting (MCQ; $N = 399$), and the Balloon Analogue Risk Task (BART; $N = 232$). The best fitting model for each task was then used to identify differences in cognitive model parameters between opiate and stimulant users.

Results: Machine-learning models achieved high out-of-sample classification accuracy (OD AUC = 0.88; SD AUC = 0.83) and revealed that individuals dependent on opiates and stimulants were characterized by distinct multivariate personality, psychiatric, and neurocognitive profiles. Heroin users were uniquely characterized by elevated callous/unemotional facets of psychopathy, greater impulsivity under negative emotional states ("negative urgency"), increased trait anxiety, and lower risk-taking. Amphetamine users were characterized by greater sensation-seeking, motor impulsivity, anxiety sensitivity, and delay discounting, and lower depression and trait anxiety. The impulsive/antisocial facet of psychopathy was the only feature common to both drugs.

The cognitive modeling approach revealed differences in decision making, delay discounting, and risk taking between opiate and stimulant users that traditional methods alone did not detect. Delay discounting on CGT and MCQ tasks was particularly pronounced in stimulant users. Reduced sensitivity to loss in opiate users was one of the most consistent finding across different tasks and cognitive models and could represent a potential biomarker for opiate addiction.

Conclusions: Combining theory-driven and data-driven computational approaches could complement recently developed neuroscience-based frameworks for the clinical assessment of addictions and increase our understanding of different mechanisms involved in subtypes of addiction. Our findings suggest that quick, economical, and easy to administer neurobehavioral measures can identify objective behavioral markers of distinct addiction risk profiles, which may facilitate the development of reliable risk assessment batteries and could increase the precision of targeted behavioral interventions for addictions.

Disclosure: Nothing to disclose.

31.3 The Addictions Neuroclinical Assessment: Deep Phenotyping for Alcohol Addiction

Laura Kwako

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Background: Similar to other dimensional approaches to psychiatric disorders, the Addictions Neuroclinical Assessment (ANA) focuses on three neuroscience domains relevant to addiction and grounded in basic and clinical research. These domains comprise Incentive Salience, Negative Emotionality, and Executive Function. Domain-specific measures are currently being collected as part of a long-term screening and natural history protocol (SNHP) of alcohol use.

Methods: Participants included individuals seeking treatment for AUD at NIAAA in Bethesda, MD, USA, and those screened in the NIAAA outpatient clinic for participation in research. The SNHP includes physiologic assessments, questionnaires, and collection of blood for genetic testing; ANA measures are behavioral and self-report. Statistical tests included factor and latent class analyses.

Results: The first results include a factor analysis of measures in the SNHP, which identified three factors largely corresponding to the ANA domains. These domains significantly differentiated between individuals with and without AUD. The area under the curve (AUC) for Incentive Salience was 0.96, the AUC for Negative Emotionality was 0.86, and for Executive Function was 0.85. The second set of results comprise a latent class analysis using the same measures included in the factor analysis, in which two classes were identified; Class 2 drank more average drinks per drinking day ($\chi^2 = 259.63$, $p < 0.0001$) and had more total heavy drinking days ($\chi^2 = 404.60$, $p < 0.0001$) than Class 1. The third and final set of data presented will include the most current findings of the ANA substudy. At present, we have enrolled 148 individuals, of whom 43% are seeking treatment for AUD. In this early sample, 45% are women and 52% Caucasian; the mean age is 42 years and mean years of education is 15. Twenty-six percent of participants were diagnosed with a lifetime cannabis use disorder, and 5.5% with a lifetime opioid use disorder. Approximately 20% of the sample were diagnosed with PTSD.

Conclusions: This presentation will include an introduction to the Addictions Neuroclinical Assessment deep phenotyping approach, and will include background and novel data. We will discuss potential applications of computational models for ANA and how this deep phenotyping may be brought to bear on addressing the critical problem of heterogeneity within addiction.

Disclosure: Nothing to disclose.

31.4 Computational Neuroeconomic Decision-Making Trajectories as Predictors of Clinical Outcomes for Opioid Use Disorder

Silvia Lopez-Guzman

Universidad del Rosario, School of Medicine, Bogota DC, Colombia

Background: Decision-making is a principal target of computational investigation of both normal and pathological behavior. It is notably altered in addiction, where impulsive and risky behaviors are common and associated with changes in neural circuits related to reinforcement learning, reward valuation, and choice selection. While it is clear that decision-making behavior differentiates addicted individuals from controls, a more clinically-relevant question is whether it is informative in predicting deleterious outcomes such as relapse and treatment dropout. Several studies have pointed to personality and sociodemographic variables as potential prognosis predictors for these outcomes, but few have also incorporated individual decision-making task measures and taken into account their dynamics in time. To address this issue, we measured changes through time-in-treatment using three established neuroeconomic assays, offering an algorithmic framework for studying impulsivity, tolerance for known risks, and tolerance for unknown risks, in a cohort of patients with opioid use disorder (OUD) followed for up to seven months of medication for OUD (MOUD).

Methods: 74 patients with OUD were assessed for as many as 15 sessions over the course of MOUD in an outpatient treatment setting. In each session, subjects completed a delay discounting task, a (known) risk attitude task, and an ambiguity (unknown risk) attitude task. All choices from the tasks had an equal probability of counting towards a monetary bonus at the end of the session thus incentivizing subjects to choose according to their true preferences. We derived three individual computational decision-making parameters from these tasks: a discount rate, a risk tolerance parameter, and an ambiguity parameter. Data on symptom severity, and other impulsivity, risk, and personality self-report scales, as well as sociodemographic variables were also collected. Opioid relapse (10 or more days of use within a period of 28 days) and treatment dropout were extracted from medical records. We employed cross-validated LASSO logistic regression, a robust machine-learning method that is useful for variable selection and prevention of over-fitting, to determine which factors contributed to the prediction of relapse.

Results: Most variables did not survive LASSO regression for relapse. Notably, the coefficients of several subscales of personality impulsivity and risk self-report scales were reduced to zero, suggesting most of these personality factors, while useful for diagnosis, are not determinants of prognosis. Interestingly, the dynamics through time-in-treatment of computational decision-making parameters and symptom intensity (craving, anxiety, and withdrawal symptoms) were significant predictors of relapse compared to baseline measures, such that progressive increases in impulsive and risky decision-making —the slope of the trajectories of these parameters— were associated with a higher risk of relapse.

Conclusions: Neuroeconomic approaches offer a promising framework for algorithmic modeling of altered decision-making in addiction. We conclude that in-treatment dynamics of these neuroeconomic parameters may contribute along with other demographic, personality, and psychiatric comorbidity factors, to the construction of a relapse phenotype that could aid in targeted intervention selection for individualized care.

Disclosure: Nothing to disclose.

Panel

32. The Power of Transdiagnostic Circuit, Physiologic, and Behavioral Data to Support and Refine Critical RDoCs Domains

32.1 Exploring Negative Valence Systems: Interactions Between Anxiety, Pain, and Aversive Learning

Lauren Atlas

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Background: Pain is a subjective, emotional experience that is the most common reason individuals seek medical care and lies at the foundation of the current opioid epidemic in the United States. Pain is also highly comorbid with psychiatric disorders, including anxiety and depression, yet we know little about the mechanistic links between pain and anxiety. In this talk, I will explore the link between pain and negative valence systems, focusing on a series of studies designed to measure potential links between anxiety, fear/threat learning, and acute pain.

Methods: I will present published and unpublished work measuring links between anxiety, acute pain, and aversive learning. All studies employ conditioning with or without instructions and measure pain ratings and autonomic responses to noxious thermal stimulation. Study 1 measured cue-based expectancy effects on subjective pain in healthy and clinically anxious youth ($n = 63$; Michalska et al., 2018). Study 2 ($n = 59$) compared the effects of instruction and aversive learning on cue-based expectancy effects on pain and autonomic responses during a pain reversal learning task and measured associations with state and trait anxiety within healthy volunteers. Study 3 ($n = 49$) compared instructions and aversive learning in healthy and clinically anxious youth ($n = 49$). All studies include both male and female participants.

Results: Consistent with previous work in healthy volunteers, participants in all studies showed significant cue-based modulation of pain, such that pain was higher when the same medium temperature was preceded by a high pain cue relative to a low pain cue. In Study 1, when expectations were manipulated through both learning and instruction, expectancy effects did not differ between healthy and anxious youth: both groups showed strong expectancy-based modulation ($B = 1.72$, $t(41) = 10.48$, $p < 0.001$). However, when we separately manipulated instructions and learning (Study 2), associations with anxiety emerged. Interestingly, individuals with high state anxiety were more likely to update pain upon instruction (Group x State anxiety interaction: $p = 0.016$), but also maintained elevated autonomic arousal based on initial learning irrespective of instruction or contingency reversals ($p = 0.005$). Study 3 revealed that youth with anxiety showed larger anticipatory SCRs during feedback-driven learning, but these differences were abolished upon instructed reversal ($p = < 0.05$), and we saw no differences in response to pain itself, as both groups showed strong expectancy-based modulation of subjective pain.

Conclusions: These studies indicate promise for exploring pain as a unique negative valence dimension. We observe unique interactions with other negative valence dimensions, including anxiety and fear, which emerge when considered through the lens of dynamic learning. When cue contingencies are fully instructed, we see no influence of anxiety on acute pain. However, when contingencies are learned through experience, or when contingencies change over time, anxiety influences both pain and autonomic responses. Interestingly, we see dissociations between subjective and physiological responses, suggesting that anxious individuals may use cognitive information to update behavioral reports, but maintain elevated arousal for initial learning. Future studies of clinical anxiety and negative valence dimensions should compare pain with other aversive and appetitive outcomes to determine whether these relationships are unique to pain, or whether they reflect alterations in associative learning or negative valence systems more generally.

Disclosure: Nothing to disclose.

32.2 Leveraging Latent Neurocognitive Reward Dimensions to Predict Mood Symptoms in Teens

Roselinde Kaiser

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Background: Neurocognitive models of mood pathology propose that altered reward processing is central to the etiology of unipolar and bipolar disorders, which commonly emerge in adolescence and young adulthood. However, reward processing is a multifaceted construct, and much remains unknown about the specific dimensions of reward processing that distinguish among clinical symptom profiles – or that can predict future symptom trajectories in youth. This study aimed to address this gap by decomposing reward processing into (sub-)dimensions using a latent variable approach, and evaluating relationships between individual differences in reward dimensions and mood symptoms.

Methods: The transdiagnostic sample included n = 155 (ages 15–25, n = 86 current mood diagnosis); n = 42 completed neuroimaging and n = 123 completed an eight-week daily diary following the research session. Confirmatory factor analyses (on behavioral data from a pooled dataset of n = 368) extracted latent dimensions reflecting the ability to adapt behavior in order to achieve reward (reward learning) or the extent to which behavior is disrupted by receipt of reward (reward interference). Task-related functional connectivity (TFC) in corticostriatal networks in response to a reward (dice guessing) task was evaluated using a task-weighted general linear model. Daily diary data were subjected to hierarchical analysis to estimate within-subject models predicting mood symptoms by daily stress, and partition subjects by model features using k-means clustering. Analyses tested relationships between latent reward dimensions and (1) mood symptoms at baseline, (2) TFC at baseline, (3) symptom trajectory cluster membership.

Results: Poorer reward learning ability was associated with higher baseline severity of mood symptoms (either anhedonia or mania), rs = −0.22 and −0.29, ps < 0.01, hypoconnectivity between ventral striatum and ventral prefrontal cortex in response to reward, and higher likelihood of symptom trajectories characterized by stress-reactive anhedonia, Wald $\chi^2 = 3.91$ and 4.58, ps < 0.05. Higher reward interference was associated with higher mania at baseline, r = 0.24, p < 0.01, (but not anhedonia, r = 0.08, p > 0.05), hyperconnectivity between striatal regions and areas of default network, and higher likelihood of a symptom trajectory characterized by stress-reactive mania, Wald $\chi^2 2 = 4.24$, p < 0.05.

Conclusions: Findings from this transdiagnostic youth sample indicate the presence of separable neurocognitive reward dimensions, with distinct relationships to clinical health and corticostriatal functioning, and possibly reflecting vulnerabilities to different profiles of mood symptoms in the near future.

Disclosure: Nothing to disclose.

32.3 Examining Impaired Emotion Regulation as a Transdiagnostic Domain

Harold Koenigsberg

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Background: Affective instability (AI) is a prevalent and behaviorally destabilizing feature of many psychiatric disorders, yet the mechanisms underlying AI are not well understood. We have shown that in borderline personality disorder (BPD), AI is associated with impairments in the ability to employ the highly adaptive emotion regulatory process of cognitive reappraisal by emotional distancing and failure to adequately engage pre-frontal cortical regions that are typically activated during reappraisal (Koenigsberg et al, Bio Psych 2009). The present study examines whether impaired cognitive reappraisal reflects a dimension associated with impaired emotion regulation transdiagnostically. This has important implications for developing treatments across diagnoses as well as for better understanding mechanisms of resilience.

Methods: We present data on a preliminary sample of unmedicated subjects recruited, independent of diagnosis (excluding those with psychotic, neurological or substance use disorders), covering a wide range affective instability. As 3T BOLD images were obtained, subjects performed an affect regulatory task in which they were instructed to either simply look at or regulate by distancing a series of IAPS negative emotional pictures and then rate their affective response to the pictures after performing the looking or distancing task.

Results: The sample (n = 31) captured a wide range of affective instability (Affective Lability Scale (ALS) scores ranging from 7 to 106 (mean 44.2 ± 30.3)) and included 16 subjects without psychiatric diagnoses (HCs), 9 with anxiety disorders, 2 with bipolar II disorder, 3 with adjustment disorders and 6 with personality disorders Whole brain imaging demonstrated that overall, subjects engaged the ventrolateral prefrontal cortex (VLPFC) bilaterally during reappraisal by distancing vs. looking at negative pictures (x = −40, y = 52, z = −2; k = 1241 voxels, p < 0.001; x = 22, y = 52, z = 30; k = 1149; p < 0.001). This is consistent with meta-analyses demonstrating that the VLPFC is activated in HCs during reappraisal. Affective Instability (ALS) was positively correlated with activity in the right amygdala (x = 22, y = −6, z = −16; k = 53, p < 0.001) and left posterior insula (x = −42, y = −12, z = 0; k = 167, p < 0.001), across the sample, as subjects were endeavoring to reappraise by distancing (vs. looking). We identified no regions showing a negative correlation with ALS during distancing. Behaviorally, ALS did not anti-correlate with reappraisal success, as measured by reduced negative affect ratings when distancing vs. looking (r = 0.012, ns).

Conclusions: In a transdiagnostic sample, we replicated the finding that the VLPFC is engaged during cognitive reappraisal. Consistent with our hypothesis, we found that increasing affective instability was associated with a reduced capacity to down-regulate amygdala and insula activity by means of reappraisal by distancing. However, behaviorally we did not find a relationship between affective instability and reappraisal success. While we must revisit the negative behavioral finding as we continue to increase sample size (n = 88 subjects will give 90% power to detect associations of r = 0.3 at alpha < 0.05), our findings suggest that neuroimaging techniques may provide a particularly sensitive approach to identify biologically mediated transdiagnostic psychopathological domains.

Disclosure: Nothing to disclose.

32.4 Amygdala Connectivity During Emotional Face Perception in Psychotic Disorders

Aprajita Mohanty

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Background: Schizophrenia is characterized by prominent emotional face perception (EFP) deficits. The National Institute of Mental Health Research Diagnostic Criteria (RDoC) initiative has recommended examining reception of facial communication (measured via EFP) as a basic dimension of functioning that spans normal to abnormal human behavior. However, EFP impairment and its association with symptoms or functioning

has been examined largely in the domain of schizophrenia. The present study adopted a dimensional approach recommended by RDoC to examine the association of behavioral and neural measures of EFP with psychotic symptoms and global functioning across individuals with schizophrenia spectrum and other psychotic disorders. Neurally, the study focused on the functional connectivity of the amygdala during EFP because this region is frequently implicated in EFP and bears extensive structural connectivity with other brain regions supporting EFP.

Methods: Participants were sampled from the Suffolk County Mental Health Project, a longitudinal study of first admission psychosis. Data were collected from 55 male and female cases with psychotic disorders – 26 with schizophrenia spectrum disorders and 29 with other psychotic disorders and a comparison group of 29 never-psychotic participants (NP). Participants matched expressions of emotional faces and the identity of neutral faces while behavioral accuracy and functional magnetic resonance imaging (fMRI) data were recorded. Seed-based functional connectivity analyses were conducted to examine connectivity of amygdala to other regions of the face processing network during the EFP task.

Results: Results revealed that cases showed worse accuracy, $F(1,74) = 10.57$, $p < 0.005$, greater inferior frontal gyrus (IFG) activation, and greater amygdala-insula connectivity ($p < 0.05$, corrected for multiple comparisons) while matching emotional and neutral faces compared to NP. However, for emotional vs. neutral faces in cases 1) worse accuracy was associated with worse negative symptoms, $r = 0.378$, $p < 0.009$, social functioning, $r = -0.324$, $p < 0.026$ and marginally worse global functioning, $r = -0.273$, $p < 0.064$, and 2) greater IFG activation, as well as amygdala-insula and amygdala-IFG connectivity was associated with worse negative symptoms as well as social and global functioning ($p < 0.05$, corrected), even after controlling for antipsychotic medication status. Importantly, hierarchical regressions examining transdiagnostic nature of these relationships showed non-significant symptoms/functioning x diagnosis interaction terms indicating that these relationships transcended diagnostic categories.

Conclusions: Present findings help bridge the gap between basic EFP-related neuroscience research and clinical research in psychosis, and highlight amygdala functional connectivity during EFP as a potential symptom-specific marker that tracks global functioning transdiagnostically across psychotic disorders.

Disclosure: Nothing to disclose.

Panel

33. Neural Circuit Dysfunction in Schizophrenia – Opportunities for Novel Treatments Beyond Dopamine Receptor Blockade

33.1 SEP-363856, a Novel Psychotropic Agent With a Unique, Non-D2 Receptor Mechanism of Action

Abstract not included.

33.2 Circuit Mechanism Mediates Sub-Chronic Ketamine-Induced Increase in Dopamine Synthesis

Abstract not included.

33.3 An Intracellular Trace Amine-Associated Receptor, TAAR1, Regulates G-Protein Signaling and Transporter Trafficking in Dopamine Neurons

Abstract not included.

33.4 The Development and Characterization of Highly Selective Trace Amine-Associated Receptor 1 Agonists

Abstract not included.

Panel

34. Multimodal Imaging Results From the Four Human Connectome Projects (HCP) Examining Dimensions of Anxious Misery

34.1 Dimensional Symptoms Across Anxious Misery Disorders Predict Brain Network Connectivity Measures

Yvette Sheline

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Patients with "anxious misery" disorders, including major depression, posttraumatic stress disorder (PTSD), social anxiety disorder, generalized anxiety disorder and persistent depressive disorder, exhibit heterogeneous symptom profiles, characterized by the RDoC negative valence constructs of "loss" and "response to sustained threat". Studies using resting-state functional magnetic resonance imaging (rsfMRI) have described large-scale brain network differences from controls in a variety of DSM diagnoses but have not examined symptom correlations across different types of "anxious misery" disorders.

Methods: Participants ($n = 100$; age: 18-59; sex: 66 females) were recruited with a score > 10 on the PHQ-9, completed a battery of clinician administered and self-report measures and were scanned using the Human Connectome Project (HCP) multiband rsfMRI protocols. Clinical data consisting of 162 individual items from the nine symptom scales (HAMD, MADRS, MASQ, SHAPS, ISI, ASI, BIS-BAS, NEO-N and CTQ) underwent data reduction using symptom network analysis, resulting in nine symptom clusters: anhedonia, general depression, somatic anxiety, psychic anxiety, sleep problems, rumination, negative internalizing, history of sexual abuse or physical neglect, h/o emotional/physical abuse or emotional neglect. Data-driven analysis of within and between network connectivity of the 10 Power networks produced 55 brain connectivity features. Clinical and network features were controlled for age and sex. These brain network features were correlated using multidimensional canonical correlation analyses (CCA) with the nine symptom clusters.

Results: A significant correlation with the first pair of CCA modes was observed: canonical correlation $r = 0.92$, $p < 0.0002$ (permutation test); FDR-corrected $p = 0.02$). The first network CCA mode was significantly associated with ten of the 55 original network variables, including within network connectivity in the default mode network (DMN), and between network connectivity of DMN-visual (VIS), DMN-subcortical (SUB), DMN-auditory (AUD), DMN-dorsal attention network (DAN), DAN-frontoparietal (FPN), SUB-VIS, DAN-VIS, DAN-AUD, DAN-cingulo-opercular network (CON). There were specific correlations of the emotional/physical abuse or emotional neglect, negative internalizing, somatic anxiety, sleep problems and general depression clinical clusters with the first CCA mode.

Conclusions: Data driven network modeling of rsfMRI suggests that within- and between-network connectivity in particular networks is associated with specific depressive and anxious symptom clusters. These symptom cluster correlations were present across different types of "anxious misery" disorders, supporting the RDoC framework. Future analyses will test these relationships in an individual validation testing set.

Disclosure: Nothing to disclose.

34.2 Intrinsic Functional Architecture Predicts Progression of Future Pathology in a Normative Pediatric Sample and in the Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA) Connectomes Related to Human Disease (CRHD)

Susan Whitfield-Gabrieli

MIT, Cambridge, Massachusetts, United States

Background: We face an ever-increasing crisis of mental health in children and adolescents, especially with the increased rates of anxiety and depression in teenagers. While current diagnoses are largely based on symptoms, neuroimaging techniques may provide biomarkers for early detection which could potentiate early intervention and possible prevention of these psychiatric disorders. Resting-state networks (RSNs), which reflect the intrinsic functional architecture of the human brain, may provide such early biomarkers. Understanding the neurodevelopmental trajectory of these RSNs in relation to the developmental trajectory of psychiatric symptoms is important for developing early interventions.

Methods: First we examined, in a normative pediatric sample ($N = 94$), whether RSNs can predict individual children's internalization problems characteristic of major depression (MDD).

We acquired baseline RSNs at 7 years of age and performed longitudinal behavioral and imaging follow-ups each year for four years. Subgenual anterior cingulate (sgACC) seed-based prediction analyses were performed to identify biomarkers which could predict individual developmental trajectories towards behavioral problems as measured by the Childhood Behavioral Checklist (CBCL) empirically based syndrome scales, such as internalization problems (which combine the Anxious/depressed, Withdrawn, and Somatic complaints subscales). Next, we sought to replicate/extend this finding with the BANDA CRHD sample, which is a longitudinal study following teens who were diagnosed with anxiety/depression ($N = 160$).

Results: In the normative pediatric sample, weaker resting-state connectivity at age 7 between the sgACC and dorsolateral prefrontal cortex (DLPFC) predicted the development of internalization problems by age 11. Logistic regression analyses of resting state metrics revealed that RSNs were a more accurate predictor than initial behavioral measures of whether a child would progress to a subclinical CBCL scores, which are highly predictive of a future psychiatric diagnosis. After testing this model on the BANDA data set, we again found that weaker sgACC-DLPFC baseline connectivity in teens who were diagnosed with anxiety/depression predicted subsequent worsening of internalization one year later.

Conclusions: Such neuroimaging biomarkers are promising for the early identification of vulnerabilities in neural systems and may support preventive treatment of at-risk children prior to the emergence of full-blown psychiatric disorders of MDD. In addition, identifying which teenage adolescents who were already diagnosed with anxiety/depression are more vulnerable (or resilient) to worsening pathology may aide in developing/augmenting a personalized treatment program.

Disclosure: Nothing to disclose.

34.3 Using Human Connectome Imaging Within an RDoC Framework to Characterize Disordered Emotional States

Leonardo Tozzi

Stanford University, Stanford, California, United States

Background: In our Human Connectome Project for Disordered Emotional States (HCP-DES), we characterize emotional states that cut across disorders such as depression and anxiety based on neuroimaging of large-scale neural circuits that govern emotional, cognitive and self-reflective functions. Circuit data is integrated with phenotypic measures of symptoms, psychological functions and behavior. This multi-modal approach thus spans across different units of analysis compatible with the research domain criteria initiative (RDoC). In particular, we focus on the constructs of acute threat and loss (negative valence system), reward evaluation and responsiveness (positive valence system), and working memory (cognitive system). We also focus on the default mode network relevant to self-directed thought during rest. Our hypothesis is that individual variations in circuit dysfunction account for the heterogeneity of disordered emotional states, independent of diagnosis. An important first aim is to establish a frame of reference, demonstrating harmonization of our data with the umbrella Human Connectome Project (HCP).

Methods: Data are being acquired for 250 participants with mood and anxiety disorders and 50 healthy controls, all aged 18 to 35. HCP-DES takes advantage of the cutting-edge protocols developed by the HCP for acquisition, analysis and sharing of MRI data. We use an HCP-equivalent scanning protocol on a 3T GE Discovery scanner including multi-band fMRI (resting state and task) and multi-band multi-shell diffusion-weighted imaging. Our tasks are designed to probe the RDoC constructs of interest: matching negative faces (acute threat), gambling (reward responsiveness) and n-back (working memory). We also collect several questionnaires measuring anxiety and depression, quality of life, emotion regulation and trauma history, and an extensive behavioral battery assessing cognitive functions. To investigate the harmonization between our site and the central connectome facility, we compared 30 healthy controls from HCP-DES with 30 matched controls from the HCP healthy young adult data release. After preprocessing all data with the HCP minimal preprocessing pipelines, we compared temporal signal to noise ratio (tSNR), task activations, average resting state functional connectivity in established brain networks and structural properties of automatically segmented white matter fiber tracts between the two datasets.

Results: We demonstrate higher fMRI tSNR on our GE Discovery scanner compared to the Siemens Connectome Skyra (mean tSNR $= 95.33 \pm 44.21$ and 55.71 ± 26.78, $t = -707.79$, $p < 0.01$). In both datasets we show activation of the amygdala in the matching task (pFWE < 0.05), of the caudate in the gambling task (pFWE < 0.05) and of the dorsal lateral prefrontal cortex in the n-back task (pFWE < 0.05). At rest, we found higher connectivity for HCP-DES in the parieto-occipital network ($t = 3.91$, $p < 0.01$) and lower coupling in the medial parietal ($t = 2.70$, $p < 0.01$) and mouth supplementary motor networks ($t = -2.87$, $p < 0.01$).

Conclusions: Data collected by HCP-DES provide an RDoC-inspired insight in the circuit dysfunctions underlying depression and anxiety. By comparing imaging data between our GE platform and the umbrella HCP project, we have established a frame of reference for interpreting dysfunctional circuits and for future multi-site clinical connectome analyses.

Disclosure: Nothing to disclose.

34.4 Modulation of the Functional Connectome in Treatment-Resistant Depression by Fast-Acting Therapies

Katherine Narr

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Background: Resting-state functional magnetic resonance imaging (rsfMRI) studies show differences in the functional

connectivity (FC) of large-scale brain networks in major depression compared to non-depressed controls, most frequently implicating the default mode (DMN), executive control, limbic and salience networks. Perturbation of brain network connectivity could thus play a role in successful treatment response. Both low-dose ketamine infusion treatment and electroconvulsive therapy (ECT), via pharmacotherapy or neurostimulation, are shown to elicit a rapid therapeutic response in patients with treatment resistant depression (TRD). However, it remains unclear how these treatments modulate the depression functional connectome and relate to clinical outcome.

Methods: Patients with TRD clinically eligible to receive ECT (n = 26, mean age 36.38 ± 11.71, 69% female) or ketamine treatment (n = 45, mean age 37.26 ± 10.82, 41% female) were scanned using Human Connectome Project (HCP) multiband rsfMRI acquisition protocols (TR/TE = 800/37ms, FA = 52o, MB = 8, 2 mm isotropic voxel size, TA = 13:22 minutes). Imaging data and clinical assessments were acquired prior to treatment, and after patients received either a clinically prescribed ECT index series, or after one, and four intravenous infusions of ketamine (0.5 mg/kg), respectively. Functional data was processed with the HCP minimal preprocessing pipelines and denoised using FSL's FIX. Data-driven functional segmentation of the timeseries data was performed using ICA (FSL's MELODIC) and dual regression to extract 25 resting state (RS) nodes. Network modeling using FSLNets with L1 regularization (lambda=10), hierarchical clustering of the group-average full correlation NetMat using Ward's method implemented in Matlab, generated a TRD functional connectome. Each subject's partial correlation NetMat was then unwrapped into a single row and combined across subjects to create a Subject x Edges matrix. To evaluate the effect of each fast-acting treatment on the extracted functional connectome, changes in FC were compared across time and in association with change in depressive symptoms.

Results: Patients showed significant reductions in depressive symptoms following both single ($p < 0.001$) and serial ($p < 0.0001$) ketamine infusion therapy, and after ECT treatment ($p < 0.001$). Following single ketamine infusion, decreases in FC were observed between the anterior DMN and executive control fronto-parietal network (FPN) ($p = 0.03$, FWE corrected). Changes in the pattern of FC differed after the fourth ketamine infusion to show increased FC between somatosensory and visual networks ($p = 0.04$, FWE corrected). Changes in network FC pre- and post ECT showed increases in FC between the DMN and executive control networks ($p = 0.0014$, uncorrected) in this currently smaller sample. Post-hoc analyses showed changes in FC were associated with improvements in depressive symptoms ($p < 0.05$).

Conclusions: Data-driven network modeling of rsfMRI data suggest changes in FC between DMN and executive control FPN nodes contribute to rapid treatment response, in line with previous studies implicating these networks as relevant to the systems-level pathophysiology of major depression. However, the pattern of FC changes within these networks also appear to differ across treatment modalities. Further, results suggest that ongoing ketamine treatment leads to changes in FC that encompass functional plasticity of sensory networks. Future analyses will directly compare changes in networks FC across treatment modalities.

Disclosure: Nothing to disclose.

Panel

35. Targeting Balance Among Limbic and Cortical Networks to Prevent Suffering and Suicide

35.1 The HOPES Project: Help Overcome and Prevent the Emergence of Suicide

Anne-Laura van Harmelen

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Background: Globally, suicide is the second most common cause of death for adolescents and young adults. Suicidal thoughts and behaviours (STBs) include suicidal ideation, plans, and attempts and are most often reported in individuals suffering from a mood disorder. The risks for STBs are elevated significantly by adolescence, and the incidence of suicide rises sharply from childhood to adolescence (i.e. from 1.2 to 19.2 per 100.000). To improve treatment and preventative interventions for teenage groups, it is critical to identify mechanisms that confer risk to adolescent STB. Here, I will introduce the MQ- Help Overcome and Prevent the Emergence of Suicide (HOPES) project. The HOPES project is a global multidisciplinary international research consortium that aims to elucidate the neurobiological mechanisms that underlie risk for STBs during adolescence. In this talk, I will also present the first findings from the HOPES project. Specifically, I will present findings from a machine learning approach to investigate the neural underpinnings of suicidality in 133 young people with severe depression, and discuss how these neural underpinnings interact with negative experiences in the social environment (e.g. abuse, victimization) in young people suffering from suicidality.

Methods: We examined structural brain alterations underlying suicidal ideation in youth with severe depression (the MR-IMPACT sample; N = 122, mean age ± standard deviation = 15.44 ±1.27).

Suicidal severity rating was performed using the Columbia Suicide Severity Rating Scale (C-SSRS).

High resolution T1-weighted sequences were acquired in the sagittal plane using a 3D-MPRAGE sequence. Pre-processing of the structural images was performed using Freesurfer version 6.0.0. The full Freesurfer pre-processing pipeline was performed. After pre-processing, cortical thickness, surface area and mean curvature were extracted region-wise using the Desikan-Killiany atlas. Eight subcortical regions were also extracted hemisphere-wise from the pre-processed images namely the: Cerebellum, Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, and Nucleus Accumbens. Least absolute shrinkage and selection operator (LASSO) was used to identify the brain anatomical regions that are most relevant to suicidal ideation severity. Deviance was used to assess goodness of fit through cross validation for generalisation of the Lasso.

Post-hoc regression analyses were utilized to examine whether these neural underpinnings identified using Lasso interact with negative experiences in the social environment (i.e. child abuse, peer victimization) in order to predict level of suicidality in young people.

Results: In our analyses, we find preliminary support that suicidality is associated with alterations in thickness of the ventromedial prefrontal cortex (VMPFC) including the orbitofrontal cortex, the paracentral gyrus, the inferior parietal cortex, and the insula (Lambda MSE min = 0.25).

Conclusions: We find support for the notion that suicidality in young people is associated with alterations in the VMPFC regions, and discuss how these findings interact with negative social experiences. VMPFC regions and their connections may be important in the excessive negative and blunted positive internal states that can stimulate suicidal ideation.

Disclosure: Nothing to disclose.

35.2 Probing Structural and Functional Subcortical Regions Implicated in Youth Depression

Randy Auerbach

College of Physicians & Surgeons, Columbia University, New York, New York, United States

Background: Prior structural and functional neuroimaging research in adolescent major depressive disorder (MDD) has consistently implicated abnormalities in subcortical regions (Auerbach et at., 2014; Luking et al., 2016). However, research has often relied on sample sizes that limit power to detect effects that are presumed to be small. Additionally, heterogeneity in disease course and treatment history undoubtedly affects the reliable identification of structural and functional abnormalities among unaffected, high-risk youth as well as youth diagnosed with MDD. To reconcile inconsistent structural and functional neuroimaging findings, the presentation will leverage data from the Adolescent Brain and Cognitive Development (ABCD) Study and Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA). ABCD is a multi-site project that was designed to assess normal variability in adolescent brain and cognitive development among 9-10-year-old children. By contrast, BANDA is a human connectome project that aims to characterize neural circuitry underlying depression and anxiety in adolescents ages 14-16 years. Collectively, these projects afford a unique opportunity to probe subcortical abnormalities in at-risk and currently depressed youth.

Methods: The ABCD Study acquired structural MRI data from 9-10-year-old children ($n = 4{,}521$). Of these children, 29.7% ($n = 1{,}343$) had a parental depressive history. Secondary analyses also tested whether subcortical brain differences were present in youth with a lifetime depressive disorder history. For BANDA, adolescents ($n = 141$) completed an incentive processing task while fMRI data were collected. Primary analyses probed differences in subcortical activation, and secondary analyses will test whether blunted activation within striatal regions related to anhedonia and a history of suicidal thoughts and behaviors.

Results: Several findings emerged. Within ABCD, relative to low-risk youth, high-risk participants with a maternal, but not paternal, depression history exhibited smaller volumes of the right putamen, right accumbens, and left pallidum (FDR-corrected $p < 0.05$, $p < 0.002$, $t < -2.57$) as well as smaller left amygdala volumes (this latter finding did not pass FDR correction). As expected, depressive disorders were more common among those with a parental history of depression (15.96% [parental depressive history] vs. 8.72% [no parental depressive history]; $\chi2(1) = 47.36$, $p = 5.90$ x 10–12), but there were no significant associations (after FDR correction) between subcortical volumes and children's depressive disorder history. Among all BANDA participants, there was greater activation in the nucleus accumbens for reward versus loss ($t(140) = 10.00$, $p < 0.001$). Preliminary analyses showed that the reward-loss contrast activation was blunted in adolescents with depression and anxiety ($B = -0.47$, $t = -2.29$, $p = 0.02$). For adolescents with depression and anxiety, incentive-related activation was altered in a number of other regions in whole brain analyses, including reduced anterior insula and anterior cingulate activation as well as increased activation in the mPFC and posterior cingulate.

Conclusions: Structural and functional neuroimaging approaches in high-risk and currently depressed youth highlight subcortical abnormalities, which may contribute to MDD and suicide risk during a critical developmental period.

Disclosure: Nothing to disclose.

35.3 The Study of the Amygdala-Ventromedial Prefrontal Emotion Regulation Brain System to Reduce Hopelessness and Suicide Behavior Across Mood Disorders

Anjali Sankar

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Background: The amygdala-ventromedial prefrontal (vmPFC) system and the emotion regulation (ER) functions it subserves are increasingly implicated in suicide thoughts and behaviors (STBs). Differences in the structure and function of this system have been observed by our group in adolescents and young adults with previous and future suicide attempts across mood disorders. This talk will (a) present novel multimodal structural, and functional connectome-based findings from a dataset of individuals with STBs across adolescent to older adult epochs, and discuss an approach to identifying biotypes that are predictive of STBs, (b) identify brain circuity patterns that underlie the important suicide risk factor, hopelessness, and provide a model for its association with ER dysfunction, and (c) show data supporting salutary effects on brain circuitry and reducing suicide propensity of a 12-week psychobehavioral intervention, Brain Emotion Self¬-Monitoring and Regulation Therapy for Daily Rhythm Regularization (BE-SMART-DR), designed to alter the target ER brain system via bottom up DR mechanisms.

Methods: Clinical, behavioral and imaging data were acquired in 946 subjects (14-59 years; 50% with a mood disorder, 50% healthy comparison). Grey matter volume, white matter connectivity, and functional connectome-based analyses using intrinsic connectivity distributions were examined to identify brain systems that differentiate suicide attempters (SA) from non-attempters (NSA). Analyses also assessed brain patterns associated with hopelessness and the relationship with ER. Analyses of imaging data from before to after BE-SMART-DR in adolescents/young adults (ages 16-24 years) with bipolar disorder examined whether targeted improvements in ER brain system functioning were associated with reductions in suicide propensity.

Results: Across mood disorders, structural and functional connectome-based networks in an amygdala-vmPFC ER brain system differentiated SAs from NSAs ($p < 0.001$), supportive of a suicide-related biotype. Within this ER system, reduced activation in the medial orbitofrontal cortex (mOFC) during ER of negative emotions was associated with hopelessness ($p < 0.001$). Pre-to-post BE-SMART-DR increases were observed in ER, functional connectivity in the mOFC, and reductions in amygdala activation that were associated with reductions in suicide propensity (CHRT scale) ($r > 0.46$).

Conclusions: Multimodal structural and functional connectome-based models showed associations of the amygdala-vmPFC ER system with hopelessness and STBs. Early evidence suggests that a psychobehavioral intervention that targets the functioning of this system could lead to reductions in suicide propensity.

Disclosure: Nothing to disclose.

35.4 In Search of a Depression Switch: Electrophysiological Changes With Initial Exposure to Therapeutic Subcallosal Cingulate DBS

Helen Mayberg

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Background: Stereotypical behavioral effects of deep brain stimulation (DBS) can be reliably elicited in patients with treatment

resistant depression (TRD) with first stimulation of the white matter in and around the subcallosal cingulate (SCC) during implantation surgery (1-2). Cumulative improvements in negative mood and psychomotor slowness, symptoms that play important roles in suicide, are observed with repeated bilateral testing at the optimized DBS target, and these 'first' antidepressant effects often persist for 1-2 weeks post-op without additional stimulation. Electrophysiological mapping provides an important perspective on the contribution of these initial changes to long-term effects of chronic DBS.

Methods: Ten TRD patients were implanted using individualized DTI targeting methods (3). During awake intraoperative DBS testing, right and left sided SCC local field potentials (LFPs) were continuously recorded. Analyses compared (1) 60 sec pre-stim baseline; (2) 60s after consecutive 2-min stim trials at each of the 8 DBS contacts; and (3) 60s after repeated bilateral stimulation (2-5 min blocks at 130Hz, 60us, 6mA at the behaviorally confirmed target later used for chronic DBS) using power spectral density and a logistic regression classifier trained on predefined spectral features.

Results: Both analyses identified significant changes from baseline in left and right beta (20-30Hz) and right alpha (9-12 Hz) power. Classifier accuracy was significant for baseline versus bilateral stim ($n = 5$; $p < 0.0001$), but not for baseline versus post consecutive stim of all single contacts. HDRS scores one week after surgery showed a significant decrease relative to pre-op baselines (mean 41%; range 19-65%) with some residual effects out to 4 weeks (mean = 25% decrease). In addition, baseline beta power significantly correlated with baseline severity as measured with the HDRS ($n = 5$, $r = 0.91$, $p = 0.03$).

Conclusions: These findings demonstrate that bilateral SCC DBS during implantation surgery evokes rapid changes in neural dynamics and associated clinical effects that persist for several weeks. Beta band changes suggest a first candidate biomarker of emergent antidepressants effects measurable during chronic therapeutic DBS using longitudinal LFP recordings.

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UH3 NS103550-02; Hope for Depression Research Foundation. FDA IDE G130107; Clinicaltrials.gov NCT01984710

Disclosure: Abbott Labs, Consultant; Abbott Labs, Patent

Mini Panel

36. The Molecular Genetics of Neurodevelopmental Disorders: Insights From Diverse Animal Models

36.1 High-Throughput Behavior-Based Screens in Zebrafish Models of Autism Risk Genes

Abstract not included.

36.2 Animal Models to Understand Social Attachment Deficits in ASD

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Background: Social attachments play a central role in most, if not all, levels of human interaction, from parent-child attachment, friendship and social affiliation, to enduring partnerships with mates. Social attachment behaviors are clinically relevant, as devastating conditions such as autism spectrum disorders (ASD) and schizophrenia often manifest with a dramatic collapse of inter-personal interactions. It has been difficult to study social attachment because none of the traditional genetic lab model exhibits adult social attachment behaviors. Prairie voles, in contrast, display social attachment as adults such that mating partners form an enduring pair bond and display complex attachment behaviors, such as social monogamy and bi-parental care. Using the prairie vole as a model system 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 and environmental perturbations that correlate with the incidence of ASD affect the function of these circuits to disrupt social bonds.

Methods: Using CRISPR-mutagenesis, we have generated voles mutant for genes associated with ASD. Briefly, we have generated 2 alleles of Shank3 and 3 alleles of Scn2a, both genes whose mutation is highly associated with ASD. We have developed a battery of behavioral assays to determine phenotypes in attachment and non-attachment related behaviors that result from the mutation of ASD-associated genes (n = 8-10 per genotype/sex, WT vs mutant/gene, power = 0.8, alpha = 0.05). We have begun to characterize the deficts in pair bonding and adult social attachment behaviors in animals heterozygous for Shank3 and Scn2a null alleles in both sexes.

Results: We have identified deficits in social attachment behaviors that result from the heterozygous loss of Shank3 or Scn2a. We have identified male-specific deficits in pair bonding in voles heterozygous for Shank3 null alleles ($p < 0.05$), and deficits in social behavior in Scn2a mutants of both sexes. 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 social attachment behaviors.

Conclusions: Using parameterized behavioral characterization and molecular approaches to identify the neuronal populations involved in attachment behaviors, we can now begin to determine the specific deficits in attachment that result at distinct developmental stages from mutations in genes implicated in autism, and the differences in neuron populations and patterns of gene expression in distinct components of this circuitry.

Disclosure: Nothing to disclose.

36.3 Autistic-Like Behaviors and Atypical Brain Connectivity in SHANK3 Mutant Macaques

Abstract not included.

Panel

37. Identifying Cholinergic Mechanisms That Shape Striatal Dopaminergic Dysfunction in Psychosis

37.1 PET Measures of Presynaptic Vesicular Cholinergic Transporter in Schizophrenia as a Probe for Local Regulation of Dopamine in Striatum

Anissa Abi-Dargham, Stony Brook University, Stony Brook, New York, United States

Background: Multiple lines of evidence implicate the cholinergic system in schizophrenia: including the rate of smoking, postmortem, genetic and imaging studies. In addition to these, the

well-established observation that the nicotinic system regulates DA release in striatum, independently of DA cell firing, was most intriguing to us, due to the fact that our own data showed a dissociation of striatal vs. midbrain DA release. This dissociation suggested to us that local mechanisms in the striatum may be responsible for dysregulated DA release. In order to test this hypothesis, we examined indices of cholinergic transmission in the brains of patients with SCZ and matched healthy controls.

The ACh system in the striatum includes intrinsic striatal cholinergic interneurons (CINs), which form dense arborizations that are intertwined with dopaminergic terminals, allowing close interactions between these two systems. In cholinergic cells, ACh is loaded into presynaptic vesicles by the vesicular acetylcholine transporter (VAChT). The quantity of ACh stored and capacity for transmitter release are closely related to VAChT levels, and therefore VAChT imaging provides a measure of capacity for cholinergic transmission. Biophysical studies have shown that the amount of ACh stored per vesicle depends on the amount of VAChT expressed and that VAChT is likely rate limiting for ACh release (Prado, Bioch J, 2013). Therefore, VAChT imaging is a powerful tool for studying the capacity for cholinergic transmission.

Methods: We used a novel radiotracer for the VAChT, [18F]VAT. This tracer has better kinetic properties compared to previous tracers for this target. We have acquired preliminary PET data with [18F]VAT in n = 7 SCZ and n = 7 HC matched for age, gender, ethnicity, smoking and sociodemographic status of the parents. We measured volume of distribution, a correlate of vesicular transporter availability, and its relationship to psychosis.

Results: [18F]VAT VT: There were no group level differences in injected cold mass (HC = 1.01 ± 0.2 μg, SCZ = 1.12 ± 0.02 g, p = 0.22) or injected activity (HC = 3.82 ± 0.95 mCi, SCZ = 3.74 ± 0.62 mCi, p = 0.86). Group mean VT was higher in SCZ than HC in all striatal subdivisions. In associative striatum (AST) the effect size for the group difference is 0.75.

[18F]VAT VT relationship to psychosis: In the SCZ participants there was a strong relationship between hallucinations (PANSS positive p3) and [18F]VAT VT in the associative striatum and its subdivisions (in AST: r = 0.76 for P3 vs VT).

[18F]VAT VT in cortex: VT was lower in SCZ than HC but effect sizes were smaller than in striatum.

Conclusions: Despite the relatively small sample of patients and healthy controls we present here, the observations in this preliminary sample are compelling for the following reasons:

1-The topography of the VAChT expression changes coincide exactly with the topography of the dopamine dysregulation in the striatum, with a similar pattern of striatal vs. extrastriatal changes;

2-The relationship of striatal VAChT to psychosis symptoms adds internal validity;

3-ACh and DA are known to regulate each other in the striatum.

The data collection is ongoing and more definitive results will be presented at the meeting.

Disclosure: Nothing to disclose.

37.2 Probing Low Striatal Availability of the α7 Nicotinic Acetylcholine Receptor in Recent-Onset Psychosis Using [18F]ASEM PET

Jennifer Coughlin

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Background: Low availability of the α7 nicotinic acetylcholine receptor (α7-nAChR) in hippocampus in patients with recent-onset psychosis was found in our study using [18F]ASEM with positron emission tomography (PET). This finding builds on evidence of similar, low α7-nAChR distribution reported from study of postmortem hippocampal tissue, as well as in other brain regions in psychosis. Here we build on our initial focus on hippocampus, and investigate the striatum for low [18F]ASEM binding in individuals with recent-onset psychosis compared to healthy controls. Since we observed a difference in [18F]ASEM binding between patient subgroups in our earlier investigation of hippocampus, we also tested whether individuals with non-affective psychosis (NP) have lower [18F]ASEM binding in striatum compared to individuals with affective psychosis (AP).

Methods: Patients with recent (within five years) onset of psychosis and well-matched healthy controls (HCs) completed [18F]ASEM PET as well as neuropsychological testing and structural magnetic resonance imaging. Participants were non-smokers and, among patients, treatment was restricted to current monotherapy (lithium, atypical antipsychotic) or no medication. Total distribution volume (VT) in striatum was estimated from images after partial volume correction (PVC) using Logan analysis with metabolite-corrected arterial input function.

Results: A one-way ANCOVA revealed lower [18F]ASEM VT in striatum in patients compared to HCs after adjusting for age. There was no difference in [18F]ASEM VT in striatum in NP compared to AP. Secondary analysis without adjusting for age, or using [18F]ASEM VT in striatum that was derived from images without PVC did not change the results. Among patients, [18F]ASEM VT in striatum positively correlated with verbal memory and visual memory domains after adjusting for age. These partial correlations were not observed among HCs.

Conclusions: These [18F]ASEM PET data are consistent with low striatal α7-nAChR availability in patients with recent-onset psychosis compared to HCs, and lack of difference in striatal binding between NP and AP. The relationship to cognitive impairment and other clinical findings in psychosis warrants further investigation.

Disclosure: Nothing to disclose.

37.3 Cortical Afferents Expressing CB1 Receptors Control Accumbal Phasic Dopamine Release Caused by Selective Activation of Cholinergic Interneurons: Implications for Psychosis

Abstract not included.

37.4 Regulation of Striatal Dopamine Signaling by Muscarinic Acetylcholine Receptors: Implications for Treatment Different Symptom Domains in Schizophrenia Patients

P. Jeffrey Conn

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Background: Previous studies suggest that activators of M1 and/or M4 subtypes of muscarinic acetylcholine receptors (mAChRs) could provide a novel approach for improving multiple symptom clusters in schizophrenia patients. We have discovered highly selective positive allosteric modulators (PAMs) for M1 and M4 that could be used to understand the specific roles of each receptor and to advance to clinical testing for potential efficacy in schizophrenia patients. Exciting new studies provide insights into the mechanisms by which M1 and M4 regulate specific behavioral domains that are relevant for positive symptoms and motivational deficits in schizophrenia patients through specific effects on DA signaling in ventral and dorsal striatum.

Methods: We have used novel M1 and M4 PAMs in electrophysiology, fast scan cyclic voltammetry, genetic, optogenetic, and in vivo imaging, and behavioral approaches to develop an understanding of the specific roles of M1 and M4 in brain circuits involved in the pathophysiology underlying schizophrenia.

Results: We have established a novel mechanism in which M4 muscarinic receptors interact with the metabotropic glutamate (mGlu) receptor mGlu1 to selectively inhibit dopamine release in the dorsal striatum, but not ventral striatum (nucleus accumbens; NAc) or prefrontal cortex. This regional specificity allows targeting of mGlu1 to induce robust antipsychotic-like effects in rodent models, without inducing motivational deficits associated with reduced dopamine signaling in the NAc, or cognitive deficits associated with reduced dopamine signaling in the cortex. Interestingly, activation of M1 increases dopamine release in the NAc and directly activates D1-expressing medium spiny neurons in the NAc. Further, M1 PAMs induce robust increases in motivational responding in rodent models. Interestingly, we also found that some M1 PAMs can display stimulus bias and potentiate coupling of M1 to activation of phospholipase C without potentiating M1 activation of phospholipase D, and may have fundamentally different effects depending on whether they potentiate all or only a subset of signaling pathways that are activated by the M1 receptor.

Conclusions: Highly selective M1 and M4 PAMS may provide efficacy in treatment of different symptom domains in schizophrenia patients. M1 PAMs are now in phase I clinical development and M4 PAM clinical candidates are advancing to clinical testing to allow studies to assess potential efficacy in reducing symptoms in schizophrenia patients. Our new data reported here provide exciting new insights into the effects of M1 and M4 PAMs on dopamine signaling and related behaviors that may be relevant for treatment of positive symptoms and motivational deficits in these patients. In addition, our studies reveal specific properties of M1 PAMs that are required for maximizing efficacy while avoiding adverse effect liability.

Disclosure: Boeringer Ingleheim, Grant; Lundbeck, Grant.

Study Group

38. Artificial Intelligence as a Transformative Force for Research and Practice in Neuropsychiatric Disorders: A Realistic Aspiration or a Magical Fantasy?

Dilip Jeste*, John Torous, John Krystal, Ellen Lee, Martin Paulus, Sarah Lisanby, Michele Ferrante, Munmun De Choudhury, Ho-Cheol Kim

Study Group Summary: Artificial intelligence (AI) is omnipresent in modern life, what with Google, Alexa, social media, fitness monitors, and smart homes. However, we are far from routine adoption of AI in healthcare, especially for neuropsychiatric disorders. Morbidity and mortality in the mentally ill are high; yet there is a severe shortage of mental healthcare providers. AI could help identify high-risk individuals and provide scalable interventions to prevent or treat mental illnesses. The number of published studies using AI in neuropsychiatry is limited, but good examples of AI's use include electronic health records, brain imaging, sensor-based monitoring systems, and social media platforms, to predict, classify, or subgroup mental illnesses as well as problems like suicidal attempts. Machine learning technology can potentially transform neuropsychiatric research and practice through identification of patient-specific biomarkers, inform prognosis, facilitate early detection, enable better monitoring, help optimize pharmacotherapy, and uncover novel mechanisms and treatments. However, much of the published empirical literature is early proof-of-concept work rather than definitive.

The goal of this Study Group is to foster a discussion of major challenges in applying AI to neuropsychiatry and consider novel strategies to overcome them. Non-ACNP-member participants of the Study Group include researchers in mental health-related technology and ethics (JT), computational neuroscience (MF), social media (MDC), and technology and aging (EEL), along with IBM Co-Director of AI Center for Healthy Living (HCK). ACNP member participants (JK, DJ, SL, MP) bring computational psychiatry and neuroscience research perspectives. We will probe several issues.

(1) To discover new relationships between mental illness and latent variables using deep learning, very large datasets are needed. How do we ensure that these models are clinically interpretable and not a "black box"? How do we build a robust platform for data sharing across institutions?
(2) Clinically there are the challenges to integrating AI technology into practice. How will such technology fit into reimbursement systems? Will it only be available to a portion of the population, worsening inequality in healthcare? How do we address unique challenges to adopting AI in specific groups like older adults?
(3) Psychiatric practice can benefit from interactive AI that involves an agent like the IBM "debater" that is capable of human-machine adaptive dialogue. How do we use a reinforcement learning paradigm that keeps the history or memory of sequences of decisions and acts to improve symptoms?
(4) A major need in neuropsychiatric AI portfolio is designing AI algorithms that include a life-long learning framework, so that these are adaptable and build on their own knowledge instead of suffering 'catastrophic forgetting'. Just as a human becomes wiser with age, how can we help an algorithm develop "artificial wisdom" with time, building on its experiences and using them to inform future predictions?
(5) There are ethical considerations for using AI in neuropsychiatry. How to "trust" the algorithms that make important and sensitive inferences about a person's mental health? Who is liable in the case of errors? How can researchers harness social media on the population level to better characterize, prevent, and treat neuropsychiatric problems?

Disclosure: I am Co-Director of UCSD-IBM Center on Artificial Intelligence for Healthy Living (2018-2022). This is a grant to UCSD from IBM. However, I have no commercial interest in IBM or any other AI-related companies., Grant.

Study Group

39. Should MDMA and Psilocybin be Used for the Treatment of PTSD?

Eric Vermetten*, Rachel Yehuda, Rick Doblin, Michael Mithoefer, Ann Mithoefer, Matthew Johnson, Benjamin Kelmendi

Study Group Summary: Results of the early investigations with psychedelics in psychiatry were mixed, with studies often poorly designed. Due to class I scheduling in the 70's, research into the potential therapeutic use of these substances was halted, preventing definitive conclusions about whether or how these compounds might best be utilized. This study group will critically evaluate emergent research that has shed new light on the therapeutic possibilities of two compounds in the treatment of posttraumatic stress disorder (PTSD) and depression:

methylenedioxymethamfetamine (MDMA) and 4-phosphorloxy-N, N-dimethyltryptamine (psilocybin). Although the FDA has granted MDMA-assisted psychotherapy for PTSD and psilocybin for depression, breakthrough therapy status there are many questions about the efficacy, neurobiology, and exact use of these compounds in these disorders, which this study group will also address.

We will present the latest published and unpublished data from phase 2 trials, and supporting neuroscience observation pre and post-treatment for these increasingly hyped, but poorly understood treatments. It is now more important than ever for the ACNP community to have the facts and latest knowledge, as there is a growing interest by the public in psychedelic use for trauma related symptoms, including depression and anxiety, as evidenced by Michael Pollan's best-selling book "How to change your mind." Additionally, phase 3 trials are now in progress for both MDMA and psilocybin, so it is important to separate fact from fiction, and understand, if these compounds do work, how they work, and how this informs us about biological mechanisms of resilience.

Among the questions addressed:

1. What are the similarities and differences in the way MDMA and psilocybin act from a clinical perspective? Do these compounds produce similar psychological states? What are the underlying neurobiological correlates, as demonstrated by neuroimaging studies?
2. When in the course of a therapy might these compounds be indicated? Are they for treatment resistant conditions? Should they be first line treatments?
3. Must these therapies be utilized in the context of psychotherapy?
4. What types of psychotherapy are recommended with MDMA and psilocybin?
5. What are the dangers regarding the potential for abuse of these medications and in whom are these treatments contra-indicated?
6. How can emerging neurobiological data obtained before and after treatment with MDMA and psilocybin permit a reverse translation towards understanding molecular and brain circuits involved in recovery?

Brief presentations will occur to set the stage for the discussion. Dr. Michael Mithoefer will describe the results of phase 2 trials using MDMA assisted psychotherapy in PTSD. Annie Mithoefer will describe the psychotherapy used in connection with MDMA as well as other critical features of the approach. Dr Johnson will describe early data for psilocybin, and whether its consideration for depression makes it a good candidate for PTSD. Dr. Kelmendi will present fMRI data on MDMA and Dr Yehuda will dis cuss putative mechanisms of actions that underly effect of these compounds. They also will describe the data that resulted in their evolution from being extremely weary of these treatments to finding them the most promising therapies on the horizon for PTSD. Dr Doblin will discuss risk mitigation strategies for these drugs in the treatment of PTSD and depression.

Disclosure: Nothing to disclose.

Panel

40. Intersectional Neurobiology of Pain, Addiction & Negative Affect

40.1 Cell-Type-Specific Bidirectional Modulation of Pain-Related Behaviors in the Central Amygdala

Yarimar Carrasquillo

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Background: Maladaptive and adaptive experiences can strongly and bidirectionally shape how individuals perceive and respond to pain, amplifying or suppressing pain in both normal and pathological states. The neural and circuit mechanisms underlying the bidirectional control of pain remain largely unknown. Work over the last 15 years has demonstrated that the central nucleus of the amygdala (CeA) is a brain region that promotes hypersensitivity in pathological states. In a contradictory manner, earlier studies demonstrated that the CeA is an important locus for analgesia, promoting pain reduction secondary to stress or pharmacological manipulations. The mechanisms underlying these apparently dual and seemingly opposing functions of the CeA in pain modulation remain unknown.

Methods: The sciatic nerve cuff model of neuropathic pain was used in adult (8-16 week old) male Swiss-Webster, C57Bl/6NJ, Prkcd-cre, Sst-cre, Prkcd-cre::Ai9 or Sst-cre::Ai9 mice. The acetone test, Hargreaves test, von Frey filaments assay and Randall Selitto test were used to measure sensitivity to cold, heat, tactile and pinch stimulation of the hindpaw, respectively. Paw responses to the different stimuli were measured 1-2 weeks after the sciatic nerve surgery. Multidisciplinary approaches that included cfos and pERK immunostaining ($n = 4$ mice per group), chemogenetics ($n = 4$-7 per treatment) and slice electrophysiology ($n = 5$-21) were used to evaluate the contribution of CeA cell types to pain-related behaviors.

Results: In all mice, cuff implantation in the sciatic nerve induced robust ($p < 0.000$; t-test) cold, heat and tactile hypersensitivity in the paw ipsilateral to nerve treatment. To determine which cell types in the CeA are activated by pain, we focused our experiments on cells expressing either protein kinase C delta (CeA-PKCδ) or somatostatin (CeA-Som) because these constitute the majority of CeA neurons and represent largely non-overlapping populations. Immunostaining for pERK and c-Fos following nerve injury demonstrated that nerve injury-induced pERK and c-Fos was preferentially localized to CeA-PKCδ neurons. Consistently, ex-vivo electrophysiological experiments in acute amygdala slices demonstrated significant ($p < 0.001$; two-way ANOVA) increases in the excitability of CeA-PKCδ neurons following cuff implantation, compared to sham treatment. Experiments using chemogenetic manipulations of CeA-PKCδ neurons demonstrated that activation of these cells is both necessary for and sufficient to promote increases in pain-related behaviors. In marked contrast to the CeA-PKCδ neurons, sciatic nerve cuff implantation resulted in significant ($p < 0.05$; chi-square test) silencing of neuronal activity in CeA-Som cells and chemogenetic manipulations revealed that activation of these CeA cells is both necessary for and sufficient to promote suppression of pain-related behaviors.

Conclusions: Our experiments uncovered that the CeA can function as a pain rheostat, amplifying or suppressing pain-related behaviors in mice. The dual and opposing function of the CeA is encoded by opposing changes in the excitability of CeA-PKCδ and CeA-Som neurons. Together, these results demonstrate that the CeA can amplify or suppress pain in a cell-type -specific manner, uncovering a previously unknown mechanism underlying bidirectional control of pain in the brain.

Disclosure: Nothing to disclose.

40.2 Neurobiological Mediators of Hyperalgesia After Chronic Alcohol & Chronic Morphine

Nicholas Gilpin

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Background: Chronic alcohol and opioid use lead to heightened pain states and exacerbation of pre-existing pain states. This is problematic because individuals are prescribed opioid drugs to treat pain and they self-medicate pain with opiates and alcohol. Chronic opiates or alcohol leads to neuroadaptations that produce hyperalgesia in absence of drug. We are working to identify neurobiological mediators of hyperalgesia in rats chronically exposed to alcohol or morphine, with a focus on limbic forebrain and midbrain circuits important for mediating affective components of pain and descending modulation of pain.

Methods: We hypothesized that chronic alcohol and chronic morphine each produce neuroadaptations in central amygdala (CeA) and periaqueductal gray (PAG) that contribute to hyperalgesia after removal of drug. We used adult male Wistar rats to test the effects of chronic intermittent high-dose alcohol (>6 weeks of alcohol vapor exposure) or chronic morphine (7 days of 20 mg/kg/day, s.c.) on thermal nociception, synaptic physiology in PAG, and adaptations in melanocortin protein expression in CeA and PAG. We also tested the effects of site-specific pharmacological and circuit manipulations on pain-like outcomes in animals that underwent the same exposures. Power analysis was used to determine the number of animals required for each experiment ($n = > 8$/group) to provide >80% power to detect appropriate effect sizes at a significance level of $p<0.05$.

Results: Alcohol dependence produced thermal hyperalgesia during withdrawal ($F(1,30) = 46.26$, $p < 0.01$), reduced light-evoked IPSC amplitude from CeA terminals onto ventrolateral PAG (vlPAG) neurons ($t(29) = 2.255$, $p = 0.03$) and reduced melanocortin-4 receptor (MC4R) expression in CeA ($t(14) = 2.60$, $p = 0.02$). Alcohol withdrawal thermal hyperalgesia was rescued by MC4R antagonism in CeA ($F(1,18) = 10.04$, $p < 0.01$) and also by CeA-PAG circuit stimulation ($F(1,28) = 5.13$, $p = 0.03$). Activation of MC4Rs in CeA induced hyperalgesia ($F(2,15) = 9.05$; $p < 0.01$) that was blocked by mu-opioid receptor (MOR) activation in vlPAG ($F(3,44) = 25.16$, $p < 0.01$), and a MOR agonist suppressed inhibition onto vlPAG neurons ($t(10) = 4.28$, $p < 0.01$). Chronic morphine produced thermal hyperalgesia during withdrawal that was reversed by intra-vlPAG infusions of a MOR agonist ($F(4, 36) = 13.64$, $p < 0.01$), and this effect was antagonized by co-infusions of a cannabinoid type-1 receptor (CB1R) positive allosteric modulator (PAM; $F(5,45) = 1.07$, $p = 0.39$). In the vlPAG slice, morphine withdrawal hyperpolarized neurons ($t(58) = 2.36$, $p = 0.02$) and trended to reduce the frequency of spontaneous inhibitory postsynaptic current (sIPSC) events relative to controls ($t(76) = 1.84$, $p = 0.07$). A MOR agonist suppressed inhibition onto vlPAG neurons ($F(3,59) = 3.28$, $p = 0.03$) and this effect was blunted by pre-application of a CB1R PAM (correlation between DAMGO eIPSC relative amplitude and GAT211 dose in the bath: $R = 0.29$, $p = 0.02$).

Conclusions: Our results suggest that 1) chronic alcohol & chronic morphine each produce hyperalgesia during withdrawal and overlapping but not identical plasticity in vlPAG signaling, and 2) intra-vlPAG DAMGO infusions rescue morphine withdrawal hyperalgesia and suppress inhibition onto vlPAG neurons, and these effects are blunted by a CB1R PAM.

Disclosure: Glauser Life Sciences, Inc., Stock / Equity.

40.3 A Novel Midbrain to Amygdala Anti-Nociceptive Circuit

Thomas Kash

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Background: Chronic pain and drug abuse are comorbid disorders that manifest with differing prevalence and severity in males and females. A mechanism that explains sex-specific pain and drug interactions has yet to be identified. Recent evidence from our lab suggests that dopaminergic neurons of the ventrolateral periaqueductal grey (vlPAGDA+) contribute to the anti-nociceptive effects of morphine and alcohol use.

Methods: We used a combination of chemogenetics, optogenetics, viral based gene deletion and calcium imaging in awake behavior animals to assess causal roles of this vlPAG circuit in pain related behaviors. We used optogenetic assisted circuit mapping to probe cellular mechanisms.

Results: Following up on these studies, we found that activation of vlPAGDA+neurons to a primary output region, the bed nucleus of the stria terminalis (BNST), relieves thermal and mechanical nociception in males but not females. This effect persists during pathological pain, with vlPAGDA+/BNST activation attenuating heightened pain sensitivity in males following treatment with the inflammatory agent Complete Freund's Adjuvant (CFA). Preliminary studies on the physiological properties of this pathway show a notable sex difference in inhibitory transmission to vlPAGDA+ neurons following morphine application, as well as divergences in DA release and local connectivity of vlPAGDA+ terminals in the BNST. Downstream of vlPAGDA+ neurons, we examined a population of pain- and drug-sensitive corticotropin releasing factor (CRF) neurons in the BNST. Genetic deletion of CRF from the BNST reduces thermal and mechanical nociception and exacerbates escalations in alcohol consumption without altering pain-related affect and anxiety-like behaviors in male and female mice. In vivo miniscope calcium imaging of BNSTCRF+ neurons further reveal robust and synchronized recruitment of these neurons during acute exposure to pain and alcohol in both sexes

Conclusions: Taken together, these findings support the notion that vlPAGDA+ and BNSTCRF+ neurons differentially contribute to sex-specific interactions of pain and drug use. This knowledge will be informative for future approaches to treating chronic pain and drug abuse, as it identifies new morphine- and alcohol-sensitive mechanisms that are capable of attenuating pain in both a sex-dependent and -independent manner.

Disclosure: Nothing to disclose.

40.4 Developing TMS as a Tool to Decrease Pain and Promote Opiate Sparing: Orderly Evaluation of Three Potential Cortical Targets

Colleen Hanlon

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

Background: Effective control of chronic pain is a top priority in the United States, as approximately 10% of adults have severe chronic pain. However, despite the advances in neuroscience over the past 20 years, we still largely treat chronic pain with opiate narcotics. Now, through the use of non-invasive transcranial magnetic stimulation (TMS), there is an emerging body of work suggesting it may be possible to dampen pain and promote opiate-sparing in patients with chronic pain. Currently, there is literature supporting several possible neural targets for TMS-based interventions for chronic pain: the primary motor cortex (PMC), the dorsolateral prefrontal cortex (DLPFC), and the medial prefrontal cortex (MPFC). Until recently however, there has not been an orderly and comparative evaluation of these targets (target engagement), followed by a biologically-informed, double-blind sham controlled clinical trial.

Methods: We have completed 2 clinical trials, and are currently conducting a third trial evaluating the optimal TMS strategy for

dampening pain and decreasing demand for opiates among chronic pain patients. First, we conducted an early Phase 2 trial comparing the efficacy of 10 days of PMC versus DLPFC TMS (110% motor threshold, 10Hz) on pain in chronic pain patients currently using prescription opioids (NCT03319138, n = 30). Next, for the first time we evaluated the MPFC as a potentially fruitful TMS target (given its structural and functional connectivity to the cingulate cortex and insula – nodes of the Pain network. In this 'target engagement' study we quantified the effect of a single session of DLPFC versus MPFC TMS on the brain response to pain using functional MRI (NCT03681769, n = 60).

Results: The initial Phase 2 study demonstrated that DLPFC stimulation was more effective at attenuating limbic aspects of pain than PMC stimulation, but the subsequent target engagement study demonstrated that the probability of responding to DLPFC TMS was not different from sham ($\chi 2 = 0.667$, $p = 0.41$). In contrast the probability of responding to MPFC was significantly greater than sham (($\chi 2 = 20.17$, $p = 0.0001$). Finally, as a logical extension of these studies, we will present the results of an interim analysis of an ongoing Phase 2 trial (NCT03576781), which is evaluating the relative efficacy and durability of 24 sessions of DLPFC versus MPFC TMS (2x/day, 12 days) as tools to decrease subjective pain ratings and demand for opiates (measure via delayed discounting).

Conclusions: Considered together this body of work suggests that TMS to the DLPFC is likely more effective at attenuating pain than PMC stimulation for individuals with chronic pain, but the MPFC may also be a novel, biologically-informed treatment strategy for this population – which is currently underserved by existing pharmacotherapeutic approaches.

Disclosure: Nothing to disclose.

Panel

41. Responses to the Opioid Epidemic: Government, Industry and Academic Perspectives

41.1 Diversity of "Bias" in Developing MOR Agonists

Laura Bohn

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Background: Genetic models of mice lacking Barrestin2 show an improved therapeutic profile in response to morphine, wherein the development of tolerance and respiratory suppression were significantly limited. This spawned the interest in developing MOR agonists that could continue to signal through G protein signaling pathways yet avoid the recruitment of Barresitn2. Some compounds have progressed to clinical development. However, while cell-based signaling assays may reveal a separation between the two pathways, it remains unclear whether divergence in signaling persists in vivo downstream of activation by these agonists.

Methods: We have developed a series of agonists that preferentially activate MOR to signal through G protein pathways over recruiting Barrestins and have compared these compounds across diverse signaling assays in cell-based assays. We have also looked for an interaction between these compounds and conventional opioid therapeutics, both in cells and in mice.

Results: We find that while two compounds may look like similarly biased agonists based on the comparison between two signaling assays (i.e. they may both stimulate G protein signaling and not recruit Barrestin2), however, the two compounds can fundamentally differ on how they interact with the receptor to produce downstream responses and adaptations in cells and in mice. In behavioral studies, we find that some of the biased MOR agonists are competitive with morphine-induced behavioral responses, while other classes of biased MOR agonists are additive with morphine-induced behaviors.

Conclusions: These findings emphasize that compounds cannot be uniformly grouped as "biased" based on how they perform in a few cellular assays and that temporal and contextual factors will contribute to how the ligand will ultimately perform in vivo. Further evaluation of endogenous opioid receptor signaling, modulation and adaptation will be essential for future drug development efforts.

Disclosure: Goldfinch, Bio, Consultant.

41.2 NIDA as Catalyst: Facilitating a Pipeline of Next Generation Treatments to Address the Opioid Crisis

Kurt Rasmussen

NIDA, Bethesda, Maryland, United States

Background: The rampant misuse of opioid drugs (both prescribed and illegal) in America, now known as the Opioid Crisis, has had grave effects on both the public health and the well-being of our society. The National Institute on Drug Abuse (NIDA) is pursuing creative ways to serve as a catalyst to speed the development of novel treatments for Opioid Use Disorder (OUD) and opioid overdose.

Methods: In pursuit of this goal, NIDA is leveraging multiple resources, including awarding non-dilutive funds via cooperative granting opportunities, conducting preclinical and clinical studies on a contract basis, and serving as consultants to both private and public sector entities for the development of novel small and large molecules, devises, and psychosocial treatments for OUD and overdose. Toward this end, a streamlined grant funding opportunity has substantially reduced the time from application to funding decision and has generated substantial interest from both the public and private sectors.

Results: Thus far, these efforts have facilitated a pipeline of novel treatments representing the full spectrum of treatment development from early preclinical to Phase III testing. The non-confidential component of this pipeline will be presented.

Conclusions: Preclinical development projects to be highlighted include GPR151 antagonists, mu/delta opioid receptor heterodimer agonists, and fentanyl monoclonal antibodies and vaccines. Clinical phase projects include trials of guanfacine, ketamine, suvorexant, and tDCS augmentation of buprenorphine and CBT. In addition, the development of longer-acting implant and sustained-release injection formulations of FDA-approved medications (e.g., buprenorphine and naltrexone) and, for the treatment of opioid overdose, the development of a nasal spray containing nalmefene, a longer acting alternative to naloxone will be discussed.

Disclosure: Nothing to disclose.

41.3 The Heal Initiative: NIH's Role in Responding to the Opioid Epidemic

Abstract not included.

41.4 ITI-333: An Investigational Drug for the Treatment of Opioid Use Disorder

Kimberly Vanover
Intra-Cellular Therapies, Inc., New York, New York, United States

Background: New approaches to the treatment of opioid use disorder (OUD) are needed. ITI-333 is an investigational new drug in development that is predicted to ease the somatic symptoms of

opioid withdrawal while mitigating the dysphoria and psychiatric comorbidities of mood and anxiety disorders that drive opioid abuse. ITI-333 combines high affinity binding (Ki < 50 nM) to three receptors that individually have been associated with treatment of substance use disorders and psychiatric comorbidities, functioning as a biased mu opioid (MOP) ligand with partial agonist activity, a serotonin 5-HT2A receptor antagonist and dopamine D1 receptor antagonist.

Methods: The behavioral pharmacology and safety profile of ITI-333 was characterized using in vivo preclinical models including reversal of DOI-induced head twitch to assess functional activity as a 5-HT2A receptor antagonist, morphine-induced hyperactivity to assess functional activity as a MOP partial agonist, a battery of analgesic assays to assess effects on acute and neuropathic pain, a battery of assays to assess effects on opioid dependence and withdrawal, self-administration to assess potential for abuse liability, gastrointestinal motility and pulmonary function assays to assess potential MOP-mediated side effects.

Results: ITI-333 blocked DOI-induced head twitches in mice (EC50 = 0.44 mg/kg PO) indicating strong functional activity as a 5-HT2A antagonist. ITI-333 (0.1 mg/kg SC) attenuated hyperactivity induced by morphine (32 mg/kg SC) in mice without significant effects on spontaneous locomotor activity. In mice, ITI-333, alone (0.01-1 mg/kg SC; $p < 0.05$; 1-10 mg/kg PO; $p < 0.05$), produced naloxone-sensitive analgesia in the tail flick assay, while ITI-333 (0.3-3 mg/kg SC; $p < 0.05$) attenuated morphine (5 mg/kg SC)-induced analgesia. Moreover, in a rat model of diabetic neuropathy, ITI-333 (1-10 mg/kg SC; $p < 0.05$) dose-dependently attenuated cold, tactile, and mechanical allodynia. In drug abuse assays, ITI-333 (0.3-3 mg/kg SC; $p < 0.0001$) dose-dependently suppressed the somatic and behavioral signs of opioid withdrawal precipitated by naloxone injection in oxycodone-dependent mice. Chronic (28 day q.d. treatment) of ITI-333 (0.3 or 3mg/kg SC) did not result in tolerance or physical dependence in rats. ITI-333 was not self-administered IV by heroin-maintained rats (0.003-0.01 mg/kg/inj) or rhesus monkeys (0.01-0.1 mg/kg/inj). Acute doses of ITI-333 (0.3 or 3 mg/kg SC) did not induce GI or pulmonary side effects in rats.

Conclusions: In summary, preclinical evidence supports a role for ITI-333 in mitigating symptoms of opioid withdrawal and supports its potential as a treatment for OUD and pain. First-in-human clinical studies to evaluate the safety and pharmacokinetics of ITI-333 are planned.

Disclosure: Intra-Cellular Therapies, Employee.

Panel

42. Molecular and Neural Mechanisms of Risk and Resilience in Neuropsychiatric Disorders of Aging

42.1 Synaptic Resilience to Psychosis in Alzheimer's Disease

Abstract not included.

42.2 Enhanced Molecular Senescence Changes in Major Depression and its Links With Structural Brain Changes, Cognitive Impairment, and Medical Morbidity Across Lifespan

Breno Diniz

Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Background: There is growing evidence that the biological mechanisms of depression significantly overlap with those observed during the aging process, leading to an acceleration of brain and systemic aging in depressed individuals. We will present recent data supporting that molecular senescence changes (I.e. SASP index) are linked with microstructural brain changes, cognitive impairment, and medical comorbidities in individuals with major depression across the lifespan. We will also show additional data demonstrating have increased expression of senescence markers p16INK4a in the prefrontal cortex and hippocampus of mice under mild chronic stress model.

Methods: We included subjects from both sexes from different ongoing cohorts of young and middle-aged subjects (NESDA cohort [Netherland Study of Depression and Anxiety], n = 1156) and older adults with major depression (LLD cohort, n = 111). The SASP index biomarkers were measured in the plasma. We also analyzed the expression of p16INK4a in the brain tissue (I.e. prefrontal cortex and hippocampus) of 2 month old mice under mild chronic stress (i.e., 3 days, 3 weeks, and 5 weeks).

Results: Subjects with major depression had increased SASP index when compared to healthy controls in both cohorts ($p < 0.001$). In older adults, SASP index was associated with worse neurocognitive performance in executive function ($p = 0.004$) and processing speed ($p < 0.001$) domains. Finally, SASP index was associated with higher mean diffusivity (MD) in the left and right cingulate bundle, after controlling for age and cognitive performance ($p = 0.02$ and $p = 007$, respectively). In young and middle-aged adults, the association between molecular senescence and major depression was significantly moderated by metabolic status (depression*overweight interaction, $p = 0.027$), with those with major depression and overweight having the highest SASP index scores compared to other groups ($p < 0.001$). Finally, we showed that young mice under mild chronic intermittent stress had a significant increase in cellular senescence marker p16INK4a in the pre-frontal cortex and hippocampus ($p < 0.001$, respectively). Increased expression of the p16INK4a occurs as early as after 3 days of stress and are sustained over the course of 5 weeks.

Conclusions: Our results demonstrate that MDD is associated with enhanced molecular senescence changes across the lifespan. Molecular senescence changes in MDD are significantly moderated by medical comorbidities, especially metabolic disorders like overweight/obesity. Also, they can be mechanistically linked to neurocognitive impairment (e.g., executive dysfunction and slower processing speed) and microstructural brain changes in critical circuits related to these cognitive domains. Finally, the dysregulation of senescence-related biological cascades can provide a molecular link between depression and accelerated brain and systemic aging across the lifespan.

Disclosure: Nothing to disclose.

42.3 Multi-Modality Imaging of Neurodegeneration in Late Life Cognitive Decline and Depression

Gwenn Smith

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

Background: Molecular imaging methods to visualize the neuropathology of Alzheimer's disease (AD) in vivo provide an unprecedented opportunity to understand the neuropsychiatric (NPS) and cognitive symptoms observed in early stage AD by testing hypotheses informed by human neuropathology and animal models. A fuller understanding of the neurobiology of early AD and its clinical progression is essential to identify individuals at risk and to identify targets for prevention and treatment. To maximize the benefit from disease-modifying therapies, individuals must be identified and treated in the early stages, including mild cognitive impairment (MCI). Only by doing so, is it possible to

prevent progressive spreading of neuropathology and emergence of cognitive deficits and NPS.

Methods: Magnetic resonance imaging (Phillips 3T Achieva) and multi-radiotracer high resolution positron emission tomography (HRRT) scans of Tau ([18F]--T807; beta-amyloid (Aβ [11C]-PiB) and serotonin transporter binding (5-HTT [11C]-DASB) were performed in amnestic, multi-domain, MCI (aMCI-MD; n = 53) and cognitively normal elderly (n-46).

Results: In aMCI-MD, progressive, cortical and limbic serotonin degeneration was observed, linked to network dysfunction, that was greater and more widespread than cortical Aβ, cerebral atrophy or cerebral blood flow deficits (5-HTT differences significant at a cluster-level $p \leq 0.001$ (FDR corrected) and peak voxel-value of $p \leq 0.001$ (uncorrected) and extent threshold (k) = 50 voxels). Cortical and limbic serotonin degeneration was a more powerful predictor of cross-sectional and longitudinal memory impairment than Aβ (likelihood ratio test $p < 0.001$).

Conclusions: In vivo imaging of 5-HTT combined with Tau and Aβ, may represent a powerful predictor of cognitive decline and emergence of NPS. Elucidating the role of 5-HT in relation to Tau and Aβ in cognitive decline in aMCI-MD will have fundamental implications for the design of prevention and intervention studies targeting serotonin and studies of other neurotransmitters vulnerable to neurodegeneration (norepinephrine).

Disclosure: Nothing to disclose.

42.4 Biomarkers of Treatment Response to Memantine Combination With Escitalopram in Geriatric Depression With Subjective Cognitive Impairment

Helen Lavretsky

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

Background: Geriatric depression is frequently accompanied by subjective memory complaints, thus increasing risk for dementia. New treatment strategies targeting both depression and cognition are urgently needed. We examined biomarkers and predictors of response to the combined memantine and escitalopram can improve mood and cognitive outcomes in geriatric depression.

Methods: We conducted a 6-month double-blind placebo-controlled trial to assess the efficacy and tolerability of escitalopram + memantine (ESC/MEM) compared to escitalopram + placebo (ESC/PBO) in geriatric depression and subjective memory complaints with 12-month follow up (NCT01902004). Remission was defined as HAM-D scores of <6 at 6 months. We collected FDDNP PET at baseline and multimodal MRI and gene expression at baseline and follow up to examine biosignatures of treatment response in geriatric depression.

Results: Of the 97 randomized participants, 65 completed the study. Dropout and tolerability did not differ between treatment groups. Remission rate in ESC/MEM group was 69.7% compared to 51.7 % in ESC/PBO group ($\chi2(1) = 2.0$, $p = 0.15$). Both groups improved significantly in depressive symptoms on the HAM-D during follow up. At 6 months, MADRS scores ($F(1,57) = 6.5$, $p = 0.01$) and HAM-A scores ($F(1,57) = 4.2$, $p = 0.04$) improved greater in ESC/MEM vs. ESC/PBO. At 12 months, the ESC/MEM group improved greater in delayed recall ($F(2,82) = 4.3$, $p = 0.02$) and executive functioning ($F(2,82) = 5.1$, $p = 0.01$) compared to ESC/PBO. Frontal lobe [18F]FDDNP binding was associated with improvement in executive functions at 6 and 12 months Gene expression pathways related to immune response and cellular proliferation were enrichment following EsCIT-PBO treatment, while EsCIT-MEM treatment involved upregulation of chromatin remodeling and factors related to maintaining cellular pluripotency.

Conclusions: Our results indicate that the combination of memantine with escitalopram was well-tolerated and more effective compared to escitalopram and placebo in reducing severity of depression and anxiety at 6 months and improving cognitive outcomes at 12-month follow-up in older adults with major depression and subjective memory complaints. Our results suggest that gene expression and [18F]FDDNP binding may serve as relevant biomarkers predictive of clinical and cognitive response with antidepressant treatment, and provide insight into underlying mechanisms of response.

Disclosure: Allergan, Grant.

Mini Panel

43. Novel Mechanisms by Which Maternal Signals During Sensitive Periods Impact the Developing Brain: Neuro-Inflammation, Neuronal Circuits and Vulnerability to Mental Illness

43.1 Maternal Infection and Depression and Fetal Brain Development: Evidence for Sex-Dependent Effects on the Fetus and Placenta of Maternal Inflammation and HPA Axis Activation

Robert Freedman

University of Colorado at Denver, Aurora, Colorado, United States

Background: Epidemiological studies found that mothers' infection and depression both have long-lasting effects on the unborn child, including increased risk for schizophrenia and autism later in life. The mechanism of these effects when infection and depression converge, as they do frequently, has not been investigated in prospective studies.

Methods: Pregnant women (N = 172) were studied from 15 weeks gestation with periodic ratings of infection and depression. Blood levels of cytokines and C-reactive protein (CRP) were analyzed at 16 weeks, and cortisol and cortisone were analyzed in maternal hair at 28 weeks and in fetal hair at birth. Maternal hair integrates maternal cortisol levels from the past 10 weeks; the child's hair at birth integrates fetal corticosteroid levels from the last 12-14 weeks gestation. At 1-month of age, auditory P50 evoked potential inhibition to repeated stimuli was recorded from the newborn to assess fetal development of neuronal inhibition. The Infant Behavioral Questionnaire (IBQ-R) was assessed behavior at 1 years. Male and female offspring were analyzed separately.

Results: By 16 weeks' gestation, 40% of women had experienced an infection, generally respiratory or genito-urinary; both have been associated with later offspring mental illness. Infection increased stress and depression ($d' = 0.52$) and elevated maternal CRP ($d' = 0.48$) and IL-6 ($d' = 0.44$) levels. Increased CRP levels adversely affected the development of neuronal inhibition in male fetuses ($\beta = 0.40$). This effect did not occur in females.

Depression was associated with activation of the maternal HPA axis, measured by increased levels of cortisol in her hair. Cortisol inhibits neuronal development in vulnerable areas like the hippocampus, but the placenta enzyme 11β-Hydroxysteroid dehydrogenase-2 (11BHSD2) detoxifies cortisol to cortisone. In the babies of mothers who had not experienced infection earlier in gestation, maternal cortisol correlated with cortisone in baby's hair at birth ($\beta = 0.39$), indicating that their placentas had detoxified the mother's cortisol. However, if the mothers had experienced infection, maternal cortisol correlated significantly

with cortisol in baby's hair (β = 0.80). Increased levels of fetal cortisol are correlated with decreased development of newborn P50 response inhibition. However, opposite to the increased sensitivity to inflammation in males, it is the females who are more sensitive to cortisol (β = −0.32) than the males.

Effects of both maternal inflammation and hypercortisolemia persisted in 1-year IBQ-R behavior measurements.

Conclusions: Stress and infection are both linked in animal models to inflammation of the placenta, to decreased levels of 11BHSD2, and to problems in fetal brain development. This prospective study demonstrates in humans the effects on fetal development of neuronal function in early gestation, when inhibitory neurons are first differentiating, of both inflammation and of decreased placenta detoxification of cortisol. Effects of inflammatory peptides and cortisol depended upon the sex of the fetal-placental unit. Both maternal inflammation and HPA-axis activation contribute to decreased development of neuronal inhibition, childhood behavior problems, and potentially are first steps in the pathogenesis of future mental illnesses.

Disclosure: Nothing to disclose.

43.2 Mother's Stress During Pregnancy and Childhood Maltreatment Affect the Next Generation: Placental DNA Aging, Fetal Functional Brain Connectivity, and Behavior

Catherine Monk

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

Background: Increasingly, neuropsychiatric disorders are considered neurodevelopmental in etiology. Maternal prenatal distress may contribute by altering children's brain development and mental health trajectories. Earlier birth is a primary outcome predicting future neurodevelopmental risk; males are more vulnerable to both. Maltreatment also is a risk factor for developing psychopathology, yet little is known about how mother's maltreatment as a child may be transmitted across generations. In addition, no studies to date have used fetal brain imaging to examine these influences.

Methods: Two samples of healthy pregnant women were studied (A) N = 184, ages 18–45 at Columbia University Medical Center in New York; (B) N = 60, ages 18-38 at Wayne State University in Detroit. During the 3rd trimester, both cohorts self-reported stress levels (Perceived Stress Scale); group A underwent fetal neurobehavioral testing and placenta collection; group B answered questions on their own childhood maltreatment (CM) (The Childhood Trauma Questionnaire) and underwent functional MRI during pregnancy to scan the fetal brain. Birth outcome data was derived from medical records. Fetal movement (FM) and fetal heart rate (FHR) were obtained using a Toitu MT 325 fetal actocardiograph via a single transabdominal Doppler transducer. The cross-correlation of FM/FHR (coupling), an index of CNS development reflecting the coordination of somatic and ANS systems that increases over gestation, was calculated. Methylation of placental tissue (DNAm) was analysed using 450K Beadchips and bisulfite sequencing (Illumina) and Mayne's approach to calculating DNAm epigenetic age (vs chronological age) based on 62 CpG sites. Bilateral amygdala masks were used as ROI to conduct ROI-to-voxel functional connectivity analyses.

Results: In sample A, accelerated epigenetic aging in the placenta (Delta = DNAm age – chronological gestational age) predicted early birth age and lower birth weight only in male offspring (p = 0.004 and 0.012 respectively). Maternal stress was positively associated with fetal coupling behaviors (r = 0.32, p = 0.05); In sample B, controlling for current stress, maternal childhood trauma predicted greater inverse connectivity of the amygdala with frontal areas (orbitofrontal cortex, left ventrolateral prefrontal cortex, right ventromedial prefrontal cortex (the adult pattern), ps < 0.01) and greater positive connectivity with the right medial and lateral temporal lobe (ps < 0.5).

Conclusions: These studies are among the first to relate pregnant women's experiences of stress and preceding childhood maltreatment with accelerated placenta aging associated with earlier birth, fetal behavior reflecting advanced CNS development, and alterations in functional fetal brain connectivity of emotion regulation systems. Taken together, these data are consistent with hypotheses of prenatal adaptation to maternal intrauterine signals forecasting a threatening postnatal environment. This prenatal programming may predispose infants and children to risk because of a mismatch between the prenatal and postnatal contexts.

Disclosure: Nothing to disclose.

43.3 Patterns of Maternal-Derived Signals Influence the Maturation of Developing Brain Circuits Across Species, With Significant Impact on Mental Health

Abstract not included.

Panel

44. Orbitofrontal Cortex Representation, Function, and Collaboration in Decision Making

44.1 Cortico-Limbic-Striatal Networks for Reward Value Encoding and Retrieval

Melissa Malvaez

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Background: The value of an anticipated rewarding event is a crucial element in the decision to engage in its pursuit. The encoding and retrieval of this, typically, state-dependent incentive information is, thus, vital for adaptive behavior. Dysfunction in this process will lead to aberrant reward pursuit and ill-informed decision-making— cognitive symptoms that characterize myriad psychiatric diseases. The basolateral amygdala (BLA) is required for encoding and retrieving a reward's incentive value, but the neural circuitry through which it achieves this function is unknown.

Methods: To identify the specific cortical afferent contributors, we used chemogenetic and optogenetic approaches in male rats to bidirectionally modulate the activity of lateral or medial orbitofrontal cortex (OFC) projections to the BLA during the encoding and retrieval of the state-dependent incentive value of a palatable food reward. Intersectional chemogenetics was used to manipulate BLA projections to the dorsal and ventral striatum to identify the BLA cells that regulate these processes.

Results: Activity in lateral OFC to BLA projections was found to be both necessary ($F(2,26) = 5.06$, $P = 0.014$) and sufficient ($F(2,24) = 9.25$, $P = 0.001$) for encoding of a positive change in a reward's value, but not for subsequent retrieval of this information. Conversely, projections from the medial OFC were not required for incentive learning, but were found to be necessary ($F(2,25) = 9.81$, $P = 0.0007$) and sufficient ($t(15) = 3.62$, $p = 0.003$) for retrieval of a reward's value from memory to drive reward-pursuit actions. These projections were also found to support the encoding ($F(1,14) = 7.69$, $P = 0.015$) and retrieval ($F(2,20) = 4.18$, $P = 0.031$) of stimulus-reward memories. BLA neurons projecting to the nucleus accumbens (NAc) were found to be required for both positive reward value encoding and for value-guided reward seeking.

Conclusions: These data demonstrate that the BLA participates in both the encoding and retrieval of state-dependent reward memories and that it is supported in these functions by input from the OFC. BLA projections to the NAc convey this information to the ventral striatal networks that motivate reward pursuit decisions. These data reveal the cortico-limbic-striatal neural circuitry required for adaptive reward valuation and pursuit and provide insight into the dysfunction in these processes that characterizes myriad psychiatric diseases.

Disclosure: Nothing to disclose.

44.2 Medial Orbitofrontal Cortex Regulation of Different Forms of Risk/Reward Decision Making

Stan Floresco

University of British Columbia, Vancouver, Canada

Background: The medial orbitofrontal cortex (mOFC) has been implicated in refining action selection, particularly in situations requiring decisions about rewards that vary in terms of magnitude and uncertainty. Studies in humans and animals indicate that mOFC dysfunction is associated with maladaptive patterns of risk/reward decision making and altered sensitivity to response feedback when decisions are guided by internal representations of reward contingencies. The mOFC shares reciprocal connections with both the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC; homologous to Area 32 of the human anterior cingulate), yet how these distinct subcortical and cortical mOFC circuits may differentially contribute to these types of decisions is unclear. Moreover, there is a dearth of preclinical studies investigating how the mOFC influences decisions guided by external cues that inform about the likelihood of obtaining rewards.

Methods: We dissected the contribution of the mOFC and its cortical/subcortical circuits in the mediation of two distinct forms of risk/reward decision making, wherein well-trained rats chose between small/certain rewards or larger rewards delivered in a probabilistic manner. Decision making guided by internal representations of reward history was measured using a probabilistic discounting task, where the odds of obtaining larger rewards changed systematically over a session. Cue-guided decision making was probed with a novel "Blackjack" task that more closely resembles assays used with human subjects. Here, rather than being guided by reward history, choice was guided by discriminative stimuli presented pseudorandomly, that informed about the relatively probability of obtaining larger rewards.

Results: Bilateral mOFC inactivation increased risky choice during probabilistic discounting via an increase in win-stay behaviour, suggesting that under these conditions, this region the tempers urge to chase larger/risky rewards and focus on immediate reward feedback. Moreover, selective disruption of mOFC projections to the BLA and mPFC revealed distinct contributions of these circuits. Specifically, chemogenetic disruption of top-down mOFC-to-BLA (but not bottom-up BLA-to-mOFC) circuits increased risky choice via an enhanced sensitivity to negative feedback and increased lose-shift tendencies. Conversely, disrupting intracortical communication between the mOFC and mPFC induced suboptimal patterns of decision making, reducing and increasing risky choice when reward probabilities were high or low, respectively. In comparison, mOFC inactivation induced a risk-averse pattern of choice during cue-guided decision making. This was again accompanied by an inappropriate increase in sensitivity to feedback after recent choices, rather than using external stimuli to guide more optimal choice patterns.

Conclusions: Collectively, these data reveal dissociable and multifaceted contribution of the mOFC in optimizing different forms of decision making guided by internal generated vs externally-cued information about risk/reward contingencies. They further demonstrate that separate cortico-amygdala and cortico-cortical circuits play distinct yet complementary roles in these processes. More generally, these findings highlight that the mOFC promotes optimal reward seeking by reducing emphasis of recent action outcomes, and instead promoting integration of broader information about reward history or external stimuli to guide choice towards more profitable options.

Disclosure: Nothing to disclose.

44.3 Orbitofrontal Cortex, Decision Making, and Anticipatory Autonomic Arousal

Betsy Murray

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Background: The primate orbitofrontal cortex (OFC) was once thought to have expansive and general functions in reward-based learning, decision-making, and behavioral inhibition, as exemplified by reversal learning. Recent findings, however, have demonstrated that many previous ideas about OFC's function resulted from disconnecting prefrontal areas outside OFC via white matter damage. Instead, the primate OFC has a more specific function. Experiments using the devaluation task have revealed that it links cortical representations, such as representations of objects, with updated desirability valuations of necessary resources, such as specific food items and fluids. OFC also plays a well-known role in autonomic arousal, and now that we have isolated OFC's core function this facet of its output is due for re-examination. We therefore studied the role of OFC in the acquisition of autonomic arousal that occurs with learning.

Methods: We studied four rhesus monkeys with selective, excitotoxic lesions of OFC (Walker's areas 11, 13 and 14) and four unoperated controls. All 8 monkeys were trained on an appetitive Pavlovian association at the rate of one session per day. One visual stimulus (CS+) predicted reward; another (CS-) predicted no reward. As the monkeys fixated a central point, a 1-s CS period was followed by a 0.5-s trace (delay) period and then reward delivery (for CS+ trials). Pupil dilation served as the measure of arousal. Criterion was set at 4 consecutive sessions in which pupil diameter during the CS period was significantly greater for the CS + relative to the CS-. Control conditions included unsignaled rewards and luminance changes. The monkeys also learned an instrumental visual discrimination that matched the Pavlovian task in timing and stimulus material.

Results: Three analysis periods followed CS onset (0 ms) in consecutive time windows: CS (250-1250 ms); trace (1250-1750 ms); and reward (1750-2250 ms). Controls rapidly acquired a robust conditioned autonomic response (mean ± SEM = 9 ± 2.8 sessions to criterion) and then continued to show this robust anticipatory autonomic response across sessions. They showed an increased pupil diameter to the CS+ relative to the CS- during all three analysis periods. In contrast, 3 of the 4 monkeys with OFC lesions failed to attain criterion (i.e., failed to exhibit consistent conditioned responses), even after ~48 sessions. All monkeys showed pupil dilation after unsignaled rewards and responded appropriately to changes in luminance. Finally, monkeys with OFC lesions learned the instrumental visual discrimination at the same rate as controls. We can rule out accounts of these results in terms of motivation because monkeys with OFC lesions learned the discrimination task at the same rate as controls, and showed the same trial-completion rates and reaction times as controls.

Conclusions: The primate OFC is necessary for the acquisition of autonomic arousal in anticipation of positive emotional events.

We know that neurons in OFC encode associations between visual stimuli and reward value, so it seems likely that these value-coding signals give rise to the autonomic arousal observed in the controls. Although the full underlying circuit is not yet known, these data are relevant to one of the key symptoms of depression, anhedonia, especially anticipatory anhedonia. More generally, the present results support the idea that the primate OFC links arbitrary visual stimuli to updated valuations of a predicted outcome's desirability.

Disclosure: Nothing to disclose.

44.4 Human Orbitofrontal Networks are Necessary for Outcome-Guided Behavior

Thorsten Kahnt

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Background: Adaptive decisions require knowledge about the current value of expected outcomes. Experiments in rats and non-human primates have shown that the orbitofrontal cortex (OFC) is necessary for making such choices, but a causal role for human OFC in outcome-guided behavior has not been established. Here we used non-invasive connectivity-guided continuous theta burst stimulation (cTBS) to temporarily disrupt human OFC networks prior to devaluation of food odors.

Methods: Hungry subjects learned associations between visual cues and two food odors, which were selected to be matched in subjective pleasantness. In a baseline choice task, subjects made decisions between cues predicting the two food odors. We then applied cTBS to a coordinate in the lateral prefrontal cortex that was individually selected based on maximal resting-state functional magnetic resonance imaging (rs-fMRI) connectivity with the intended target area in the central OFC. Subjects ($N = 56$, 32 female) were randomly assigned to either the STIM or SHAM group, and cTBS was applied before the devaluation phase of the task. Devaluation was implemented by consumption of a meal corresponding to one of the two food odors. Next, subjects repeated the choice task in extinction.

Results: Analysis of rs-fMRI data acquired immediately after cTBS confirmed that cTBS reduced the connectivity of central OFC with the rest of the brain in STIM compared to SHAM subjects ($P < 0.001$). Importantly, whereas subjects in the SHAM group directed their choices away from the cues predicting the devalued food odor ($P < 0.001$), subjects in the STIM group continued to choose cues predicting devalued food odor ($P = 0.19$). This effect was significantly different between groups ($P = 0.006$). Importantly, cTBS had no effect on the devaluation of food odors themselves, as assessed by changes in odor pleasantness from pre to post the meal ($P = 0.46$), or on the ability to make value-based choices in general ($P = 0.85$).

Conclusions: These results suggest that OFC is necessary for inferring the current value of specific outcomes, as required for outcome-guided behavior, but not for economic choice per se. More generally, these results demonstrate the feasibility of targeting human OFC using non-invasive stimulation techniques, which may provide the basis for new treatments of psychiatric conditions associated with disrupted OFC function.

Disclosure: Nothing to disclose.

Panel

45. Anhedonia as a Target for Novel Therapeutics: Clinical Characterization and Assessment, and Proof-Of-Principle From Early Clinical Trials Involving Unprecedented Mechanisms

45.1 The Anhedonia Trifecta: Clinical, Neuroimaging and Molecular Associations of Anhedonia and Antidepressant Response

Sidney Kennedy

St. Michael's Hospital, Toronto, Canada

Background: Anhedonia is a primary symptom across depression, but is also common to other psychiatric disorders. In order to develop a fulsome characterization of anhedonia, the Research Domain Criteria approach would recommend evaluating the construct across various units of analysis. While data suggest that anhedonia is associated with impairment in mesocorticolimbic regions, it is not clear how these deficits integrate with clinical presentation and molecular underpinnings.

Methods: Data from a Canadian Biomarker Integration Network in Depression (CAN-BIND) trial will be used to evaluate clinical, neuroimaging and inflammatory markers of anhedonia (211 MDD and 112 healthy control participants). All patients underwent an 8-week open-label trial of escitalopram, and non-responders received an additional 8 weeks of adjunctive aripiprazole. At baseline, week 8 and week 16, anhedonia scores using the Dimensional Anhedonia Rating Scale (DARS) and the Snaith Hamilton Pleasure Scale (SHAPS) were collected. At baseline, 2 weeks, 8 weeks and 16 weeks blood samples for molecular analyses were collected, and at baseline, 2 weeks and 8 weeks participants completed an anhedonia task evaluating anticipation and reward outcome under fMRI conditions.

Results: Overall, anhedonia had moderate correlations with depression severity. Based on patterns of response, there were three distinct trajectories: 'fast' responders, 'slow' responders and non-responders. Notably, slow responders and non-responders had greater baseline anhedonia compared to fast responders and healthy controls. Anhedonia was associated with dampened frontostriatal activity during reward anticipation. Furthermore, less severe baseline anhedonia and early increases in frontostriatal connectivity during reward anticipation correlated with depression improvement. Preliminary molecular analyses identified IL-17 as predictive of antidepressant response.

Conclusions: Antidepressant response was associated both with baseline anhedonia and cytokine status. However, while anhedonia was correlated with a change in depression scores during treatment, it also represents a distinct construct that needs to be evaluated separately from depression severity. The trajectory analysis method provides an opportunity to explore the biological basis of individual differences in treatment response and advance precision medicine.

Disclosure: Alkermes, Allergan, Janssen, Lundbeck, Otsuka, Servier, Advisory Board; Abbott, Janssen, Grant; Lundbeck, Servier, Honoraria

45.2 The Utility of Anhedonia as a Biomarker in Depression: Implications From Anhedonia Scale Development, Antidepressant Response and Neuroimaging

Sakina Rizvi

St. Michael's Hospital, University of Toronto, Toronto, Canada

Background: Anhedonia has been historically conceptualized as a "loss of pleasure", although neuroscientific studies support multi-faceted and unique aspects of reward processing including

interest, anticipation, effort and consummatory pleasure. Moreover, published studies of reward in Major Depressive Disorder (MDD) tend to focus on a single task and clinical scales primarily focus on consummatory pleasure, which does not capture the full spectrum of reward processing abnormalities. It is important to develop measures of anhedonia that are reflective of the full range of reward processing deficits observed in MDD.

Methods: This presentation will review data from three antidepressant clinical trials, demonstrating the validity of the Dimensional Anhedonia Rating Scale (DARS), a new anhedonia scale that incorporates multiple facets of reward (interest, anticipation, motivation, effort, and consummatory pleasure), and its correlations with clinical response, dopamine D2/D3 receptor binding, as well as brain activity during reward processing. Data will be presented from: (1) a 16-week Canadian Biomarker Integration Network for Depression trial (CAN-BIND-1) involving 210 MDD and 111 healthy controls; (2) a Deep Brain Stimulation for treatment resistant depression study (TRD; n = 35), and (3) a small study (n = 25) that involved an extensive reward processing battery to evaluate interest, associative learning, anticipation, expectation, consummatory pleasure, and feedback integration before and after an 8-week trial of desvenlafaxine in MDD patients.

Results: Results from CAN-BIND data demonstrate strong internal consistency, reliability and validity of DARS in MDD patients and healthy controls. DARS scores improved in responders to escitalopram over 8 weeks and baseline scores were able to distinguish subsequent responders from non-responders to adjunctive aripiprazole. Data in TRD patients demonstrated increased dopamine receptor binding in the dorsolateral prefrontal cortex among individuals with high anhedonia. With respect to neural correlates of reward processing, the DARS showed a significant negative correlation with frontostriatal connectivity during reward anticipation, while the gold standard anhedonia scale, the Snaith Hamilton Pleasure Scale (SHAPS), did not. These data will be validated against results from the desvenlafaxine trial.

Conclusions: In conclusion, these data demonstrate the validity of the DARS, its change with successful antidepressant treatment, and its association to brain reward processing deficits in depression. Correlations of the DARS with D2/D3 binding potential may reflect lower dopaminergic tone associated with greater levels of anhedonia, which may explain its utility in predicting aripiprazole response. Overall, these data support further investigation of anhedonia as a useful biomarker of treatment response.

Disclosure: Janssen Pharmaceuticals, Advisory Board; Pfizer Canada, Grant; Allergan, Grant.

45.3 The Relationship Among Anhedonia Measures Included in the NIMH Fast-Mas Trial of the Effects of Kappa Opioid Receptor Antagonism in Patients With Mood and Anxiety Spectrum Disorders and Anhedonia

Andrew Krystal

UCSF, Oakland, California, United States

Background: As part of the NIMH Fast-Fail Mood and Anxiety Spectrum Disorders (FAST-MAS) Program we carried out a clinical trial aimed at determining if it was possible to establish Proof of Mechanism (POC) that kappa opioid receptor (KOR) antagonists have potential for treating anhedonia, an entity represented in several reward-related Research Domain Criteria (RDoC) Constructs ("Reward Responsiveness", "Reward Learning", and "Reward Valuation"). We sought to establish POC by assessing if a potent and selective KOR antagonist favorably impacts brain circuitry hypothesized to mediate reward-related function. Although our study was focused on evaluating the effects of KOR on an fMRI-based measure of neural circuitry, it included a number of other measures of anhedonia representing all 3 units of analysis – brain circuitry, behavior, and self-report. A secondary goal of this study was to determine the relationships among our various measures of anhedonia. Here, we present the results of these analyses as a means of improving our understanding of anhedonia measures and our capacity to select measures for use in future clinical trials.

Methods: Subjects 21-65 years of age meeting DSM-5 criteria for a mood or anxiety disorder who had anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] score ≥ 20), were randomized to 8 weeks of double-blind treatment with JNJ-67953964 10 mg (N = 45) or placebo (N = 44). Primary outcome was assessed with fMRI in conjunction the MID task. Measures included in this study were two MID fMRI measures (ventral striatal activation in anticipation of gains and losses), three self-report anhedonia measures (SHAPS, Visual Analogue Scale of Anhedonia and the Temporal Experience of Pleasure Scale), two behavioral measures (the probabilistic reward task [PRT] and the Effort Expenditure for Rewards Task), and several clinical scales (Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, the Cognitive and Physical Functioning Questionnaire, and the Clinical Global Impression Scale). Statistical analysis consisted of generating the correlation matrix for this set of measures and carrying out latent class analysis to determine if there were patterns of findings on these measures that defined clinically important subgroups of subjects in terms of severity or treatment response.

Results: The neuroimaging measures of ventral striatum activity in anticipation of reward and loss were significantly correlated ($p < 0.01$) as were all of the self-report measures ($p < 0.05$). PRT response bias was correlated with mean fMRI ventral striatal activity during anticipation of gain in the MID ($p < 0.05$). LCA indicated that there were two subgroups of subjects defined primarily by self-reported anhedonia severity who differed in terms of depression severity ($p < 0.05$) and had a differential treatment response ($p < 0.05$).

Conclusions: Statistically significant correlations among variables were found primarily within domains of assessment. The only exception was that PRT results were significantly correlated with the primary fMRI measure. These findings and LCA, which identifies subgroups that differ in treatment response, provide potential guidance for choosing measures and thresholds for subject selection for future anhedonia-related trials.

Disclosure: Janssen, Eisai, Neurocrine, Idorsia, Consultant; Janssen, Patent (Other Immediate Family Member); Janssen, Jazz, Ferring, Galderma, Harmony Biosciences, Takeda, Merck, Physician's SealAdvisory Board;, Axsome, Reveal Biosensors, Jazz, Grant,

45.4 Effects of Immunomodulatory Drugs on Anhedonia and Reward Circuitry

Gayle Wittenberg

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Background: Anhedonia, decreased reactivity to pleasurable stimuli, is one of the core symptoms of major depressive disorder (MDD) that has been tied to a dysfunction in reward processing in depression. The presence of immune system dysregulation among a subset of depressed patients has been well-established and has become a target for potential precision medicine approaches. Recent work demonstrated that antidepressants with a dopaminergic effect have greater efficacy among MDD patients with higher levels of C-reactive protein (CRP). Further, it has been

shown that dopamine release in reward-related brain regions its and association with motivation and anhedonia can be bi-directionally influenced by pro- or anti-inflammatory stimuli. Here we present data from two randomized, placebo-controlled clinical trials in psoriasis and MDD patients to evaluate whether targeting pro-inflammatory cytokines may lead to improvements in the anhedonic component of MDD.

Methods: The VOYAGE-2 study is a phase 3 clinical trial evaluating the efficacy and safety of guselkumab, an anti-IL-23 antibody, in patients with moderate-to-severe plaque psoriasis. Anhedonic Depression was measured using the Hospital Anxiety and Depression Scale-Depression Score (HDS). Patients with HDS ≥11 were classified as depressed at baseline. Changes in HDS score from baseline to weeks 8 and 16 between the guselkumab and placebo groups were evaluated in a mixed effects model with repeated measures, with and without adjustment for the Psoriasis Area and Severity Index (PASI) score. The CNTO136MDD2001 study investigated the efficacy of sirukumab, an anti-IL-6 antibody, as adjunctive treatment to antidepressant therapy. Subjects were diagnosed with MDD with suboptimal response to the current standard oral antidepressant therapy and screening high sensitivity C-Reactive Protein (hsCRP) ≥ 3.00 mg/L. Anhedonia symptoms were measured with the SHAPS scale at week 12. In both studies the assessment of anhedonia was included as part of the secondary outcome measures.

Results: Among moderate-to-severe plaque psoriasis patients with high depressive symptoms (n = 111, 12.1%), guselkumab treatment produced significantly better improvements in HDS score compared to placebo (p = 0.0007/1.7E-6 at week 8/16). Improvement at week 16 remained significant after adjustment for the PASI score (p = 0.064/0.013 at week 8/16). Sirukumab was more effective than placebo in decreasing anhedonia symptoms measured with the SHAPS at week 12 (p = 0.014); greater clinical effect was seen with increasing baseline hsCRP levels.

Conclusions: Among patients with MDD, those with higher inflammation have a lower response rate to current therapies; likewise, among patients who respond to antidepressants, anhedonia is frequently a residual symptom. These results suggest treatments targeting cytokines may be effective in treating symptoms of anhedonia in MDD, particularly among patients with immune dysregulation, potentially filling an unmet need among patients today.

Disclosure: Janssen Research & Development, LLC, Employee, Johnson & Johnson, Stock / Equity.

Panel

46. Dopamine D1 Family Receptor Mechanisms in Psychiatric and Neurodegenerative Diseases

46.1 Preclinical Pharmacology and Early Clinical Development of D1 Positive Allosteric Modulators With Therapeutic Potential for Neuropsychiatric Disorders

Abstract not included.

46.2 The D1 Positive Allosteric Modulator, DETQ, Improves Cognition and Negative Symptoms in Subchronic Phencyclidine (PCP)-Treated and Aged Mice

Abstract not included.

46.3 The Novel Dopamine D1R Agonist, PF-3628, is the First Agonist to Excite Delay Cells in Primate Dorsolateral Prefrontal Cortex: Greater Potential for Treating Cognitive Disorders

Amy Arnsten

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Background: It has been known for 40 years that dopamine (DA) is essential to the working memory functions of the dorsolateral prefrontal cortex (dlPFC), especially through its actions at D1 receptors (D1R). DA D1R signaling produces an inverted U dose/response on working memory, where either too little or too much impairs cognitive function. DA D1R is altered in cognitive disorders such as schizophrenia, yet D1R agonists have yet to translate to human use. A major problem has been that unlike DA itself, which has low affinity for D1R, existing D1R agonists had very high affinity for the D1R, and thus evoked only suppressive actions. As D1R antagonist data indicated that endogenous DA could excite dlPFC neurons, agonists that better mimicked the enhancing effects of DA were needed. The current presentation will discuss data with the novel D1R agonist, PF-3628, which has lower affinity for D1R and thus better mimics endogenous DA actions.

Methods: PF-3628 was iontophoresed onto dlPFC neurons in aging rhesus monkeys performing an oculomotor delayed response task, to assess drug effects on Delay cell firing. Delay cells exhibit persistent firing across the delay epoch, maintaining spatial information for the neuron's preferred direction in working memory. The aging monkeys performing the task have naturally-occurring DA depletion, and naturally-occurring reductions in Delay cell firing, thus allowing for "replacement therapy" with a D1R agonist. We also examined the expression of D1R in monkey and human postmortem dlPFC using immunoEM and microarray profiling using laser capture microdissection, respectively.

Results: Iontophoresis of low doses of PF-3628 onto dlPFC neurons increased Delay cell firing for the preferred direction (p = 0.0002), thus enhancing the representation of visuospace held in working memory. The enhancement was blocked by a D1R antagonist, consistent with actions at D1R. This is the first evidence that a D1R agonist can excite neurons in monkey dlPFC. Higher doses suppressed firing, as had been previously seen with high affinity D1R agonists. As D1R are enriched on pyramidal cell spines, including in the post-synaptic density, PF-3628 may increase firing by enhancing NMDAR synaptic actions. We will show evidence of D1R expression in the post-synaptic density of glutamatergic synapses in the primate dlPFC.

Conclusions: These data suggest that a lower affinity D1R agonist that better mimics endogenous DA actions may have greater potential to succeed as a therapeutic for cognitive disorders such as schizophrenia. As the field has spent decades trying to identify a D1R agonist that could replace critical DA actions in patients, this may provide a therapeutic break through.

Disclosure: Shire/Takeda, Royalties; Lundbeck, Consultant; Roche, Consultant (Spouse)

46.4 Dopamine Induces Oscillatory Activities in Human Midbrain Neurons With Parkin Mutations

Abstract not included.

Study Group

47. What Should the General Psychiatrist Know About Genetics?

Wade Berrettini*, Dorothy Grice, James Kennedy, James Potash, Daniel Mueller, Gwyneth Zai, David Ross, Antonia New, E. Cabrina Campbell, Takahiro Soda, John Nurnberger

Study Group Summary: During the 20th century, through twin and family studies, it was established that most psychiatric disorders are characterized by substantial genetic risks. The past decade has seen an explosion of genetic knowledge for many psychiatric disorders through the application of genome-wide genotyping and sequencing. Psychiatrists are now faced with many questions related to genetic influence on risk: affected persons ask about risk to their children, unaffected persons with ill parents ask about personal risk, parents ask about genetic analysis for their affected young children, many ask about 'DNA tests' to determine their risk, validate diagnosis, predict response to medications, etc.

As an example, any psychiatrist who evaluates and treats individuals with autism, intellectual disability and neurodevelopmental disorders, must be familiar with genetic testing and the implications and interpretation of results, including information related to copy number variation findings. Because the field of gene discovery is dynamic and moving ahead at great pace, ongoing education related to this area is necessary so that psychiatrists can provide up to date information and counseling to patients and their families.

A polygenic risk score (PRS) might be used in the future to augment clinical diagnoses and guide medication selection. For example, consider the following scenario: A unipolar depressed patient presents to a psychiatrist with family history of a parent who has schizophrenia. Review of the parent's medical record confirms the diagnosis provided by the unipolar patient. The unipolar patient has a high PRS for schizophrenia. Will future research reveal that this patient may be better treated with an atypical antipsychotic, compared to an antidepressant?

While the utility of currently available pharmacogenetic tests for antidepressants may be debated, one could envision in the future a polygenic risk score with substantial predictive validity for various pharmacologic classes of antidepressants, mood stabilizers and antipsychotics, etc. The application of such polygenic risk score tests for various classes of psychotropic medications may become fairly routine in the next few decades, providing a precision medicine aspect to psychiatric pharmacotherapy.

These and other clinical scenarios will be discussed from various perspectives, including those of psychiatric genetics investigators (John Nurnberger, Jimmy Potash, Wade Berrettini), scientists developing such tests (e.g., Gwyneth Zai, Daniel Muller, Jim Kennedy), psychiatric residency training program directors (Dorothy Grice, Cabrina Campbell, David Ross and Antonia New) and developers of neuroscience curricula for physicians (David Ross). In these discussions, ethical considerations will be formulated by Takohira Soda, MD, PhD, a member of the International Society of Psychiatric Genetics Ethics Committee. This study group will attempt to define a core set of information critical to psychiatrists and psychiatric training. This core information should reflect both the current knowledge of psychiatric genetics, and it should prepare the physician to use future tools for the benefits of patients.

Disclosure: Nothing to disclose.

Panel

48. Neuroinflammation in Psychiatric Diseases: Preclinical and Clinical Data

48.1 Consequences of Microglial-Mediated Recruitment of Inflammatory Monocytes to the Brain With Psychological Stress

Jonathan Godbout

The Ohio State University, Columbus, Ohio, United States

Background: Psychological stress contributes to the development of anxiety and depression. Recent clinical studies have reported increased inflammatory leukocytes in circulation of individuals with stress-related psychiatric disorders. Parallel to this, our work in mice shows that stress causes release of inflammatory monocytes into circulation. In addition, stress caused the development of prolonged anxiety that was dependent on inflammatory monocytes in the brain. Therefore, we hypothesize that chronic stress drives the production of inflammatory monocytes that are actively recruited to the brain by microglia, and these monocytes augment neuroinflammatory signaling and prolong anxiety.

Methods: WT, Capsase-1 KO, and IL-6 KO mice were subjected to 6 cycles of repeated social defeat, and immune and behavioral parameters were determined 14 hours later.

Results: Here we show that repeated social defeat (RSD) in mice activated threat appraisal centers in the brain that spatially coincided with microglial activation and endothelial facilitation of monocyte recruitment. Moreover, microglial depletion with a CSF1R antagonist prior to stress prevented the recruitment of monocytes to the brain and abrogated the development of anxiety. Cell-specific transcriptional profiling revealed unique mRNA signatures of monocytes in the blood, monocytes in the brain and microglia in the brain after RSD. For example, microglia selectively enhanced the expression of key chemokines, while monocytes highly expressed IL-1β, MMP9 and Ly6C. Consistent with these profiles, the recruited inflammatory monocytes with stress adhered to IL-1R1+ neurovascular endothelial cells and this interaction was blocked by microglial depletion. Furthermore, disruption of IL-1β signaling by caspase-1KO specifically within bone marrow-derived cells revealed that monocytes promoted anxiogenesis through stimulation of neurovascular IL-1R1 by IL-1β.

Conclusions: Collectively, the development of anxiety during stress was caused by microglial recruitment of IL-1β-producing monocytes that stimulated brain endothelial IL-1R1. Thus, monocyte IL-1β production represents a novel mechanism that underlies behavioral complications associated with stress-related psychiatric disorders.

Disclosure: Nothing to disclose.

48.2 Maternal Immune Activation by Combined Environmental Stressors Disrupts Thalamo-Cortical Development, Social Behavior, and Microglial Phenotype in a Mouse Model of Autism

Staci Bilbo

Duke University, Durham, North Carolina, United States

Background: Maternal immune activation (MIA) during pregnancy, e.g. by environmental factors such as infection or toxins, is associated with an increased risk of neurodevelopmental disorders in the offspring of humans and in animal models, including autism spectrum disorder (ASD) and schizophrenia. Despite the critical role for microglia in neural development, few studies have examined the impact of MIA on microglial development or long-term function.

Methods: We developed a novel mouse model in which pregnant C57BL/6 mouse dams are exposed intermittently throughout pregnancy to diesel exhaust particles (DEP), a proxy for air pollution, vs control. Half of the dams in each group were further exposed to stress during the last third of pregnancy, using a restricted nest material paradigm. Both of these environmental exposures robustly activate the maternal immune system and are associated during pregnancy with increased ASD risk in humans.

We performed multi-circuit neurophysiological assessments during concurrent social behavior to identify potential circuit abnormalities, and to explore the neuroimmune mechanisms that may underlie their disruption, e.g. microglial sculpting of synapses.

Results: DEP exposure alone altered embryonic microglial colonization and neural-glial interactions in the cortex of juvenile males, but not females ($p < 0.05$); however, no overt impacts on behavior were observed in either sex. In contrast, offspring exposed prenatally to combined DEP + maternal stress (MS) showed striking, persistent deficits in communication and sociability, which was most pronounced in males ($p < 0.05$, for all). Multi-circuit neurophysiological recordings in the mice during a social interaction test revealed multiple circuit abnormalities in offspring exposed to DEP/MS, and a pronounced disruption within the thalamocortical projections into the anterior cingulate cortex (ACC), a brain region that has been implicated in many autism studies in humans. DEP/MS males had a more than two-fold increase in the number of glutamatergic (VGLUT2+) synapses within the ACC at postnatal day (P)8 ($p < 0.001$), followed by a decrease in synapse number by P15 that persisted into adulthood ($p < 0.05$, for each). These changes are similar to the early brain overgrowth followed by atrophy that is reported in autism. Finally, we observed a striking shift in the phenotype and phagocytic capacity of microglia within the synaptic layer of ACC in DEP/MS males.

Conclusions: These data suggest combined environmental exposures which activate the maternal immune system may persistently impact brain and behavioral development in males via impacts on microglial phagocytic and inflammatory function.

Disclosure: Nothing to disclose.

48.3 Consequences of Peripheral Inflammation Leading to Neuroinflammation: A Novel Role for Meningeal Innate Lymphoid Cells in Modulating Microglial Activation to Peripheral Cytokine Storm

Noel Derecki

Janssen Research and Development, San Diego, California, United States

Background: The relationship between peripheral inflammation and central nervous system (CNS) pathologies—including psychiatric disorders—represents a burgeoning area of inquiry anticipated to reveal novel therapeutic pathways. While numerous analyses of clinical data reveal significant comorbidity of somatic immune dysfunction and psychiatric disease, our understanding of the immune-CNS connection remains largely phenomenological. Accordingly, a major interest of our group is the elucidation of targetable mechanisms. To that end, we are systematically probing microglial and meningeal responses to peripheral challenge with LPS, Poly I:C, and Imiquimod (IMQ). Our goal is to elucidate and exploit the neuroimmune interplay occurring at the borders of the brain as a point of leverage in ameliorating deleterious CNS effects of peripheral inflammation.

Methods: First, we compared LPS, Poly I:C, and IMQ challenge in terms of their peripheral, meningeal, and CNS effects by FACS, multiplex analysis of cytokines, immunolabeling of brain and meninges, and 2-photon analysis of microglia. We also looked at behavioral responses. After probing WT mice using the above, we began to parse out the relative contributions of adaptive and innate immune cell subsets, particularly in the meninges, in terms of their ability to affect neuroinflammatory sequelae. T cells and innate lymphocytes (ILCs) have both been demonstrated to drive inflammation, and both are plentiful in periphery and meninges. Thus, we compared WT, T cell deficient Rag2−/−, and T cell and ILC-deficient Rag2−/−Il2rg−/− mice. We focus most heavily on these experiments and IMQ challenge as they represent our most novel dataset.

Results: Each challenge—LPS, Poly I:C and IMQ—was associated with a unique neuroinflammatory profile. As such, we and others have observed that psoriatic inflammation induced in mouse by topical application of IMQ is accompanied by microglial inflammation and invasion of brain by peripheral immune cells. Of particular note, was that while skin pathology was severe in WT mice, moderate in Rag2-/- mice, and abolished in Rag2-/-Il2rg-/- mice, neuroinflammatory responses were reversed; in fact, ILC-deficient mice showed increased immune infiltration, Evans blue leakage into brain, and microglial cytokine release following IMQ treatment. Moreover, ILC-deficient mice also showed greater suppression of locomotion. These results strongly suggested that ILCs were somehow able to suppress neuroinflammation, BBB permeability and behavioral responses—all more severe in their absence. Subsequent RNAseq of meningeal ILCs revealed factors produced by activated ILC2s with ability to suppress inflammation and reinforce barrier integrity in peripheral systems, e.g. gut. Accordingly, when ILC-deficient mice were passively transferred with ILC2s, these cells engrafted in meninges and suppressed neuroinflammatory sequelae.

Conclusions: These data suggest ILC2s play a previously unanticipated role in BBB protection, and show the functional ability to mitigate neuroinflammation related to peripheral inflammatory disorders like psoriasis. Our findings also suggest the possibility of cell therapeutic applications for ILC2s in suppression of neuroinflammation linked to psychiatric disorders.

Disclosure: Nothing to disclose.

48.4 Disease Progression and Blood Serum Biomarkers as Predictors of Gliosis in Affective Disorders

Abstract not included.

Panel

49. Neurobiological Risk for Affective Disorders: Evidence From Developmental and Cross-Species Investigations

49.1 Developmental Shifts in the Neurobiological Basis of Risk for Anxiety

Abstract not included.

49.2 Continuities and Discontinuities in the Developmental Correlates of Anxiety Disorders

Daniel Pine

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

Background: Anxiety disorders exhibit both continuities and discontinuities with development. On the one hand, most adult anxiety disorders have their onsets in childhood, and anxiety disorders respond to similar treatments during childhood, adolescence, and adulthood. On the other hand, most pediatric anxiety disorders remit by adulthood. Previous brain-imaging research emphasizes findings on the neural correlates of anxiety that manifest similarly in children, adolescents, and adults. The current presentation will focus on unpublished data revealing strong age-related differences in the correlates of anxiety disorders.

Methods: Findings from two sets of fMRI studies will be reviewed. The first study is based in a sample of 150 adolescents who were first identified during infancy, based on the infants' level

of behavioral inhibited temperament. This sample has been followed longitudinally since infancy through age 17, with both psychiatric and brain imaging assessments. Longitudinal data will be presented for the dot-probe task, a threat-attention-paradigm, where more than 50 subjects have at least two assessments. The second study is based on a cross-sectional data set including 200 medication free subjects between nine and 45 years-of-age. All subjects underwent a threat conditioning and extinction task using faces as conditioned stimuli and an aversive scream as an unconditioned stimulus. Psychophysiology was assessed. Subjects returned to the clinic three weeks later, during which time they underwent an extinction recall paradigm, in the fMRI scanner.

Results: Findings from the longitudinal study examine changes in the relationship between anxiety symptoms and amygdala-prefrontal connectivity on the dot-probe task. These findings reveal an increasingly strong relationship between amygdala-prefrontal connectivity and anxiety ($p < 0.05$) as subjects undergo repeated scans across development. Moreover, this developmental trend appears particularly strong in the adolescents who had manifested a behavioral inhibited temperament during infancy and preschool. Findings from the cross-sectional study examine age differences in the relationship between anxiety and prefrontal function during extinction recall. These findings reveal greater dorso-lateral prefrontal cortex function in healthy adults, as compared to adults with anxiety disorders, during the appraisal of extinguished threat cues ($p < 0.05$). No such anxiety-related differences arose in children and adolescents, who manifested distinct prefrontal function patterns during memory recall tasks but not during the appraisal of fear evoked by extinguished threat cues.

Conclusions: Considerable previous data from brain-imaging studies demonstrate similarities between pediatric and adult anxiety disorders. However, age-related discontinuities have been less comprehensively examined in past research. The current presentation will highlight data revealing such discontinuities while also noting findings where no such discontinuities manifest.

Disclosure: Nothing to disclose.

49.3 Studies in Young Children and Young Nonhuman Primates Focused on Mechanisms Underlying the Risk to Develop Anxiety and Depression

Ned Kalin

University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States

Background: Early life temperamental anxiety is a risk for the later development of anxiety disorders, depression, and comorbid substance abuse. To understand mechanisms underlying this risk we are performing parallel studies in young rhesus monkeys and at-risk preadolescent children. Longitudinal neuroimaging studies in children are being performed alongside chemogenetic and molecular studies in nonhuman primates.

Methods: Studies in preadolescent children with subsyndromal anxiety and anxiety disorder ($n = 120$) are performed using multimodal neuroimaging strategies along with physiological measures to assess responses to potential threat and uncertainty. Studies in preadolescent rhesus monkeys are ($n = 47$) using laser capture microscopy and RNAseq to understand molecular alterations in the extended amygdala and DREADDs technology in the dorsal amygdala to test mechanistic hypotheses.

Results: In children with anxiety disorders results demonstrate structural and functional alterations in prefrontal-medial temporal lobe connectivity (ps < .05). Inhibition of primate dorsal amygdala neurons with DREADDs results in a reversible reduction in threat related freezing behavior and vocalizations. Studies using nonhuman primate brains reveal transcripts in the central nucleus of the amygdala that are associated with individual differences in anxiety, including PKCdelta.

Conclusions: Taken together, these data implicate altered regulation of prefrontal-amygdala circuits in mediating early life pathological anxiety. The chemogenetic data point to the primate dorsal amygdala as a core, mechanistic component of maladaptive anxiety and the RNAseq data have identified potential molecular substrates that may underlie the neural circuit alterations.

Disclosure: CME outfitters, Elsevier, Pritzker Consortium, American Psychiatric Association, Honoraria, Actify Neurotherapies, Advisory Board, Seattle Genetics, Stock / Equity.

49.4 Adolescence as a Critical Period for the Induction of Resilience in a Genetic Model of Internalizing Temperament

Abstract not included.

Panel

50. Cannabinoids: Risks and Benefits Across the Lifespan?

50.1 A Placebo-Controlled Double-Blind Trial of Cannabinoids in Children and Adolescents With Autism Spectrum Disorder

Francisco Castellanos

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Background: Reduced endocannabinoid "tone" has been posited in the pathophysiology of ASD animal models; children with ASD have been found to have lower peripheral endocannabinoid levels. Additionally, anecdotal reports suggest cannabinoids may be beneficial for some aspects of ASD.

Methods: Double-blind placebo-controlled comparison (NCT02956226) of whole plant cannabis extract containing cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) in a 20:1 ratio and (2) purified CBD and THC in the same ratio. Participants were 150 children and adolescents with ASD, both males (80%) and females (mean age 11.8 +/- 4.1 yrs). They received either placebo or cannabinoids for 12-weeks (testing efficacy) followed by a 4-week washout, and crossed-over to receive another treatment for 12 weeks to further assess tolerability.

Results: There were no treatment related severe or serious adverse events. None of the outcomes differed significantly between cannabinoid preparation, in either treatment period. Considering cannabinoids together, in the first period, 43% of 90 children who received cannabinoids were either much or very much improved on the CGI-I compared with 21% of 47 on placebo ($p = 0.009$). Placebo-cannabinoid differences were not significant on the other primary outcome, the Home Situations Questionnaire for ASD (HSQ-ASD). A positive response on the Social Responsiveness Scale-2 (SRS-2) was defined as 15% decrease or better from baseline. In the first treatment period, 44% of participants who received cannabinoids had a positive response compared with 19% on placebo ($p = 0.013$). In terms of possible mediators of treatment effects on the SRS-2, male sex and milder ASD symptoms at baseline were independently associated with better response to cannabinoid treatment.

Conclusions: Novel pharmacological treatments for the core and comorbid symptoms of ASD are urgently needed. Preclinical studies implicate the endocannabinoid system in the pathophysiology of ASD. In a controlled study of 150 children, a combination of CBD and THC, in a 20:1 ratio, either as a whole plant extract or as pure cannabinoids, improved disruptive behaviors and an index of ASD core symptoms, with relatively

few adverse events. These data suggest that further investigation of cannabinoids in ASD is likely to be promising.

Disclosure: BOL Pharma, Stock / Equity.

50.2 Data and Theory Driven Investigations of Cannabis's Effects on Adolescent Neurodevelopment

Hugh Garavan

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Background: The recent increases in the availability and potency of cannabis raise concerns that it may negatively impact adolescent development. However, the cross-sectional and correlational nature of human research makes it challenging to arrive at definitive conclusions. Well-powered, longitudinal studies offer valuable insights: By helping to identify brain differences that precede or follow cannabis use they can suggest possible causes and consequences.

Methods: We report data from the IMAGEN study, a ten-year study of 2,000 participants recruited at age 14. To identify possible causes for cannabis use (i.e., differences that precede use) we performed machine-learning analyses assessing thousands of multi-modal variables acquired at age 14 for their value in predicting cannabis use two years later. A theoretical interest in limbic reactivity as a predictor of cannabis use motivated a specific analysis of amygdala hyperactivity in response to angry visual stimuli. To assess consequences, we compared grey matter volumes of participants who at age 14 reported just one or two lifetime uses of cannabis against cannabis-naïve participants. We also assessed changes in amygdala reactivity after five years in those participants who were using cannabis at age 14 and continued to use by their age 19 scan.

Results: The exploratory approach to identifying the predictors of cannabis use identified a sparse number of predictive features that included personality, youth alcohol and cigarette use, parental cannabis use, and a number of structural and functional brain measures. Curiously, prediction was better for future female users despite the females being lighter users and fewer in number than males. We found that amygdala reactivity at age 14 in cannabis-naïve participants significantly predicted levels of cannabis use five years later. Turning to the possible consequences of cannabis use, we found differences in brain volumes between those 14 year olds reporting just one to two lifetime uses compared to naïve controls. These effects were most pronounced in areas that were rich in cannabinoid receptors and were areas that the preceding analysis revealed to predict future use. Together, this suggests brain changes that may arise from the very first uses of cannabis in an adolescent. Finally, regarding amygdala reactivity in those who used continuously from age 14 to age 19, we observed a reversed pattern to effects observed in cannabis-naïve controls: Whereas non-users showed an age-related increase in amygdala reactivity, continuous users, who were hyperactive at age 14, showed age related decreases in activity.

Conclusions: The results from this very large longitudinal study of adolescent development suggest that cannabis use can be predicted using both exploratory, data-driven methods and by hypothesized differences in amygdala functioning. The results suggest that a profile of future user is possible while the "normalization" of amygdala reactivity may suggest a biological system related to the reinforcing, sustained use of cannabis throughout adolescence. The evidence that brain changes may emerge from the very first, early uses of cannabis offers an intriguing possibility that these initial changes may presage prolonged use or abuse potential, a possibility that will be explored in larger longitudinal studies such as ABCD.

Disclosure: Nothing to disclose.

50.3 A Chronic Low Dose of Delta-9-Tetrahydrocannabinol Restores Cognitive Function in Old Mice by Histone Acetylation

Abstract not included.

50.4 Maternal Prenatal Cannabis Use and Human Fetal Hippocampal Functional Connectivity

Moriah Thomason

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Background: Increasing evidence supports a link between maternal prenatal cannabis use and altered brain and physiological development of the child. However, whether cannabis use is reflected in altered human brain development prior to birth, and specifically, whether maternal prenatal cannabis use relates to connectivity of fetal functional brain systems, remains an open question. It is known that Delta-9-tetrahydrocannabinol (THC), the psychoactive chemical in cannabis, readily crosses the placenta and binds to and mimics the action of endogenous cannabinoids receptors. These receptors are densely located in the basal ganglia, hippocampus and cerebellum and play a central role in neuronal proliferation, arborization, and differentiation. In the hippocampus, cannabinoid receptors are found primarily on GABAergic interneurons, where binding of exogenous cannabinoid suppresses GABA release. Here, we investigate the hypothesis that maternal prenatal cannabis use is associated with altered human fetal hippocampal functional connectivity. Specifically, we predict that maternal cannabis use, which has been linked to reduced GABAergic inhibitory control, will be associated with increased hippocampal to limbic connectivity in the human fetal brain.

Methods: Prenatal resting-state functional magnetic resonance imaging (MRI) data was obtained in 230 human fetuses. 111 of participating women also received drug urine toxicology screening during pregnancy. Subjects were excluded if they were positive for any substance other than THC. Those retained for analysis were 30 positive for maternal THC, and 51 control cases that tested negative across the drug panel. Groups did not differ in gestational age at scan, age at birth, quality of MRI data, motion during MRI, or demographic variables. Subject-specific voxel maps of bilateral hippocampal connectivity were generated using the CONN toolbox, following standard preprocessing methods, linear detrending, nuisance regression, despiking, and band-pass filtering at 0.008 to 0.09 Hz. Hippocampal functional connectivity was then compared between groups using a 2-sample t-test, controlling for gestational age at scan.

Results: Fetuses prenatally exposed to THC showed increased functional connectivity between the hippocampus and regions of the cerebellum, nucleus accumbens, posterior cingulate cortex, and orbitofrontal cortex. In contrast, THC-exposed fetuses showed reduction of hippocampal connectivity to regions of the anterior cingulate cortex, insula, dorsolateral prefrontal cortex, and sensorimotor cortex. Statistical tests used a significance threshold of $p < 0.05$, corrected for multiple comparisons.

Conclusions: This is the first human fetal study to report on global brain connectivity differences that relate to maternal prenatal cannabis use. These findings support a role for exogenous cannabis substrates in influencing fetal neural connectivity patterns and supports the hypothesis that medial temporal, limbic, and cerebellar structures may be targets of that programming. However, this study raises a number of new questions as to whether and how biological and psychosocial

factors influence this association, and what the relevance of these fetal neural differences is to future child neurological health. Therefore, next steps should include prospective longitudinal approaches suited to identification of environmental and health modifiers that buffer or exacerbate these programming effects, and evaluation of associations between THC-related corticolimbic system connectivity and functional outcomes in infancy and childhood.

Disclosure: Nothing to disclose.

Panel

51. Biomarkers in Autism Spectrum Disorder: Promise for Differentiation, Subtyping, and Treatment

51.1 Electrophysiological Biomarkers of Autism Spectrum Disorder (ASD) in Early Infancy: Implications for Early Detection and Intervention

Shafali Jeste

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Background: Converging evidence from genetics suggests that disruptions in the development of healthy neural circuits underlie and precede behavioral signs of autism spectrum disorder (ASD). Examination of functional connectivity patterns in infants at risk for ASD, well before behavioral signs emerge can elucidate early brain changes that relate more directly to putative biological mechanisms. Here, we discuss two studies that have integrated EEG with behavioral assays to examine early neural network changes in infants at high risk for atypical development and ASD: (1) infants with older siblings with autism (familial risk) and (2) infants with Tuberous Sclerosis Complex (TSC).

Methods: In study 1, participants included 49 familial-risk and 35 low-risk infants. High density (EGI Inc.) EEG was acquired longitudinally (at 3, 6, 9, and 12-month) while infants passively watched a video of bouncing soap bubbles ("spontaneous EEG") and while listening passively to a continuous stream of syllables. In study 2, 35 infants with TSC and 20 low-risk infants were studied at 12 and 24 months with spontaneous EEG. Clinical outcomes were assessed at 18 and 36 months using standardized measures of cognition and autism symptoms. After cleaning using independent component analysis, EEG data were transformed into current source density estimates using a Laplacian transform. Alpha phase coherence (APC) was computed between all electrode pair combinations, peak alpha frequency (PAF) was estimated using a robust curve-fitting procedure for three regions of interest: frontal, central and occipital. Nonparametric permutation testing, with FDR correction, was used to examine differences between groups in alpha coherence, and non-parametric Kendall's tau correlation was employed to examine relationships between cognitive function and peak alpha frequency.

Results: In study 1, significant differences in APC were identified in both conditions between the ASD+ and ASD- groups as early as age 3 months. Specifically, in the spontaneous recording, a combination of reduced long-range APC and increased frontal APC predicted ASD symptoms ($R = 0.81$, $p < 0.01$). During language processing, ASD+ infants show significantly reduced APC in frontotemporal networks as early as 3 months that persist across the first year of life ($p = 0.016$). In study 2, infants with TSC demonstrated reduced interhemispheric APC compared to controls at 12 months of age ($p < 0.01$), most pronounced at 24 months in infants who later developed ASD ($p < 0.01$). Across all infants and within the TSC group alone, PAF at 24 months was associated with verbal and non-verbal cognition at 36 months (0.314, $p = 0.020$ whole group, 0.389, $p = 0.016$ for TSC group). The robust data processing methods mitigated data loss, with up to 98% data retention.

Conclusions: EEG is a scalable method to identify the earliest changes in brain development and function in infants prior to the diagnosis of ASD. Despite heterogeneity in genetic risk, EEG changes in long-range connectivity can differentiate infants who develop ASD as early as 3 months of age, while peak alpha frequency relates to cognitive function. These studies necessitate larger-scale collaborations and replication in independent samples, both of which are the focus of ongoing studies. Ultimately, the goal is to more accurately identify those infants with the highest likelihood of atypical development in order to initiate early screening and intervention. These methods also have been applied to stratification in both syndromic and non-syndromic ASD, with the goal of identifying EEG biomarkers for clinical trials.

Disclosure: Nothing to disclose.

51.2 The Autism Biomarkers Consortium for Clinical Trials: EEG and ET Biomarkers for Use in Clinical Trials With Children With ASD

Sara Webb

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Background: The NIMH Autism Biomarker Consortium for Clinical Trials (ABC-CT) aims to identify social communicative biomarkers for use in clinical trials with children with ASD age 6 to 11 years of age. The objective of the ABC-CT is to validate (bio)markers that can be used to reduce heterogeneity of samples via stratification, to indicate early efficacy, and to demonstrate target engagement. This naturalistic longitudinal study includes collection of a large battery of clinical, behavioral, EEG and Eye-Tracking (ET) measures occurring across 5 sites. From this battery, we report data from two social attentional experiment (one EEG and one ET); as a contrast, we present data the Visual Evoked Potential response to checkerboard as a measure of basic visual processing.

Methods: Our interim sample included 161 children with ASD (IQ 60-150) and 64 typically developing children (TD) at baseline (T1), +6 weeks (T2), and +24 weeks (T3). Interim results assessed feasibility of administration; discriminant validity, test-retest reliability, and relation to demographic factors. Average age was 8.7 years (SD 1.6-1.8) in both groups. As expected, the TD group had higher IQ, as well as fewer autism behaviors ($ps < 0.01$). The protocol included 2 visits per timepoint with ET collected on both days and EEG on the 2nd day. The latency of the N170 ERP to upright faces was used to assess early stage face processing; a composite score (% looking at the head) was used to assess social attention; the amplitude of the P1 was identified as a measure of basic visual processing.

Results: Across the three timepoints, 96% of participants had valid acquired data. (1) The Face Upright N170 latency variable validity differed by group with more participants in the TD (92%) compared to the ASD group (74%) providing artifact free data. At baseline, the N170 latency was faster in the TD than the ASD group ($p < 0.01$; $AUC = 0.66$). Test-retest was adequate (T1-T2 ICCs $= 0.67$). The relation over time differed (T1-T3): decreasing in the ASD group ($ICC = 0.45$) and increasing in the TD group ($ICC = 0.78$). Latency was correlated with age in both groups ($rs = -0.36$–0.49) with faster response in older individuals. (2) The ET composite variable validity did not differ by group (>97%). The ASD group looked less at the head region ($p < 0.01$; $AUC = 0.78$). Test-retest was excellent (ICCs = 0.77–.82). The ET composite was correlated with age in the TD group ($r = 0.28$–0.43) but not the

ASD group (r = 0.13–0.15). (3) The VEP validity did not differ by group. The VEP P1 also did not differ by group (p = 0.15; AUC = 0.58). Test retest was good (All ICC = 0.62–.80). None of the variables correlated with sex, nor IQ.

Conclusions: The final data set for the ABC-CT will include 280 children with ASD and 119 TD children. Preliminary analysis of the interim sample suggests acquisition of data was high, with more data loss in experiments that required greater attention (e.g., Faces ERP). While test-retest was good over at 6-week period, the N170 showed more change over the 24 weeks than the VEP P1 or ET composite. Even in a relative narrow age range, significant age effects were found in relation to social-communication (bio) markers. This study suggests that (bio)markers of social communication and basic visual processing are viable for use in clinical trials with children with ASD.

Disclosure: Nothing to disclose.

51.3 EEG Response to Simple Sensory Stimuli as a Potential Biomarker for Predicting Outcomes and Differentiating Syndrome-Specific Profiles in Autism

Jennifer Foss-Feig

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Background: EEG represents a promising tool for developing biomarkers with which to stratify individuals with autism, track biological changes, and predict outcome as a function of both natural development and in response to intervention during clinical trials. Syndromic forms of autism represent an opportunity to develop biomarkers in more homogenous populations where impacted biological pathways are better understood, and clinical trials are often initiated. This talk will present the results of two studies: in the first, we use EEG markers of attention to sensory input to examine differential predictors of the development of psychosis in individuals with and without autism. In the second, we examine habituation of neural response to repeated tones in three syndromic forms of autism alongside idiopathic autism and typically developing controls.

Methods: Study 1: Using EEG data recorded at baseline visit for the NAPLS2 clinical high risk for psychosis (CHR) consortium, we examined the ability of P300 amplitude to infrequent target (10%) and novel (10%) stimuli from visual and auditory oddball tasks to predict conversion to psychosis over the next 24 months in CHR patients with and without autism. Study 2: In ADNP syndrome, Phelan-McDermid syndrome (PMS), FOXP1 syndrome, idiopathic autism, and controls, we presented four tone sequences and compared N1, P2, and N2 amplitude to the first tone, as well as habituation of these components to subsequent tones. Both males and females were included in both studies and ANOVAs tested both between and within group effects.

Results: EEG data revealed dissociable profiles regarding neural response to sensory stimuli in psychosis converters, depending on autism status. In particular, P300 amplitude to novel visual stimuli was smaller in converters (n = 71) versus non-converters (n = 220) without autism, but larger in converters (n = 4) versus non-converters (n = 14) with autism (p = 0.06). Study 2: Relative to typical controls (n = 14), individuals with idiopathic autism (n = 19) had reduced response to tone 1 (p = 0.04) with no change in habituation (ps > 0.05). Patients with PMS (n = 19) showed both weaker response to tone 1 (p = 0.02) and more habituation across tones 2-4 (ps < 0.04). Qualitatively, those with ADNP syndrome (n = 9) showed strong initial response with greater habituation, and those with FOXP1 syndrome (n = 4) showed typical initial response but reduced habituation; statistical analyses are pending larger sample sizes in these two syndromes.

Conclusions: Our results show that: 1) EEG response reflecting attention to sensory stimuli can be useful in the prediction of later psychiatric symptoms in patients with autism, and 2) the pattern of neural responsiveness to simple auditory stimuli differs across various forms of syndromic autism where fundamental biological alterations also differ. Reliability of these markers across sessions and their sensitivity to detecting treatment effects are currently being explored. Taken together, these findings support the role of EEG as a promising tool for developing multi-functional biomarkers in ASD.

Disclosure: Nothing to disclose.

51.4 Differential Patterns of Visual Sensory Alteration Underlying Face Emotion Recognition Impairment and Motion Perception Deficits in Schizophrenia and Autism Spectrum Disorders

Daniel Javitt

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Background: Impaired face-emotion recognition (FER) and abnormal motion processing are core features in schizophrenia (SZ) and autism spectrum disorder (ASD) that have been linked to atypical activity within visual cortex. Despite overlaps, only a few studies have directly explored convergent versus divergent neural mechanisms of altered visual processing in ASD and SZ. We conducted two studies to compare processes across groups. The first employed a multimodal imaging approach to evaluate FER and motion perception in relation to functioning of subcortical and cortical visual regions. The second investigated scan patterns while viewing static faces with congruent vs. incongruent emotion features.

Methods: Subjects for study#1 were 20 high-functioning adults with ASD, 19 SZ patients and 17 control participants (Ctl). Behavioral measures of motion-sensitivity and FER were obtained along with electrophysiological and functional MRI measures of visual pattern and motion processing. Resting-state fMRI was used to assess the relationship between cortico-cortical and thalamo-cortical connectivity and atypical visual processing. Subjects for study#2 were 21 ASD, 23 SZ patients and 21 Ctl. Fixation patterns and both stimulus- and fixation-onset ERP were assessed during viewing of static emotion faces with either congruent vs. incongruent eye and mouth components. Analyses were by ANOVA and multiple regression. Both sexes were included.

Results: In study#1, SZ and ASD participants showed equivalent and intercorrelated deficits in FER and motion-sensitivity but markedly different profiles of physiological dysfunction. SZ participants showed patterns consistent with reduced visual activation/functional connectivity, including increased decreased stimulus-induced theta and alpha ERD (p < 0.01) whereas ASD participants showed hyperactivity/hyperconnectivity, including increased theta (p < 0.001) and alpha ERD (both p < 0.001). In both groups, activation of the pulvinar correlated with dysregulation of visual alpha activity and increased clinical symptoms. Together, these multimodal measures discriminated SZ from ASD participants with 97% accuracy. In study#2, as expected both groups showed reduced FER vs. Ctl (p < 0.05). ASD showed significantly less fixation to eyes vs. mouth relative to Ctl (p = 0.034). Both groups also used eye information to a lesser extent than Ctl when processing incongruent faces (p < 0.001). Deficits in activation correlated with impaired alpha and delta frequency activity.

Conclusions: ASD and SZ are associated with convergent deficits in FER and social cognition, but divergent underlying mechanisms. Whereas patterns in SZ are, in general, associated with reduced activation/connectivity, patterns in ASD are, in

general, associated with increased activation/connectivity. The measures can be used to both distinguish groups and assess underlying mechanisms.

Disclosure: NeuroRx, Glytech, Inc/LLC, Stock / Equity, NeuroRx, Board Member, Biogen, Phytecs, Promentis, Advisory Board, Autifony, SK Life Sci, Cadence, Pfizer, Consultant, Cerevance, Grant.

Panel

52. Modeling and Dissection of Decision-Making Deficits Across Mood, Anxiety, Substance, and Psychotic Disorders

52.1 Computational Models of Information Processing as a Link Across Species Allowing Translation From Fundamental Discoveries to Clinical Practice

Aaron Redish

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Background: There has been a recent backlash against the idea that fundamental neuroscientific discoveries in non-human animals can translate to human clinical practice, particularly in the fields of psychiatric and pharmacological research. We will argue here for a computational understanding of the information processing underlying decision making as a bridge across that chasm. Although individual species (including humans) have evolved specific ethologies underlying their actions, current theories of computational information processing suggest strong similarities across species, if tasks are designed to access those specific ethologies.

Methods: We approach this question from three synergistic directions: (1) species-specific tasks framed in the ethology of a given species, but with parallel computational requirements across tasks, (2) computational models of the necessary information processing, and (3) clinical consequences as disruptions of that information processing.

Results: We will present a variety of results as an explanation of this new methodology from two task sets with potential translational and clinical relevance. (1) Data from rats and mice on the Restaurant Row task (foraging for food) and humans on the Web-Surf task (foraging for online videos). In these tasks, subjects forage for reward with a time limit. On entry into a restaurant or video-gallery, subjects are presented with a delay before reward will be delivered ("offer zone"), which starts counting down once the subject decides to stay (by entering a "wait zone"). We will show the power of behavioral translation, such that all three species show a significant sensitivity to sunk costs only after committing to the decision (on entering the wait zone) and different decision-making processes in the two zones ($N = 64$ mice, 32 rats, 65 humans) . We will also present consequences of cocaine and morphine on mouse decision making in this task ($N = 32$), clinical relationships to human cocaine users ($N = 12$), and demonstrate how these decision making patterns differ from other phenotypically distinct clinical samples (e.g. anorexia nervosa, $N = 17$). (2) Data from rats on an anxiety-inducing food-foraging / predator-attack task in which a robotic predator interferes with a path to food reward. We will show that this task allows a differentiation between fear and anxiety in rats with pharmacological translational validity ($N = 14$), and that these effects entail different computational information processes in the rodent hippocampus ($N = 2$).

Conclusions: By working at a computational level, similar processes can be identified between species, providing a more robust translation. Because each species empowers different experimental paradigms (optogenetics in mice, neural ensemble recording in rats, pharmacology in rodents, fMRI in humans, clinical phenotyping in humans), computational processes can be delineated through cross-species experimentation. Clinically relevant maladaptive behavior can be seen as a dysfunction in one or more of the information processing pathways, particularly in how those pathways interact with the environment. Interestingly, these data suggest that treatment potential can be achieved by repairing the computational dysfunction or by compensating for it (either through enhancing parallel information processing decision systems or changing the environment to alleviate the dysfunction).

Disclosure: Nothing to disclose.

52.2 Using Computational Models to Examine Effort-Based Decision-Making in Psychopathology

Jessica Cooper

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Background: Effort-based decision-making paradigms have emerged as useful tools to assess motivational deficits in psychopathology and have been widely used in populations with schizophrenia and major depression. While these tasks provide rich information about decision processes, common methods of analysis rely on summary statistics (i.e. percentage of high-effort selections) that may obscure clinically relevant information. Here, we apply a series of computational models to effort-based decision-making (EBDM) data to examine: the degree to which EBDM behavior is guided by trial-wise reward and probability in schizophrenia and depression, associations between decision variables and symptom severity, and relationships between in-lab behavior and behavior in daily life using ecological momentary assessment (EMA).

Methods: We analyzed data collected using the Effort Expenditures for Rewards Task (EEfRT) from previously collected samples of patients with schizophrenia, an ongoing study of patients with major depression, and an additional ongoing study in which a transdiagnostic sample of participants completed in-lab behavioral tasks followed by 6 weeks of EMA. All studies included participants of both sexes. In the EEfRT, participants choose to allocate effort (speeded button presses) for rewards over the course of many trials, choosing between a low effort/low reward option and a high effort/high reward option. The choice behavior of each subject was fit with computational models that provided estimates of decision consistency, effort aversion, and sensitivity to probability. Comparison to a null model using BIC was also used to examine the extent to which trial-wise information was utilized to guide choice. EMA data was used to quantify pursuit of effortful activities in daily life and was compared to in-lab performance on the EEfRT.

Results: We found that individuals with schizophrenia ($n = 150$) were less likely than healthy control participants ($n = 105$) to make choices that were guided by available trial-wise information $X2(2, N = 255) = 12.253$, $p = 0.002$. Among patients with schizophrenia, systematic effort allocation was related to differences in cognitive functioning ($p < 0.018$). In contrast to schizophrenia, patients with depression from an ongoing study ($n = 43$) were more frequently fit by models indicating systematic allocation of effort for rewards, similar to what has been observed in healthy controls. However, within this sample, patients exhibited aversion to effort that was related to psychomotor slowing as assessed by the Quick Inventory of Depressive Symptomatology (QIDS), Spearman's $r = 0.449$, $p = 0.011$. Finally, preliminary analysis of EMA data suggests that model-estimated effort aversion from the EEfRT is correlated with completion of activities in daily life with

lower relative expected effort (as compared to activities that were considered but not completed), Spearman's $r = -0.752$, $p = 0.012$.

Conclusions: Our results demonstrate the potential of computational modeling approaches for studying motivation to exert effort for rewards in psychopathology. Ongoing studies are assessing relationships with behavior in daily life and symptom severity in individuals with depression.

Disclosure: Nothing to disclose.

52.3 Modelling Addiction in the Intersection Between Endophenotypes and the Role of Environment Complexity

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Background: Substance use disorder is often described as caused by aberrant instrumental conditioning. This computational theory assumes that substances of abuse hijack the reinforcement learning mechanism, causing dopamine to signal the presence of non-compensable prediction errors (i.e. action-outcomes are always interpreted as more rewarding than expected). This theory successfully explains compulsive drug consumption despite adverse consequences, but poorly accounts for the heterogeneity of behavioral phenotypes in addiction and treatment response. Furthermore, addiction is today also diagnosed under conditions that are not associated with dopamine-releasing substances, as for instance in pathological gambling and videogaming, suggesting that other decision-making vulnerabilities may be interacting with the described ones.

Methods: To expand on the existing computational theories and allow validation across Marr's levels of analysis, we used a neural model, simulating neural dynamics and plasticity in multiple cortico-striatal circuits, and a normative model, based on reinforcement learning (RL). In the neural model, we varied the connectivity weights between dorsal and ventral cortico-striatal circuits ($N = 330$ agents, 11 endophenotypes). In the RL model, we varied a parameter controlling the weighed competition between model-based (MB) and model-free (MF) components ($N \approx 600$ agents, 6 endophenotypes). For both models, the environment presented multiple choices, one of which simulated an addictive reward. If selected, the addictive option triggered dopamine-dependent associative plasticity in the neural model. The agents were then tested under a second, reward-deprived phase to quantify the compulsive behavior. In this phase, the selection of the addictive reward was suboptimal: it resulted in prediction error-based learning processes and it was followed by stochastic negative outcomes simulating negative social and health-related consequences. To simulate conditions of non-drug addiction, we did not disrupt the MF component and allowed for compensable prediction errors.

Results: Both models revealed that the agents characterized by high dominance (i.e. asymmetrical ventral-dorsal connectivity or MB-MF balance) expressed significantly ($p < 0.001$) higher preference for the addictive selections in comparison with balanced agents. Furthermore, the RL system was vulnerable to suboptimal choice selections if deliberation and habit formation exceeded the capabilities of the artificial agents. The presence of the stochastic negative after-effects overloaded the agents, resulting in further phenotypical differentiation. We found that even temporarily reduced cognitive resources (as, for instance, it has been suggested may be caused by stress) resulted in increased likelihood to develop addiction, measured as number of individual choice preferences towards the addictive reward ($p < 0.001$ in the comparison between populations characterized by either 50 or 500 model based updates per step).

Conclusions: We found evidence, across neural and algorithmic levels of analysis, that two so far neglected dimensions are likely to play a critical role in clinical heterogeneity in addiction. We suggest these two vulnerabilities interact with those already described in literature and play a prominent role in non-pharmacological forms of addiction, as they do not rely on differential physiological reactions to drug consumption.

Disclosure: Nothing to disclose.

52.4 Anxiety and Decision-Making Under Ambiguity

Sonia Bishop

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Background: Theoretical accounts have linked anxiety to intolerance of ambiguity. However, this relationship has not been well operationalized empirically. The computational decision-making literature has valuably operationalized alternate forms of uncertainty, in particular differentiating 'ambiguity' from 'risk'. 'Ambiguity' is used to refer to situations where the information required to estimate action-outcome contingencies is partially or totally missing. This leads to imprecision when estimating outcome probability, i.e. it is not possible to obtain a sharp point estimate. This is effectively a form of second-order uncertainty (Bach et al., 2011).

We tested the hypothesis that high trait anxious individuals would show heightened ambiguity aversion and that this would increase as a function of the level of missing information (i.e. as second-order uncertainty increases). We also tested the hypothesis that trait anxiety would be associated with an altered dorsal anterior cingulate cortex (dACC) response to level of missing information given the reported role of the dACC in processing second-order uncertainty resulting from other manipulations (Behrens et al., 2007).

Methods: Behavioral and fMRI data were obtained from 31 healthy human volunteers (18-38yrs, 21 females). Participants completed the Spielberger State-Trait Anxiety Inventory. They then performed an Ellsberg style urn task while fMRI data were acquired. On each trial, participants chose between two urns. Drawing an 'O' was linked to receipt of electrical stimulation. Both the proportion of 'Os' and magnitude of potential stimulation (subjective pain levels were calibrated initially) differed between urns and across trials. On 50% of trials, tokens were occluded in one urn, making it harder to estimate the proportion of 'Os'. Eight levels of missing information (MI) were used ($MI = 1 - \sqrt{(n/50)}$, where n = tokens revealed). Logistic and linear regression were used to investigate the influence of missing information upon urn choice and dACC activity, respectively.

Results: Participants showed a bias towards choosing the unambiguous (versus ambiguous) urn which increased with level of missing information (MI). This effect of MI on choice was significant: $t(30) = 5.8$, $p = 2.3e\text{-}6$ and increased positively with trait anxiety, $r(29) = 0.35$, $p = 0.027$. DACC activity increased with MI level, $t(30) = 3.5$, $p = 0.0015$. This activation pattern was strongest when participants went on to choose the ambiguous urn. The extent of differential DACC activity on trials where participants engaged with versus avoided ambiguity positively correlated with trait anxiety, $r(29) = 0.36$, $p = 0.049$.

Conclusions: We demonstrate that elevated trait anxiety is associated with increased avoidance of ambiguous options as a function of level of missing information. This quantifiable sensitivity of trait anxious participants to missing information might lead to sub-optimal choices when confronted with ambiguous situations in everyday life.

DACC activity increased with level of missing information. This was primarily observed on trials where participants went on to choose the ambiguous urn. This differential activation was strongest in high trait anxious individuals. These results are

consistent with dACC activity facilitating rational evaluation of options under second order uncertainty and being recruited to override engagement in ambiguity avoidance. The extent of activation required to support choice of the ambiguous urn was greatest in those individuals (high in trait anxiety) and those conditions (with high levels of missing information) characterized by elevated ambiguity avoidance.

Disclosure: Nothing to disclose.

Panel

53. Developmental Origins of Adult Health and Disease (DoHAD)-Relevance in Psychiatry

53.1 Schizophrenia Risk, Placenta Gene Expression and Early Child Development

Abstract not included.

53.2 Developmental Regulation of Neuronal Chloride Homeostasis and the E/I Switch: Interaction of NRG1 Genetics and Perinatal Choline Supplementation

Amanda Law

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Background: Genes involved in maturation of GABAergic neurotransmission, including Neuregulin1 (NRG1,[8p21-p12]) and CHRNA7 [15q13.3], are associated with neurodevelopmental disorders, including schizophrenia (SZ). Our studies in human brain have demonstrated that a molecular mechanism of genetic risk in NRG1, in SZ involves rs6994992, a promoter polymorphism associated with elevated transcription of the NRG1 isoform, (NRG1-IV) and reduced brain levels of the CHRNA7 receptor (α7nAChR). Signaling via the α7nAChR is a critical driver of the GABA excitatory/inhibitory (E/I) shift, mediated via the chloride cotransporters, NKCC1 and KCC2; and deficits in α7nAChR expression are a potential mechanism of observed increases in the NKCC1/KCC2 ratio in SZ patients and associated E/I deficits. NRG1 is a regulator of α7nAChR expression; the role of NRG1-IV is unknown. Choline is a α7nAChR agonist, and a novel prenatal supplementation strategy in humans shown to improve early behavior; the neuromolecular mechanisms are unknown. Here we studied the developmental transcriptional regulation of the NKCC1/KCC2 switch in mPFC of NRG1-IVtgNSE-tTA (male and female) transgenic mice, and assessed the impact of perinatal α7nAChR agonism, via maternal dietary choline supplementation.

Methods: We developed a transgenic mouse (NRG1-IVtgNSE-tTA) engineered to overexpress human NRG1-IV exclusively in brain. mPFC was used for quantitative RNA profiling to assess the developmental trajectories of NKCC1 & KCC2 expression. Mice at postnatal (P) days, P0, P6, P9 and P13 were studied, either exposed to a normal (1g/kg) or choline-supplemented (5g/kg) maternal diet during gestation through weaning.

Results: In male and female mice exposed to a standard choline diet, a main effect of postnatal age was observed on the NKCC1/KCC2 ratio ($N = 102$; ANOVA, $p < 0.0001$), whereby NKCC1/KCC2 ratios were dramatically higher at P0, declining to reach adult levels by P13. These molecular data parallel the developmental shift in GABA E/I balance. An interaction of sex*age was observed on the NKCC1/KCC2 ratio (ANOVA, $p = 0.002$) with all female mice showing higher ratios than males at P0. All mice exposed to maternal dietary choline supplementation showed developmental acceleration of the molecular switch (main effect of diet; $N = 183$; ANOVA, $p < 0.0001$). Finally, male and female NRG1-IVtgNSE-tTA exposed to a normal choline diet showed elevated NKCC1/KCC2 expression ratios ($n = 27$, $p < 0.05$), at P13, when the molecular switch is complete, and similar to findings observed in adult patients with SZ. Maternal gestational choline supplementation prevented this deficit ($n = 17$, main effect of genotype $p = 0.885$). We also present novel data demonstrating reduced α7nAChR neuronal distribution in NRG1-IVtgNSE-tTA mice. and impact of gestational choline supplementation to prevent adult neurobehavioral deficits in NRG1-IVtgNSE-tTA mice.

Conclusions: Our data demonstrate a novel biogenetic interplay between NRG1-IV, CHRNA7 and developmental regulation of the NKCC1/KCC2 switch, necessary for maturation of E/I balance. We show that a molecular mechanism of choline's effects in utero, involves accelerated maturation of neuronal chloride homeostasis, via altered regulation of NKCC1/KCC2 transcription.

Disclosure: Nothing to disclose.

53.3 Placental and Cord DNA Methylation Markers Associated With Child Outcome in Prospective Autism Studies

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Background: DNA methylation acts at the interface of genetic and environmental factors relevant for autism spectrum disorder (ASD). Placenta and cord blood, normally discarded at birth, are potentially rich sources of DNA methylation patterns predictive of ASD in the child. Males have a 3:1 bias for developing ASD compared to females, but potential epigenetic alterations in the intergenerational dynamics of X chromosome inactivation and reactivation has not been previously explored at a genome-wide level.

Methods: We performed whole genome bisulfite sequencing (WGBS) analyses of placentas and cord blood from a prospective study MARBLES (Markers of Autism Risk in Babies-Learning Early Signs) of high-risk pregnancies and offspring of both sexes. We also performed replication in a similar cohort (EARLI) and using alternative approaches of DNA methylation analyses, including Infinium 450k and EPIC arrays and pyrosequencing of specific gene loci. Differentially methylated regions (DMRs) were identified using dmrseq and modified custom scripts.

Results: Placental ASD associated DMRs were significantly enriched at promoters, mapped to genes functionally enriched in neuronal development, and overlapped genetic ASD risk. Cord blood methylation analysis revealed a male-specific significant hypomethylation in global CpG methylation in ASD compared to typically developing (TD) ($p < 0.042$ discovery, 0.016 replication, 0.002 pooled), correlating with the enrichment of hypomethylated blocks and DMR enrichment on the X chromosome. Cell type deconvolution also revealed and increase in newborn red blood cells in ASD compared to TD cord. Cord blood ASD DMRs showing replication were significantly enriched for synaptic functions, neuronal development, ASD genetic risk, and X chromosomal location.

Conclusions: Together, these results suggest that DNA from placenta and cord blood samples contains DNA methylation marks that can inform the complex etiology and possibly be used for prediction and early intervention of ASD in high risk families.

Disclosure: Nothing to disclose.

53.4 Maternal Childhood Adversity Impact on Fetal Adrenal Volume: Potential Pathway for Sex-Specific Intergenerational Transmission of Stress

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Background: Preclinical research suggests that maternal early life stress (ELS) can be "transmitted" to the offspring, influencing risk or resilience for a host of physical and behavioral outcomes in a sex-varying manner. While mechanisms mediating the intergenerational transmission of stress effects are unknown and likely to be multifactorial, particularly in humans, we have previously published that ELS has an enduring impact on maternal glucocorticoid response to stress postnatally, in both humans and mice. Here we focus on fetal and infant effects (by sex) of maternal ELS on adrenal volume and cortisol response to an acute stressor, respectively.

Methods: Pregnant women completed the Adverse Childhood Experiences (ACE) Questionnaire and underwent 3-D ultrasound (US) at 21.5 (1.4) and 29.5 (1.4) wks to assess fetal adrenal volume and fetal total weight. Maternal ($n = 147$) and infant ($n = 62$ female, $n = 74$ male) demographics were summarized by high (2+, $n = 76$) versus low (0-1, $n = 71$) maternal ACE score (0-10). Weight-adjusted fetal adrenal volumes (WaFAV) were modeled in separate linear regressions at the first and second US visits. The primary predictor was ACE group, and other covariates included fetal sex as determined at birth, maternal age, maternal body mass index (BMI) at first prenatal visit, race, Perceived Stress Scale and Edinburgh Postnatal Depression scores at US, gestational age (GA) at US and the interaction between infant sex and maternal ACE. Acute stress (restraint, loud noise) effect on cortisol response (log-transformed, peak cortisol controlling for baseline) at 6 mos of age is currently available for a subset ($n = 66$) of these offspring, hence these data are considered preliminary in nature though an interaction between fetal sex and maternal ACE group was explored.

Results: At visit 1 ($n = 134$), there was a significant interaction between ACE group and infant sex ($p = 0.001$). ACE effect was significant in boys, with boys of high ACE mothers having lower WaFAV than boys of low ACE mothers ($p < 0.001$). In the low ACE group, girls had smaller WaFAV than males ($p < 0.001$). GA also had significant effects on WaFAV ($p < 0.001$), with later GAs associated with lower average WaFAV. The interaction between ACE group and infant sex was not significant ($p = 0.127$) at Visit 2. Maternal BMI and GA were the only significant predictors of weight-adjusted WaFAV at visit 2 ($p = 0.001$, $p = 0.046$). Among the subset ($n = 38$ low ACE; $n = 28$ high ACE) of 6 month-old infants for which there are currently data available, there was a significant maternal ACE by sex interaction ($p = 0.02$), with larger peak cortisol response to an acute stressor in high compared to low ACE males and smaller response in high compared to low ACE females.

Conclusions: Maternal ACE impacts fetal adrenal development in mid-gestation in a sex-specific fashion, with greatest impact observed in males. Though the ACE effect on WaFAV is diminished in late-gestation, our preliminary data from 6 month-old infants suggests an enduring effect of maternal ACE x infant sex on offspring stress response. To our knowledge this is the first study to provide evidence of ELS impact on fetal HPA-A development in humans. Cortisol levels from the remaining infant cohort are expected imminently and will be used to assess the enduring and potential clinical relevance of maternal ACE x sex effects on WaFAVs.

Disclosure: Sage Therapeutics, Consultant, Sage Therapeutics, Honoraria, Sage Therapeutics, Grant

Panel

54. Neurosteroids and Oxysterols Modulate Neuroinflammatory Signaling: Translational Insights

54.1 The Endogenous Neurosteroid (3α,5α)-3-Hydroxypregnan-20-One (3α,5α-THP) Inhibits Pro-Inflammatory Toll-Like Receptor (TLR)-MyD88-Dependent Signaling and Enhances Anti-Inflammatory Signaling in Immune Cells and Brain

A. Leslie Morrow

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Background: 3α,5α-THP has therapeutic activity in addictions, depression, traumatic injury and epilepsy. These conditions are regulated by multiple TLRs, suggesting that 3α,5α-THP may inhibit TLR signaling. We have recently shown that 3α,5α-THP inhibits TLR4 activation in RAW264.7 macrophages and the brain of alcohol-preferring (P) rats. However, its effect on human macrophages, other TLR signals and the potential difference between males and females, are currently unknown.

Methods: We examined the effect of 3α,5α-THP on agonist-induced activation of the TLR2, TLR4 and TLR7 signals, which are MyD88-dependent and the TLR3 signal, which is TRIF-dependent in RAW264.7 cells, human macrophages and rat brain.

Results: We found that Pam3Cys (10 μg/ml; 24h) activates TLR2 signaling, evidenced by increased levels of TRAF6, pERK1/2, pCREB and pATF-2. Increased expression was completely inhibited by 3α,5α-THP (1 μM, $p < 0.05$). Imiquimod (1 μg/ml; 24h) activated TLR7 signaling, resulting in pIRF7 increase (30%) that was completely inhibited by 3α,5α-THP (1 μM, $p < 0.05$). By contrast 3α,5α-THP did not inhibit the Poly-IC- (TLR3 agonist; 25 μg/ml; 24h) induced increase in CXCL10, suggesting that 3α,5α-THP selectively inhibits the activation of signals that function through MyD88. Similar results were found in cultured human macrophages. Consistent with the findings for RAW264.7 cells, 3α,5α-THP inhibited MCP-1 and pIRF7, but had no effect on pIRF3 levels in P rat nucleus accumbens (NAc). We found a sex difference in baseline MCP-1 (55% higher in male vs. female) and pIRF7 (45% higher in female vs. male). In both sexes, 3α,5α-THP (15 mg/kg; IP) administration significantly reduced the levels of MCP-1 (40% in females; 25% in males) and pIRF7 (55% in males and females). 3α,5α-THP inhibition of MCP-1 levels was also found in the P rat ventral tegmental area, amygdala, hypothalamus and hippocampus, indicating that 3α,5α-THP inhibits pro-inflammatory TLR signal activation throughout brain. However, TLR activation can also increase anti-inflammatory signals. Significantly, 3α,5α-THP administration increased the NAc levels of CX3CL1 in both female (45%, $p < 0.05$) and male (30%, $p < 0.05$) P rats, suggesting that it simultaneously shifts proinflammatory signaling to anti-inflammatory signaling via multiple pathways.

Conclusions: Collectively, the data indicate that the therapeutic potential of 3α,5α-THP involves modulation of proinflammatory MyD88-dependent TLR signaling pathways as well as the enhancement of anti-inflammatory pathways resulting in diminished pro-inflammatory signal activation, both in immune cells and throughout the brain.

Disclosure: Nothing to disclose.

54.2 Structure-Activity Profile of the Anti-Inflammatory Effects of Neurosteroids in Vitro

Steven Mennerick

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Background: A neurosteroid was recently approved by the FDA for treating women with postpartum depression. Clinical studies are in press demonstrating efficacy for major depressive disorder. These results fuel a desire to understand basic mechanisms of neurosteroid action. Best known effects of this class are on ion channels, particularly GABA-A receptors. However, as far as is known, other GABA receptor modulators are not antidepressant. This suggests that other mechanisms may be at play. Hints from the literature suggest that neurosteroids may have anti-inflammatory effects, so we tested structure-activity characteristics of anti-inflammatory effects in an in vitro model.

Methods: We used BV2 cells, a microglial-derived cell line, with lipopolysaccharide (LPS) stimulation to induce neuroinflammatory responses in vitro. We co-incubated cells with neurosteroids with LPS for 6 h, and measured transcriptional changes to pro-inflammatory cytokines, IL-6, IL-1beta, and TNF-alpha using qPCR.

Results: We found that the anti-depressant neurosteroid allopregnanolone reduced LPS-induced pro-inflammatory transcription. The unnatural enantiomer of allopregnanolone was similarly effective. Without LPS, baseline cytokine transciption was below detection, and neither compound increased levels to detectable. In contrast with the anti-inflammatory effects of allopregnanolone and its enantiomer, progesterone and its unnatural enantiomer were ineffective a reducing pro-inflammatory cytokine transcription.

Conclusions: Unnatural enantiomers are interesting drug candidates because they are expected to resist metabolism and thus may have longer half life with fewer off-target effects. We conclude that the enantiomer of allopregnanolone has anti-inflammatory properties without GABAergic sedative effects.

Disclosure: Sage Therapeutics, Grant

54.3 Neurosteroids as Biomarker Candidates and Novel Therapeutics: Pregnenolone Decreases Low Back Pain - Results From a Randomized Controlled Trial

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Background: Extensive data support anti-inflammatory and analgesic roles for neurosteroids (NS). Inflammation mediates key components of pain perception, and NS such as 3α,5α-THP (allopregnanolone, ALLO) are decreased in clinical populations reporting pain symptoms (Naylor et al 2015; Kilts et al 2010). Ameliorating NS deficits with exogenous supplementation may thus hold promise as an approach that is mechanistically anchored and potentially disease-modifying. Current pharmacological treatments for chronic pain, including opioids, are often suboptimal and associated with substantial risk for adverse sequelae such as overdose and addiction. Alternative interventions for pain that are safe, efficacious, and biomarker-informed are thus urgently needed. Given the pronounced anti-inflammatory actions of NS, these molecules represent logical therapeutic options for the treatment of pain. We therefore conducted a 6-week, randomized, placebo-controlled trial of pregnenolone (PREG) vs. placebo to determine possible therapeutic utility for treatment of chronic low back pain in Iraq/Afghanistan-era veterans. We also investigated potential NS associations with inflammatory markers in two independent cohorts to explore mechanistic underpinnings of its therapeutic efficacy.

Methods: Iraq/Afghanistan-era veterans with chronic low back pain received PREG or placebo for 4 weeks. Participants ($n = 94$) were randomized to fixed escalating doses of PREG to 500 mg per day ($n = 45$) or placebo ($n = 49$). The primary endpoint was change in average daily pain intensity ratings. Outcomes were estimated using mixed regression modeling procedures. Primary hypothesis tests were based on differences in model-based estimates of least square mean outcomes at the final study time point. NS and inflammatory markers were quantified in serum samples from two independent cohorts (INTRuST and MIRECC).

Results: Participants randomized to adjunctive PREG showed significantly greater improvements in low back pain compared to placebo on pain diary scores ($p = 0.024$) and pain recall ($p = 0.010$). Pain interference scores for "work" ($p = 0.040$) and "activity" ($p = 0.031$) were also improved in veterans randomized to PREG compared to placebo. Consistent with these clinical trial results, higher NS levels were associated with lower levels of pro-inflammatory markers in two independent cross-sectional cohorts. Specifically, in MIRECC discovery and replication cohorts, CRP was inversely correlated with ALLO ($p = 0.47$, $r = -0.23$, $n = 82$; $p < 0.0001$, $r = -0.26$, $n = 480$) and PREG ($p < 0.0001$, $r = -0.33$, $n = 479$). These inverse correlations of CRP with PREG and ALLO were replicated in the independent INTRuST Biorepository cohort ($p < 0.001$, $r = -0.27$, $n = 259$ and $p < 0.057$, $r = -0.12$, $n = 257$, respectively). IL-6 was similarly inversely associated with NS in both MIRECC (PREG, $p < 0.0001$, $r = -0.25$, $n = 479$; ALLO, $p < 0.0001$, $r = -0.22$, $n = 480$) and INTRuST cohorts (PREG, $p < 0.001$, $r = -0.245$, $n = 259$; ALLO, $p < 0.001$, $r = -0.264$, $n = 257$).

Conclusions: Treatment with PREG significantly decreased low back pain in this randomized controlled trial, demonstrating promise as a new intervention for pain that is safe, well-tolerated, non-habit-forming, and potentially efficacious. Inflammatory markers are inversely associated with PREG and other NS in two independent cohorts. The anti-inflammatory actions of PREG and other NS may contribute to their analgesic actions.

Disclosure: Nothing to disclose.

54.4 The Oxysterol 25-Hydroxycholesterol as a Mediator and Amplifier of Neuroinflammation: Implications for Neurodegenerative Disorders

Steven Paul

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Background: The oxysterol 25-hydroxycholesterol (25HC) has been shown to be an important immunomodulator in peripheral hematopoietic cells, such as macrophages and lymphocytes. In the CNS, 25HC is synthesized from cholesterol via cholesterol 25-hydroxylase (CH25H), a cytochrome P450 enzyme expressed predominantly in microglia. 25HC is further metabolized by both astrocytes and oligodendrocytes (but not microglia) to 7α -25 dihydroxycholesterol (7α25diHC) via the enzyme Cyp7b1. 7α25diHC is a high affinity ligand for the G-protein coupled receptor GPR183/Ebi2 where it has also been shown to mediate chemotaxis of lymphocytes. The importance of 25HC as an immune modulator has been demonstrated primarily in peripheral immune cells. Consequently, we have investigated its role in modulating innate immunity in the brain.

Methods: We have used primary cultures of mouse microglia to study the impact of activating innate immunity on the synthesis and secretion of 25HC as well as various cytokines (IL-1β). We have also studied the effects of 25HC treatment on cytokine production and secretion by primary microglia. In addition, primary microglia prepared from apoE targeted replacement mice were used to study the impact of the various apoE isoforms on 25HC and cytokine production and secretion.

Results: We first investigated the role of 25-HC and CH25H in the microglia-mediated innate immune response. We demonstrated that the TLR4 agonist lipopolysaccharide (LPS) markedly upregulates both CH25H expression and 25-HC secretion in/from primary microglia isolated from wild type mice (10–50-fold, $p < 0.01$). We also found that 25-HC itself enhances the effects of LPS on stimulating pro-inflammatory cytokine (IL-1β synthesis and secretion in microglia (approximately 5-10-fold, $p < 0.01$). Elimination of 25-HC production by genetically deleting CH25H reduces LPS-induced IL1β production by microglia (−30–40%, $p < 0.05$), suggesting that 25-HC may function as an "amplifier" of IL1-mediated inflammatory signaling in microglia. Furthermore, we found that 25-HC also enhances IL1β production in microglia treated with pathophysiological concentrations of Aβ42 oligomers. Finally, microglia expressing human apolipoprotein E4 (APOE4), a well documented genetic risk factor for late-onset Alzheimer's, disease produce significantly greater amounts of 25-HC and secrete higher levels of IL1β in response to 25HC treatment than APOE2-expressing microglia (approx. 5–10-fold, $p < 0.01$) following combination treatment with LPS and 25-HC.

Conclusions: Our data demonstrate that the immunomodulatory oxysterol 25-HC is produced by microglia in an apoE isoform-dependent manner (E4>>E2/EKO) following stimulation with LPS and markedly potentiates LPS-mediated cytokine secretion from microglia, also in an apoE isoform-dependent manner (E4>>E2). Thus, 25HC may function as an "amplifier" of neuroinflammation, promoting cytokine-mediated inflammatory signaling and neurodegeneration.

Disclosure: Nothing to disclose.

Study Group

55. Ethical Issues in the Use of Digital Technology for the Assessment and Treatment of Psychiatric Conditions

Scott Kollins*, Ellen Frank, John Torous, Kimberly Resnick, Phyllis Foxworth, Jennifer Kanady, Michael Waitzkin

Study Group Summary: The entire field of medicine is in the midst of a digital revolution. Technology is impacting all aspects of health care, and across therapeutic areas. Digital approaches for assessing, monitoring, and treating psychiatric conditions have proliferated in recent years, and products are on the market or in development for nearly all disorders, including autism, ADHD, anxiety, mood disorders, addiction, sleep difficulties, and schizophrenia/psychosis. While the rapid growth in this field holds great promise, there are myriad ethical issues, consideration of which has not kept pace with the increase in products. The purpose of this study group is to consider a range of ethical issues with input from a range of perspectives including clinical research, legal aspects of digital health, patient advocacy, and commercial development. The broad categories to be considered, along with specific questions include:

1. Data privacy, consent, and confidentiality in an era of remote, digital assessment/treatment and passive monitoring

What are the boundaries of privacy with the collection of real-time data via digital technologies
How can we ensure proper consent for research participation and clinical care using digital technologies?
What steps are companies and investigators taking to ensure confidentiality and integrity of collected data from potentially large numbers of affected individuals?
What are the legal issues that can arise in the collection, storage, and use of digital health data?

2. Quality standards and clinical validation for digital products

What defines efficacy and safety for digital products and what are the distinctions from traditional pharmaceutical or device products?
What kinds of study designs are best suited to conducting efficacy/effectiveness trials to ensure high quality products in the marketplace?
Who are the appropriate entities to provide regulation and oversight for the use of digital technologies in the assessment and treatment of psychiatric conditions?

3. Ethical challenges for monitoring risk and safety in real time

What kinds of procedures are needed to address risk and safety issues that may arise in the context of real-time monitoring of behavior?
Where are the boundaries of risk prediction that can/should be acted upon? Eg., if we develop reliable ML/AI driven algorithms for predicting suicidality, what actions could be ethically taken in the absence of patient reported risk?
How can providers of digital products manage ancillary information/inadvertent information they may receive that relates to patient/consumer risk and safety?

Disclosure: Akili Interactive, Stock / Equity, Bose, Grant, Akili Interactive, Grant.

Panel

56. Using Genome Editing Technologies to Understand the Mechanisms of Neuropsychiatric Disorders

56.1 Chromatin-Mediated Alternative Splicing of Srsf11 Regulates Cocaine Reward Behavior

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Background: Cocaine drives alternative splicing to a far greater extent than differential mRNA expression, yet this mechanism of gene regulation is understudied in the context of drug abuse and addiction. During development, alternative isoform expression confers neuronal identity and is maintained throughout life. We posit that in adulthood, alternative exon expression maintained by stably-associated hPTMs, underlies chronic disease states, such as addiction. We and others have recently reported that alternative splicing is correlated with H3K36me3 enrichment in brain, a histone posttranslational modification (hPTM) which is also regulated by cocaine. H3K36me3 is catalyzed by the histone methyltransferase, SET2.

Methods: We generated three within-sample, RNA/ChIP datasets from NAc of mice following either SET2 overexpression, 1-day or 28-days of abstinence following cocaine-self administration. In each dataset, we analyzed alternative isoform expression and splice junction enrichment of H3K36me3. To examine the direct causal relevance of H3K36me3 to alternative splicing, we expressed either full-length SET2 or locus-targeted dCas9-SET2 in NAc (control: catalytically dead SET2(R195)). Differential splicing analysis was performed by MAJIQ, using thresholds of FDR < 0.05 and ΔPSI < 0.1 (10% change in Percent Spliced In), and validated by PCR. Samples sizes were 10-12 mice (pooled 2 mice per n =

6 seq samples, n = 2 biological replicates) or 6-10 samples (qPCR, PCR) per each biological replicate. Statistical analysis for cocaine behavior was performed by 1-way repeated measures ANOVA. All experiments were performed in 8-10 week old male or female mice on a C57 background.

Results: Across three datasets, we identified exons that were both differentially expressed and enriched for H3K36me3 at the respective splice junction (FET $P < 0.05$). This group included Serine and arginine rich splicing factor 11 (Srsf11). We selected this gene given that the Srsf11 target motif was enriched globally in spliced genes following cocaine- and SET2-treatment. Targeted enrichment of H3K36me3 by dCas9-SET2 to the relevant Srsf11 splice junction was confirmed by CUT&RUN-seq in N2a cells. This manipulation increased inclusion of the targeted skipped exon (n = 6 samples, 3 replicates) and increased cocaine conditioned place preference (n = 6 mice).

Conclusions: Taken together, the combination of bioinformatic and epigenetic editing approaches provide conclusive evidence of the functional relevance of H3K36me3 enrichment at splice junctions to expression of specific isoforms. We are currently working to determine the precise mechanism by which this histone modification contributes to alternative splicing, either via direct recruitment of splice factors or regulation of the kinetics of RNA polymerase.

Disclosure: Nothing to disclose.

56.2 Circuit-Specific CRISPR Gene Editing in a Mouse Model of Cocaine Seeking

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Background: Activation of ventral hippocampus (HPC) CA1 glutamatergic projections to nucleus accumbens (NAc) drives seeking of cocaine, but the mechanism by which cocaine shapes the function of this vCA1-NAc circuit is poorly understood. ΔFosB is induced throughout HPC by cocaine and we have shown that its regulation of gene expression in dorsal HPC CA1 pyramidal neurons is critical for learning and memory and cell excitability. Here, we investigate cocaine effects on vCA1-NAc physiology and use novel circuit-specific CRISPR tools to knock out FosB gene expression specifically in the vCA1-NAc circuit and assess effects on cell physiology and cocaine reward and seeking.

Methods: Male and female C57Bl6/J mice from Jackson Labs were used in this study and all experiments were performed in accordance with IACUC-approved protocols. Viral vectors were injected by stereotaxic surgery into vHipp (3° angle; −3.2 mm AP, ±3.4 mm ML and −5.0 mm DV), and NAc (10°; +1.6 AP; ±1.5 ML; −4.4 DV). Mice were implanted with chronic indwelling jugular catheters and singly housed. After a 3-day recovery period, mice underwent training for cocaine self-administration (0.5 mg/kg, infused over 5 s) using nose-poke on fixed ratio one schedule over the course of 14 days. Following one week of abstinence, mice were reintroduced to the chamber, and non-cocaine-reinforced responding was used as a measure of cocaine seeking. Electrophysiological recordings were performed 1 day following 10 days of experimenter administered cocaine (20 mg/kg); coronal slices (250 μm) were prepared in oxygenated artificial cerebrospinal fluid at 30–32 °C and recordings made using a computer-controlled amplifier (MultiClamp 700B), digitized (Digidata 1440), and acquired with Axoscope 10.1 (Molecular Devices). Circuit-specific translating ribosomal affinity purification (TRAP) was performed using Rosa26eGFP-L10a mice and antibodies 19C8 and 19F7 (Memorial Sloan-Kettering).

Results: We found that cocaine, similar to ΔFosB expression, reduces vCA1-NAc excitability, suggesting that cocaine induces ΔFosB leading to decreased neuronal excitability ($F10,130 = 3.31$, $p < 0.001$). Studies are ongoing to identify the ion channel mechanism underlying this change. We next sought to determine whether ΔFosB expression in vCA1-NAc neurons is necessary for cocaine reward and seeking. We used circuit-specific, viral-mediated CRISPR silencing of the FosB gene (FosB KO) in vCA1-NAc and assessed both place preference for cocaine and cocaine seeking after forced abstinence. FosB KO in vCA1-NAc neurons decreased cocaine reward and seeking (reward: $F1,29 = 4.74$, $p = 0.038$; seeking: $t15 = 2.17$, $p = 0.046$). Circuit-specific TRAP-RNA-Seq in non-drug-exposed vCA1-NAc neurons indicates that these effects are driven by specific patterns of ΔFosB-mediated gene expression, however future studies will identify the cocaine-specific ΔFosB transcriptional targets underlying vCA1-NAc physiology and behavior.

Conclusions: Collectively, these findings demonstrate that cocaine induces ΔFosB expression in vCA1-NAc projection neurons, leading to functional reshaping of this circuit and driving cocaine-dependent behaviors. Furthermore, they suggest that ΔFosB and its gene targets in hippocampus afferents may serve as promising therapeutic inroads for treating drug addiction.

Disclosure: Nothing to disclose.

56.3 CREB-Mediated Activation of Zfp189 in Nucleus Accumbens Drives Behavioral Responses to Psychostimulants, but Not Opiates

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Background: Repeated administration of psychostimulants or opiates elevates cyclic AMP-responsive element binding protein (CREB)-mediated transcription in the nucleus accumbens (NAc), a major brain reward region. Viral over-expression of CREB in NAc decreases the rewarding effects of both psychostimulants and opiates, suggesting that CREB activity in this region can regulate the addictive properties of these drugs. However, manipulations of this kind cause transcriptional changes at hundreds or thousands of gene loci, limiting mechanistic insight. To clarify this complexity, we generated a novel fusion construct consisting of the nuclease-dead, RNA-guided, DNA-binding protein Cas9 tethered to the active form of CREB (S133D) (dCas9-CREB). When combined with viral delivery methods, this tool enables us to target active CREB to specific gene loci within mouse brain. Here, in mouse NAc, we targeted CREB to the Zfp189 gene, which is observed to be activated by CREB in animal models of psychostimulant abuse, and assessed the causal contribution of the CREB-Zfp189 interaction to psychostimulant (cocaine) versus opiate (morphine) induced behaviors.

Methods: Both male and female C57Bl/6J mice, aged 8–10 weeks, were utilized in these studies. dCas9 fusion constructs and sgRNAs (Zfp189 targeting or non-targeting control) were packaged in herpes simplex virus (HSV) and injected as a viral cocktail by stereotaxic surgery bi-laterally to NAc (10°; +1.6 AP; ±1.5 ML; −4.4 DV). For conditioned place preference (CPP), one side of a CPP box was repeatedly paired with cocaine (7.5 mg/kg; intraperitoneal injection) or morphine (5 mg/kg; subcutaneous injection) then on the test day mice were allowed to move freely in the box. For locomotor sensitization, mice were administered cocaine (10 mg/kg) or morphine (10 mg/kg) for seven sequential days and locomotion was quantified. Sample sizes are 10-15 mice per group and statistical analyses were performed with two-tailed t-tests or two-way ANOVAs, comparing the test group (HSV-dCas9-CREB + HSV-Zfp189-sgRNA) and the control group (HSV-dCas9-CREB + HSV-non-targeting-sgRNA).

Results: We observed that co-delivery of HSV-dCas9-CREB and HSV-Zfp189-sgRNA to NAc is capable of elevating Zfp189 gene expression (mRNA) relative to non-targeting controls ($P < 0.05$). Using these approaches to induce CREB-mediated activation of Zfp189 in both male and female mice reduces conditioned preference behaviors for cocaine ($P < 0.05$), but does not affect morphine preference ($P > 0.9$). Further, inducing CREB-Zfp189 interactions potentiates locomotor response to cocaine ($P < 0.05$), yet do not alter locomotor responses to morphine ($P > 0.5$). Using cell-type specific analyses, we observe that cocaine exposure specifically induces chromatin opening at the Zfp189 gene in D2R-expressing medium spiny neurons (MSNs).

Conclusions: These experiments indicate that CREB's action at Zfp189 causally contributes to CREB's ability to reduce the rewarding effect of psychostimulants. However, CREB-Zfp189 interactions in the NAc did not affect behavioral responses to morphine; suggesting that CREB's capacity to reduce the rewarding properties of opiates not mediated by CREB's action at Zfp189. We hypothesize that our cocaine effect is driven by CREB-Zfp189 interactions in D2-MSNs. This work is evidence that in vivo neuroepigenetic editing allows us to model a single drug-induced molecular interaction and identify its causal contribution to the broader syndrome.

Disclosure: Nothing to disclose.

56.4 Cocaine-Induced Neuron Subtype Differential Regulation of the EGR3-NAB2 Transcriptional Feedback Loop

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Background: Early growth response 3 (Egr3) induction in nucleus accumbens (NAc) dopamine receptor 1 (D1)-medium spiny neurons (MSNs) and reduction in dopamine receptor 2 (D2)-MSNs drives behavioral responses to cocaine. However, it is unclear if Egr3 expression in MSN subtypes mediates relapse-like behavior after long term abstinence from cocaine. Additionally, Egr3 transcriptionally activates and represses its own expression, the latter through a negative feedback loop whereby Egr3 activates its corepressor NGF1-A binding protein 2 (Nab 2). It is unknown if differential Egr3 expression in MSN subtypes, after repeated cocaine, is mediated through this Egr3-Nab2 feedback. Finally, CRISPR tools that alter endogenous transcription of Egr3 and Nab2, in a time selective and cell type specific manner are critical for defining the precise temporal role of these molecules in drug self-administration and relapse-like behavior.

Methods: D1-Cre and A2A-Cre mice underwent 10 days of cocaine (0.5mg/kg/infusion) self-administration followed by NAc infusion of adenoassociated viruses (AAVs) to knockdown Egr3 in D1-MSNs (AAV-DIO-Egr3-miR-mCitrine) or overexpress in D2-MSNs (AAV-DIO-Egr3-EYFP). Three weeks after self-administration, mice underwent extinction followed by cocaine (7.5. mg/kg) induced reinstatement. D1-Cre-RiboTag (RT) and A2A-Cre-RT mice were used to examine Nab2 mRNA in NAc MSN subtypes after repeated cocaine (20mg/kg, 7 days) exposure. Finally, using the blue light activated CIBN/Cry2 dimerization system we developed optogenetic-CRISPR tools to alter Egr3 and Nab2 transcription. We combined DIO-CIBN-nuclease dead(d)Cas9 and DIO-Cry2-lysine demethylase 1 (KDM1A) or Cry2-p300 histone acetyltransferase (termed Opto-CRISPR-KDM1A and Opto-CRISPR-p300) with gRNAs targeting Egr3 and Nab2 promoters, or lacZ control. Vectors and Cre-recombinase were expressed in Neuro2A cells. Following blue light (473nm) exposure, cells were collected for quantitative RT-PCR. Samples sizes in each group are 6-9 (per sex; behavior), 4-6 (pooled 4 mice; RiboTag experiments), and 3 (cell culture). Two-way- or One-way-ANOVAs and 8-10 week old male or female mice on a C57 background were used.

Results: Reduced cocaine-induced reinstatement occurred in female mice with Egr3 overexpression in D2-MSNs ($P < 0.05$). D1-MSN Egr3 knockdown had no effect on reinstatement behavior. Nab2 mRNA was reduced in D1-MSNs and enhanced in D2-MSNs after repeated cocaine ($P < 0.01$). Blue light activated Opto-CRISPR-KDM1A histone demethylation at the Egr3 promoter enhanced Egr3 mRNA ($P < 0.05$), while at the Nab2 promoter reduced Nab2 ($P < 0.01$) and increased Egr3 mRNA ($P < 0.05$). In contrast, Opto-CRISPR-p300 histone acetylation at the Egr3 promoter led to enhanced Egr3 and Nab2 mRNA ($P < 0.01$), while at the Nab2 promoter caused enhanced Nab2 and reduced Egr3 mRNA ($P < 0.01$).

Conclusions: Our data implicate a temporal, cell type specific, and sex specific role for Egr3 in cocaine-induced reinstatement. Further, our studies show that Egr3 differential regulation in MSN subtypes may occur through the Egr3-Nab2 feedback loop. Finally, we demonstrate that Opto-CRISPR tools can alter Egr3 and Nab2 transcription. We can now begin to utilize these tools in vivo in a sex specific and cell type specific manner during precise time points in cocaine self-administration and relapse-like behavior.

Disclosure: Nothing to disclose.

Panel

57. Shared Risks for Brain and Heart Across the Lifespan: Impact of Sex

57.1 Multi-Morbidities of Insulin Resistance: Diabetes, Dementia and Depression

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Background: Premature and accelerated brain aging trajectories started to be recognized in cognitive and neural responses, but specific mechanisms for the course of cognitive aging remain to be elucidated. Insulin resistance (IR) is known to change with age, affect cognition in older and elderly adults as well as in patients with affective disorders. It is unknown whether IR can predict cognitive decline in individuals younger than age 50 without overt mental illness. Studies in younger adults afford a unique opportunity to assess whether IR mediates cognitive and correlating neural processes decades before the manifestation of cognitive decline.

Methods: We use an innovative accelerated longitudinal design to characterize trajectories of cognitive and neural biomarkers and to: 1) describe baseline cognitive and neural biomarkers of brain function across the spectrum of IR in persons of both sexes ages 25–50; 2) assess how the baseline IR and change in IR at a younger age affects the pattern of decline in cognitive and neural biomarkers and 3) explore the effects of baseline IR on changes in cognitive and neural variables of interest. Utilizing an accelerated longitudinal design we are recruiting overweight/obese individuals (total $N = 120$) aged 25–50. Based on semi-longitudinal data, this design will allow us to examine outcome development over 25 years between ages 25–50 after 3-year follow-up.

Results: Initial results are available for 46 participants who completed the second time point. Insulin resistance as measured by serum glucose levels after glucose challenge with insulin clamp was associated with increases in time to complete DKEFS Trail 2 from year 1 to year 2 (Pearson correlation 0.386, $p = 0.010$) and with baseline levels of depression (Pearson correlation $= 0.240$,

p = 0.019) but not with changes in depression scores. Age, BMI, lipid panel, and fasting glucose were not associated with changes in DKEFS or Hamilton depression scores from year 1 to year 2.

Conclusions: Serum glucose and insulin resistance have distinct effects on performance in specific cognitive domains, separate from aging or other measures of metabolic impairment. Insulin resistance may contribute to impairments in cognitive flexibility over time. Additional data from the third planned time point will help to confirm or deny and to further expand these findings.

Disclosure: Nothing to disclose.

57.2 Developmental Programming by Glucocorticoids of Adult CardioMetabolic and Neuroendocrine Function: A Sex and Brain Perspective

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Background: Using a rat model of developmental exposure to glucocorticoids, we have shown that prenatal treatment of pregnant dams causes long lasting increases in cardiovascular responses to stress and alterations in metabolism in adulthood. Moreover, these effects are female-biased and can be alleviated using the angiotensin II Receptor I (AT1R) antagonist Losartan.

Methods: We explored the changes that might program the comorbidity of cardiometabolic changes with neuroendocrine dysregulation. Timed-pregnant Sprague-Dawley rat dams were treated with the synthetic glucocorticoid, dexamethasone (0.1–0.4 mg/kg BW/day) from gestation day (GD) 18-21. Offspring were allowed to grow to adulthood and cardiovascular function was determined using remote radio telemetry. Baseline and stress responsive heart rate, blood pressure and heart rate variability were determined in male and female offspring. N-Counter technology (Nanostring Inc.) was used to examine changes in adult and neonatal mRNA expression within the paraventricular nucleus of the hypothalamus (PVN), a brain region that controls neuroendocrine and autonomic function and feeding, metabolism and behaviors. In situ hybridization and immunohistochemistry was used to map changes in mRNA and protein expression in PVN sub regions.

Results: Prenatal dexamethasone treatment decreased brain weight and body weight at birth. In adulthood offspring showed an increased pressor response to restraint in adult offspring and an increase in Low Frequency component of HRV suggesting an imbalance of autonomic regulation. 2 way ANOVA showed significant age and treatment effects in the development of vasopressin mRNA across prepubertal and adult life in both sexes. Changes in some Renin-Angiotensin System (RAS) genes were also detected, as were changes in neurosteroid synthesis enzymes, 5 alpha reductase and 3 beta Hydroxysteroid dehydrogenase (3b-HSD).

Conclusions: The results of these studies identify some specific gene targets for programming of the adult hypothalamus by prenatal glucocorticoid overexposure. These changes suggest a dysregulation of the autonomic nervous system which further implicates preautonomic neurons that are found within the paraventricular n. of the hypothalamus.

Disclosure: Nothing to disclose.

57.3 Shared Prenatal Programming of Sex Differences in Major Depression and Cardiac Dysregulation With Midlife Memory Decline

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Background: Major depressive disorder (MDD) is a primary cause of disability worldwide. Women are at twice the risk than men, with a high comorbidity for cardiovascular disease (CVD) and risk for memory decline later in life. Thus, understanding shared pathophysiology of MDD, CVD, and memory decline across the lifespan is critical for developing therapeutics targeted to early intervention and prevention. We have been testing the hypothesis that this shared risk has prenatal origins involving abnormalities in immune-stress and cardiac pathways with sex-dependent consequences. Previously, we demonstrated abnormalities in maternal prenatal TNF-α exposure were significantly related to sex differences in risk for MDD and loss of cardiac tone (heart rate variability- HRV) by age 43. Here, we tested the association of prenatal maternal immune markers (IL-6, IL-β, and TNF-α) at mid-gestation on memory function and circuitry in early midlife and whether it was mediated by MDD and associated with structural abnormalities in shared brain regions between mood, cardiac tone, and memory.

Methods: 212 early midlife adults (ages 47-54), equally divided by sex, underwent cognitive, MRI/fMRI assessments. They were adult offspring whose mothers were followed through pregnancy and sera stored at NIH for >50 years, from which prenatal maternal cytokines (TNF-α, IL-1β, IL-6, IL-10 at early 3rd trimester) were assayed. MDD was based on SCID interviews 10 years earlier. Cytokines were assessed using a multiplexed, bead-based immunoassay on a Luminex 3D detection platform and run in duplicate. Face-Name Associative Memory and 6-Trial Buschke Selective Reminding Test were used. MR data were acquired on a Siemens Tim Trio 3T MRI scanner with a 12-channel head coil using spin echo T2*-weighted sequences and analyzed using a semi-automatic segmentation MRI tool. General linear models were used to relate prenatal exposures to structural volumes of memory/mood circuitry regions and cognitive function, controlled for potential confounders.

Results: Using mixed linear models adjusted for intrafamilial correlation, race, parental SES, and weeks gestation of serum draw, maternal prenatal IL-6 levels were significantly negatively associated with FN among postmenopausal women ($\beta = -0.18$, $p = 0.05$), and not among pre- or peri-menopausal women or men. Interaction between IL-6 and reproductive status was significant ($p = 0.0018$), and postmenopausal women did not significantly differ from men. Further, interaction of IL-6 with MDD status on FN was significant in postmenopausal women ($F = 8.06$, $p = 0.01$), affecting right caudal ACC thickness ($\beta = -0.07$, $p = 0.002$) and FN performance ($\beta = -0.59$, $p = 0.03$). Among men, esp. men with recurrent MDD, high maternal TNF-α levels were significantly associated with lower FN memory ($\beta = -0.67$, $p = 0.05$). Right HIPP mediated this, as high maternal TNF-α was also associated with lower right HIPP volume in men ($\beta = -405.98$, $p = 0.004$), which was associated with lower FN performance ($\beta = 0.0004$, $p = 0.001$).

Conclusions: Taken together, these findings provide initial evidence that MDD and HRV in mid-adulthood and deficits in memory circuitry later in early midlife are associated with shared prenatal immune exposures, dependent on sex, and related to reproductive aging in women. Findings suggest immune system dysregulation beginning in fetal development may provide a window into potential early biomarkers for intervention for comorbidity.

Disclosure: Cala Health, Consultant.

57.4 Non-Invasive Vagal Nerve Stimulation: A Novel Therapeutic for Targeting the Comorbidity of Major Depression and Cardiovascular Disease

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Background: Patients with major depressive disorder (MDD) and decreased vagal tone are at increased risk for developing cardiovascular disease (CVD). Conversely, patients with CVD are more likely to have poor outcomes if they develop MDD. Thus, treatments that address comorbid illness will have a great impact on public health. Recently, transcutaneous auricular vagus nerve stimulation (taVNS) has emerged as a non-invasive alternative to implanted VNS in the treatment of MDD, and experimental studies suggest it also modulates the autonomic nervous system physiology. The mechanisms of action and neural pathways mediating these effects are still unclear. However, neuroimaging and physiological studies from our group show that taVNS effects are mediated by modulation of nucleus tractus solitarii (NTS), from which projections synapse with brain regions involved in mood and autonomic regulation [central autonomic network (CAN)]. Further, as NTS operate in response to changes in cardiopulmonary function, we have proposed gating taVNS to variations in respiration could enhance its modulatory effects in mood and cardiovascular physiology in MDD patients.

Methods: Twenty women with recurrent MDD in an active episode were scanned twice within one week to assess effects of taVNS gated to exhalation vs gated to inhalation in modulation of CAN, depressive symptomatology and peripheral autonomic function. Functional MRI (fMRI) data were acquired on a Skyra 3T MRI scanner (TR = 1250 ms, TE = 33 ms, slice thickness = 2mm). A mild visual stress challenge preceded and followed a 30-minute session of respiratory-gated taVNS delivered to the left cymba conchae of the ear (region innervated by the auricular branch of the vagus nerve). An electrocardiogram (ECG) was collected during the fMRI sessions and point-process algorithms were used to compute variations in instantaneous estimates of the high frequency component of heart rate variability (HF-HRV). In a separate study, 20 hypertensive subjects underwent two experimental sessions on non-consecutive days. In each session subjects received 30 minutes of exhalatory-gated taVNS or sham stimulation. Continuous ECG and blood pressure signals were collected and point process analyses of heartbeat and blood pressure dynamics were performed.

Results: In MDD patients, exhalatory-gated taVNS resulted in significantly greater activations of NTS, subgenual anterior cingulate and orbitofrontal cortices ($p < 0.01$), as well as acute reduction in BDI values (-8.21 ± 7.4 vs -3.58 ± 4.83, $p = 0.03$) and increase in cardiovagal output (HF-HRV percent change = $48.3 \pm 33.6\%$ vs $23.56 \pm 27.34\%$, $p = 0.01$) when compared with inhalatory-gated taVNS. In hypertensive subjects, exhalatory-gated taVNS resulted in significant reduction of systolic blood pressure values compared to sham intervention (-5.0 ± 10.5 mmHg vs 2.7 ± 7.5 mmHg, $p = 0.01$).

Conclusions: Our results demonstrate the enhanced impact of a novel, respiratory-gated auricular taVNS technique in CAN modulation with associated reduction of depressive symptomatology, and increased peripheral autonomic regulation in MDD subjects, as well as blood pressure reduction in hypertensive patients. Furthermore, this data provides initial evidence supporting the therapeutic potential of this technique for its use in MDD patients with comorbid CVD.

Disclosure: Nothing to disclose.

Panel

58. Precision Neurostimulation for Treatment of Psychiatric Disorders

58.1 Antidepressant-Responsive Brain Signatures in Major Depression Defined by Electroencephalography

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Background: Though antidepressants are some of the most-widely prescribed medications, their efficacy relative to placebo has come into question. While the history of repetitive transcranial magnetic stimulation (rTMS) research is more recent than that of antidepressant medications, real rTMS has likewise not differentiated from sham rTMS. One reason may be that the clinically-defined diagnosis of major depression is itself composed of largely unknown, but critical, neurobiological heterogeneity, which contributes to varying treatment outcomes.

Methods: We sought to identify antidepressant treatment-responsive neurobiological phenotypes vis a vis prediction of treatment outcome. To do so, we designed a novel latent-space machine learning algorithm tailored for resting-state electroencephalography (rsEEG), and applied it to several data sets. These data included a large randomized placebo-controlled trial of sertraline versus placebo for depression (EMBARC study), a clinic-based depression dataset wherein patients received rTMS treatment, and a third depression data set that included concurrent TMS/EEG assessment of neural excitability.

Results: Symptom change was robustly predicted in a manner both specific for sertraline (versus placebo) and generalizable across different study sites and EEG equipment. Using a second independent depression data set, we then tested for two properties of the predictive signature: convergent validation and neurobiological significance. We calculated in the second sample outcome predictions derived from the rsEEG model we trained in our first sample, as well as predictions from a task-based fMRI classifier we developed in our first sample in a prior analysis. These two predictions were found to correlate in the second sample, providing convergent multi-modal evidence for a treatment-response phenotype within the broader clinical diagnosis of depression. We also found that the rsEEG-derived outcome predictions in the second sample indexed prefrontal neural excitability, as measured by concurrent TMS/EEG, thereby elucidating neurobiological significance. Finally, in a third depression treatment data set we found that the greater the rsEEG-predicted symptom improvement with sertraline, the poorer the response to 1Hz rTMS treatment over the right dorsolateral prefrontal cortex.

Conclusions: Our findings thus advance the neurobiological understanding of depression and antidepressant treatment through an EEG-tailored computational model, as well as provide a clinically applicable avenue for personalized treatment approaches in psychiatry with the possibility of differential treatment prediction.

Disclosure: Akili Interactive, Advisory Board, Mindstrong Health, Advisory Board.

58.2 Individualized Functional Connectome Targeting for Repetitive Transcranial Magnetic Stimulation (rTMS) Protocols in Patients With Mild Traumatic Brain Injury and Neurodevelopmental Disorders

Abstract not included.

58.3 Optimization of TMS Delivery in the Temporal Domain

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Background: It is one thing to precisely locate in space, on an individual basis, a functional network to be modulated by brain stimulation. However, getting to the right location is only part of what is needed for network engagement and modulation: when the stimulation occurs plays a key role in whether it is effective. In TMS, the dynamics of stimulation generates differential effects on physiology and behavior at a number of time scales, from the temporal shape of the individual pulse waveform in the millisecond range, to the frequency and pattern of trains of pulses over seconds, to the duration, placement and number of sessions of TMS over minutes to days. Further, it has also become clear that the dynamic interaction of stimulation with ongoing cortical processing is also important: understanding state dependence is vital to optimizing efficacy. The focus of this presentation will be on two aspects of TMS timing: first, the acute effects on behavior of the placement of stimulus trains relative to ongoing cortical processing, and second, the longer lasting effects of controlling state dependency by stimulating relevant networks while they have been activated with ongoing tasks and cognitive therapy.

Methods: Acute behavioral effects of TMS were explored using a working memory task. In three previous studies, an fMRI-guided rTMS paradigm was developed that demonstrated temporal placement of 5 Hz rTMS trains immediately before participants were cued to respond in the task acutely enhanced their performance. Here, 34 healthy volunteers (17 young adults (YAs) and 17 older adults (OAs)), in a repeated measures design, were given active and sham 5Hz rTMS to three locations over occipital and premotor cortex and the supplementary motor area.

A second paradigm in which five patients with MDD were given 10 Hz rTMS over 20 sessions while simultaneously receiving a form of CBT demonstrated the control of cortical state in achieving longer lasting modulation. The patients were scanned using fMRI before and after the course of TMS, and the pre-post scans were compared to two groups of controls.

Results: In the working memory study, both YAs and OAs showed significant performance enhancement relative to sham TMS. Both groups also showed a significant worsening of performance in response time and accuracy with premotor stimulation. No effects were seen with SMA stimulation. A subset of YAs and OAs were brought back for a follow-up session in which the 5 Hz rTMS was applied to premotor cortex in the seconds immediately before the trials started instead of during the delay period after the stimulus set was presented. This time YAs showed significant performance enhancement, while the OAs showed smaller deficits.

In the depression study, all 5 patients remitted. In univariate MRI analyses, they showed increased pre-post activation in cortical and limbic regions associated with depression. Multivariate analyses of pre-post data comparing the patients receiving TMS and therapy with groups receiving only therapy and with healthy controls showed significant increases in fronto-temporal connectivity in the patients receiving TMS and therapy.

Conclusions: The two studies demonstrate the sensitivity of TMS effects to temporal placement of stimulation relative to ongoing cortical processing at both acute and longer-lasting time scales. The working memory effects, whether enhancing or disrupting performance, only last a few seconds, while cumulative effects, demonstrated using the working memory paradigm or within depression treatment, can last for days or months. The optimization of TMS effects via temporal control is discussed.

Disclosure: Nothing to disclose.

58.4 Towards Individualized Seizure Therapy

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Background: Despite advances in antidepressant interventions, none has replaced electroconvulsive therapy (ECT) in its acute efficacy and speed of action in severely depressed patients, including in psychotic depression, catatonia, and acutely suicidal patients. However, ECT carries a risk of significant adverse effects including cognitive and physiological side effects, some of which can be long term. The side effects are thought to be related to stimulation of brain areas beyond those implicated in depression. While these advances have improved the safety and tolerability of seizure therapy, a risk of cognitive side effects remains, and none of the currently used procedures individualize the current amplitude for each patient despite knowledge that anatomical variation significantly impacts the strength of the current delivered to the brain. We propose a first-in-human safety and feasibility study of this approach (termed "individualized low amplitude seizure therapy", or iLAST).

Methods: iLAST introduces three areas of improvement over conventional ECT. 1) Conventional ECT uses two large disc electrodes that are spaced widely apart, which leads to a nonfocal electric field distribution in the brain. In iLAST, we use a multi-electrode array to selectively target different regions of the brain similar to one employed in high-definition tDCS studies. This is coupled with state-of-the-art computational electric field modeling on an individual patient basis to examine the current flow in the brain. 2) Conventional ECT uses a high and fixed current amplitude (800 mA). This current amplitude is much higher than necessary to elicit an adequate seizure, as demonstrated in our computational studies, pre-clinical research in nonhuman primates, and early pilot studies in humans. The fixed current amplitude also results in a different amount of current entering the brain, possibly leading to variability in clinical outcome. In iLAST, we explore a dosing strategy in which the stimulus is titrated in the current amplitude domain. Not only does current amplitude titration minimize over-exposure of the brain to strong tetanic electrical stimulation, it also compensates for inter-individual variation in head anatomy and brain excitability. 3) Conventional ECT monitors seizure induction with two-channel EEG recording in the prefrontal cortex, which does not characterize seizure topography. In iLAST, we use high-density EEG electrodes that are weaved into the multi-stimulation electrode array so that topographical ictal EEG is recorded.

Results: Electric field simulation in a group of 67 ECT patients show marked variability in the induced electric field with conventional right unilateral electrode placement. The maximum E-field strength induced in the brain is 513 +/- 113.2 V/m. For bilateral ECT, the largest cluster of white matter voxels where the E-field strength is significantly correlated with the post-treatment MADRS score includes parts of the right inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, anterior thalamic radiation, and the corticospinal tract.

Conclusions: With advanced computational modeling, particularly anatomically-realistic finite-element head models derived from individual structural MRI data, combined with neuroanatomical targeting multi-electrode configurations and rational dosimetry, we can now develop personalized seizure therapy.

Disclosure: Nothing to disclose.

Panel

59. Turned on by Psychedelics: Putting LSD, Psilocybin, and MDMA to Work to Treat Psychiatric Disease

59.1 Durable Improvements in PTSD Associated With Early Life Stress Following MDMA-Assisted Psychotherapy

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Background: Recent data from a series of studies indicate that either 2 or 3 doses of 3-4 methylenedioxymethamphetamine (MDMA, ranging from 75mg-125mg per dose) can effectively attenuate symptoms of post-traumatic stress disorder (PTSD) in adult populations. However, less is known about the penetrance and durability of MDMA-assisted psychotherapy, especially in those suffering from treatment resistant PTSD as the result of childhood stress and trauma. Because those with early life trauma often present as treatment resistant, it is important to determine whether novel therapies can effectively mitigate PTSD symptoms in this population. We hypothesize that durability of the effects of MDMA-assisted psychotherapy will be similar in those suffering from early life stress and trauma and those suffering from other forms of PTSD.

Methods: Childhood trauma (ACE) was assessed at the baseline visit. PTSD symptomology (CAPS) was assessed at baseline and then again after each experimental session by a blinded, independent rater who had no prior experience with the subject. In order to ensure this blinding, participants were scheduled with a different independent rater for each CAPS assessment. After attending 3 psychotherapy-based preparatory sessions with a pair of psychotherapists, 36 subjects (17 ♀) meeting criteria for PTSD (CAPS > 34) were administered 3 doses of MDMA (80 or 120 mg with a supplemental half-dose 1.5 to 2 hours after the initial dose) at monthly intervals. MDMA was administered in the presence of the psychotherapists and at the beginning of an 8-hour psychotherapy session. Psychiatric medications were discontinued at least five half-lives plus one week before the first Experimental Session to avoid possible interactions with MDMA.

Results: There was a significant decrease in CAPS score between baseline and endpoint (CAPS at baseline = 45.67 +/− 1.19, versus CAPS post 3rd dose = 16.03 +/− 1.96; $p < 0.0001$). There was no significant difference in ACE childhood trauma scores between male and female subjects. Those with both high and low ACE scores responded equivalently to MDMA as assessed by the CAPS-5. While there was a trend towards male subjects having higher baseline CAPS scores than female subjects, there was no significant sex difference in the change in CAPS score between baseline and endpoint.

Conclusions: These data provide further evidence to suggest that MDMA is effective in attenuating symptoms of PTSD.

Disclosure: Nothing to disclose.

59.2 Social Reward Learning-Developmental Mechanisms and Therapeutic Opportunities

Gul Dolen

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Background: A critical period is a developmental epoch required for proper circuit organization and learning. Recently, we have identified a novel critical period for social reward learning, and demonstrated the ability of the psychedelic drug MDMA to reopen this critical period. However, it remains unclear whether LSD is also able to reopen this critical period, and whether these effects are dependent on serotonin 2A receptor activation in the Nucleus Accumbens

Methods: Here we measured social reward learning using the social conditioned place preference (social CPP) assay in male and female mice, two days (48 hours) following treatment with MDMA, LSD, along with either ketanserin, a serotonin 2A receptor antagonist, or saline control. Roughly 30 mice were used for each condition. For electrophysiological experiments, whole cell patch clamp recordings of medium spiny neurons in the nucleus accumbens were made, and both evoked and miniature excitatory postsynaptic currents (EPSCs) were recorded before and after administration of drug in in male and female mice. Between 6-10 cells were recorded for each condition. Within animal or cell comparisons of pre versus post values were analyzed using paired t-tests, whereas between animal comparisons of normalized and subtracted preference scores or normalized EPSCs were analyzed using unpaired t-tests.

Results: Here we show that both the therapeutic and macro doses of LSD (50 and 1 μg respectively) were like MDMA able to reinstate social reward learning in adults, raising the possibility that hallucinogens as a broad class are able to open critical periods. In contrast neither cocaine nor anesthetic doses of ketamine were able reopen the critical period.

Conclusions: These studies build on our previous work identifying a social reward learning critical period, and provide evidence that hallucinogens including MDMA and LSD reopen the social reward critical period. These findings have important implications for understanding the mechanisms underlying the therapeutic efficacy of these drugs for neuropsychiatric disease.

Disclosure: Nothing to disclose.

59.3 In Patients With Major Depressive Disorder, Psilocybin Administration is Associated With Reduced Amygdala Response to Negative Affective Stimuli and Normalization of Cortical Glutamate One Week After Psilocybin, and Improved Cognitive Flexibility One and Four Weeks After Psilocybin

Frederick Barrett

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Background: Current approved treatments for major depressive disorder (MDD) have limited effectiveness and patient adherence. Many patients remain refractory to treatment in many symptom domains, notably with cognitive deficits. We and others have recently shown psilocybin treatment (careful patient preparation followed by 1-3 administrations of psilocybin under closely monitored conditions) to greatly reduce depression severity in patients with depression and anxiety secondary to a cancer diagnosis, as well as patients with treatment resistant depression. However, the enduring effects of psilocybin on cognition and the neurobiological correlates of affective dysfunction that are associated with MDD have not yet been determined.

Methods: In a preliminary, randomized waitlist-controlled trial, 21 patients who were diagnosed with MDD (15 F, 6 M; mean age = 40.3 [range = 20-59]) were randomized using Urn randomization to either immediate (N = 12) or delayed (N = 9) treatment consisting of two psilocybin administration sessions (20 mg/70 kg and 30 mg/70 kg). Three weeks before session 1, and 1 and 4 weeks after session 2, a subset of patients (N = 18) completed behavioral measures of cognitive flexibility (the Penn Conditional Exclusion Task, or PCET) and verbal reasoning (the Penn Verbal Learning Test). Three weeks before session 1 and 1 week after session 2, a subset of patients also completed neuroimaging measurements including proton magnetic resonance spectroscopy (MRS) of the anterior cingulate (N = 10), right hippocampus (N = 10), and left hippocampus (N = 7), and an amygdala reactivity task (N = 12) during measurement of blood-oxygenation level-dependent (BOLD) signal. In the amygdala reactivity task,

patients matched one of two emotional facial expressions on the bottom of a display with a target emotional facial expression at the top of a display. Matching of vertical and horizontal ellipsoids was used as a control condition. Imaging data were collected with a Philips 7T MRI, with BOLD data collected using a 3D T2-prep sequence that corrects for field inhomogeneity distortions encountered at 7T, and with MRS data collected using a short-TE (13ms) point-resolved spectroscopy (PRESS) pulse sequence.

Results: One week after psilocybin session 2, compared to 3 weeks before session 1: (1) glutamate increased in the right hippocampus ($d = 0.59$) and decreased in the anterior cingulate cortex ($d = 0.53$); and (2) BOLD response to negative affective stimuli decreased in the amygdala ($t = 2.01$, p[FWE] $= 0.026$, $d = 0.61$). Cognitive flexibility also improved, with greater accuracy on the PCET 1 week ($t = 2.07$, $p = 0.045$) and 4 weeks ($t = 2.51$, $p = 0.016$) after psilocybin session 2 compared to 3 weeks before session 1 (f2 effect of time $= 0.34$). No effect of psilocybin on verbal reasoning was observed. Reduced amygdala response to negative affective stimuli was associated with reduction in depression severity assessed 1 week after session 2 using the GRID-HAMD ($r = 0.417$).

Conclusions: Reduced amygdala reactivity, normalized cortical glutamate, and increased cognitive flexibility may represent neural and psychological mechanisms underlying antidepressant effects of psilocybin in patients with MDD.

Disclosure: Nothing to disclose.

59.4 Harnessing Psilocybin: Synaptic Mechanisms Underlying the Antidepressant Response

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Background: Major depressive disorder is a leading cause of disability worldwide. Selective serotonin reuptake inhibitors, the standard-of-care treatment, typically do not relieve symptoms for weeks-to-months necessitating the development of faster, more effective therapies. Psilocybin has recently been shown to produce a significant improvement in patient-reported depression scores within days, with improvements persisting for up to 3 months. The FDA has since given psilocybin a fast-track designation for depression. We report here the first preclinical study on antidepressant-relevant behavioral responses to psilocybin in rodents and begin to address the underlying mechanisms.

Methods: Male rats and mice were subjected to chronic multimodal stress. Behavioral responses in reward tasks, such as the sucrose preference test, were compared before and after injection of psilocybin (1mg/kg). Tissue was harvested from stressed and unstressed animals with and without psilocybin for electrophysiological analyses of synaptic transmission.

Results: Chronic stress leads to maladaptive changes in reward-related behavioral responses that are accompanied by weakening of excitatory synaptic strength in several key nuclei of reward circuits. Restoration of normal reward behaviors by antidepressants is accompanied by a restoration of synaptic strength in these circuits. SSRIs restore synaptic strength by a 5HT1BR-triggered synaptic potentiation involving postsynaptic plasticity of AMPARs. We hypothesize that psilocybin engages the same mechanisms because it is a pan-serotonergic receptor agonist with high potency. Our data indicates that a single injection of psilocybin restores sucrose preference within 24 hrs ($p < 0.05$) and restores the strength of temporoammonic-CA1 cell excitatory synaptic transmission ($p < 0.05$), measured with AMPA:NMDA ratios in ex vivo brain slices. We also found that the effects of the SSRI fluoxetine on synaptic transmission and sucrose preference were unaffected by co-administration of the 5HT2R antagonist ketanserin (no significant difference to psilocybin alone).

Conclusions: We conclude that psilocybin induces a rapid antidepressant-like response in rodent models of stress-induced behavioral deficits in reward behavior, allowing the study of its mechanisms of action under well controlled experimental conditions. Because ketanserin blocks psilocybin-induced hallucinations in humans, our finding that ketanserin does not block SSRI actions, offers hope that psilocybin can be combined with ketanserin to produce a hallucination-free, rapid antidepressant treatment for depression.

Disclosure: Nothing to disclose.