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ABSTRACTS COLLECTION

ACNP 59th annual meeting: panels, mini-panels and study groups

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Study Group

1. Inclusion and Diversity Efforts Within Large Scientific Organizations: Tangible Methods: That Work

April Thames*, Sade Spencer, Lisa Eyler, Shawn McClintock, Erika Nurmi

Study Group Summary: Owing to the scarcity of women and underrepresented minorities in science especially in senior and leadership roles, diversity and inclusion are aspirational "buzz-words" that are used widely across institutions, organizational settings, and the scientific community. At federal, state and private sector levels, billions of dollars have been allocated to "fix" this longstanding systemic problem. Unfortunately, there remains no clear consensus on methods deemed effective to improve institutional diversity and inclusion. Moreover, those who are tasked with initiatives to create systemic change are often members of underrepresented groups who are given many responsibilities, but little to no authority or support. Consequently, these individuals often report feeling as though they are "preaching to the choir" and/or end up sustaining a career cost from engaging in such efforts. To create lasting change while minimizing burden on underrepresented individuals, it is important to ensure that efforts to promote diversity and inclusion are evidence-based and rely on methods with demonstrated positive transformation. Given that effective strategies are often based on social psychological and behavioral change theories tested with clinical trial methodology, it is particularly important for members of scientific societies, such as the American College of Neuropsychopharmacology (ACNP), to be aware of optimal practices in this area. The proposed study group will introduce specific methods, tailored towards fostering inclusion and diversity efforts in large scientific organizations and institutions. Drs. April Thames, Associate Professor of Psychology at the University of Southern California and Lisa Eyler, Professor of Psychiatry at the University of California San Diego will discuss methods of enhancing inclusion and diversity efforts from an organizational perspective that includes developing and sustaining workgroup efforts, identifying tangible outcomes and "products," use of social media, collaboration with international colleagues, and co-advising from organizational executive leadership. Dr. Erika Nurmi, Associate Professor of Psychiatry at UCLA and Greater Los Angeles VA, will discuss the development and integration of strategies and activities to promote inclusion and diversity in medical and scientific education and training; she will present data illustrating successes and challenges in designing and implementing these programs at UCLA and nationally. Dr. Shawn McClintock will present on how inclusion and diversity can be infused into the continuing education and scientific programs as part of the ACNP conference, as well as strategies to translate knowledge from the conference to the membership's place of work. Dr. Sade Spencer (co-Chair) will lead an interactive discussion and exercise to engage the audience in determining an action intention to take back with them to their spheres of influence based on what they have learned in the symposium. Overall, this timely and innovative work group sets the stage within and beyond the ACNP conference to ensure successful integration, implementation, and long-lasting state-of-the-art diversity and inclusion practices.

Disclosure: Nothing to disclose.

Study Group

2. Clinical High Risk (CHR) for Psychosis: Where Do We Go Next?

Cheryl Corcoran*, Carrie Bearden, Robin Murray, Raquel Gur, Scott Woods, Sarah Morris, Brandon Staglin, Michael Sand, Yulia Landa, Michael First, Rolando Castillo-Passi, Jerome Taylor, Robert Bilder

Study Group Summary: The field of research and services on clinical or ultra-high risk for psychosis (CHR/UHR) has evolved over time, engendering some controversy as to potential ethical concerns and relative merit. CHR is no longer circumscribed to risk for psychosis, or even risk itself, as the construct was included in the DSM-5 as "Attenuated Psychosis Syndrome" (APS), a "condition for further study". Ethical concerns about stigma remain and are the focus of empirical research. CHR programs exist worldwide, with increased funding for CHR research and services, and sustained efforts for harmonization of research methods and tools. Promising biomarkers of psychosis risk have been identified and replicated, however, there is still no evidence-based pharmacological treatment for CHR. Our study group has representation from NIMH, pharma, charitable nonprofits, the DSM, the CHR research community, and investigators who can contextualize CHR research in the broader effort of early identification and prevention of schizophrenia. The ACNP community is the ideal forum for a discussion of CHR research, and where to go next. We aim to have a lively discussion in which all perspectives are presented, with input from presenters and the audience. There are several questions to consider. (1) One set of questions addresses the CHR construct itself. How important is

psychosis outcome, given decreasing rates of transition among CHR worldwide? What are the ramifications for broadening of outcomes of interest in CHR research? While this leads to greater focus on comorbidity, cognition, negative symptoms, function and recovery, are we moving toward a general psychiatric risk construct for young people? What are the roles of healthy and patient controls for understanding specificity? Heterogeneity in CHR, once considered a threat to validity, is now a research priority. Is it worthwhile to consider what features and mechanisms are common across CHR? How important is risk? What can be done about variability in nomenclature and criteria? How similar should CHR and APS remain, and have we made progress in the "further study" of the APS "condition"? (2) A second set of questions focuses on intervention. How do we aggregate promising biomarkers so as to understand mechanisms that may inform treatment? How does academia work with pharma to develop treatments, given the large sample sizes needed to address heterogeneity and length of time needed to determine outcome? Which outcomes should we focus on? Should we integrate pharmacology with the network of coordinated specialty care for CHR funded by SAMHSA and other funding agencies? (3) A third set of questions address ethical concerns, including limited resources. To what extent has the field addressed the problem of stigma related to CHR? How can we best include in our research planning individuals with lived experience and their families, who are key stakeholders in the CHR research and services endeavor? Also, more broadly, in the context of limits in resources and funding, is the CHR approach the most optimal to advance early identification and prevention of serious mental illness? Namely, can advocates of the CHR approach answer the criticism that only a small proportion of individuals who develop a first episode of psychosis have attended CHR services, and therefore a public health approach that diminishes exposure to risk factors (e.g. heavy cannabis use) may prove more cost effective in preventing psychosis?

Disclosure: Nothing to disclose.

Panel

3. Translational Approaches in Identifying Novel Mechanisms and Treatment Targets for Alcohol Use Disorder

3.1 Oxytocin Reduces Alcohol Drinking and Relapse Behavior Through Signaling in Extended Amygdala in Mice

Howard Becker

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

Background: Oxytocin (OT) has emerged as a potential therapeutic for alcohol use disorder (AUD) and stress-related psychiatric illnesses. We previously showed that systemic administration of OT reduced binge-like alcohol drinking, operant oral self-administration, and stress-induced relapse-like behavior in male and female mice. It is not known whether these effects are mediated by OT release and signaling at oxytocin receptors (OTR) in brain or due to peripheral effects of OT. The present series of studies used pharmacological and chemogenetic approaches to address this research question.

Methods: Adult male and female C57BL/6J or OT-IRES-Cre mice (n = 6–12/group) were used to study binge-like alcohol drinking (limited access to 20% alcohol) and operant oral self-administration (responding (FR4 schedule) for 12% (v/v) alcohol (20 ul) during daily 20-min sessions). After 14 days of extinction testing, mice were exposed 15 min to a predator odor (TMT) for reinstatement testing. For chemogenetic studies, OT-IRES-Cre mice were injected with AAV-DIO-hM3Dq-mCherry or control virus to target excitation of OT neurons in the hypothalamus (PVN), or retroAAV-DIO-hM3Dq-mCherry or control virus was injected to target their projections to the central amygdala (CeA) and bed nucleus of the stria terminalis (BNST). CNO (3 mg/kg) was injected (IP) to activate the excitatory DREADD 30 min prior to testing. Mice were injected (IP) with the peripherally-restricted OTR antagonist Atosiban (1 mg/kg) or central OTR antagonist L368,899 (10 mg/kg) 45 min prior to injection of OT (0.5 mg/kg) or vehicle, which was given 30 min prior to testing.

Results: Chemogenetic activation of PVN OT neurons reduced binge-like drinking and operant alcohol self-administration, mimicking the effects of systemic OT treatment. CNO had no effects in mice with control virus. This effect was blocked by pretreatment with L368,899 but not Atosiban in the binge model. Activation of PVN OT neurons projecting to BNST or CeA also reduced binge-like drinking. The centrally active OTR antagonist L368,899, but not the peripherally-restricted OTR antagonist Atosiban, blocked the ability of OT to reduce binge-like drinking and stress-induced alcohol relapse-like behavior, with females less responsive to OTR antagonism.

Conclusions: Chemogenetic activation of OT neurons in the PVN reduced alcohol intake in two models in a similar manner as systemic administration of the neuropeptide. This effect was reversed by pretreatment with a centrally-active OTR antagonist. Also, pharmacological antagonism of OTR in the brain, but not in the periphery, blocked the ability of systemically injected OT to reduce binge-like drinking and stress-induced reinstatement of alcohol seeking behavior. Finally, targeted activation of PVN OT neurons that project to CeA and BNST reduced alcohol binge-like drinking as well. Collectively, these results suggest that OT effects in reducing alcohol drinking and relapse are mediated by signaling within extended amygdala circuitry and support the therapeutic potential for OT in treating AUD.

Disclosure: Nothing to disclose.

3.2 The Ghrelin System as a Potential Novel Pharmacological Target to Treat Addictions: Recent Translational Findings

Abstract not included.

3.3 From Big Networks to Small Metabolites, Novel Targets for Diagnosis and Treatment

Olivier George

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

Background: The rational development of novel therapeutic interventions for the treatment of alcohol use disorder and substance use disorders requires the identification of novel targets. Unbiased approaches, such as single-cell whole-brain imaging, microbiome profiling, and untargeted metabolomics, offer new opportunities to identify brain regions and metabolites that are specifically dysregulated in individuals with addiction-like behaviors. However, such approaches have been underused in the addiction field. To address this gap, we performed single-cell whole-brain microbiome profiling and untargeted metabolomics in animal models that are relevant to alcohol use disorder and opioid use disorder.

Methods: In Study 1, mice were given access to alcohol and exposed to chronic alcohol vapor to produce alcohol dependence. Brains were harvested after 1 week of abstinence, and single-cell whole-brain imaging of the immediate early gene c-fos using iDisco+ was performed. Hierarchical clustering, graph theory, and multiple regression analysis were performed. In Study 2, heterogeneous stock rats were given access to intravenous oxycodone

self-administration. The effect of microbiome depletion on oxycodone self-administration was tested using an oral non-absorbable antibiotic cocktail. Microbiome profiling using 16S rRNA sequencing and whole-blood metabolomics using tandem mass spectrometry and the XCMS platform were performed to identify biomarkers of vulnerability.

Results: In Study 1, alcohol abstinence resulted in the whole-brain reorganization of functional architecture in mice and a pronounced decrease in modularity that was not observed in nondependent moderate drinkers (published). Structuring of the alcohol abstinence network revealed three major brain modules—(1) extended amygdala module, (2) midbrain striatal module, and (3) cortico-hippocampo-thalamic module—that are reminiscent of the three-stage theory of addiction. Multiple regression analysis identified the central nucleus of the amygdala, midbrain reticular nucleus, posterior hypothalamic nucleus, parasubthalamic nucleus, dorsal peduncular area, basolateral amygdala, preoptic nucleus, and postsubiculum as independent predictors of addiction-like behaviors. In Study 2, antibiotic treatment depleted the gut microbiome and increased oxycodone self-administration in a subpopulation of vulnerable rats. Vulnerable rats exhibited an increase in the abundance of verrucomicrobia and a decrease in proteobacteria. Untargeted metabolomics identified a decrease in propionylcarnitine and an increase in taurocholic acid in vulnerable rats.

Conclusions: These results demonstrate that single-cell whole-brain imaging can identify novel brain regions and brain networks that are involved in addiction-like behaviors and that microbiome profiling and metabolomics can identify gut microbial phyla and small metabolites in the blood that are dysregulated in animals that are vulnerable to opioid self-administration. Such approaches have the potential to identify novel biomarkers for diagnosis and targets for medication development.

Disclosure: Nothing to disclose.

3.4 A Preliminary Double-Blind, Placebo-Controlled Study of Mifepristone Treatment of Alcohol Use Disorder

Barbara Mason

The Scripps Research Institute, La Jolla, California, United States

Background: The cortisol response of the brain's stress system becomes blunted with chronic heavy alcohol use. Blunted cortisol response in AUD is associated with increased alcohol craving and drinking. In prior work we found mifepristone, a potent glucocorticoid receptor antagonist, increased cortisol production and decreased responsivity to alcohol in preclinical and human laboratory models of AUD. This project sought to extend these findings to a population of individuals seeking treatment for AUD in order to learn how mifepristone may optimize AUD treatment outcome.

Methods: We conducted a Phase II, single-site, parallel groups, placebo-controlled study with random assignment to 1-week of treatment with double-blind mifepristone or matched placebo (2:1 ratio) in 103 male and female outpatients with current AUD of greater than or equal to moderate severity. Individuals also attended 8 weekly individual counseling sessions and one 3-month follow-up visit. Outcome data were collected weekly over 12 weeks, beginning with the first dose of study medication. Number of drinks per day was the primary outcome measure and was analyzed using latent growth curve models.

Results: Treatment groups did not differ significantly on average drinks per day over the entire 12-week post-baseline period. Exploratory post-hoc descriptive analyses suggested less daily drinking with mifepristone compared to placebo during the week on drug and for the following 2 weeks, consistent with the half-life of mifepristone. A latent growth model focusing on this period found evidence ($p < 0.05$ 1-tailed) that mifepristone was most effective for decreasing drinking in individuals who did not have abstinence as a treatment goal. Effectiveness in this group was linearly related to mifepristone plasma level. Model-predicted average drinks per day for such individuals were more than twice as high at Day 21 for placebo participants vs participants with a median mifepristone plasma level, with equivalent efficacy for men and women (about 40% of participants were female). Individuals who entered treatment with abstinence as a treatment goal did well with counseling, regardless of whether their assigned drug was mifepristone or placebo. Mifepristone was associated with significant ($p < 0.05$) improvement in liver function test values and Pittsburgh Sleep Quality Index scores, and with good safety and tolerability.

Conclusions: Future studies of pulsed dosing with 1-week of mifepristone at 3-week intervals may optimize long-term AUD treatment outcome. The significant effects of mifepristone on improving sleep and hepatic function are of particular interest in an AUD population.

ClinicalTrials.gov number NCT02179749; funding from NIAAA R01AA023152.

Disclosure: CV Sciences: Advisory Board (Self)

Panel

4. Using Animal, Pharmacological and Computational Models to Understand the Pathophysiology Behind Aberrant Inferences in Psychosis

4.01 Paranoia as a Deficit in Non-Social Belief Updating

Philip Corlett

Yale University, New Haven, Connecticut, United States

Background: Paranoia is the belief that harm is intended by others. It may arise from selective pressures to infer and avoid social threats, particularly in ambiguous or changing circumstances. We propose that uncertainty may be sufficient to elicit learning differences in paranoid individuals, without social threat.

Methods: We used reversal learning behavior and computational modeling to estimate belief updating across individuals with and without mental illness ($n = 32$), online participants ($n = 307$), and rats chronically exposed to methamphetamine ($n = 9$), an elicitor of paranoia in humans.

Results: We observed an interaction between task block and paranoia group ($F(1) = 5.344$, $P = 0.028$): Prior beliefs differed between high and low paranoia in both blocks (block 1, $F(1) = 4.232$, $P = 0.048$, $CI = [0.005,1.312]$; block 2, $F(1) = 7.497$, $P = 0.010$, $CI = [0.406, 2.789]$), but only low paranoia subjects significantly updated their priors between block 1 and block 2 ($F(30) = 39.841$, $P = 5.85E\text{-}07$, $CI = [1.017, 1.99]$). Online participants demonstrated significant effects of block ($F(1) = 64.652$, $P = 1.54E\text{–}11$, $CI = [0.980,1.627]$) and paranoia ($F(1) = 6.366$, $P = 0.014$, $CI = [0.191, 1.628]$). Rats showed a similar effect following methamphetamine exposure with a significant time by treatment (methamphetamine, saline) interaction ($F(1) = 5.159$, $P = 0.038$, pre versus post methamphetamine effect: $F(15) = 12.186$, $P = 0.003$, $CI = [-0.493, 2.037]$). Random effects meta-analyses confirmed significant cross-experiment replication of elevated priors on volatility in human participants with paranoia (in laboratory and online version 3; $MDMETA = 1.110$, $CI = [0.927, 1.292]$, $zMETA = 11.929$, $p = 8.356E\text{-}33$) and across humans with paranoia and rats exposed to methamphetamine ($MDMETA = 2.090$, $CI = [0.123, 4.056]$, $zMETA = 2.083$, $p = 0.037$). Both paranoid humans and rats administered chronic methamphetamine had strong beliefs that the task contingencies would change rapidly and

unpredictably – in other words, they expected frequent reversal events. Methamphetamine exposure made rats behave like humans with high paranoia.

Conclusions: Paranoia is associated with a stronger prior on volatility, accompanied by elevated sensitivity to perceived changes in the task environment. Methamphetamine exposure in rats recapitulates this impaired uncertainty-driven belief updating and rigid anticipation of a volatile environment. Our work provides evidence of fundamental, domain-general learning differences in paranoid individuals.

Disclosure: Nothing to disclose.

4.2 Striatal Dopamine Mediates Hallucination-Like Perceptions in Mice

Katharina Schmack

Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, United States

Background: Hallucinations are a core symptom of schizophrenia, a debilitating disorder that has long been thought to be caused by excessive dopaminergic neurotransmission. However, the neural circuit mechanism linking dopamine and hallucinations remains elusive, mainly because hallucinations have been difficult to measure in model organisms. Here, we aimed to establish a novel readout of hallucinations that easily translates from humans to mice. Our goal was to provide a circuit-level description of the suggested link between dopamine and hallucinations.

Methods: Our rationale was that hallucinations can be operationalized as false perceptions of non-existent signals that are experienced with high confidence. We developed a psychometric auditory detection task with confidence reports for both humans and mice. In this task, false alarm rate and confidence in false alarms provide quantitative measures of hallucination-like perceptions. To validate the task, we performed online testing of human participants with varying degrees of hallucinations, as well as pharmacological and behavioral manipulations in mice. To measure and manipulate dopamine activity during this task, we used fiber photometry and optogenetics in behaving mice. Behavioral and neural data were analyzed using a computational model of statistical confidence.

Results: Both humans and mice were able to consistently perform the task. Their choices were closely fitted by a psychometric curve and confidence behavior significantly correlated with the predictions of the statistical confidence model. We found evidence across species that hallucination-like perceptions were a valid readout of hallucinations. In humans, self-reported hallucinations were correlated with hallucination-like perceptions. In mice, hallucinogenic manipulations using ketamine or prior expectations consistently induced more hallucination-like perceptions. Finally, neural circuit investigations in mice showed that elevated baseline dopamine in both ventral and tail of striatum preceded hallucination-like perceptions. Computational modeling suggested that ventral striatal dopamine was consistent with prediction error encoding, whereas the tail of striatum dopamine signaled prior expectation of hearing a signal. In line with this, optogenetic stimulation of dopaminergic activity in the tail of the striatum induced more hallucination-like perceptions.

Conclusions: Our results suggest that hallucination-like perceptions can serve as a translational marker of hallucinations across humans and mice, and indicate a causal role for dopamine-dependent striatal circuits in hallucinations. Thereby, our findings provide circuit-level evidence for the long-standing dopamine hypothesis of schizophrenia and open up new avenues to develop urgently needed circuit-based treatments for schizophrenia.

Disclosure: Nothing to disclose.

4.3 The Inner Life of the Auditory ERP: Entrainment, Functional Ensembles, and Their Interaction

Daniel Javitt

Columbia University, New York, New York, United States

Background: Schizophrenia (Sz) is associated with deficits in auditory sensory processing that contribute both to symptoms and neurocognitive impairments. Auditory event-related potentials (ERP) such as mismatch negativity (MMN), auditory steady-state response (ASSR) and P300 (P3) index specific stages of auditory processing and may be decomposed using time-frequency (TF) analyses into underlying spectral components, which may reflect function of differential underlying neural ensembles. Here, using TF analyses, we evaluated both neural mechanisms underlying impaired auditory ERP generation in Sz, as well as relations to both symptoms and neurocognitive impairments.

Methods: In data set 1, auditory steady-state responses (ASSR) were collected on a group of 102 Sz and 82 HC. Time-frequency (TF) analyses isolated responses within delta (1-4 Hz), theta (5–7 Hz), alpha (8–12 Hz), beta (12–24 Hz), and gamma (>24 Hz) frequency bands.

In dataset 2, 20 SzP and 20 HC underwent both aERP and rsfMRI assessments. Modulation of posterior alpha activity was used as a metric of task-engagement.

Results: In the ASSR data set, SzP showed significant reductions in single-trial power within the delta ($p < 0.05$), theta ($p < 0.05$), beta ($p < 0.01$) and gamma ($p < 0.01$) frequency ranges. The combination of theta and gamma single-trial power and gamma ITC best-distinguished groups with an accuracy of ~90%. Correlations with auditory hallucinations occurred primarily to activity within the alpha frequency band ($p < 0.05$), whereas impairments in tone matching and verbal learning correlated primarily with reductions in gamma response ($p < 0.05$).

In the second data set, patients again showed marked reduction in the theta frequency band to stimulus onset ($p = 0.02$), as well as in the delta frequency ($p = 0.03$) reflecting impaired entrainment across trials, reductions in auditory P3 amplitude correlated highly with reduction in delta power to the target stimulus ($p < 0.001$), which, in turn, correlated with impaired ongoing delta ($r = 0.55$, $p < 0.01$). In rsfMRI, deficits in entrainment correlated with rsfMRI connectivity between auditory and visual networks across groups, as well as hand network specifically in HC and the cingulo-opercular network specifically within SzP.

Conclusions: These findings highlight the significant deficits that are apparent in early auditory processing in Sz and their relationship to both symptoms and neurocognitive impairments. Deficits are observed both within and across frequency bands. The studies show for the first time how different aspects of auditory sensory dysfunction map to different components of underlying TF response, and thus help map behavioral deficits to regional- and ensemble-level impairments in Sz.

Disclosure: Glytech, Inc/LLC, NeuroRx, AASI: Stock / Equity (Self); NeuroRx, Biogen, Promentis: Advisory Board (Self); Glytech, LLC, Columbia University: Patent (Self); Cerevance: Grant (Self); Autifony, SK Life Sci, Boehringer Ingelheim: Consultant (Self)

4.4 Computational Modeling Reveals a Consistent Loss of Cortical Synaptic Gain in Schizophrenia Across Four EEG and fMRI Paradigms

Rick Adams

University College London, London, United Kingdom

Background: It is widely hypothesised that a fundamental pathology in schizophrenia is the loss of synaptic gain, i.e. the ability to amplify postsynaptic responses to neural inputs, due to hypofunction of NMDA receptors in particular. Most evidence for this is indirect (e.g. genetic or postmortem), however, and it is unclear whether gain in excitatory or inhibitory neurons is most affected, and how this relates to symptoms. Computational modeling of brain imaging data permits in vivo functional analysis of synaptic gain (and other parameters) at the individual subject level, but, in schizophrenia, it has so far been restricted to small samples and single paradigms. Here, synaptic gain was explored in a larger sample of subjects who had each undergone four imaging paradigms.

Methods: Participants (male and female) with schizophrenia (n = 108), their relatives (n = 57), and controls (n = 107) underwent three electroencephalography paradigms (resting, mismatch negativity, and 40 Hz auditory steady state response, ASSR) and resting state functional magnetic resonance imaging (rsfMRI). We analysed their brain responses using dynamic causal modeling and parametric empirical Bayes.

Results: The schizophrenia group had typical abnormalities in the EEG paradigms: (i) in the resting EEG, increased theta (p(corr) = 0.035), decreased beta p(corr) = 0.022 and increased gamma (p (corr) = 0.040) power; (ii) in the mismatch negativity, a decreased mismatch response (SPM analysis, p(unc) < 0.001); and (iii) in the 40 Hz ASSR, reduced gamma power (p < 0.05) and peak frequency (p = 0.015). In the modeling analysis, across all four paradigms, the schizophrenia group showed evidence of decreased synaptic gain (i.e. greater self-inhibition) on pyramidal cells (all posterior probabilities p > 0.95). Across three paradigms, abnormal auditory perceptions were linked to disinhibition in auditory areas in schizophrenia, and pyramidal cell gain correlated with cognitive performance in controls (all posterior probabilities p > 0.95). Synaptic gain parameters also correlated within subjects, between EEG and fMRI paradigms (both posterior probabilities p > 0.95).

Conclusions: These results suggest some interesting conclusions: First, the loss of synaptic gain on pyramidal cells was a very consistent finding across paradigms, suggesting well-replicated effects in these three EEG paradigms in schizophrenia are all attributable to the same underlying pathophysiology. Second, auditory perceptual symptoms related to disinhibition – not gain loss – in auditory areas in EEG and rsfMRI, and not just auditory but all other positive and negative symptoms also related to disinhibition in the same network in rsfMRI. Psychotic symptoms may therefore not be the direct result of synaptic gain loss but of the subsequent restoration of excitatory/inhibitory balance (i.e. compensatory disinhibition of pyramidal cells) in neural circuits. Third, synaptic gain was consistently related to cognitive performance in controls, indicating this measure is also highly relevant to brain function. Finally, I evaluate synaptic gain's potential as a computational biomarker for schizophrenia.

Disclosure: Nothing to disclose.

Panel

5. Irritability: Translational and Transdiagnostic Approaches to Neural Circuitry, Development, and Treatment

5.1 Mouse Model of Frustration Reveals a Role for Striatal Dopamine at the Intersection of Reward and Aggression

Neir Eshel

Stanford University, Stanford, California, United States

Background: Aggression is a universal component of social behavior, and all too often the grim subject of the daily news. One of the most reliable triggers of aggression is frustration or failing to receive an expected reward. This state can be adaptive, energizing behaviors to overcome barriers. But it can also lead to anger and violence. Despite its clinical toll, the neurobiology of frustration remains poorly understood. Here we use a new mouse model of frustrative nonreward to examine the role of dopamine (DA), a neuromodulator uniquely situated to link reward processing with aggression.

Methods: We have combined two validated behavioral paradigms—associative conditioning and the resident-intruder assay—into a new task to probe the neural circuits of frustration and aggression. We trained food-restricted mice (n = 61, 25 female) to nose-poke for sucrose reward, which was paired with an audiovisual cue. After training, the mice underwent a 'frustration' session, in which they received the first 9 rewards as usual, but on the 10th trial, the cue was presented without reward. After a brief pause, we then placed an intruder mouse into the chamber. Throughout each session, behavior was recorded with an overhead camera, and both aggressive and nonaggressive social interactions were scored using artificial intelligence-based tracking software. Before behavioral training, a subset of the mice (n = 13 mice, 7 female) were injected with a virus carrying the DA sensor GRABDA, and implanted with a fiber optic over the nucleus accumbens. We used fiber photometry to record DA levels during the reward task and aggression. Linear mixed models and two-sided *t* tests were used to assess learning and the effect of frustration on behavior. Fiber photometry data was z-scored and effects of reward and aggression were determined with signed-rank tests.

Results: During training, mice rapidly reduced both their latency to enter the reward port after cue presentation (main effect of day, p = 0.007) and their number of unnecessary pokes (main effect of day, p = 0.0009). On the 'frustration' sessions, omission of reward triggered an increase in poking for the next 2 min (*t* test, p < 0.0001), as well as increased bouts of aggression against an intruder (*t* test, p = 0.0028), when compared to sessions in which reward was received.

Consistent with prior work, DA levels in the nucleus accumbens increased when mice were rewarded (signed-rank test, p = 0.0002) and decreased when reward was omitted (signed-rank test, p = 0.003). Aggressive attacks were also associated with DA release, but interestingly, DA tended to increase several seconds before initiation of an attack, rather than during the attack (pre- vs- post-attack DA level: signed-rank test, p = 0.03). This is in stark contrast to non-aggressive encounters in the same session, which tended to elicit post-encounter DA release (post- vs pre-encounter: signed-rank test, p = 0.04). There was a positive association between the magnitude of an animal's DA responses to reward and its probability of being aggressive (Pearson's r = 0.9, p = 0.002).

Conclusions: We have developed a new behavioral paradigm in which omission of expected reward reliably intensifies goal-directed behavior and aggression in male and female mice. Preliminary recordings have demonstrated a potential role for DA in the initiation of aggression, which can be separated from its role in movement or other social behaviors.

Disclosure: Nothing to disclose.

5.2 Neural Mechanisms of Pediatric Irritability: New Methods and Findings in Frustrative Nonreward

Katharina Kircanski

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

Background: Irritability is a common psychiatric symptom in children and adolescents (Vidal-Ribas et al., 2016), yet its neural correlates are ill-defined. Because clinical irritability typically manifests in the context of frustrative nonreward (FNR), i.e., omission of expected reward or blocking of goal attainment (Amsel, 1958), FNR is an important research focus. (Brotman et al., 2017; Leibenluft, 2017). We have developed new fMRI FNR paradigms and analytic methods to investigate specific outstanding questions. In Study 1, we developed a child-friendly paradigm to assess whether FNR modulates reward learning and its neural substrates in irritable youth. In Study 2, we advance multivariate methods by examining cross-task associations between FNR and threat processing, another construct pertinent to irritability (Kircanski et al., 2018).

Methods: Our research includes transdiagnostic samples of youth and quantifies irritability dimensionally (ARI; Stringaris et al., 2012). Study 1 is ongoing (current $N = 28$; M age = 13.95; 64% male; M parent-report ARI = 4.25). Here, the Carnival paradigm presents participants with a series of probabilistic reward learning games; halfway through the paradigm, a separate, rigged game occurs to induce FNR. The current data were analyzed using whole-brain linear mixed effects analyses, testing level of irritability and task phase (pre-FNR vs. post-FNR) in relation to neural activity during reward learning (voxelwise threshold $p < 0.005$; $k >= 24$). Study 2 is a novel analysis of fMRI data acquired across two separate tasks (shared $N = 85$; M age = 13.09; 58% male; M parent-report ARI = 4.19). Participants completed both an Affective Posner task probing FNR and a Dot-Probe task probing threat processing. We are conducting canonical correlation analysis (CCA) between the two tasks to elucidate correlated neural networks across FNR and threat processing.

Results: In Study 1, the new paradigm was successful in inducing FNR assessed via frustration ratings ($p < 0.001$, $\eta p2 = 0.33$). Higher irritability was associated with marginally higher frustration ratings during the rigged game ($p = 0.05$, $r = 0.37$). In the fMRI analyses, virtually all significant effects of irritability involved interactions between irritability and task phase. Specifically, higher irritability was associated with relative decreases in activity across several prefrontal and parietal regions from pre- to post-FNR (all $ps < 0.005$, whole-brain corrected). This included a relative decrease in activity in the lFG during reward stimulus selection, and relative decreases in activity in the IFG, dlPFC, and inferior parietal lobule when receiving feedback indicating any outcome (reward or no-reward). Data will be further analyzed using a computational model of reinforcement learning. In Study 2, the between-task CCA is ongoing. Preliminary ROI analyses indicate significant correlations between bilateral amygdala activity following FNR and during threat orienting ($ps < 0.05$, $rs = 0.24–0.31$). Final analyses will be presented.

Conclusions: These new methods and findings advance our understanding of neural mechanisms of pediatric irritability. In Study 1, an FNR induction significantly modulated the neural correlates of irritability during reward learning, such that following FNR, youth with higher irritability exhibited relative decreases in activity in regions mediating attentional and executive functions. Study 2 provides a means to examine multimodal neural networks across FNR and threat processing. Continued translational research on FNR may facilitate mechanism-based treatments for pediatric irritability.

Disclosure: Nothing to disclose.

5.3 The Clinical Threshold for Severe and Impairing Irritability in Middle and Late Adolescence: Genetic and Structural Imaging Validators

Giovanni Salum

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

Background: Disruptive Mood Dysregulation Disorder (DMDD) is a new diagnosis designed to capture pathological manifestations of irritable mood and temper outbursts in children. Given the newness of DMDD, data-driven approaches are needed to evaluate appropriate thresholds for DMDD and consider the need to refine diagnostic criteria. We recently showed the utility of data-driven approaches based on epidemiological evidence to guide a revision of the DMDD diagnostic criteria in a large birth cohort (Pelotas Birth Cohort), however our previous work was restricted to early adolescence and solely based on psychometrics and associations with other symptomatic domains. Here, we expand this methodology to middle and late adolescents and investigate associations between data-driven DMDD diagnostic criteria with cortical thickness and polygenic risk scores.

Methods: Participated in this study 736 middle adolescents (14–17 years) and 824 late adolescents (18–21 years) which are part of the Brazilian High-Risk Cohort Study (BHRCS, 3rd wave). Diagnostic Assessment was performed using the Development and Well-Being Behavior Assessment (DAWBA). Measures of cortical thickness were extracted from T1-weighted images processed with Freesurfer version 6.0. Psychiatric genetic risk was indexed by polygenic risk scores (PRSs) using large genome-wide association study results calculated from the Global Screening Array.

Results: First, clinical thresholds for irritable mood were similar between middle and late adolescents. Clinical thresholds for outbursts were more variable between the two groups, indicating important differences for assessing the clinical threshold for outbursts over development. Second, the latent class analysis suggested a two-class solution is the best way to capture a clinically impaired group and ROC analysis suggests that in both age groups irritable mood can be best captured with 2 out of 8 indicators and outbursts with 2 out of 10 indicators; whereas impairment in at least one setting would be sufficient for a DMDD diagnosis. Third, the prevalence of DMDD in the middle adolescent sample was 11.1% using the OR rule and 4.7% using the AND rule; whereas in the late adolescent sample it was 14.6% using the OR rule and 7% using the AND rule. Comorbidity was frequent with 32% of those with DMDD meeting criteria for an anxiety disorder, 39% for major depression; and 6% for ADHD. Finally, we found significant differences between those and without DMDD in polygenic risk scores for depression in all polygenic risk score thresholds ($p = 0.000015$) and not in ADHD polygenic risk scores (even after adjusting for co-occurring major depression), but failed to find between-group differences in cortical thickness.

Conclusions: The clinical threshold for DMDD varies in middle and late adolescence, especially regarding the clinical significance of some behaviors occurring during temper outbursts. DMDD seems to be prevalent among adolescents and clustering together with anxiety and depression, and not with ADHD, both phenotypically and genetically. Contrary to our initial predictions we failed to find widespread reductions in cortical thickness in those samples.

Disclosure: Nothing to disclose.

5.4 Consistent Associations Between Irritability and Active Suicidal Ideation in Adults With Major Depressive Disorder: Findings From Two Randomized Controlled Trial and One Open Label Study

Manish Jha

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

Background: Irritability is unique among depression-related symptoms as it is considered a criterion symptom of Major Depressive Disorder (MDD) in adolescents but not in adults. Yet, epidemiologic studies suggest that irritability is a prominent feature of MDD in 40–50% of adults. Recent studies suggest that irritability during childhood and adolescence is associated with subsequent suicide-related outcomes. Yet, to date, no study has evaluated the longitudinal association between irritability and suicidality in adults with MDD. The objective of this report was to determine whether irritability is associated with suicidal ideation (SI) at the same visit (i.e., concurrently) and whether early changes in irritability with antidepressants predict subsequent levels of SI.

Methods: Participants of two randomized trials, Combining Medications to Enhance Depression Outcomes (CO-MED, n = 665, aged 18–75 years, 68% females) and Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care (EMBARC, n = 296, aged 18–65 years, 66% females), and one open label trial, Suicide Assessment Methodology Study (SAMS, n = 266, n = 266, aged 18–75 years, 71% females). All participants were adults with MDD and were recruited either from six primary care and nine psychiatric practices (CO-MED and SAMS) or from four academic medical centers (EMBARC). Participants were randomized to escitalopram-plus-placebo, bupropion-plus-escitalopram, or venlafaxine-plus-mirtazapine in CO-MED; or to sertraline or placebo in EMBARC. Participants of SAMS received open label treatment with citalopram, escitalopram, fluoxetine, paroxetine, or sertraline. Outcomes of these unplanned secondary analyses were (1) concurrent association throughout the trial between irritability (5-item irritability domain of Concise Associated Symptom Tracking scale) and SI (3-item suicidal thoughts factor of Concise Health Risk Tracking scale), and (2) prediction of subsequent levels of SI based on early changes in irritability even after controlling for early changes in overall depression. Additional analyses controlled for anxiety or insomnia.

Results: Irritability was significantly associated with SI concurrently (total n = 1227, Pearson's r = 0.31–0.73). The concurrent association between irritability and SI was significant even after controlling for overall depression; estimates (standard error) were 0.18 (0.02, $p < 0.0001$), 0.64 (0.02, $p < 0.0001$), and 0.26 (0.04, $p < 0.0001$) in CO-MED, EMBARC, and SAMS respectively. Greater baseline-to-week-2 reductions in irritability predicted lower levels of subsequent SI; estimates (standard errors) were −0.08 (0.03, $p = 0.023$), −0.50 (0.05, $p < 0.0001$), and −0.12 (0.05, $p = 0.024$) in CO-MED, EMBARC, and SAMS respectively. Controlling for anxiety or insomnia produced similar results.

Conclusions: Irritability and SI were consistently linked in adults with MDD. These findings support careful assessment of irritability in suicide risk assessment.

Disclosure: Acadia Pharmaceuticals: Grant (Self), NACCME, Global Medical Education: Honoraria (Self)

Study Group

6. Loneliness and Social Isolation in the COVID-19 Era: New Directions for Neurobiology and Mental Health Research

Dilip Jeste, Nancy Donovan, Dag Aarsland, Dennis Charney, Steven Cole, Michael Green, Julianne Holt-Lunstad, Ellen Lee, Lisbeth Nielsen

Study Group Summary: The behavioral pandemic of loneliness and social isolation (L/SI) has contributed to rising rates of suicide and opioid-related deaths in the last two decades, and to the first decline in average US longevity since the 1950s. Loneliness is a modestly heritable trait, with specific genetic and gene expression signatures. Subjective loneliness is related to, yet distinct from, objective social isolation. L/SI has damaging effects on physical health similar to those of smoking and obesity. Longitudinal studies show L/SI to be a serious risk factor for major depression, anxiety disorders, and Alzheimer's and other dementias. Animal models of social isolation in rodents and loneliness in monkeys suggest multidimensional brain-body predictors of susceptibility versus resilience to social stresses. The new pandemic of COVID-19 and social distancing policies have increased L/SI in people with mental illnesses.

This study group aims to foster a discussion of challenges to advancing empirical mechanistically-based neuropsychiatric research on L/SI, as well as developing efficacious interventions. The participants include investigators in L/SI focusing on genomic and animal model research (Cole), neurobiology of L/SI and cognitive decline (Donovan), serious mental illnesses (Green), public health implications (Holt-Lunstad), social and behavioral mechanisms (Nielsen), mental health issues in the Covid-19 epicenter (Charney), artificial intelligence (AI) technologies and sensor-based objective assessments (Lee), biological and behavioral interventions (Jeste), and community-based remote interventions (Aarsland). We will discuss several issues.

(1) What novel approaches are needed to advance the study L/SI? How do we improve the behavioral taxonomy of these constructs in animals and humans? How may objective assessments approximate the subjective state of loneliness? How can real-time ecological momentary assessments be used to examine loneliness as a state, rather than a trait? What is the role for AI technologies in analyzing social behaviors linked with L/SI in different species?
(2) What are the neurobiological mechanisms underlying the development of Alzheimer's disease in people with L/SI? How are the genetic risk factors and gene expression differences related to markers of risk and resilience to social stress in depression, anxiety disorders, and PTSD?
(3) What key biological, psychosocial, and environmental factors are driving the loneliness pandemic, compounded by social isolation during the Covid-19 pandemic? Are there sex-specific differences or other individual characteristics or group-level explanatory factors? What would be the broader public health implications of a widespread social recession in the wake of the Covid-19 pandemic?
(4) What are the major challenges to developing neurobiologically and psychosocially grounded interventions for L/SI? Using precision medicine approach, how can interventions be tailored for different subgroups? How can the findings about effects of drugs like antidepressants in rodent models of social defeat stress be translated into clinical treatment paradigms? How can large population-based datasets and remote interventions be leveraged to reduce L/SI at community level? How can societal changes associated with physical distancing (living, working, and public spaces) be counteracted to mitigate or prevent L/SI?

Disclosure: Nothing to disclose.

Panel

7. Sex Differences in Depression: External and Internal Environments Differentially Affect Females or Males

7.1 Stress Effects on Microglia Activation and Behavior: Sex Matters

Georgia Hodes, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, United States

Background: Women account for 2/3rds of people diagnosed with depression. Imaging studies indicate microglia, the innate immune cells in the brain, are more activated in people with depression. Preclinical studies demonstrate baseline differences in microglia activation between males and females but only a few have examined the effects of stress on microglia activation in both sexes. We examined the effects of 6 and 28 day variable stress on microglia activation in the nucleus accumbens (NAc) and the dentate gyrus of the hippocampus.

Methods: Male and female mice were exposed to 6 days or 28 days of stress ($n = 80$). Microglia activation was examined using immunohistochemistry from tissue harvested 24 h after stress or in later studies following a behavioral test battery. Additional studies examined the dose dependent effects of a classical microglia activation inhibitor, minocycline on stress susceptibility in females following 6 days of stress ($n = 69$).

Results: Mice expressed region specific activation of microglia. In NAc, only females expressed a greater proportion of triggered and activated microglia indicated by morphology (p values < 0.05), skeleton analysis ($p < 0.05$), and co-expression of IBA-1/CD-68 ($p < 0.05$). In the dentate gyrus 6 and 28 days of variable stress both impacted activation in both sexes in the dentate gyrus ($p < 0.05$). There were dose and test dependent effects of minocycline with an indication that in unstressed female mice minocycline at high doses produced stress-like behavioral effects ($p < 0.05$) and had opposite effects on microglia activation in non-stressed vs. stressed mice ($p < 0.05$).

Conclusions: The data presented here demonstrate sex and region specific effects of stress on microglia activation. These data suggest that systemic treatments to block classical microglia activation in females may not match results found in males.

Disclosure: Nothing to disclose.

7.2 An Animal Model for SSRI-Resistant Depression at Altitude: Brain Serotonin and Antidepressants Based on Bioenergetics

Shami Kanekar

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

Background: Rates of major depressive disorder (MDD) increase with altitude. People living at altitude are exposed to hypobaric hypoxia and can exhibit physiological deficits even at moderate altitude. Healthy people living at 4500ft exhibit a deficit in blood oxygen levels vs. those at sea level, as well as a forebrain deficit in creatine (a brain bioenergetic marker) similar to that seen in MDD. Using a novel sex-based animal model, we find that depression-like behavior (DLB) in the forced swim test (FST) increases in female rats after housing for 2wks at altitude (4500ft, 10,000ft) vs. at sea level. At altitude, both sexes do not respond to most selective serotonin reuptake inhibitors (SSRIs) and SSRI-resistance is linked to low brain serotonin. Since serotonin synthesis is oxygen-dependent and may be altered by hypoxia, we studied the impact of altitude on brain serotonin. We also tested the bioenergetic compounds, creatine monohydrate (CRM) and cyclocreatine (CyCR), for the antidepressant potential at altitude. Dietary CRM treatment improves brain energetics in healthy volunteers and preclinically shows promise towards improving DLB. CRM use is limited by poor brain access, but its lipophilic analog CyCR crosses the blood brain barrier without a transporter, has improved brain access, and replaces creatine in cell energy pathways to improve brain energetics.

Methods: (1) Serotonin Study: M/F rats were housed at altitude (4500ft, 10,000ft) vs. sea level for 1–5 wks, then sacrificed and brain serotonin assayed by ELISA. DLB in the FST was tested in a subset.

(2) Dietary Study: M/F rats housed at 4500 ft were given dietary CRM (4%, 5 wks) or CyCR (1%, 3wks), vs food. Rats were then tested for DLB in the FST, and blood or brain regions assayed for creatine or serotonin.

Data was analyzed separately by sex, by one-way or two-way ANOVA ($n = 9–20$, Significance: $p < 0.05$).

Results: (1) Serotonin Study: After 2 wks at altitude (4500ft, 10,000ft) vs. sea level, serotonin decreased significantly in the female prefrontal cortex (PFC), striatum (STR), hippocampus (HIP) and brainstem (BST), but increased with altitude in the male HIP and BST ($p < 0.01$). In rats housed at 4500ft for 1-5wks, serotonin decreased in the female PFC, STR and BST from 1wk onwards, but males did not vary. With duration (2wk, 24 days) at sea level or 4500ft, female brain serotonin increased and DLB decreased with altitude, with no effects of duration. In males, significant interactions of altitude and duration were noted in the PFC, HIP and BST, with a transient increase in serotonin at 2 wks; male DLB did not vary.

(2) Dietary Study: (A) CRM: Dietary CRM increased serum creatine in both sexes. In females, CRM improved levels of both creatine and serotonin in the PFC and STR. In males, CRM improved creatine levels but reduced serotonin in the STR and HIP. Dietary CRM was antidepressant in only females, with efficacy equal to the TCA desipramine ($p < 0.01$). (B) CyCR: Dietary CyCR increased female PFC serotonin, but reduced male STR serotonin. CyCR was antidepressant in both sexes at altitude ($p < 0.05$).

Conclusions: In our model, housing at altitude causes sex-based changes in rat brain serotonin and depression status, and females may be more vulnerable to chronic hypoxic stress at altitude. Targeting brain bioenergetics may be an effective treatment strategy for MDD at altitude: CRM and CyCR are antidepressant in female rats at altitude, and CyCR is also effective in males.

Disclosure: Nothing to disclose.

7.3 Adverse Childhood Experiences: Risk Factors for Negative Affect and Executive Dysfunction After Surgical Menopause

Abstract not included.

7.4 Sex-Dependent Effects of Prenatal Immune Programming on the Association Between Depressed Mood and Central Autonomic Dysregulation

Ronald Garcia

Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts, United States

Background: Cardiac autonomic dysregulation has been implicated in the comorbidity of major depression (MDD) and cardiovascular disease (CVD). It has been suggested that this maladaptive physiological response may be the result of abnormalities in the fetal development of specific regions in the stress response circuitry and central autonomic network that are morphologically and functionally sexually dimorphic. In this study we evaluated the hypothesis that high concentrations of maternal pro-inflammatory cytokines during fetal development could be associated with sex-dependent functional alterations of the central autonomic network and reduced cardiac parasympathetic activity in adult offspring.

Methods: We assayed concentrations of three pro-inflammatory cytokines [interleukin (IL)1-β, IL-6 and tumor necrosis factor (TNF)-α] in maternal serum collected at the end of the second and beginning of the third trimester in subjects included in the New England Family Study, a pregnancy cohort enrolled between 1959 and 1966. In addition we recruited adult offspring from this cohort (22 males, 28 females, age = 45.5 ± 5 years) including healthy controls and individuals with MDD, bipolar psychosis and schizophrenia who attended an experimental session where functional magnetic resonance imaging (3T) and physiology (cardiac pulse) data were acquired during a mild visual stress reactivity challenge. The Profile of Mood States questionnaire was collected and a mean split of the depression/dejection subscale score was used to classify subjects into high or low levels of depressed mood. Associations between maternal immune activity and central and peripheral autonomic response to negative stimuli as well as its relationship with depressed mood in adult offspring were evaluated using GLM analyses.

Results: Maternal concentrations of pro-inflammatory cytokines (IL1-β, IL-6) were significantly associated with increased activation of hypothalamus (IL1-β: $\beta = 0.07$, $p = 0.009$, Adj $R2 = 0.4$; IL-6: $\beta = 0.17$, $p = 0.001$, Adj $R2 = 0.57$), left anterior insula (IL1-β: $\beta = 0.06$, $p = 0.004$, Adj $R2 = 0.5$; IL-6: $\beta = 0.14$, $p = 0.002$, Adj $R2 = 0.56$) and bilateral orbitofrontal cortex (IL1-β: $\beta = 0.08$, $p = 0.03$, Adj $R2 = 0.3$; IL-6: $\beta = 0.18$, $p = 0.025$, Adj $R2 = 0.34$) during exposure to negative images in female adult offspring with depressive symptoms, whereas no significant associations were observed in men with high or low depressed mood scores. Furthermore, in women with depressed mood, activation of hypothalamus, left anterior insula and orbitofrontal cortex was significantly associated with lower cardiovagal activity (reduced high frequency power of heart rate variability) ($p < 0.05$) with no significant associations in other groups.

Conclusions: Our results suggest that variations in maternal immune activity during pregnancy have significant sex-dependent effects on the development of functional alterations in the stress response circuitry and central autonomic network associated with reduced cardiovagal activity in adult offspring with depressed mood. These findings provide a potential pathophysiological mechanism for previously observed sex differences in the comorbidity of major depression and cardiovascular disease.

Disclosure: Nothing to disclose.

Panel

8. Integrating Common and Rare Genetic Risk Factors for Psychopathology

8.1 Higher Depression and PTSD Prevalence Among Women Using Hormone Replacement Therapy (HRT) May Be Due to Shared Genetic Effects

Laramie Duncan

Stanford University, Redwood City, California, United States

Background: Fluctuating gonadal hormone levels are thought to contribute to the higher prevalence of major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) among women. Prior studies have found that exogenous versions of these hormones – in birth control pills and hormone replacement therapy – may influence risk for these disorders.

Methods: In this study, we tested whether the use of hormone replacement therapy (HRT) was associated with depression and PTSD in women participating in the UK Biobank, a large and well-phenotyped cohort. We investigated phenotypic and genetic associations among women who used (n = 12,545) and did not use (n = 175,826) estrogen-containing medications.

Results: Our phenotypic results indicate significant positive associations between the use of estrogen-containing medication and both depression (OR=1.383, s.e. = 0.04, $p = 1.01 \times 10{-}15$) and PTSD (OR = 1.184, s.e. = 0.05, $p = 3.01 \times 10\text{-}4$). Our genome-wide association study (GWAS) comparing women taking hormone replacement therapy to those not taking such medications revealed a known locus for menopause-related hot flashes (in the TACR3 gene). Further, positive genetic correlations were found between genetic influences on estrogen medication use and depression ($rg = 0.231$, s.e. = 0.055, $p = 2.81 \times 10\text{-}5$). Statistical power for analyses in populations other than those of European ancestry was too low for informative results.

Conclusions: This analysis provides novel insight into our understanding of how hormone replacement therapy may impact mental health by identifying shared genetic effects between depression and menopause-related symptoms, and it highlights the fact that genetic factors must be accounted for in observational studies like the UK Biobank. Specifically, psychiatric outcomes correlated with medication use may actually be linked via shared genetic influences on medication use and psychiatric disorders. Further research is needed to quantify the magnitude of genetic and environmental effects (including the effects of hormone replacement therapy) on depression and PTSD.

Disclosure: Nothing to disclose.

8.2 Rare Variant Discovery in Bipolar Disorder Pedigrees

Fernando Goes

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

Background: Bipolar Disorder (BD) is a common, complex disorder that ranks among the leading causes of disability worldwide. Based on its prominent heritability, intensive efforts have been taken to uncover both common and rare variation associated with susceptibility to bipolar disorder. While common variant studies have focused on case-control cohorts, rare variant studies may particularly benefit from family-based designs, since multiplex families may be enriched for highly penetrant variants. In this presentation, we discuss the results from the Family Subgroup of the Bipolar Sequencing Consortium (BSC).

Methods: The BSC Family Subgroup has collated samples from 12 international research groups, representing an ethnically diverse collection of over 220 pedigrees with at least 2 affected family members with Bipolar Disorder. The number of affected family members per pedigree is 2–14, with an average of 3.4 affected members per pedigree. BAM files were obtained for each affected individual and a combined sequence-based genotype file was recalled using GATK and annotated with Variant Effect Predictor and Annovar.

Results: Out of an initial 1.1 million variants, we identified 8034 rare exonic variants (minor allele frequency <0.1%) that segregated in at least one family. Of these, 3511 variants were defined as damaging (defined by a CADD score >15) and 300 were defined as disruptive (nonsense, frameshift indel, and canonical splice site). Slightly over half of the sequenced pedigrees (N = 109) carried at least one disruptive variant (mean 2.8 disruptive variants, range 1–14). In the analysis of damaging missense variants, we found 432 genes with at least 2 segregating variants, including 25 genes with 4 or more segregating variants. Initial geneset enrichment analyses showed significant overlap with genes previously association with common (P = 0.03) and rare variants studies in schizophrenia (P = 0.008) as well as rare variants in autism (P = 0.02)

Conclusions: Our initial analyses of this largest combined sample of Bipolar Disorder families provides initial evidence for convergence among a moderately small number of genes. A full discussion of the results, as well as gene-set enrichment analyses, will be shown along with appropriate permutation to determine experiment-wide significance. In addition, we will present follow up of promising findings in a parallel case-control exome sequencing effort, seeking independence evidence of association from both family-based and case-control designs

Disclosure: Janssen: Grant (Self)

8.3 Influences of Common and Rare Genetic Variations on Human Brain Organization

Armin Raznahan

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

Background: The past decade has seen a rapid expansion in the identification of both common and rare genetic risk factors for neuropsychiatric disorders. A major challenge for our field is understanding how these two forms of genetic risk combine to shape risk for human brain disorders – both at the level of clinical outcome, and with respect to underlying neurobiology. Genetically-defined neuropsychiatric disorders caused by rare chromosomal or sub-chromosomal copy number variations (henceforth collectively "CNVs") provide a powerful entry point for grappling with this challenge. This talk will present several complementary lines of ongoing research that capture the integrated effects of common and rare genetic variation through (i) clinical characterization of families impacted by pathogenic CNVs, and (ii) imaging-genetic analyses in CNV carriers and a large general-population cohort (UK biobank, UKB).

Methods: Deep-phenotypic studies in CNVs: We have collected high-dimensional behavioral, cognitive and neuroimaging data from >300 probands with sex chromosome aneuploidies (SCAs), and unaffected relatives. These data are used to map effects of rare X- and Y-chromosome dosage variation on human brain organization and psychopathology. Outcome variability within each patient group is modeled against family-level data capturing background genetic and shared environmental modifiers of risk. Imaging-genomic analyses in UKB: Application of Genome-wide Complex Trait Analysis (GCTA) in a general population sample of ~14,000 individuals is used to quantify and localize the influence of common X-chromosome genetic variation on human neuroanatomical variation – allowing comparison with the influence of rarer X-chromosome aneuploidies.

Results: Sex chromosome aneuploidies induce a patterned increase in risk for psychopathology and neurocognitive impairment with greatest penetrance for domains of attention, language and social functioning. However, outcomes are highly variable within any one SCA group, and - for some domains - proband outcomes can be reliably modeled by family phenotype proxies for background genetic and environmental variation. Imaging genetic analyses in SCA cohorts and the UKB revealed a convergent pattern of regionally selective effects on rare and common X-chromosome variation on neuroanatomical variation in brain circuits for attention, language and social cognition.

Conclusions: Taken together, our results demonstrate how (i) clinical outcomes in carriers of rare and high-impact genetic risks for psychopathology can be modulated by background genetic and environmental variation, and (ii) both common and rare forms of genetic variation from the same genomic region can have spatially convergent effects on human brain anatomy. We suggest that the genetic patterning of human brain organization may scaffold the convergent effect of common and rare genetic variation on risk for neuropsychiatric impairment.

Disclosure: Nothing to disclose.

8.4 Precision Psychiatry in a Population: Integrating Common and Rare Genetic Risk Factors for Psychopathology

Thomas Werge

Institute of Biological Psychiatry, Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark

Background: While genomic discovery has made headway in recent year tabulating thousands of common and rare variants that impact on human traits, relatively little actionable insight into disease mechanisms has been achieved and clinical-grade predictions are still lacking. Most studies that have massively improved our basic understanding of the heritability of complex human traits have been based on convenience samples with little clinical or background information beyond an inclusion diagnosis and highly susceptible to ascertainment bias. In fact, it is generally agreed that the prerequisite to achieve precision health is access to real-world data that unbiased and comprehensively represent health and disease as it is realized in a dynamic population. However, the collection of such data sets is clearly beyond reach of any research program, however large or fine-grained collections might be performed, and can only be obtained by systematically leveraging nationwide and egalitarian healthcare systems.

Methods: The Danish iPSYCH Initiative, to study five major mental disorders, schizophrenia, bipolar disorder, depression, ADHD and autism, combines the complete Danish genealogy including all individual alive in Denmark in the past 70, all hospital in- and out-patient admissions and corresponding diagnoses over the past 50 years, all prescriptions made over the past 30 years as well as detailed socioeconomic and demographic person-level information. The iPSYCH Initiative has generated a case-cohort of 130,000 individuals including all subjects born since 1980 and assigned one (or more) of the five selected diagnoses until 2016 (80,000 individuals) as well as a truly random cohort of 2% of the entire study population. All individuals have been genotyped on SNPs arrays, approximately 35,000 subjects have been whole-exome sequenced.

Using the iPSYCH case-cohort, we have studied the impact at the population level on life-course disease trajectories and clinical heterogeneity within diagnostic classes of both rare copy-number variants and common SNPs.

Results: Using the iPSYCH case-cohort, we estimate the true population prevalence, mortality, fertility as well as 30 years disease trajectory recurrent CNVs at the six genomic loci as well as four sex chromosome aneuploidies. In exploratory analyses, we report on somatic disorders overrepresented among individuals carrying chromosomal aberrations. Furthermore, using sequence analyses to compute diagnostic trajectories in all individuals with schizophrenia in the case-cohort, we find that the temporal patterns of psychiatric comorbidities are highly structured and stable over time, and allow for grouping of schizophrenia patients into clusters with distinct clinical features and differential association with known risk factors of schizophrenia. Finally, we explore clinical heterogeneity in ADHD examining the heritability of 30 features in ADHD case-case comparisons, and select early/adult diagnosis, comorbid substance abuse and comorbid autism as significantly heritable. Subsequent we use GWA studies to identify a locus specific to ADHD-autism and show distinct genetic correlation of the three ADHD-traits with other brain-traits.

Conclusions: Our studies demonstrate the power of population-based studies that capitalize on decades of collected information in nationwide healthcare systems to inform on

questions on the clinical impact of genomic variants, as well as on the etiology of clinical heterogeneity as it presents in real-world clinical settings.

Disclosure: Nothing to disclose.

Panel

9. Translational Models of Deep Brain Stimulation: New Approaches to Circuits of Reward, Motivation, Habit, and Impulse

9.1 Targeted Modulation of the Ventral Pallidum to Reduce Maladaptive Reward Seeking

Meaghan Creed

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

Background: The ventral pallidum (VP) is a critical node in the reward system, receiving inputs from both direct and indirect pathways of the nucleus accumbens and modulating downstream structures including the lateral habenula (LHb) and ventral tegmental area (VTA). It is thus directly modulated and/or connected to the stimulation target during striatal DBS. Our prior work has established that distinct sub-populations within the VP are strongly modulated by opioids, and these populations powerfully modulate both the hedonic value of reward and maladaptive reward seeking despite aversive consequences. Moreover, drug-induced synaptic adaptations at efferents to the VP and within VP cell bodies have been implicated in the persistent behavioral symptoms of addiction, such as craving and negative affect, in animal models. Finally, clinical case reports of deep brain stimulation (DBS) applied to ventral segment of the pallidum indicate that targeting the VP could be well tolerated in patient populations. Therefore, we posited that modulation of VP activity and plasticity with DBS could reduce drug seeking following drug withdrawal.

Methods: Mice underwent oral, home-cage oxycodone self-administration. Briefly, mice were acclimated to a two-chamber home-cage sipper device and liquid consumption was monitored over 24h. Following habituation, mice were exposed to 5 days of escalating oxycodone concentration in the drinking water (0.1, 0.3, 0.5 mg/mL), before 10 days of free-choice between regular drinking water and oxycodone (1.0 mg/mL). Mice voluntarily consumed >180 mg/kg/day of oxycodone in this paradigm, and following 3 weeks of withdrawal, developed somatic withdrawal signs and exhibited context-induced reinstatement of drug seeking when re-exposed to the drinking apparatus ($n = 20$). Using patch-clamp electrophysiology, we next characterized oxycodone-evoked synaptic adaptations at inhibitory inputs into the VP originating from the NAc, as well as intrinsic excitability changes in defined neurochemical populations within the VP. Finally, we asked whether DBS was able to modulate transmission at NAc to VP synapses or excitability of VP neurons, or whether it could reduce oxycodone-induced adaptations.

Results: In two separate experiments, classical DBS (high frequency stimulation, >130 Hz) applied to the VP reduced both on-going drug self-administration ($n = 8$/group, $F = 11.98$, $p < 0.01$), and suppressed drug seeking following withdrawal from orally self-administered oxycodone, without affecting somatic signs of withdrawal ($n = 7$/group, 2Way ANOVA $F = 3.11$, $p = 0.02$). Our patch clamp results demonstrate that DBS induced transient hyperpolarization of cell bodies in the VP, without affecting plasticity at the major afferent population to the VP, the nucleus accumbens (PPR pre vs. post: 0.79 ± 0.09, 0.82 ± 0.13, $t = 0.02$, $p = 0.83$, Rvm pre vs. post: -65.1 ± 7.2 mV, -73.2 ± 5.7 mV, $t = 2.86$, $p = 0.040$). The effects of DBS on cell bodies were not dependent on prior drug history of the animal ($n = 8$ cells from 4 mice), and there were no differences in efficacy of NAc to VP synapses following DBS.

Conclusions: Our results support the idea that DBS of the VP holds promise for treating multiple behavioral symptoms of addiction emerging after drug withdrawal. While classical DBS potently suppresses drug-seeking, these effects are transient and do not alter synaptic plasticity in the NAc to VP circuit. These results pave the way for optimizing DBS parameters to exert long-term effects on VP excitability, or to apply classical DBS in a closed loop manner to attenuate reward seeking only under conditions of drug craving.

Disclosure: Nothing to disclose.

9.2 Closing the Loop on Loss of Control Over Eating: From Mouse to Man

Casey Halpern

Stanford University, Stanford, California, United States

Background: Loss of control (LOC) eating, characterized by uncontrolled binge-like eating behavior, is a significant contributor to the present-day obesity epidemic. LOC eating is associated with refractory responses to pharmacologic therapy and bariatric surgery. While the pathophysiologic mechanisms are poorly understood, prior evidence suggests that the hedonic properties of calorically dense food, shown to drive LOC eating in animal models, are mediated, in-part, by dopaminergic projections to the Nucleus Accumbens (NAc).

Methods: Utilizing a mouse model of LOC eating in both male and female mice, we examined the impact of deep brain stimulation (DBS) on LOC eating and optimized a stimulation strategy to be tested in a human trial guided by local field potential recordings. We then launched a human study (NCT03868670) under an Investigational Device Exemption to use responsive DBS to ameliorate LOC in treatment-refractory obese participants. This is a single site, early feasibility study with a randomized, single-blinded, staggered-onset design. Six subjects will undergo bilateral responsive DBS of the NAc for LOC eating using the Responsive Neurostimulator (RNS)® System (NeuroPace, Inc). Eligible participants must have treatment-refractory obesity with body mass index (BMI) 40-60 kg/m2. Electrophysiological signals of LOC will be characterized using ambulatory recording capabilities and controlled, clinical tasks. We have developed novel behavioral tasks utilizing Virtual Reality and eye-tracking paired to NAc recordings to capture anticipatory signals for LOC eating in clinic.

Results: We observed a dose-dependent, attenuation of LOC eating in mice ($n = 6$), measured as decreased high-fat (HF) food intake, following open-loop, chronic DBS to the NAc [$t(17) = 4.74$; $p < 0.0001$]. However, a tolerance effect was observed over time when DBS was delivered chronically and continuously. Further, given that as in mice, LOC eating in humans is episodic, we sought to leverage a closed-loop, responsive DBS strategy to attenuate LOC eating. We identified a biomarker of increased delta-frequency-band power within field potential recordings from the NAc. Delta power was higher in mice prior to binge eating ($n = 6$), was specific to HF intake vs chow or social interaction, and was observed seconds immediately prior to HF intake ($F = 6.165$, $P < 0.001$). We adapted a responsive DBS strategy, guided by delta-band power, and demonstrated effective attenuation of LOC eating behavior in mice [$T(5) = 4.29$, $P < 0.01$]. Further, responsive DBS was associated with a more durable attenuation of LOC behavior. We then piloted these same biomarkers in a patient with an RNS with a NAc depth electrode. We identified similar increases

in delta-band power before bites of a high-caloric, palatable food in a buffet vs during bites in standard meals. We currently have one participant enrolled with planned electrophysiological and behavioral assessments ongoing.

Conclusions: Our mouse to human study suggests the feasibility and promise of a responsive DBS approach for LOC eating, based on NAc delta power. These studies' findings emphasize the importance of preclinical testing and may have broad impact across impulse control disorders.

Disclosure: Boston Scientific, Ad-Tech: Consultant (Self)

9.3 Cross-Species, Closed Loop Enhancement of Cognitive Control With Striatum/Capsule Deep Brain Stimulation

Alik Widge

University of Minnesota, Minneapolis, Minnesota, United States

Background: Deep brain stimulation (DBS) of the ventral internal capsule and striatum (VCVS) can relieve intractable major depression (MDD) and obsessive-compulsive disorder (OCD). In both indications, however, clinical trial outcomes are mixed. This arises in part because DBS' mechanisms are unknown. The similar effects across two disparate disorders suggest that an RDoC perspective may help identify mechanisms. DBS may act on cognitive deficits that cut across disorders.

We previously showed one possibility: top-down cognitive control (the ability to switch response strategies when needed). In a retrospective study, MDD and OCD patients with VCVS DBS performed better on a cognitive control task when their stimulators were active. We now show validation of this effect across species and show how it can be used for real-time monitoring and enhancement of cognitive control in humans.

Methods: 1: 6 patients undergoing invasive pre-surgical epilepsy monitoring, with electrodes passing near the VCVS, performed the Multi-Source Interference Task (MSIT), a standard cognitive control assay. During task stimulus presentation, we gave 130 Hz (DBS-like) bursts of stimulation to the left or right, dorsal or ventral VCVS, on a randomly selected 50% of MSIT trials. We verified that patients were blind to the presence/absence of stimulation.

2: 20 Long-Evans rats performed an extradimensional Set-Shifting task that approximates the human MSIT. In separate cohorts, we stimulated ventral, middle, or dorsal striatum in close homology to human VCVS. We stimulated on a random 50% of testing days, continuously throughout the task (similar to our prior human experiments).

3: In a further 3 epilepsy patients, we applied a real-time behavior modeling engine to estimate MSIT performance (trial response time, RT, accounting for changes in conflict level). When RT rose above a threshold (signifying lapses of cognitive control), we again applied brief DBS-like stimulation.

All studies included males and females and analyzed results through the same generalized linear mixed-effects model.

Results: 1: As in our prior study, patients were significantly faster ($p < 0.03$ for GLM coefficients, FDR corrected) during stimulation. Right dorsal VCVS stimulation produced the largest effect (74 ms vs. 42 ms for the less-effective ventral site).

2: Rats mirrored the human pattern: faster RTs (47 ms with mid-striatal stimulation, $p < 0.001$) without more errors, and the effects were larger at a more dorsal site dorsally ($p = 0.44$ for ventral stimulation).

3: Closed-loop stimulation was more effective than (1)'s open loop ($p < 0.001$, permutation test), and possibly more efficient (additional 2 ms per stimulation event, n.s.). There were no adverse events, and one patient reported subjective relief of anxiety.

Conclusions: Across species, VCVS DBS (especially more dorsally in the capsule/striatum) augments cognitive control. The effects can be controlled in closed loop, and rapidly change in response to stimulation. It may be possible to improve DBS programming for patients, e.g. by performing this closed-loop titration as they perform a cognitive control task.

Further, we back-translated the cognitive control effect to rodents, where we can dissect circuits and mechanisms in detail. This may represent a more reliable translational model for DBS compared to traditional "depression" or "OCD" assays. Together, these tools offer a new, RDoC-driven approach to studying and optimizing psychiatric DBS.

Disclosure: Medtronic: Grant, Patent (Self)

9.4 Cell-Based Strategies for Long-Lasting Therapeutic Benefits in a Mouse Model of Parkinson's Deep Brain Stimulation

Aryn Gittis

Carnegie Mellon University, Pittsburgh, Pennsylvania, United States

Background: The globus pallidus externa (GPe) contains a wealth of different cell types, but this neuronal diversity has been poorly explored as an opportunity for novel approaches to brain stimulation. In a previous study, we found that optogenetic interventions that simultaneously excite PV-containing GPe neurons and inhibit Lhx6-containing GPe neurons induce long-lasting therapeutic benefits in a mouse model of Parkinson disease (PD). To translate these discoveries into a feasible therapeutic intervention for humans, we have developed an electrical stimulation paradigm that can achieve the same degree of cell-type specificity.

Methods: We studied the impact of electrical stimulation on the synaptic and firing responses of PV and Lhx6-GPe neurons in acute brain slices. Equal numbers of male and female mice on a c57/bl6 background, age 4-6 months, were used. During high frequency electrical stimulation, Lhx6-GPe neurons received a large amplitude, fast decaying inhibitory current that was much smaller in PV-GPe neurons ($n = 10$ pairs, $p<0.05$). Leveraging this physiological difference and a machine learning approach for stimulus optimization, we identified a spectrum of stimulation protocols that dissociated the firing rates of PV and Lhx6-GPe neurons, which were then validated experimentally.

Results: Bursts of electrical stimulation, 250 ms in duration, at 175 Hz, were an optimal stimulation pattern to recruit PV-containing cells while inhibiting Lhx-containing cells.

Conclusions: These results establish the feasibility of using electrical stimulation to drive differential responses by cell-type in the central nervous system. They suggest the potential for developing a more robust toolbox for deep brain stimulation therapies. These rapidly translatable stimulation protocols can immediately be tested in various PD models across species and have the added benefit of falling within current FDA approved frequency ranges for human use.

Disclosure: Nothing to disclose.

Panel

10. Defining the Molecular, Circuit, and Behavioral Effects of Opioids in the Nucleus Accumbens

10.1 A Dorsal Raphe to Nucleus Accumbens Medial Shell Circuit Underlies Mu-Opioid Receptor Control of Motivation

Daniel Castro, University of Washington - Seattle, Seattle, Washington, United States

Background: Overdose deaths involving opioids have skyrocketed nationally over the last 10 years. Most highly addictive opioids preferentially act on mu opioid receptors (MORs). One major site of MOR action is nucleus accumbens medial shell (NAc). Here, MOR activation has been shown to enhance the motivation for both natural and drug rewards. Despite the powerful effects of MOR activation in NAc on motivated behaviors, the mechanisms underlying their effects are largely unknown. Here, we sought to determine where, when, and how MORs mediate motivated behaviors to better understand how they may become modified in addictive states.

Methods: Male and female adult (8-16 weeks) mice were used for all studies. Behaviorally, mice were tested (8–14/group) on a food intake task in which they were allowed to freely consume sucrose pellets for 1 h. Mice were tested while ad libitum or und after an acute 24 h food deprivation. Statistically, we used parametric and non-parametric ANOVAs/t-tests. Effect sizes and confidence intervals were also calculated to supplement findings. Several mice (3-6/group) were also used for anatomical and electrophysiological experiments.

Results: MOR constitutive knockout ($p < 0.001$) or local microinjections of a MOR antagonist ($p < 0.01$) in NAc reduced food deprived enhancement of intake, but not ad libitum intake. FISH experiments showed that MORs are predominately expressed on medium spiny neurons. We crossed Oprm1fl/fl mice with dynorphin or enkephalin-cre mouse lines to delete receptors from that particular cell type. Loss of MORs on enkephalin ($p < 0.001$), but not dynorphin (n.s.), neurons resulted in decreased hunger-enhanced intake. We also deleted MORs via local or retrograde viral injections in NAc. Only retrograde deletion resulted in reduced hunger-enhanced intake. Retrograde tracing showed labeling in lateral dorsal raphe nucleus. FISH analyses revealed that MORs are expressed on more than 50% of lDRN enkephalin neurons. To test the functionality of this pathway, we injected a MOR rescue virus directly into DRN of MOR knockout x enkephalin-cre mice. This selective rescue of MORs was sufficient to restore hunger-enhanced intake. To further determine whether MORs were specifically acting on DRN-NAc terminals, we injected the calcium indicator GCaMP6s into DRN and placed an optic fiber into NAc to measure changes in fluorescence during food intake. Results show that DRN enkephalin terminals dramatically reduce their activity at the onset of consumption ($p < 0.001$), but only in the food deprived state. This inhibition is blunted by naloxone. To test the functional role of MORs on the terminal, we used the light-activated opto-XR oMOR. Initial tests show that activation of oMOR on DRN-NAc terminals was sufficient to drive intake. Finally, we used of combination of DREADD inhibition ($p < 0.05$), excitation ($p < 0.05$), cell-type specific caspase deletion ($p < 0.001$), and peptidergic deletion of dynorphin (n.s.) or enkephalin ($p < 0.001$) to demonstrate that local enkephalin from NAc D2/enkephalin neurons activate MORs to increase food intake during food deprived states.

Conclusions: These results show that MORs in NAc are selectively recruited to enhance motivated behaviors by acting on the terminals of a lDRN projection to NAc shell. Additionally, these terminal MORs are engaged by locally released NAc enkephalin. Future studies could evaluate how this system changes in response to opioid abuse (e.g., fentanyl), or how motivated systems change in response to chronic pain.

Disclosure: Nothing to disclose.

10.2 Overlapping Neuron Subtype Mechanisms in Stress and Opioid Abstinence

Mary Kay Lobo

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

Background: Previously we demonstrated that repeated social stress leads to reduced dendritic complexity in nucleus accumbens (NAc) dopamine receptor 1 (D1)-medium spiny neurons (MSNs). Restoring this dendritic complexity, by blocking the molecular mediators of dendritic atrophy in these neurons, prevented stress susceptible behaviors. Research from two decades ago demonstrates reduced dendritic complexity in NAc MSNs during abstinence from opioids. However, it is unknown which MSN subtype this occurs and if there are overlapping mechanisms occurring in stress and opioid abstinence.

Methods: Male and female D1-Cre and A2A-Cre mice, which express Cre in D1-MSNs and D2-MSNs respectively, received a Cre-inducible adenoassociated virus (AAV)-DIO-EYFP infusion into the NAc to sparsely label MSN subtypes. Following three weeks, to ensure viral expression, the subjects underwent 5 days of fentanyl (10ug/ml) in their drinking water or water for control conditions followed by 10 days of abstinence. MSN subtype morphology was analyzed by sholl analysis and dendritic length. Another cohort of male and female mice underwent the same fentanyl abstinence paradigm followed by a three-chamber social preference test. An additional male cohort underwent a subthreshold social defeat stress (SSDS) followed by social interaction. Finally, male and female D1-Cre-RiboTag (RT) and A2A-Cre-RiboTag mice, which allow ribosomal tagging in D1-MSNs and D2-MSNs respectively, underwent the same fentanyl abstinent paradigm. Ribosome-associated mRNA was collected from each MSN subtype followed by RNA-sequencing and weighted gene coexpression analysis (WGCNA).

Results: NAc D1-MSNs displayed reduced dendritic complexity in fentanyl abstinent male and female mice. Fentanyl abstinent male and female mice displayed a negative correlation between fentanyl consumption and time interacting with a novel social target. Fentanyl abstinent male mice displayed reduced social interaction after SSDS. RNA-seq analysis of D1-MSNs and D2-MSNs revealed differentially enriched genes in the fentanyl abstinent group, 439 in D1-MSNs and 137 in D2-MSNs. WGCNA analysis identified 11 cell subtype modules that were associated with fentanyl, 9 D1-MSN modules and 2 D2-MSN modules. Five of the modules included molecules related to dendritic structure and plasticity including actin cytoskeleton, glutamatergic function, and synaptic molecules.

Conclusions: Our data implicate overlapping dendritic atrophy mechanisms in D1-MSNs of stress susceptible and opioid abstinent conditions. Further, we identified distinct gene network modules mainly occurring in D1-MSNs of fentanyl abstinent mice. This included molecules that may regulate the altered dendritic complexity in these MSN subtypes. Collectively our data uncovered neuron subtype molecular and cellular mechanisms that could underlie negative affective states during prolonged opioid abstinence.

Disclosure: Nothing to disclose.

10.3 Angiotensin Converting Enzyme Degrades an Exotic Enkephalin Congener in the Nucleus Accumbens

Patrick Rothwell

University of Minnesota, Minneapolis, Minnesota, United States

Background: Extracellular peptidases are critical regulators of endogenous opioid signaling. These proteolytic enzymes degrade enkephalins and other endogenous opioid peptides after secretion, thereby limiting the duration and magnitude of opioid receptor activation. Angiotensin-converting enzyme (ACE)

degrades enkephalins and is expressed in the brain, with uniquely high expression in the striatonigral pathway formed by Drd1a medium spiny neurons (D1-MSNs). I will present evidence that pharmacological inhibition of ACE prevents the degradation of Met-enkephalin-Arg-Phe (MERF), an exotic enkephalin heptapeptide, leading to a pathway-specific enhancement of endogenous opioid signaling in the nucleus accumbens.

Methods: All experiments utilized both male and female mice, in similar numbers and on a C57Bl/6J background. Liquid chromatography-tandem mass spectrometry was used to quantify extracellular release of various enkephalin congeners, evoked by stimulation of nucleus accumbens tissue with a high concentration of potassium chloride (50 mM) for 20 minutes (n=8 mice/condition). Whole-cell patch-clamp recordings were used to monitor excitatory synaptic transmission onto D1-MSNs in the nucleus accumbens (n=5-14 cells/condition). Captopril (10 uM) was used as a pharmacological inhibitor of ACE. A floxed mouse line was used to perform conditional genetic knockout of ACE, with a control group consisting of littermate animals lacking the floxed allele.

Results: Chemical stimulation of nucleus accumbens brain slices evoked robust release of conventional Met-enkephalin and Leu-enkephalin, but only a negligible amount of MERF ($p = 0.0016$). However, in the presence of captopril, release of MERF increased 200%, with no change in levels of Met-enkephalin or Leu-enkephalin ($p = 0.0018$). Application of exogenous MERF led to a dose-dependent reduction of excitatory synaptic transmission onto both D1- and D2-MSNs ($p = 0.0005$). However, co-application of captopril and a sub-threshold concentration of MERF had a synergistic effect that was specific to D1-MSNs ($p = 0.004$), and was absent following conditional genetic deletion of ACE from D1-MSNs ($p < 0.001$). Finally, while recording excitatory synaptic current evoked by electrical stimulation, captopril caused a long-term depression in D1-MSNs that was blocked by naloxone, an opioid receptor antagonist ($p = 0.002$).

Conclusions: Our data support a model in which MERF released in the nucleus accumbens is subject to rapid degradation by ACE. Captopril inhibits ACE and reveals endogenous signaling by MERF that is specific to D1-MSNs, which express high levels of ACE. Together, these data identify fundamental but historically elusive functions for ACE and MERF in the nucleus accumbens, and uncover new therapeutic targets to manipulate endogenous opioid signaling.

Disclosure: Nothing to disclose.

10.4 Dopamine D2 Receptors Bidirectionally Regulate Striatal Enkephalin Expression to Affect Cocaine Reward

Lauren Dobbs

The University of Texas At Austin, Austin, Texas, United States

Background: A predisposing factor for cocaine abuse in humans is low dopamine D2 receptor (D2R) availability in the striatum. We recently modeled this phenomenon in mice, where a selective deletion of D2Rs from striatal indirect pathway medium spiny neurons (iMSN-Drd2KOs) induced greater cocaine seeking. While the exact downstream mechanisms by which low striatal D2R levels predispose to cocaine abuse remain relatively unknown, one potential mechanism is through D2R-mediated regulation of enkephalin, an opioid peptide implicated in cocaine reward and locomotor sensitization. Here, we assessed how manipulation of striatal D2R levels affects the enkephalin expression and tone in the striatum and how this contributes to cocaine reward.

Methods: Male and female mice were used in all experiments. We selectively manipulated striatal D2R expression ($n = 3–5$) 2 ways: (1) inducible viral approach to overexpress the human D2 receptor, and (2) genetic approach to selectively reduce D2Rs from iMSNs. Levels of pre-proenkephalin RNA were assessed using qPCR and gene chip microarray in drug naïve and cocaine treated mice. Ex vivo electrophysiological recordings of striatal GABA transmission were performed in slices from iMSN-Drd2KOs and Adora2a-Cre controls ($n = 10–11$ cells/3–4 mice). Bath application of peptidase inhibitors to prevent enkephalin breakdown was used to assess enkephalin tone in the slice. Recordings of inhibitory post synaptic currents were made from direct pathway MSNs. Control Drd2loxP/loxP mice were administered intra-accumbens enkephalin paired with systemic cocaine in a conditioned place preference experiment ($n = 9–16$). Preference was measured in a drug-free state and also following intra-accumbens administration of the mu-opioid receptor antagonist CTAP.

Results: Selective reduction of D2Rs in iMSNs using a genetic approach increased striatal enkephalin mRNA by 56%, while over-expression of D2Rs in iMSNs using a viral vector suppressed enkephalin expression by 50%. Further, repeated cocaine, which increases D2R activity, also suppressed enkephalin expression by 32% in the nucleus accumbens. Ex vivo electrophysiological recordings revealed evidence of enhanced enkephalin tone in mice with low D2Rs in iMSNs. Peptidase inhibitors suppressed amplitude of optically-evoked IPSCs by 24% in mice with low D2Rs but had no effect in controls. Exogenous bath application of met-enkephalin suppressed IPSC amplitude in both genotypes (71%–66% reduction) and was reversed by an opioid receptor antagonist, suggesting that reducing D2Rs from iMSNs enhances striatal opioid peptide tone. Microinjection of met-enkephalin, but not vehicle, into the nucleus accumbens shell of wild-type mice facilitated cocaine place preference (67% vs, 58% time on cocaine floor, respectively). Further, while the MOR antagonist CTAP blocked the expression of cocaine CPP in previously vehicle-conditioned mice, it had failed to block cocaine preference in previously enkephalin-conditioned mice.

Conclusions: Together, these data indicate that D2R activity bidirectionally regulates striatal enkephalin expression, and heightened enkephalin tone resulting from low striatal D2Rs can enhance cocaine reward. We conclude that enhanced cocaine reward resulting from low striatal D2R levels results at least in part from increased striatal enkephalin tone and a disinhibition of direct pathway MSNs.

Disclosure: Nothing to disclose.

Study Group

11. Aggression: Gaps in our Knowledge and Strategies to Enhance Research in the Field

Emil Coccaro, Nelly Alia-Klein, Jennifer Fanning, M. Mercedes Perez-Rodriguez, Michael McCloskey, F. Gerard Moeller, Neir Eshel, Alan Swann, Barbara Stanley, Matthew Nock, Neal Simon, Alan Schatzberg, Sarah Lisanby

Study Group Summary: Human aggression constitutes a multi-determined act that results in physical (or verbal) injury to self, others or objects. It appears in several forms and may be defensive, premeditated (e.g., predatory) or impulsive (e.g., non-premeditated) in nature. While defensive aggression is typically within the normal range of human behavior, premeditated and impulsive aggressive behaviors are commonly viewed as pathological and the tendency to behave aggressively represents a behavioral trait. A converging pattern of empiric data consistently link impulsive aggression, in particular, to biological, environmental, and to pharmacological and psychological treatment response, factors. Epidemiologic data suggest that recurrent,

problematic, impulsive aggression is relatively common affecting up to 8% of the adult US population. Most importantly, the tendency to be aggressive, not psychiatric illness in general, underlies the vast majority of violence, including gun violence, in the US. Despite this, research in aggression is inadequately funded and many gaps in our understanding of human aggression, from a biomedical perspective, continue to exist. This study panel will identify the many gaps in our knowledge and discuss potential strategies to address these gaps as well as strategies to increase public awareness of aggression as a target for treatment and to enhance the pipeline of investigators working in this field. The study group members will discuss these issues from both a basic science and clinically-oriented perspective.

Disclosure: Avanir: Consultant (Self); Azevan: Advisory Board (Self)

Panel

12. Children and Adolescents With Bipolar Disorder: Where Do They Come From and Where are They Heading?

12.1 Early Childhood Indicators of Bipolar Risk in Offspring of a Parent With Bipolar Disorder

Danella Hafeman

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Offspring of parents with bipolar disorder (BD) are at higher risk to develop the disorder. Previous work indicates that BD is often preceded by mood/anxiety symptoms months to years prior to diagnosis. Using clinical predictors, we previously built a risk calculator (RC) to predict BD onset in offspring with good accuracy in school-aged youth. However, we do not know how early precursors of BD are evident in these youth. Here, we present data from offspring of parents with BD in the Pittsburgh Bipolar Offspring Study (BIOS) initially assessed during preschool years (2–5 years old) to test whether early childhood symptoms predict later risk trajectories and bipolar spectrum disorder (BPSD) onset.

Methods: We assessed 106 offspring of parents with BD 1–2 times during preschool years (2–5 years old) and then followed them up approximately every two years for a mean of 7.6 years. We used mixed models (nested within individual and family), adjusting for age and gender, to assess whether average scores on Child Behavior Checklist (CBCL) subscales (Internalizing and Externalizing) and Emotional Activity, and Sociability (EAS) temperament subscales were associated with later risk scores, based on the log-transformed BIOS RC. Analyses were further adjusted for preschool diagnosis and bipolar parent depressive symptoms. Next, we limited assessments to younger ages (e.g. <4 years old) to test if these also predicted later risk scores. Finally, we conducted survival analyses to assess the degree to which early symptoms predicted later onset of BPSD and depressive disorder.

Results: Our risk score prediction analyses included 223 follow-up observations, nested within 90 youth in 69 families. Both Internalizing and Externalizing symptoms were predictive of later risk score trajectories (Internalizing: $\beta = 0.027$, S.E. $= 0.008$, $p = 0.002$; Externalizing: $\beta = 0.026$, S.E. $= .007$, $p = 0.0002$). Internalizing symptoms showed slight negative interaction with assessment age, indicating that effects were stronger at younger ages ($p = 0.03$). Findings remained significant after adjusting for parental depressive symptoms and preschool diagnoses. Even when the sample was limited to assessments prior to 4 years old (n=47), Internalizing and Externalizing symptoms were still predictive of school age risk scores (Internalizing: $\beta = 0.030$, S.E. $= 0.011$, $p = 0.01$; Externalizing: $\beta = 0.018$, S.E. $= .009$, $p = 0.04$). Finally, we found that externalizing symptoms during preschool years predicted later BPSD onset (Externalizing: HR $= 1.07$, 95% CI: 1.02, 1.11; $p = 0.001$). Preschool CBCL symptoms did not predict depressive disorder onset. We did not find any relationships between EAS subscales and either risk trajectories or BPSD onset.

Conclusions: These unpublished results provide initial prospective evidence that, as early as 2–5 years old, youth who will later have elevated RC scores are already showing symptomatology. Further studies including larger samples are warranted to replicate these findings. These findings point to the need for even earlier assessment of neural risk markers and development of early interventions.

Disclosure: Nothing to disclose.

12.2 Differences in Limbic Microstructure and Connectivity Among Youth With Attentional Deficits With and Without a Family History of Bipolar Disorder

Abstract not included.

12.3 Predicting Individualized Risk for Mood Recurrences in Youth and Adults With Bipolar Disorder

Abstract not included.

12.4 Differential Association of Cardiovascular Risk Factors With Structural Neuroimaging Phenotypes in Youth With Bipolar Disorder

Benjamin Goldstein

Sunnybrook Health Sciences Centre, Toronto, Canada

Background: Bipolar disorder (BD) is associated with increased risk of excessive and premature cardiovascular disease (CVD). Elevated lipid levels and reduced cardiorespiratory fitness (CRF) are evident in BD, and associated with mood symptoms. Studies in other populations have identified neurostructural correlates of lipids and CRF. However, no prior studies have examined either of these CVD risk factors in relation to brain structure in BD. We evaluated whether the association between these CVD risk factors and regional brain structure differs among adolescents with BD vs healthy control adolescents (HC).

Methods: 3-Tesla Magnetic Resonance Imaging measures of brain structure were analyzed using Freesurfer in adolescent females and males, ages 13–20 years, and examined in relation to: fasting blood lipid levels ($n = 55$ BD, $n = 47$ HC) and CRF ($n = 54$ BD, $n = 43$ HC). Power (watts/kg) during a 20-min bout of moderate-intensity exercise (60–80% of maximum) on a bicycle ergometer served as a previously validated proxy for CRF. Diagnoses were determined using validated semi-structured interviews. Region of interest analyses were complemented by vertex-wise analyses. Analyses controlled for age, sex, intracranial volume and, for lipid analyses only, body mass index.

Results: Lipid levels were elevated in adolescents with BD vs. HC. In region of interest analyses there were significant lipid-by-diagnosis effects on hippocampal volume and anterior cingulate cortex volume and area ($p = 0.02$ to $p = 0.001$). Elevated lipids were associated with smaller brain structure to a significantly greater extent in BD vs. HC. Vertex-wise results similarly showed that elevated lipids were associated with smaller brain structure to a significantly greater extent in BD vs. HC in frontal, parietal, temporal, and occipital regions. CRF was reduced in adolescents with BD vs. HC (0.91 ± 0.32 vs.1.01 ± 0.30, $p = 0.03$). Within the BD group, female sex, greater depression symptoms ($r = 0.31$, $p = 0.02$), and lower physical activity ($r = 0.48$, $p = 0.001$) were

associated with reduced CRF. There were no significant region of interest findings for CRF. In vertex-wise analyses there were significant CRF-by-diagnosis interaction effects for several clusters in frontal, parietal and occipital cortices. The direction of these findings was inconsistent. Controlling for second-generation antipsychotics did not alter any of these results.

Conclusions: Lipid levels are elevated and CRF is reduced among adolescents with BD. Each of these cardiovascular risk factors is differentially associated with brain structure in adolescents with BD vs. HC. Interventions targeting lipids or CRF in BD are thus far lacking, and offer multiple potential near-term and long-term benefits.

Disclosure: Nothing to disclose.

Panel

13. Neural Indices of Risk for Developmental Psychopathology in Infancy and Adolescence: Findings From Longitudinal Samples of Underrepresented Groups

13.1 Neural Noise at 8-Months Predicts Infant Internalizing and Externalizing Behavior at 18 Months of Age

Koraly Perez-Edgar

Penn State University, University Park, Pennsylvania, United States

Background: Adaptive information processing depends on efficient communication between neurons. Information processing may, however, be disrupted when neuronal networks are synchronized too strongly (over-coupling) or too weakly (under-coupling). Neural noise may serve as a safety mechanism that prevents pathological coupling. A moderate level of noise facilitates information processing, whereas extreme high and low levels may lead to cognitive and behavioral dysfunction by disrupting neuronal synchronization. Internalizing disorders (e.g., anxiety) may reflect over-coupling of the default mode network as a result of reinforcement (e.g., rumination). High noise undercuts neuronal synchronization and is related to age-related cognitive decline, as well as cognitive dysfunction in certain disorders (e.g., ADHD). Neural noise can be measured by the EEG power spectral slope. Computational and animal models demonstrate that the spectral slope reflects the balance of synaptic excitation to inhibition in the brain. Animal models also suggest that environmental stress may impact the neural mechanisms that drive spectral slope differences. A flatter slope indicates more random neuronal activity. Here, we leverage an ethnically diverse sample drawn from three communities varying in psychosocial stress to examine how neural noise emerges in infancy and relates to childhood psychopathology.

Methods: Families were drawn from an ongoing longitudinal study examining infant temperament and attention (N=350). Spectral slopes were estimated from infant resting EEG at Cz via FOOOF. A flatter slope (lower values) indicates more neural noise, while a steeper (more positive) slope indicates more efficient information processing that may extend to over-coupling at the extreme. Preliminary data are currently available at 8- (N=124), 12- (N=88), and 18-mo (N=72). Mothers reported on infant internalizing and externalizing problems at 18-mo via the Infant-Toddler Social and Emotional Assessment (ITSEA).

Results: 8-mo neural noise was negatively associated with neural noise trajectories ($\beta = -0.85$, $p = 0.01$), suggesting that infants with lower noise at 8-mo (reflected by a higher intercept in spectral slope) were more likely to show stability in neural noise trajectories over time. Less neural noise at 8-mo also showed more internalizing ($\beta = 0.23$, $p = 0.01$) and externalizing ($\beta = 0.19$, $p = 0.01$) problems at 18-mo. Changes in neural noise from 8- to 18-mo did not predict behavior problems at 18-mo ($ps > 0.57$). Parent education predicted less neural noise at 8-mo, and paternal education predicted stable trajectories.

Conclusions: Our preliminary results converge with prior evidence to show individual differences in the shift of spectral power from lower to higher frequencies across early life, as indexed by changes in the spectral slope over time. Less noise (potentially over-coupling) at 8-months was associated with early childhood psychopathology risk. In addition, markers of the child's environment, particularly as marked by SES, also impact trajectories of early neural development. These emerging data suggest that environmental risk markers (e. g., parental SES) may also be related to the trajectory of early neural noise. Follow-up analyses will work to bring together individual neural markers, environmental risk, and early psychopathology symptoms into a single model.

Disclosure: Nothing to disclose.

13.2 Maternal Anxiety and Neonatal Brain Response to Novel Sounds as Measured With fMRI

Chad Sylvester

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

Background: Neonates with an enhanced behavioral and neural reaction to novelty (as measured by EEG) are at an increased risk for developing an anxiety disorder. Yet, almost nothing is known about the specific brain regions that respond to novelty in neonates and how variation in activity in specific brain regions relates to risk for anxiety.

Methods: We used task-based fMRI to measure regional brain activity evoked by novel auditory stimuli ("oddballs") in $n = 46$ sleeping neonates (mean age 27.8 days, 60% female, 64% African American). In a subset of $n = 41$ infants, variation in regional brain activity in response to oddball stimuli was related to maternal trait anxiety on the State-Trait Anxiety Inventory (STAI-T). All statistical analyses were whole brain corrected at a level of $p < 0.05$ using stringent cluster-based correction methods (voxelwise significance $p < 0.001$, cluster size 756mm3). Regional brain activity in neonates was related to adult functional architecture. Exploratory analyses will identify brain networks in each individual infant using functional connectivity measures in a data driven approach and relate evoked brain activity to subject-specific functional architecture.

Results: Auditory oddballs elicited robust and widespread activity across the neonatal brain, including in the thalamus, auditory cortex, dorsal anterior cingulate cortex, anterior insula, precentral sulcus, and in the right temporal lobe extending posteriorly the temporal-parietal junction. In adults, these include regions that become the salience, cingulo-opercular, and ventral attention networks. High maternal trait anxiety was associated with an increased initial response to auditory oddballs in 55 different regions distributed across the brain, including the bilateral anterior insula, ventrolateral prefrontal cortex, and multiple areas within anterior cingulate cortex. Remarkably, the brain regions underlying the increased neonatal responsivity to novel stimuli and its association with maternal anxiety overlapped with brain regions previously linked to anxiety disorders and other psychiatric illnesses in adults. Future analyses will use each participant's own functional connectivity data to identify individual-specific functional architecture, to determine the specific networks underlying the novelty response in neonates.

Conclusions: Neonates at high risk for anxiety on the basis of high maternal anxiety have increased neural responses to novel sounds across many different brain systems. Furthermore, the

specific brain regions that respond robustly to novel stimuli, and the regional responses that vary with maternal anxiety, are the same regions implicated in the response to novel stimuli and the pathophysiology of anxiety disorders in adults. These results suggest that the pathology associated with anxiety may begin already at birth and may include alterations in the basic brain mechanisms that respond to environmental change.

Disclosure: Nothing to disclose.

13.3 Brain-Based Connectivity Mechanisms Underlying Depression in Adolescent Girls

Amanda Guyer

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

Background: Depression is the leading cause of disease burden in adolescent girls, with depressive symptoms typically increasing among girls during adolescence. Theories of depression suggest certain neurocognitive processes serve as mechanisms of depression risk. Behavioral evidence has linked biases in autobiographical memory and worse recall of emotional stimuli in relation to depressive symptoms in adolescent girls. However, the neural underpinnings of these cognitive processes remain unidentified. Based on evidence that the amygdala and hippocampus are associated with negative emotional memory, we examined whether task-based functional connectivity of the amygdala and hippocampus relates to higher severity of concurrent depressive symptoms. We tested these hypotheses in an understudied sample of girls who are majority African Americans from predominantly low-income backgrounds, and thus at heightened risk for depression.

Methods: Participants were 116 girls enrolled in the Pittsburgh Girls Study of Emotions, a prospective cohort study of risk for depression. At age 16, girls completed an fMRI scan as they rated emotional faces (sad, angry, happy, neutral) presented in an event-related task; post-scan, girls indicated if they saw a previously-encoded or novel face (44 trials). Depressive symptom severity was measured with the Adolescent Symptom Inventory. CONN toolbox was used to assess seed-to-voxel functional connectivity on neural activity engaged when girls encoded negative emotions they subsequently remembered or forgot. Seed regions were bilateral amygdala and hippocampus selected based on past work, and defined using FSL atlas masks. Functional connectivity values between seed regions and any significant clusters of voxels were extracted in order to use these values as predictors of memory performance and depressive symptoms.

Results: Both the amygdala and hippocampus showed differential patterns of functional connectivity during the encoding of remembered faces displaying negative emotions versus encoding of subsequently forgotten negative faces. The amygdala demonstrated connectivity with a cluster of voxels in left occipital cortex (476 voxels; peak coordinates: −32, −92, 4), p value cluster <0.001 (corrected), p value voxel <0.001, showing greater functional connectivity during the encoding of subsequently remembered versus forgotten negative emotional faces. However, only functional connectivity between the amygdala and occipital lobe during the encoding of remembered negative faces relative to forgotten ones was significantly related to depressive symptoms, B = 0.155, rate ratio = 1.168, $p < 0.001$. Amygdala-occipital functional connectivity statistically mediated the association between stronger negative memory performance and higher levels of depressive symptoms, $p = 0.021$, accounting for 16.9% of the variance in depressive symptoms explained by negative memory.

Conclusions: In a diverse sample of adolescent girls, depression severity associated with enhanced negative memory performance may be due to relatively greater functional connectivity between the amygdala and occipital cortex during encoding. These results also fit with evidence from this sample indicating that increasing depressive symptom severity was related to greater white matter connectivity between fusiform gyrus and middle occipital gyrus. Together, findings derived from structural and functional modalities suggest potential avenues for neurobiologically-informed interventions aimed at modifying how negative information is processed in order to decrease depression risk.

Disclosure: Nothing to disclose.

13.4 Childhood Violence Exposure Predicts Adolescent Neural Network Sparsity

Leigh Goetschius

University of Michigan, Ann Arbor, Michigan, United States

Background: Adverse childhood experiences (ACEs) are a critical public health issue with negative mental and physical health sequelae that persist throughout life. Current theories suggest that ACEs have subdimensions (i.e., violence exposure versus social deprivation) that have unique neural correlates; however, past research is inconsistent likely due to heterogeneity in how the environment "gets under the skin". Thus, the present study aimed to examine how dimensional exposure to childhood adversity predicts person-specific patterns in adolescent resting-state functional connectivity (rsFC) of two networks (salience network – SN, and default mode network – DMN). We did this using a data-driven, sparse neural network approach in a large sample with many under-studied and under-served minority youth.

Methods: We analyzed resting-state fMRI in 175 adolescents (M_AGE = 15.88 years (SD_AGE = 0.53) | 98 Female, 77 Male | 171 African American) from the Fragile Families and Child Wellbeing Study with longitudinal data from birth on childhood violence exposure and social deprivation. Group Iterative Multiple Model Estimation (GIMME), a data-driven, sparse modeling approach, estimated person-specific networks with connections shared by all participants, data-driven community algorithm-detected subgroups, and unique for individuals within and between the 4 SN regions of interest (ROIs) and 3 DMN ROIs. We examined links between subdimensions of early adversity (violence exposure, social deprivation), subgroup membership, and overall connectivity patterns (network density: number of connections modeled; node degree: number of connections involving a single ROI).

Results: Adolescents with high violence exposure were 3.06 times more likely (95% CI [1.17,8.92]) to be in a data-driven subgroup characterized by high heterogeneity (i.e., few shared paths across the group) and low network density (sparsity). Furthermore, childhood violence exposure, but not social deprivation, predicted reduced adolescent rsFC density (beta = −0.25, 95% CI [−0.41,−0.05], p = 0.005), which was driven by fewer connections within the SN (beta = −0.26, 95% CI [−0.43, −0.08], p = 005) and between the SN and DMN (beta = −0.20, 95% CI [−0.38,−0.03], p = 0.023). Violence exposure specifically predicted degree of the right anterior insula (beta = −0.29, 95% CI [−0.47, −0.12], p = 0.001) and left inferior parietal lobule (beta = −0.26, 95% CI [−0.44,−0.09], p = 0.003).

Conclusions: In a prospective, longitudinal study of 175 youth, childhood violence exposure, but not social deprivation, predicted person-specific differences adolescent rsFC in regions involved in salience detection (SN) and higher-level cognitive processes (DMN). These differences were potent enough that a data-driven algorithm, blind to child adversity, grouped youth exposed to more violence together based on the heterogeneity of their neural networks, suggesting that the environment shapes the brain in unique ways that cannot be detected using standard mean-based analyses. Findings have implications for understanding how

dimensions of adversity affect brain development, which can inform future neuroscience-based policy interventions.

Disclosure: Nothing to disclose.

Panel

14. The Neurobiology of Arousal and its Relevance to Psychiatry, Anxiety and PTSD

14.1 Prefrontal Acetylcholine and Norepinephrine Structure Arousal After Stress

Alfred Kaye

Yale, New Haven, Connecticut, United States

Background: Across the cortex, neurons increase their firing when the pupil dilates, reflecting neuromodulatory control of arousal. Arousal neuromodulators such as acetylcholine (ACh) and norepinephrine (NE) have been described as operating redundantly, and show alterations following stressful experiences. The precise nature of neuromodulatory interactions and control of neural ensembles is not well understood. Here we employ neurotransmitter biosensors, microendoscope and two-photon imaging to define spatiotemporal dynamics of neuromodulatory control of prefrontal cortex following stress.

Methods: C57Bl6 mice (sample size $n = 10$ in stress and control groups) were used for (1) in vivo norepinephrine (GRAB-NE2h) and (2) acetylcholine sensor imaging (GRAB-Ach3.0), and subsequently used for pharmacological blockade of norepinephrine transporter (desipramine vs saline) in a crossover design. Pupil was recorded with infrared cameras, and simultaneous pupil-imaging datasets were analyzed with spectral and time series analysis of neural response to pupil events. An additional cohort ($n = 6$) was used for (3) two-photon GRIN lens imaging of GRAB-NE2h and genetically encoded calcium indicator (jrGECO1a) in prefrontal cortex to define spatiotemporal dynamics of NE-prefrontal ensembles (saline vs despramine, crossover design).

Results: Acetylcholine shows higher correlation to pupillary diameter than norepinephrine ($r = 0.64$ vs 0.36 $p < 0.01$). Acetylcholine shows greater coherence with the pupil at infra-slow (<0.2 Hz) whereas norepinephrine shows greater coherence with the pupil at slow (0.3–0.6 Hz) frequencies. Stress alters the Ach-NE balance by increasing infra-slow acetylcholine and decreasing infra-slow norepinephrine ($p < 0.05$) coupling to pupillary state. Surprisingly increasing NE levels by administering a NET inhibitor amplifies slow (<0.1 Hz) cholinergic dynamics in prefrontal cortex ($p < 0.001$) while diminishing slow noradrenergic dynamics ($p < 0.05$). Two-photon imaging of NE in PFC shows local NE release, as well as heterogeneous modulation of PFC ensembles.

Conclusions: Acetylcholine and norepinephrine are not redundant, but rather can be synergistic with increasing norepinephrine amplifying cholinergic dynamics. The balance of acetylcholine and norepinephrine dynamics in pupillary arousal is not constant but is plastic, and varies with emotional state. Norepinephrine dynamics are dominated by slow dynamics, which in turn reflect the action of the norepinephrine transporter, and norepinephrine release is spatially localized. Prefrontal neural ensembles are heterogeneously modulated by norepinephrine, with some neurons showing evidence of suppression by norepinephrine. These results extend our previous understanding of stress in modulating arousal states, and have implications for the conceptualization of disorders involving stress-induced hyperarousal, such as PTSD.

Disclosure: Nothing to disclose.

14.2 Prepronociceptin-Expressing Neurons in the Extended Amygdala Encode and Promote Rapid Arousal Responses to Motivationally Salient Stimuli

Jose Rodriguez-Romaguera

UNC at Chapel Hill, Chapel Hill, North Carolina, United States

Background: Dysfunctional arousal responses are a core component of many neuropsychiatric disorders. For example, patients with anxiety disorders often show hyperarousal responses to negatively salient stimuli, and patients suffering from depression show hypoarousal responses to positively salient stimuli. Elucidating the neural circuit elements that orchestrate changes in physiological arousal is thus essential for understanding maladaptive motivational states. Motivational states are complex and consist of cognitive, emotional, and physiological components controlled by neuronal networks spanning multiple brain regions. An integral component of this neural circuitry is the bed nucleus of the stria terminalis (BNST). Here, we studied a subpopulation of genetically identified neurons within BNST and their role in encoding rapid arousal responses to motivationally salient stimuli and anxiety-like behavior.

Methods: In the present study, we used cell-type-specific two-photon calcium imaging approaches to assess the role of neurons within BNST that express the gene prepronociceptin (Pnoc-BNST). We tested the role of these neurons in driving and encoding rapid physiological arousal responses to aversive and rewarding odors ($n = 1177$ neurons, $n = 7$ mice). We also used optogenetics to activate Pnoc-BNST neurons while assessing physiological measurements associated with arousal (pupillary response and heart rate), as well as locomotive and anxiety-like behaviors (open field velocity and elevated plus maze, $n = \sim 7$ mice per group, 10 groups). Lastly, we used a combination of histological ($n = 11$ mice), electrophysiological ($n = 14$ neurons, $n = 4$ mice), and single-cell RNA sequencing ($n = 24$ mice) methods to assess Pnoc-BNST neuronal diversity.

Results: Using in vivo two-photon calcium imaging, we find that responses from individual Pnoc-BNST neurons directly correspond with rapid increases in pupillary size when mice are exposed to both aversive ($p < 0.0001$) and rewarding ($p < 0.0001$) odors. Furthermore, optogenetic activation of these neurons increases pupillary size ($p = 0.039$), heart rate ($p = 0.026$) and anxiety-like behavior ($p = 0.0037$) but does not induce approach/avoidance ($p = 0.34$) or locomotion ($p = 0.999$). Further histological, electrophysiological, and single-cell RNA sequencing data reveal that Pnoc-BNST neurons are composed of genetically (overlap with Som, PKCd, Cck, and Zic1 genetic markers) and anatomically (local connectivity and projections to medial amygdala and medial preoptic area) identifiable subpopulations that may differentially tune these responses. We found that Pnoc-BNST neurons can be subdivided by expression of the genetic markers: Som, PKCd, Cck, and Zic1.

Conclusions: Our findings demonstrate a key role for a Pnoc-BNST neuronal ensemble in encoding the rapid arousal responses that are triggered by motivational stimuli. Our findings also suggest that responses in Pnoc-BNST neurons encode rapid arousal responses that modulate anxiety states. Moreover, our data indicate that perhaps targeting these neurons may modulate hyperarousal responses in patients suffering from anxiety disorders.

Disclosure: Nothing to disclose.

14.3 Startle, Heart-Rate and Skin Conductance Data in PTSD

Tanja Jovanovic

Wayne State University School of Medicine, DETROIT, Michigan, United States

Background: Arousal levels are associated with activity in the sympathetic nervous system (SNS) and brainstem circuits such as periaqueductal gray and the pons. Peripheral physiological measures, such as skin conductance level (SCL) and acoustic startle response (ASR) can be easily used to assess activity in these circuits. Research has shown that pathological arousal, such as the hyperarousal symptoms in PTSD, are associated with elevations in peripheral psychophysiology (Pole, 2007; Norrholm & Jovanovic 2018). The etiology of whether PTSD leads to altered arousal, or whether alterations in SNS lead to chronic PTSD symptoms is still unclear. Our prior research suggested that startle in the acute phase after trauma exposure is elevated compared to chronic PTSD (Jovanovic, 2012), however, this study was cross-sectional and did not address issues of whether physiological responses change over time in traumatized individuals. Some studies have found that repeated and extreme traumatization is linked with blunted physiology (McTeague, 2010; D'Andrea, 2013). We have recently shown that SCL collected a few hours after trauma exposure in the Emergency Department (ED) was predictive of future PTSD symptoms (Hinrichs, 2019). Here we compared ASR during a fear conditioning experiment between acutely traumatized individuals (approximately 1-month post ED) and chronic PTSD, and examined longitudinal changes in startle in the ED sample. We also examined sex differences in arousal, given the increased risk for PTSD in women.

Methods: The study participants N = 244, included 60 individuals recruited from the ED (24 females) and N = 184 individuals with PTSD recruited from the Grady Trauma Project (132 females). Of the 60 individuals in the acute sample, N = 41 returned for a follow-up visit 6 months later (19 females). All participants completed startle testing during a fear conditioning task, and electromyogram of the eyeblink component was recorded using Biopac MP150. All participants completed assessment of lifetime trauma exposure and PTSD symptoms (PCL-5).

Results: We found significant sex differences. Baseline startle (measured during the habituation phase of the experiment) was significantly higher in women with acute trauma compared to women with chronic PTSD, $F(1,154) = 7.58$, $p = 0.007$. On the other hand, women also showed a decrease in startle response from 1-month to 6-months, $F(1,18) = 6.93$, $p = 0.017$. Men had lower startle at 6-months compared to women, $F(1,39)=10.44$, $p=0.003$. A regression analysis controlling for demographics and lifetime trauma found that PTSD symptoms at 3-months predicted higher fear-potentiated startle at 6-months in women (R-squared $= 0.68$, $p = 0.002$).

Conclusions: These results suggest that SNS activity and physiological arousal are high initially after trauma, especially in women. As time since trauma passes, baseline startle decreases. In chronically traumatized populations, startle responses are significantly lower, which may indicate blunted arousal systems. However, in acutely traumatized women with higher PTSD symptoms, fear-conditioned physiology, which may be related more to fear circuitry activity than SNS, continues to be elevated six months after trauma exposure.

Disclosure: Nothing to disclose.

14.4 Translational Approaches to Arousal-Related Disorders: Genetics, Circuits and Clinical Biology

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

Background: Posttraumatic stress disorder (PTSD) and other trauma- and fear-related disorders are associated with states of hyper-arousal. This presentation will examine translational approaches across fear processing in mice and humans contributing to hyperarousal states. We will focus on new, cell-type specific understanding of the corticotropin releasing hormone gene (Crh) within the central amygdala (CeA) and its role in arousal, fear and fear extinction learning in mice and genetic associations of this pathway in humans with PTSD. Crh is well-established as central to stress and arousal networks, and it has recently been associated in Genome-wide Association Studies of PTSD symptoms. Finally, we will also examine enhanced sensory sensitivity across species following trauma exposure.

Methods: In mouse studies, we profiled the transcriptome of Crh-expressing neurons within the central amygdala (CeA)— the CeL (central amygdala lateral aspect) following fear conditioning and fear extinction in mice using translating ribosome affinity purification (TRAP) followed by RNA sequencing. Differential gene analysis across behavioral states, gene network analysis, and upstream regulator analyses were employed. In a large, prospective examination of patients in the aftermath of trauma (the AURORA study), structural MRI data were collected ~ 1-month after trauma exposure in 78 subjects. Multimodal MRI data fusion was completed to identify groups of structural covariance networks (SCNs), related to acute PTSD severity at 1 month, and change in symptoms from 1 to 12 months.

Results: In our mouse models, differential gene expression analyses performed after fear expression and extinction animals showed robust extinction ($F(30, 540) = 5.590$, $p < 0.0001$). These analyses revealed mRNA profiles consistent with broad decreases in neuronal activity in the CeL Crh+ population. Further, gene co-expression network analysis identified diverse sets of networks activated or inhibited by fear extinction learning (19 gene network modules with 4346 co-expressed genes). With upstream regulator analysis, we found that fear extinction is associated with reductions in expression of CREB in CeL Crh+ neurons. Conversely, viral vector-induced elevations of CREB expression in CeL Crh+ neurons increased fear expression ($F(1,13) = 8.244$, $p = 0.013$) and inhibited fear extinction. Human studies with prior data also found amygdala increased activation to arousal cues was predictive of PTSD development. Furthermore, our multimodal analyses revealed greater gray matter properties of several areas including visual cortex with 1 month PSS scores ($t(71) = 2.64$, $p = 0.010$, $\beta = 0.341$), and was associated with the change in mPSS total scores between 1 and 12 months ($t(59) = 2.280$, $p = 0.026$, $\beta = 0.349$).

Conclusions: Our mouse findings suggest that CREB, within a specific subset of CeL neurons (Crh+), functions as a molecular switch that regulates expression of fear and its extinction. Our human data demonstrated that multimodal imaging approaches find patterns, in particular underlying sensory processing, that are related to variability in PTSD symptoms in the early aftermath of trauma. The identified networks may reflect patterns of neuroanatomical organization and provide unique insight into acute posttraumatic stress. Together, translational approaches can help to identify molecular-cellular-circuit-behavior relationships that may provide insight into the biology of threat-related arousal and its dysregulation in Psychiatric disorders.

Disclosures: Alkermes, Brainsway: Consultant (Self); Janssen, Verily, Nobilis: Advisory Board (Self); Takeda: Grant (Self)

Panel

15. Imaging of Putative Neuroinflammatory Markers for Precision Medicine in Neurologic and Psychiatric Disorders

15.1 Applying PET Markers of Gliosis for Disease Stratification, Target Engagement and Characterization of State

Abstract not included.

15.2 Neurobehavioral Phenotype of Kynurenine Metabolism in Depression

Ebrahim Haroon

Emory University, Atlanta, Georgia, United States

Background: The inflammatory subtype of depression emerges as a well-defined clinical and neural phenotype. However, leveraging these insights for new drug development is complicated by the broad range of upstream and downstream targets engaged by inflammatory molecules. Herein, we examine the kynurenine pathway (KP) as one of the targets involved in mediating effects of inflammation on brain and behavior. Inflammatory cytokines activate the enzyme indoleamine 2,3-dioxygenase (IDO), leading to the production of kynurenine (KYN). KYN further undergoes sequential degradation into molecules that modulate glutamate (quinolinic acid, QA and kynurenic acid, KYNA) and promote oxidative stress (3-hydroxy-kynurenine, 3HK). Furthermore, our recently published data indicated that inflammatory mediators facilitated the transfer of KP molecules from plasma to CSF, thus amplifying KP-related neurotoxic risk. The primary objective of this study is to link plasma/CSF KP metabolites with basal ganglia glutamate (measured using magnetic resonance spectroscopy, MRS), functional connectivity (measured using resting-state functional MRI, fMRI), and examine their symptomatic correlations.

Methods: Forty medication-free depressed subjects with stable chronic medical conditions were studied. Patients underwent behavioral, cognitive, plasma/CSF sampling for KP metabolites and MRS/fMRI scans under standardized conditions (plasma-CSF sampling interval<24 h). Absolute measures of glutamate in the left basal ganglia (LBGlu) was estimated using single-voxel MRS, and creatine-normalized glutamate in the right basal ganglia (RBGluCr) was measured using multi-voxel chemical shift imaging (CSI). LC Model was used to fit MRS spectra. Resting-state fMRI was used to obtain measures of regional homogeneity (ReHo – a measure of concordance in brain oxygen level-dependent (BOLD)-oscillations among neighboring voxels), functional connectivity, and network integrity. Fatigue was measured using the Multidimensional Fatigue Inventory (MFI), and cognitive slowing was measured using Digit Symbol Substitution (DSST), Trails A, and CANTAB-Stockings of Cambridge Tests (SOC). Confirmatory Factor Analysis was used to obtain component factors representing plasma/CSF KP and Anhedonia (ANH).

Results: Of the 40 subjects, 28 (70%) were male, and 26 (65%) were African American. Plasma KP factor significantly predicted RBGluCr (Cohen's $f = 0.42$, $p = 0.02$), and plasma QA predicted LBGlu ($f = 0.60$, $p = 0.006$). The interaction between RBGlu/Cr and Plasma KP factor was associated with impaired performance on DSST ($f = 0.60$, $p = 0.01$) and Trails A ($f = 0.51$, $p = 0.02$). Seed-to-brain analysis showed that KP measures negatively modulated the connectivity from BG-to-MSPFC (basal ganglia-to-medial superior prefrontal) and LSPFC-to-PCC (left superior prefrontal-to-posterior cingulate). Path analysis indicated that the CSF KP factor directly ($z = 2.04$, $p = 0.04$), and the plasma KP factor indirectly (via CSF KP) impacted anhedonia ($z = 1.93$, $p = 0.05$). Finally, decreased network node strength was associated with greater severity of anhedonia (ANH, $f = 0.43$, $p = 0.03$), fatigue (MFI, $f = 0.45$, $p = 0.03$), longer initial thinking time on CANTAB-SOC ($f = 0.40$, $p = 0.04$).

Conclusions: Anhedonia, fatigue, and cognitive slowing increase disability in depression. The association between the plasma KP and neurobehavioral findings reiterates the role of plasma-to-CSF transfer mechanisms in depression. Blocking or limiting the transfer of KP molecules across the blood-brain-barrier using agents such as leucine may be relevant.

Disclosure: Nothing to disclose.

15.3 A PET Marker of Gliosis Distinguishes Stages and Subtypes of Alzheimer's Disease and is Related to Emerging CSF Biomarkers of Inflammation

Abstract not included.

15.4 Preclinical and Clinical Evaluation of Novel PET Radioligands for Imaging Cyclooxygenase (COX)-1 and COX-2

Abstract not included.

Study Group

16. Use of Drugs With Abuse Potential for Psychiatric Pharmacotherapy: Clinical, Ethical, Legal & Policy Implications

Paul Appelbaum*, Peter Schmidt, Carlos Zarate, Deepak D'Souza, Marilyn Huestis, Frances Levin, Robert Mikos, Nora Volkow, Bertha Madras

Study Group Summary: A wide range of drugs with abuse potential are being investigated or used for treatment of psychiatric disorders. This study group, sponsored by the ACNP Ethics Committee and comprising some of the leading researchers and experts on the therapeutic uses of these drugs, will explore the issues raised from clinical, ethical, legal, and policy perspectives. We will begin by examining 4 substances with abuse potential now being used in treatment settings, either for research or clinical care. Ketamine is associated with rapid improvements in symptoms in patients with treatment-resistant depression and suicidal ideation. Dr. Zarate will describe its use, ethical issues that arise, and evidence suggesting that research on ketamine in participants with severe mood disorders and suicide risk can be conducted safely and ethically. The serotonergic psychedelics such as psilocybin have evoked considerable interest as treatments for depression, alcoholism, and other substance use disorders (SUDs). Dr. D'Souza will describe their use and explain how, consistent with the anecdotal literature, clinical trials with psychedelics suggest that when administered in a therapeutic context and with adequate preparation, abuse liability is low. Cannabinoids have attracted attention for potential therapeutic uses in depression, anxiety, ADHD, Tourette syndrome, PTSD, and psychosis. Dr. Huestis will offer an overview of research on the efficacy of cannabinoids for psychiatric indications and will describe the potential adverse consequences. Amphetamines and related stimulants remain the most effective treatment for ADHD, but are commonly misused, particularly by adolescents and young adults. Dr. Levin will explain why long-acting formulations are much less likely to be misused and will discuss other strategies to mitigate risk. With this background on the uses of these substances, Dr. Appelbaum will review the ethical concerns associated with research and clinical use, among them difficulties in research design, risks of evoking or exacerbating SUDs, unavailability of medications after study completion, and stigmatization of participants by family members and the public. However, ethical considerations may also favor research on therapeutic use of these compounds, notably possible benefit for patients with psychiatric disorders. Prof. Mikos will describe the

legal issues, surrounding investigation and use of psychiatric pharmacotherapies. These issues include the potential liability researchers and physicians face under federal law for investigating or recommending a Schedule I controlled substance. Dr. Volkow will consider lessons learned from the opioid crisis for the use of drugs with abuse potential, focusing on opioids for management of pain, treatment of opioid use disorders, and as potential antidepressants. She will demonstrate how the crisis highlights the need for better understanding of their diverse pharmacological properties, the relevance of delivery formulations, and the importance of training healthcare providers in prescription practices. Finally, drawing on her experience as deputy director for demand reduction in the White House Office of National Drug Control Policy, Dr. Madras will describe policy challenges and approaches when drugs of abuse are used for therapeutic indications. Audience input will be solicited after each presentation and ample time reserved for discussion.

Disclosure: Nothing to disclose.

Study Group

17. Psychiatric Challenges of COVID-19

Mark Weiser*, Crystal Lewis, Mark Bradley, Celso Arango, Chunbo Li

Study Group Summary: In this international study group speakers from different countries will present different ways in which they have been dealing with the COVID-19 pandemic. The unique data will include:

Dr. Lewis from New York, the epicenter of Covid-19 in the U.S., will discuss racial disparities of COVID-19 and the disproportionate impact on psychiatric patients in hospitals and community settings. Dr. Lewis will discuss (1) fundamental underlying system- and individual-level causes of disparities, (2) initial responses to these disparities by the NYS Office of Mental Health, and (3) salient opportunities to develop innovative strategies for service delivery that prioritize prevention of disparities related to Covid-19, and future pandemics.

Dr. Bradley will discuss innovations in consultation-liaison psychiatry developed during the COVID-19 outbreak to improve psychiatric care for these patients while medically hospitalized, including interventions to proactively identify and manage psychological distress, reduce patient isolation, and prevent psychiatric emergencies that may lead to breaches of infection control. Challenges in converting to a largely telephonic and video inpatient service will be described.

Dr. Arango from Spain, the country with the largest number of infected health staff, will describe the programs put in place to take care of health professionals by the Liason Department of Psychiatry. The hospital staff has been overwhelmed by the combination of fear, guilt, knowledge that they are not saving lives that they know could be saved under different circumstances, frustration at not having a proper treatment and at not being able to predict who is going to do poorly, working in a different place and with different populations that they are used to, among many other stressful factors. He will present data on psychopathology detected in the health staff (including suicidal ideation/attempts) and results from interventions conducted with them (ventilation groups and individual counseling).

Dr. Li from Shanghai will describe his experiences in China during the pandemic, including a systematic review of the prevalence of mental problems in COVID-19 positive patients, the clinical organization of psychiatric wards and outpatient clinics, and psychological intervention for COVID-19 positive patients.

Dr. Weiser from Israel will discuss the establishment of a locked psychiatric ward located within a general hospital which treated acute psychiatric patients infected with COVID-19 from the entire country. Modifications included 2-way tele-monitors enabling remote communication between patients and staff, oxygen delivery capabilities, clothing protective both against infection with COVID-19 and also tear-proof. We admitted 17 patients during one month, all involuntary, used high doses of antipsychotics and restraints in order to minimize presence of staff in the corona infected ward. There were significant problems with false positive and false negative PCR testing.

These presentations will be clinically useful for psychiatrists currently organizing services and treating COVID-19 patients, and will also be relevant for preparing for future epidemics and natural disasters

Disclosure: Nothing to disclose.

Study Group

18. The Neuroscience Based Nomenclature (NbN): A Rational Approach to the Categorization of Psychotropic Medications

Joseph Zohar*, David Kupfer, Guy Goodwin, Barbara Sahakian, Jeremy Veenstra-VanderWeele, Kerry Ressler, Pierre Blier, Stephen Stahl

Study Group Summary: The current disease-based nomenclature of psychotropics medications does not reflect contemporary knowledge, nor does it appropriately inform the clinician about rational neuroscience-based prescribing. For example, grouping 38 drugs under "antidepressant" does not take into account, from a pharmacology perspective, that it actually includes 12 different groups of medications. Moreover, it is confusing for the patients as very often we prescribe "antidepressants" for anxiety disorders or "second generation antipsychotic" to depressed patients who show no evidence of psychosis.

Five major international neuropsychopharmacological scientific organizations joined forces together, 12 years ago, to create new nomenclature.

These organizations are:

ECNP – European College of Neuropsychopharmacology

ACNP – American College of Neuropsychopharmacology

AsCNP – Asian College of Neuropsychopharmacology

CINP – International College of Neuropsychopharmacology

IUPHAR – International Union of Basic and Clinical Pharmacology.

The mission was:

To provide a pharmacologically-driven (rather than indication-based) nomenclature that embeds contemporary neuroscience understanding of how medicines act.

To enrich our vocabulary (vis-à-vis psychotropic drugs) and to expand our toolbox by pointing out to the relevant mechanism (via pharmacology and mode of action).

To help clinicians to make informed choices when they are trying to figure out what would be the next "pharmacological step".

To decrease stigma and enhance adherence by a naming system that lays out the rationale for selecting a specific psychotropic.

NbN provides a pharmacological driven nomenclature focusing on pharmacology and mode of action. It reflects current knowledge and understanding about the targeted neurotransmitters/molecules/system being modified + mode/ mechanism of action and includes 135 compounds which cover the vast majority of psychotropics used worldwide.

There are key questions that remain in regard to the psychotropics drugs' precise pharmacology or their relevant mode of action that we would like to address in this study group. This issue is true across the board but it is more pronounce in the medications for psychosis. Part of the discussion will focus on this.

Finally, the question about the tension between pharmacological precision on one end, and how to make it 'user friendly' on the other hand, will be discussed as well. This discussion will also address the issue of using NbN as educational tool.

Disclosures: Lundbeck, Brainsway: Grant (Self); Servier, Jazz Pharma, Lundbeck: Advisory Board (Self); Janssen, Lundbeck, Abbott: Consultant (Self); SunPharma, Brainsway: Honoraria (Self)

Panel

19. Brain Initiative 2020: Progress and Promise for Next-Generation Therapeutics

19.1 Brain 2.0: Charting a Course for the Next Phase of the NIH Brain Initiative

John Ngai

NIH BRAIN Initiative, Rockville, Maryland, United States

Background: The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative® aims to revolutionize our understanding of the human brain by accelerating the development and application of innovative neurotechnologies.

The NIH BRAIN Initiative largely focuses on neural circuits and networks, and by all accounts, its first five years have been enormously successful. Over 500 awards have been made to hundreds of investigators, totaling nearly $1B in investment and resulting in over 600 publications. As the Initiative approached its halfway point, an Advisory Committee to the NIH Director (ACD) BRAIN Initiative Working Group 2.0 was convened to assess progress, and to identify key research directions and opportunities to apply new and emerging tools to revolutionize our understanding of how the brain works. This presentation highlights the findings of the ACD report, as well as BRAIN scientific advancements, tool and technology dissemination, and the new Director's vision for the future.

Methods: The new Office of the BRAIN Director (OBD) is tasked with coordinating a trans-NIH effort. Using the BRAIN Initiative Working Group 2.0 report as a guide, staff from NINDS, NIMH, NIDA, NIA, NIAAA, NEI, NICHD, NICCH, NIDCD, and NIBIB will continue to evaluate progress to date, identify remaining unmet needs, and develop future opportunities both within and outside the field of neuroscience. In addition to organizing activities at NIH, the OBD will continue to engage other Federal agencies, nonprofit organizations, International partners, and the private sector in order to advance the goals of the BRAIN Initiative globally.

Results: Plans are in place to keep BRAIN on the productive path established in the first phase of the initiative, with continuing support for technology development and targeted study of circuit components focusing on: (1) collaborative technology development (neurotechnology) (2) discovery-driven, knowledge-building science (neuroscience) (3) support for organization of science: resources related to data sharing, technology dissemination, training, public engagement, and neuroethics. Importantly, plans are being made to initiate and large-scale projects that have the potential to transform the way that neuroscience research is conducted.

Conclusions: Our vision for the next phase of the BRAIN Initiative is to identify and promote emerging technologies aimed at advancing fundamental knowledge of nervous system function, with the goal of introducing new tools for research to ultimately improve clinical practice for the prevention and treatment of human neurologic and neuropsychiatric diseases by the year 2025. The goal is to leverage advances from BRAIN to enable fundamental discoveries in neuroscience, accelerate treatments and cures based on latest discoveries, and democratize technologies for research and clinical applications. The BRAIN Initiative will provide a framework to enable IC disease-focused projects and develop a diverse workforce prepared to invent tomorrow's technologies.

Disclosure: Nothing to disclose.

19.2 Imaging Neuromodulator Dynamics With Genetically Encoded Indicators

Abstract not included.

19.3 Ultrasonic Drug Uncaging for Noninvasive Targeted Neuropsychopharmacology

Raag Airan

Stanford University, Stanford, California, United States

Background: There are myriad hypotheses for how action at a particular drug target in a specific brain region may yield therapeutic benefit for our patients. However, our ability to act upon these hypotheses has been limited since current technology does not allow us to easily apply the right drug, to the right brain target, at the right time. To this end, we have developed the technique of ultrasonic drug uncaging, in which ultrasound-sensitive drug-loaded nanoparticles, following intravenous infusion, release their drug cargo into specific brain regions upon the application of focused ultrasound.

Methods: We have screened a variety of nanoparticle formulations to optimize biodegradable and biocompatible nanoparticles so they can be loaded with a small molecule drug and bind the drug stably both in storage and in vivo, until they release the drug when ultrasound of a sufficient intensity is applied. We have also varied our nanoparticle production methods to determine processes that could readily transfer to pharmaceutical-grade contract manufacturing. Finally, to validate this technology in vivo, we have used a combination of pharmacokinetic analyses, electrocorticography, and functional neuroimaging (PET, functional ultrasound) to assess the effects of ultrasonic uncaging of drugs like propofol and ketamine.

Results: We have created an ultrasound-sensitive nanoparticle formulation suitable for ultrasonic drug uncaging that can be loaded with any of a variety of small hydrophobic drugs, with drug loading increasing with drug hydrophobicity, that are stable in storage for months, and that circulate in vivo for up to one hour. Using the anesthetic propofol as a model drug, we have seen that ultrasonic drug uncaging allows drug application delimited precisely by the size and timing of the ultrasound field with millimeters and seconds-scale resolution. Finally, we have validated a scalable, sterile, and cGMP-compatible nanoparticle production process.

Conclusions: We have developed the technology of ultrasonic drug uncaging to allow precise, targeted, and noninvasive neuropsychopharmacology. After now validating this technology at our bench and in rodent animal models, we are now well on our way towards clinical translation, anticipating first-in-human trials to start within a few years.

Disclosure: Cordance Medical: Consultant (Self); Lumos Labs: Advisory Board (Self)

19.4 Dynamic Brain Network Modeling and Decoding for Closed-Loop Neuromodulation of Mental States

Maryam Shanechi, Viterbi School of Engineering, University of Southern California, Los Angeles, California, United States

Background: Deep brain stimulation (DBS) systems can provide an alternative therapy for treatment-resistant mental disorders such as depression but have largely been open-loop with variable efficacy. Developing closed-loop DBS systems that guide the stimulation with neural activity could improve efficacy but has remained elusive to date. Developing these systems requires novel methods that can decode mood states in real time from neural activity and that can predict the dynamic neural response to ongoing stimulation in an individual.

Methods: Toward developing closed-loop DBS systems, we present a dynamical network modeling and decoding framework for distributed neural activity. We design a decoder that can identify brain regions and neural dynamics that are predictive of mood states. We also develop machine learning methods that can learn a model of how neural activity (output) responds to ongoing electrical stimulation (input). We validate our framework within both sexes. Statistical permutation tests are used and described in the Statistics section.

Results: We show that we can significantly decode mood variations from multisite intracranial human brain activity ($P<0.05$; permutation test). We also stimulate the brain with a new stochastic pulse train and use the data to learn input-output models. We show that our input-output models can significantly predict the dynamic neural response to stimulation ($P<0.05$; permutation test).

Conclusions: These results could facilitate future closed-loop personalized DBS therapies for mental disorders such as depression.

Disclosure: Nothing to disclose.

Panel

20. Functional and Systems Genomic Approaches to Psychiatric Disorders

20.1 Integrating eQTLs and Environment to Interpret GWAS

Laura Huckins

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

Background: The emergence of large-scale GWAS has enabled identification of significant genetic associations for a number of psychiatric illnesses. However, these lists of loci do not necessarily translate into biological mechanisms, actionable targets, or opportunities for therapeutic interventions, and as such the implications of these findings are as yet poorly understood.

Transcriptomic Imputation (TI) approaches combine biological insights of transcriptome data with large sample size of GWAS. TI approaches use large, well-curated eQTL reference panels to build predictors of genetically regulated gene expression (GREX) in specific tissues. These may be applied to predict GREX from genotype data (e.g., GWAS), and thus identify GREX-disease associations. We have previously shown that these methods are accurate, easy to apply, and of great utility in identifying tissue-specific associations with psychiatric disease. These approaches allow us to study gene expression for the first time at the necessary scale to identify associations with psychiatric disorders. However, these approaches model only 'static' genetically regulated gene expression, and do not include the influence of environmental factors on gene expression.

Here, we integrate genotype, RNA-seq and environmental data (such as age, BMI, smoking, alcohol use) to produce "prediXplus" predictor models. Each predictor model outputs (i) the standard genetically regulated gene expression value (GREX); and (ii) environment-plus-genetically regulated gene expression (EGREX).

Methods: Our analyses leverage large-scale brain gene expression cohorts (including >1,500 DLPFC samples from CommonMind Consortium, ROSMAP, GTEx) with extensive phenotyping data available (including data on BMI, Age, smoking, alcohol, and illicit drug use).

For each available phenotype, we have constructed gene expression predictors using elastic net regression, including (i) all SNPs in the cis-region of the gene (defined as ± 1MB surrounding a gene), following standard prediXcan methodology; (ii) trans-eQTLs (i.e., any genome-wide SNPs reaching nominal eQTL significance for the gene); (iii) the environmental variable of interest (e.g., sample BMI, smoking status). Our final models include all genes with cross-validation predictor $R2 > 0.01$. Our use of a penalized regression model means that not all gene predictors will include the environmental variable of interest; for these genes, only the standard GREX value will be output from the model.

Results: In this talk, we will present our new prediXplus models, and demonstrate their application to PGC-GWAS summary statistics, and Mount Sinai BioMeTM biobank-derived psychiatric phenotypes.

These models may be applied either to (i) more closely recapitulate the brain gene expression of a specific individual; or (ii) to perturb case/control environments in silico. For example, users may apply prediXplus to calculate EGREX of a given gene throughout the lifespan (i.e., at multiple disease-relevant ages), and test for case/control associations at each age.

Conclusions: TI approaches help to interpret and prioritize GWAS loci by leveraging large, well-curated eQTL reference panels in order to predict gene expression from genotype. TI models can be applied to any large collection of genotypes (i.e., GWAS) to obtain predicted genetically regulated gene expression in cases and controls, and thereby identify associations between gene expression and disease. This work builds on existing transcriptomic imputation methods by placing GWAS associations into both biological and environmental context.

Disclosure: Nothing to disclose.

20.2 Genome-Wide Meta-Analysis of Insomnia in Over 2.3 Million Individuals Indicates Involvement of Specific Biological Pathways Through Gene-Prioritization

Danielle Posthuma

VU University, Amsterdam, Amsterdam, Netherlands

Background: Insomnia is a heritable, highly prevalent sleep disorder, for which currently no efficient treatment exists. Previous genome-wide association studies (GWASs) with up to 1.3 million subjects identified over 200 associated loci, and showed it is extremely polygenic with many more loci yet undiscovered. The current study aims to increase statistical power and identify novel risk loci by almost doubling the sample size to over 2.3 million individuals.

Methods: We conducted a genome-wide meta-analysis, and standard post-GWAS analyses, including functional annotation (FUMA), gene-set analysis (MAGMA), stratified SNP heritability (LDscore regresssion), and tissue- and cell-type enrichment analyses. In addition, we propose a novel strategy to prioritize

plausible causal genes involved in insomnia using external biological information on genetic variants and functional interaction between genes across independent loci.

Results: We identified 554 independent genome-wide significant loci in insomnia. Gene-based association tests and gene mapping in FUMA, including positional, eQTL and chromatin interaction mapping, identified 3,073 genes. We prioritized 289 genes, and evaluated whether these genes were functionally meaningful. We found that they were significantly associated with neurons from multiple cortical layers,and enriched in gene sets related to synaptic regulation or functions as well as nervous system development.

Conclusions: We find brain-tissue expression specificity of 289 high-confidence prioritized genes and significant enrichment in specific gene-sets of synaptic signaling functions and neuron differentiation. We show that not all of our results would have been detected by conventional post-GWAS analyses, and that the novel gene prioritization strategy yields specific hypotheses on causal mechanisms underlying insomnia that can be tested in functional experiments. To the best of our knowledge this is the largest GWAS so far. We show that with increasing sample sizes different strategies can be applied to pinpoint the most likely causal genes

Disclosure: Nothing to disclose.

20.3 Using Massively Parallel Screens to Study Gene Regulatory Variation During Human Neurodevelopment

Abstract not included.

20.4 InV Perturb-Seq: Study Gene Function at Scale

Xin Jin

Harvard University, Cambridge, Massachusetts, United States

Background: Human genetics has now uncovered strong associations between genetic variants in tens of thousands of loci and complex human diseases ranging from inflammatory bowel disease to psychiatric disorders, including autism spectrum disorders (ASD). These thousands of disease risk genes and loci far outstrip our current capacity to systematically study their functions. New experimental approaches are needed for functional investigations of large panels of genes in a biologically relevant context.

Methods: Here, we developed a scalable genetic screen approach, in vivo Perturb-Seq, and applied this method for functional evaluation of 35 autism spectrum disorder (ASD) de novo loss-of-function risk genes. Using CRISPR-Cas9, we introduced frameshift mutations in these risk genes in pools, within the developing mouse brain in utero, and then performed single-cell RNA-Seq in the postnatal brain.

Results: We identified cell type-specific and evolutionarily conserved gene modules from both neuronal and glial cell classes. Recurrent gene modules and cell types are affected across this cohort of perturbations, representing key cellular effects across sets of ASD risk genes. Specifically, perturbations in 9 ASD genes (Adnp, Ank2, Ash1l, Chd8, Gatad2b, Pogz, Scn2a1, Stard9, and Upf3b) had significant effects across 5 modules (compared to the GFP control, FDR corrected $P<0.05$): the projection neuron Layer 4 and 5 module (PN1), modules representing two distinct homeostatic signatures in astrocytes (Astro1 and Astro3), the oligodendrocyte progenitor module (ODC1), and the interneuron Ndnf+ module (IN1). The linear regression analysis is performed on mean centered and standard deviation scaled module scores, so effect sizes can be interpreted in terms of standard deviations from the population mean.

Conclusions: ASD affects brain function profoundly, but its cellular and molecular substrates are not yet defined. The large number of highly penetrant de novo risk genes implicated through human genetic studies offer an entry point to identify the cell types, developmental events, and mechanisms underlying ASD origin. However, this requires scalable methods to define the function of genetic hits with cell-type specificity. Using Perturb-seq as a way to functionally test large gene sets in the developing embryo, we observed gene expression changes linked to ASD genes in different cell types and processes. Within the power of the analysis enabled by the number of cells that can be reasonably sequenced, we find that some recurrent modules are affected across more than one ASD risk gene perturbation. It is likely that this represents an underestimation of the number of convergent modules across perturbations limited by the number of embryos included in this study.

Although we focused on the neocortex in perinatal development in this study, in vivo Perturb-Seq can be applied to study gene functions systematically across other tissues in additional developmental stages, to reveal tissue-specific as well as broadly-distributed gene functions. This approach can uncover both the impact of individual or the combination of disease-associated genes and the overall set of processes that they affect. Our findings underscore the importance of using single-cell profiles as a rich, comprehensive, and interpretable phenotypic readout. In vivo Perturb-Seq can enable discoveries of pathways and cell types affected in heterogeneous genetic pathologies, directing downstream studies and informing the development of refined models for genetic disorders and mechanistic studies as we move from genetic variants to function.

Disclosure: Nothing to disclose.

Study Group

21. Tackling the Challenges of Schizophrenia Drug Development: Stakeholder Perspectives

Linda Brady*, Joshua Gordon, Sharon Mates, Michael Sand, Stephen Brannan, Tyrone Cannon

Philip Harvey, Kenneth Duckworth, Kenneth Koblan, Michael Davis, Bernard Fischer, Michael Davidson

Study Group Summary: Schizophrenia is one of the top 15 leading causes of disability worldwide, and the need for novel pharmacotherapeutics is urgent. The burden of illness is high at the personal, family, and societal levels due to its early onset, long-lasting trajectory, and the inadequacy of current treatments. Given that evidence suggests that the pathological processes underlying schizophrenia start early in development, and that a prodrome can be recognized prior to frank psychosis, early intervention is likely to be key in order to maximize the chances at recovery for individuals with schizophrenia.

This study group is focused on issues relevant to developing and testing novel pharmacologic mechanisms for early intervention in schizophrenia from the perspectives of multiple stakeholders. These include federal agencies such as the National Institute of Mental Health (NIMH) and the Food and Drug Administration (FDA); scientists in academia, biotech, and pharma; as well as individuals with lived experience and their advocates.

The study group will include perspectives from: Joshua Gordon (Director, NIMH); Tyrone Cannon (PI, North American Prodromal Longitudinal Study and Professor, Yale University); Kenneth Duckworth (Chief Medical Officer, National Alliance on Mental Illness); Philip Harvey (Professor, University of Miami); Stephen Brannan (Chief Medical Officer, Karuna Pharmaceuticals); Michael Davidson (Chief Medical Officer, Minerva Neurosciences); Kenneth

Koblan (Chief Scientific Officer, Sunovion Pharmaceuticals); Sharon Mates (Chief Executive Officer, Intra-Cellular Therapies); Michael Sand (Senior Program Leader, CNS, Boehringer-Ingelheim); Michael Davis (Clinical Team Leader, Division of Psychiatry, FDA); and Bernard Fischer (Acting Deputy Director, Division of Psychiatry, FDA).

Issues to be discussed among participants and audience include:

1. Industry perspectives on barriers for developing treatments targeting earlier stages of illness for schizophrenia, including the clinical high-risk (CHR) state
    a. Addressing negative symptoms
    b. Addressing cognitive deficits
        1. Time frame in which to expect cognitive changes to manifest
        2. How many cognitive domains need to be covered?
        3. Will function be a requirement for a co-primary? How best to assess?
    c. Addressing other symptoms commonly associated with CHR such as anxiety and depression
    d. Treatments that target underlying pathophysiology with the potential to improve multiple CHR symptom domains
    e. What would it take to test novel mechanisms in the CHR state for psychosis?
2. Clinical trial designs and measurement issues in CHR
    a. Need for predictors of trajectory and outcome(s)
    b. Potential role of an individualized risk calculator in stratification, subject selection, enrichment
    c. Endpoint selection (cognitive deficits, anxiety, and/or mood alterations vs. transition to psychosis)
    d. Role of digital measurements and measures of real-world function
    e. Trial duration
3. Industry and regulatory perspectives
    a. Which indications would be practical/measurable/approvable?
    b. How do you target probabilistic risk states like CHR?
    c. Potential acceptability of 1) theoretical indication targeting symptoms CHR patients are experiencing or 2) indication of reducing the risk of developing chronic serious mental illness
4. Recruitment issues
    a. How to find CHR subjects
    b. Role of advocacy organizations
    c. Role of patient registries

Disclosure: Nothing to disclose.

Study Group

22. Life After Compulsive Substance Use: How to Translate the Neurobehavioral Dynamics of Recovery

Steven Grant*, Jennifer Wenzel, Holly Moore, Marina Wolf, Janet Neisewander, James Jentsch, Yavin Shaham, Rainer Spanagel, Kelvin Lim, David Lydon-Staley, Hedy Kober, Silvia Lopez-Guzman

Study Group Summary: Although it is well established that substance abuse leads to adaptations in brain function, it is unclear how long these changes persist and how they contribute to relapse and/or recovery from substance use disorder (SUD). Further, while the brain mechanisms of drug action are well known, the mechanisms of "recovery" from SUD are poorly understood. Because of this, both human and animal neuroscience research has focused on the manipulation of drug action targets to prevent relapse and promote recovery, with limited success. Thus, the identification of novel treatments that can promote sustained abstinence may therefore require development of new targets and interventions, distinct from the initial targets of drug action.

This translational study group will address issues facing relapse and recovery research in both humans and animal models in order to identify the challenges in developing recovery focused therapies. This discussion is well suited for an ACNP audience as it requires an exchange of ideas from the diverse perspectives offered by clinicians and researchers represented in ACNP. In this panel, clinical and preclinical investigators will address the cognitive, behavioral and physiological changes that occur across the cycle of substance use disorder with an emphasis on changes during abstinence and interruptions of abstinence. Recent findings will be emphasized regarding how recovery involves new learning, as well as changes in decision-making and overall functional outcome.

Panelists will discuss questions such as: (1) How do we define and model relapse and recovery? (2) How do the neurocognitive effects of drug seeking and taking inform cognitive behavioral strategies in SUD treatment? (3) Looking beyond drug craving as the target in medication-assisted treatment: How do pharmacotherapies impact new learning, choice behavior, cognitive control, etc. during recovery? (4) How can translation between clinical and animal models be facilitated in order to address gaps in our knowledge and lead to treatment development?

The panelists will provide multi-disciplinary perspectives spanning preclinical and clinical research and consist of a mix of early- and mid-career and senior investigators. Although all of the clinical participants conduct research on recovery of brain function during abstinence, each brings specific perspectives including non-invasive neural interventions (Kelvin Lim), behavioral therapy for regulation of craving (Hedy Kober), decision-making and relapse (Silvia Lopez-Guzman), and changes in network dynamics during recovery (David Lydon-Stanley). Preclinical panelists have broad expertise in neural mechanisms of reinstatement of drug seeking across a variety of different drugs of abuse, using a range of model organisms. Their expertise include genetic contributions to the motivation for drugs of abuse (David Jentsch), neural circuits and environmental factors influencing drug seeking (Janet Neisewander), differences in forced versus voluntary abstinence and the incubation of drug craving (Yavin Shaham), how comorbidity of SUD with other psychiatric disorders affects relapse and recovery (Rainer Spanagel), and cellular mechanisms of drug craving and relapse (Marina Wolf).

Disclosure: Nothing to disclose.

Panel

23. Metabolic and Inflammatory Mechanisms of Anxiety and Depression: Role of Sex, Stress and Diet in Clinical and Preclinical Models

23.1 Association of Stress- and Diet-Induced Inflammation With Alterations in Neurobiology and Behavior Related to Psychopathology in Female Rhesus Monkeys and Women

Abstract not included.

23.2 Chronic Adolescent Stress Increases Vulnerability to Cognitive Impairments and Neuroinflammation Following Chronic Low-Grade Inflammation

Gretchen Neigh

Virginia Commonwealth University, Richmond, Virginia, United States

Background: Neuropsychiatric disorders often include a history of developmental stress. Alterations in cerebral metabolic activity may underlie this relationship. These mechanistic questions can be difficult to disentangle in human subjects, creating a need for animal models that demonstrate related behavioral ethograms that can be assessed on a more invasive level. A model of chronic stress during adolescent development produces sustained changes in behavior as well as alterations in physiology. Previously, we have demonstrated that adolescent stress sex-specifically alters expression of glucose transporters in the brain, suggesting that there could be further alterations in metabolism. In addition, we've shown that chronic adolescent stress alters the neuroinflammatory response to immune challenge. Given the existing knowledge regarding the impact of chronic stress on synaptic architecture and inflammation, the current study assessed the impact of chronic adolescent stress and chronic low-level inflammation on behavior and synaptosomal metabolism.

Methods: Male ($n = 24$) and female ($n = 24$) Wistar rats were exposed to chronic mixed modality stress throughout adolescence (CAS; $n = 12$) or were non-stressed (NS; $n = 12$). Adult rats received repeated lipopolysaccharide (LPS; 7.5 x 104 EU/kg; $n = 6$) or saline injections ($n = 6$) every third day for eight weeks. Learning and memory was assessed with the Barnes Maze and Y-Maze tasks while anxiety-like behavior was determined by Open Field exploration. Synaptosomal mitochondrial function was determined using the Seahorse XFe 24 analyzer. Circulating pro- and anti-inflammatory cytokines in the periphery were assessed at tissue collection. Data were analyzed using three-way ANOVA. Two-way ANOVA and Sidak's posthoc were used when appropriate.

Results: A history of chronic stress increased anxiety-like and altered memory performance. Specifically, CAS history decreased time spent in the center of the open field in adult males ($p = 0.008$), regardless of LPS treatment. During memory probe trials there was an interaction between stress history and inflammation ($p = 0.04$), whereby females with a history of CAS displayed an impairment in working memory during the Y-Maze task if they also had chronic inflammation ($p = 0.005$). Synaptosomal respiration was also altered in a sex-specific manner following chronic stress and chronic inflammation. A history of CAS interacted with chronic LPS in male rats to drive up synaptosomal respiration ($p = 0.0003$), while females with chronic inflammation had reduced mitochondrial respiration in synaptosomes ($p < 0.0001$). Chronic LPS increased peripheral cytokine levels in males ($p = 0.01$) but not in females ($p > 0.05$). Markers for synaptosome enrichment also indicated that CAS females had increased presynaptic terminals ($p = 0.04$).

Conclusions: Collectively, these data suggest that while metrics of inflammation and reactive oxygen are disrupted in males following chronic stress and chronic LPS, only the combined condition is sufficient to alter synaptosomal respiration. Conversely, females demonstrate profound shifts in synaptosomal mitochondrial function with a history of chronic inflammation. These data highlight that differential mechanisms are likely in play between the sexes and suggest influence of life experiences on mitochondrial function in the synapses.

Disclosure: Nothing to disclose.

23.3 Inflammation and Metabolism as the Two Main Biological Pathways Affected by Stress Early in Life

Annamaria Cattaneo

University of Milano, Italy

Background: Exposure to early life stress (ELS) produces widespread changes in brain function that may predispose individuals to develop a wide range of disorders later in life. Although both clinical and preclinical studies clearly support this association, the biological pathways deregulated by such exposure, and the effects of early life stress in shaping neurodevelopmental trajectories, have so far been poorly investigated. Moreover, and importantly, peripheral biomarkers associated with stress exposures and with an enhanced risk for psychiatric disorders are not available in the clinical setting.

Methods: On these bases, we performed genome-wide expression analyses in the prefrontal cortex of adult male rats exposed to stress during gestation (PNS), a model that is associated with persistent behavioral and molecular alterations relevant for psychiatric disorders, and thus useful to dissect the affected neurodevelopmental trajectories in terms of timing and to identify new targets for pharmacological modulation.

Results: We first investigated the long-lasting mechanisms and pathways affected by PNS in the PFC and found that adult animals exposed to PNS showed alterations in 389 genes ($q<FC<-1.2$) mainly involved in stress and inflammatory signaling. We then sought to establish whether PNS exposure affected neurodevelopmental trajectories in order to identify the most critical temporal window. We found that PNS rats show the most significant changes during the adolescence phase of development (between PND 40 versus PND 21), with alterations of several pathways related to stress and inflammation as well as to metabolism. Importantly, these alterations were maintained until adulthood.

Conclusions: Our preclinical data suggest that molecules related to inflammation and metabolism may serve as biomarkers to allow the identification of risk during adolescence that may lead to the development of mental illnesses later in life. We are currently testing saliva samples of adolescents characterized by childhood trauma and emotional dysregulation for a panel of molecules related to inflammation and metabolism to provide biomarkers of early risk and thus to identify adolescents at high risk of developing psychiatric disorders. These subjects could benefit from early preventive interventions with novel pharmacological or non-pharmacological strategies able to target these biological systems.

Disclosure: Nothing to disclose.

23.4 Metabolic Dysfunction and Inflammation Together Associate With Functional Connectivity in Reward Circuitry in Depression: Role of PTSD and Childhood Trauma in Women

Jennifer Felger

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

Background: Bidirectional relationships between inflammation and metabolic dysfunction may contribute to the pathophysiology

of psychiatric illnesses like depression. Metabolic disturbances drive inflammation, which in turn exacerbate metabolic outcomes including insulin resistance. Both inflammatory and metabolic challenges have been shown to affect neural activity and functional connectivity (FC) in brain regions like that are relevant to reward processing. We previously reported that elevated concentrations of endogenous inflammatory markers like C-reactive protein (CRP) were associated with low FC in classic ventral striatum (VS) to ventromedial prefrontal cortex (vmPFC) reward circuitry, which correlated with symptoms of anhedonia in both patients with major depression (MD) and in women exposed to trauma. Low FC in reward circuitry and anhedonia in MD was also associated with evidence of systemic metabolic dysfunction including protein and gene expression markers related to glucose metabolism and insulin resistance, with the greatest deficit in patients with both metabolic dysfunction and high CRP. Herein, we examined whether PTSD symptoms and history of early life trauma modified relationships between metabolic dysfunction, inflammation and FC in reward circuitry in patients with a primary diagnosis of MD.

Methods: A composite score of 5 plasma markers related to glucose metabolism (non-fasting glucose, insulin, leptin, adiponectin and resistin; higher composites scores reflecting higher values of each marker) and plasma CRP were assessed in 42 medically-stable, unmedicated MD outpatients who underwent fMRI. A targeted, hypothesis-driven approach was used to measure FC between VS and a region in vmPFC, previously found to correlate with both the glucose-related composite score and CRP as well as with symptoms of anhedonia. Comorbid PTSD was diagnosed by SCID. Early life trauma was assessed by the childhood trauma questionnaire.

Results: There was a significant interaction effect of PTSD and the glucose-related composite score on the relationship with FC in VS-vmPFC reward circuitry ($p = 0.045$) in patients with a primary diagnosis of MD ($n = 42$), were only patients with PTSD ($n = 17$) exhibited correlations between the composite score and FC. Interestingly, this interaction was significant when controlling for covariates including body mass index (BMI), and no interaction was observed for PTSD and CRP (i.e. patients with and w/out PTSD had similar relationships between CRP and FC; $r = -0.34$ to -0.42), indicating that this effect was both specific to the metabolic markers and independent of obesity. Patients with PTSD had higher glucose composite scores ($p = 0.035$) but not CRP. All but one patient with PTSD (16/17 patients) had experienced at least one form of moderate to severe early life trauma (94% versus 64% in patients w/out PTSD), and patients with PTSD were predominantly women (15/17 patients). Patients with PTSD also reported higher symptoms of anhedonia in the group as a whole and in women ($p < 0.05$).

Conclusions: These findings indicate that PTSD symptoms and history of early life trauma may have a greater impact on metabolic dysfunction in women, which may then influence reward circuit function and contribute to transdiagnostic symptoms of anhedonia.

Disclosure: Nothing to disclose.

Panel

24. Sensitive Postnatal Time Windows for Prefrontal Cortical Circuit Maturation

24.1 Activity-Dependent Maturation of Prefrontal Gamma Rhythms Sculpts Cognitive Performance

Ileana Hanganu-Opatz

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Disturbed neuronal activity in neuropsychiatric pathologies emerges during development and might cause multifold neuronal dysfunction by interfering with apoptosis, dendritic growth and synapse formation. However, how altered electrical activity during early in life impacts neuronal function and behavior of adults is unknown.

Methods: Here, we address this question by transiently increasing the coordinated activity of layer 2/3 pyramidal neurons in the medial prefrontal cortex of neonatal mice and monitoring long-term functional and behavioral consequences.

Results: We show that increased activity during early development causes premature maturation of pyramidal neurons and alters interneuron density. Consequently, reduced inhibitory feedback by fast-spiking interneurons and excitation/inhibition imbalance in prefrontal circuits of young adults result in weaker evoked synchronization in gamma frequency.

Conclusions: These structural and functional changes ultimately lead to poorer mnemonic and social abilities.

Disclosure: Nothing to disclose.

24.2 Adolescence is a Sensitive Period for Parvalbumin Interneuron Integration Into Prefrontal Circuits and Behavior

Sarah Canetta

Columbia University, New York, New York, United States

Background: Abnormalities in prefrontal cortical parvalbumin-expressing (PFC PV) interneurons are believed to contribute to cognitive and affective deficits in schizophrenia (SCZ), as well as other neurodevelopmental psychiatric disorders. However, little is known about whether developmental alterations in PV inhibitory interneuron maturation and integration into cortical circuitry could be contributing to disease onset. In particular, adolescence is a vulnerable time window for the development of psychiatric disorders like SCZ. It is also a time period in which PFC PV interneurons undergo extensive physiological development and integration into cortical circuitry, prior to attaining their mature phenotype. Such dynamic, developmental windows often prove to be sensitive periods, defined as windows in which alterations in experience can result in long-lasting effects on the development of brain circuitry, physiology and behavior.

The study of sensitive periods in PFC has been hampered by difficulty identifying experiences or manipulations that would be expected to alter circuit maturation and long-term function. In sensory cortices, experimental manipulations of activity elicited by directly manipulating the primary sensory organ can modulate the connectivity of inhibitory PV interneurons. As PFC receives no direct sensory input, we have developed a system that allows transient and reversible modulation of PFC PV activity during distinct developmental windows by virally expressing the DREADD receptor, hM4DGi, selectively in PFC PV cells. Using this system, we can ask whether adolescence is a sensitive period in which alterations in activity can result in long lasting effects on PFC PV interneuron function and behavior.

Methods: We utilized a viral and genetic approach to express the pharmacogenetic receptor, hM4DGi, in developing PV interneurons and administered the agonist for hM4DGi, clozapine-N-oxide (CNO), during a peripubertal and adolescent developmental window (P14-P50). At P90, we assayed persistent effects on the connectivity of PFC PV cells onto pyramidal neurons using optogenetics and slice electrophysiology. We also examined effects on adult attentional set shifting behavior as well as underlying prefrontal activity recorded using stereotrodes in

behaving animals. Sample sizes range from 4 to 17 and both sexes were included.

Results: We found that pharmacogenetically suppressing activity of PFC PV interneurons between P14 and P50 resulted in persistent effects on PFC PV interneuron functional connectivity in adulthood (P90) as well as impairments in adult set shifting behavior and associated task-induced prefrontal gamma activity. Moreover, we found that this same transient suppression of PFC PV interneuron activity in adulthood (rather than development) did not persistently impair animal behavior or associated prefrontal network activity.

Conclusions: Our results indicate a sensitive peripubertal and adolescent developmental period during which transient alterations in PFC PV interneuron activity can persistently affect the strength of PFC PV functional connectivity, set-shifting behavior and associated neural activity. These findings suggest early dysfunction in PFC PV interneurons can result in persistent changes in prefrontal cortical function and may give insight into disease etiology. From a therapeutic perspective, these findings may indicate a developmental period during which the brain would be particularly susceptible to interventions that engage the prefrontal cortex and thereby naturally enhance PV interneuron activity.

Disclosure: Nothing to disclose.

24.3 Experience-Dependent Maturation of Prefrontal Circuitry in Control of Social Behavior

Hirofumi Morishita

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

Background: Loneliness is increasingly being recognized as a serious threat to mental health. Social isolation during the juvenile critical window is particularly detrimental to the maturation of medial prefrontal cortex (mPFC) and establishment of appropriate levels of adult sociability However, the neural circuit mechanisms underlying these phenomena are poorly understood. While social behavior deficits are a common dimension of many psychiatric disorders, development of effective treatment strategies are hindered by an incomplete understanding of which circuits control social behavior. Identifying the specific circuits sensitive to experience-dependent modulation will likely point toward therapeutic targets for the amelioration of social processing deficits shared across a range of disorders. Here, we aimed to identify specific mPFC circuits in control of social behavior whose maturation is profoundly affected by juvenile social experience in mouse.

Methods: We integrated techniques to measure (fiber photometry imaging, patch-clamp electrophysiology) and manipulate (optogenetics/chemogenetics) the activities of selective circuits during social behavior (3chamber test, reciprocal interaction) in mice undergo juvenile social isolation (jSI: p21-p35).

Results: We find that transient juvenile social isolation leads to a failure to activate adult mPFC neurons projecting to the limbic thalamus, which relays signals to various components of the classical reward circuitry. Chemogenetic or optogenetic suppression of mPFC projection to limbic thalamus is sufficient to induce social behavior deficits without affecting preference toward rewarding food. jSI leads to reduced intrinsic excitability of mPFC neurons projecting to limbic thalamus and an aberrantly increased inhibitory drive from a subclass of deep layer somatostatin-expressing low-threshold spiking (LTS-SST) interneurons. Importantly, sociability deficits caused by juvenile social isolation can be rescued by chemogenetic or optogenetic activation of mPFC neurons projecting to limbic thalamus.

Conclusions: Our results demonstrate that mPFC->limbic thalamic projection neurons and associated mPFC LTS-SST interneurons require juvenile social interaction to establish normal circuit function necessary for adult sociability. As these circuits are sensitive to experience-dependent modulation, they are attractive circuit targets for the amelioration of social deficits shared across of range of disorders. Ultimately, our study may inspire interventions that improve social functioning in neurodevelopmental and psychiatric disorders by specifically targeting prefrontal top-down circuits to impact sub-cortical hubs, such as the limbic thalamus.

Disclosure: Nothing to disclose.

24.4 Impact of Adolescent Stress on the Development of Neural Circuits Underlying Social Behaviors

Danielle Gerhard

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

Background: Psychiatric disorders peak in prevalence during adolescence and early adverse experiences increase the lifelong risk of developing a psychiatric disease. Impairment in social behavior is a key feature of many psychiatric disorders. However, little is known about the effects of adolescent stress on the functional development of circuits mediating social behaviors, especially in females who are more likely to be diagnosed with a mood disorder. My research uses animal models for early life adversity to identify sensitive periods in social development.

Methods: To quantify development of ventral hippocampus (VH) inputs to nucleus accumbens (NAc), the anterograde tracer PHA-L was injected into the VH of P23, P30, and P60 male (m) and female (f) mice ($n = 6$/age/sex). Axon terminals containing the tracer were quantified in NAc shell as a measure of projection density of VH neurons. To assess the impact of peri-adolescent stress, male and female mice underwent ten days of chronic unpredictable stress (CUS) (P21-P31). Three-chamber test and free social interaction (FSI) tests began in adulthood (P70; m: $n = 4$/group; f: $n = 9$–11/group). In-vivo calcium imaging (fiber photometry) was used to record activity in NAc-projecting VH neurons alongside FSI in stress-naive adult females ($N = 4$). Similar experiments are currently underway to record from NAc-projecting prelimbic neurons and determine the effects of stress on activity of these two circuits during social interaction.

Results: There was significantly increased axon fiber density in NAc shell at P30 compared to P23 and P60 in males and females (m: $p < 0.0001$, $p < 0.0001$; f: $p = 0.023$, $p < 0.0001$). A sexXage comparison showed females with significantly increased axon fiber density compared to males at P23 ($p < 0.0001$). In the three-chamber test, all non-stressed mice and stressed males spent more time interacting with a novel social partner than an object while stressed females did not (m: controls: $p = 0.005$, stress: $p = 0.04$; f: controls: $p < 0.0001$, stress: $p = 0.2826$). In FSI, no effect of stress was observed on time interacting with a social partner for males ($p = 0.194$), but stressed females showed reduced time interacting with a social partner compared to controls ($p = 0.047$). For fiber photometry, social and object interaction increased VH-NAc activity. Neural activity was higher in the 2 seconds after interaction initiation than 2 seconds before ($p < 0.0001$, both). After the second bout, increased neural activity is smaller in magnitude for both social and object interaction. However, pilot data suggest that after bout 2, the difference is smaller in magnitude for social than for object interaction, where mice continue to show increased fear responses (flee) (see statistics).

Conclusions: We identified an adolescent sensitive period for sociability that is marked by changes in structural connectivity in VH-NAc circuity and affected by developmentally timed stress. We also identified sex differences in circuit trajectory that may explain

the observed differences in susceptibility to pre-adolescent CUS. Finally, increased activity in the VH-NAc circuit appears to correspond to increased fear and thus activity in this circuit may show prolonged elevation in response to social interaction in stressed females. Together, these findings inform our understanding of sex-differences in sensitive windows for social development.

Disclosure: Nothing to disclose.

Mini Panel

25. Mobile DNA in Brain Diseases

25.1 L1 Retrotransposons in Schizophrenia, Bipolar Disorder and Cocaine Use Disorder

Benjamin Reiner

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

Background: The risk for developing many psychiatric and substance use disorders, including schizophrenia (SZ), bipolar disorder (BPD) and cocaine use disorder (CUD), has substantial heritability. However, our understanding of the heritability component of risk for these disorders is frequently characterized by missing heritability, suggesting that consideration of alternative forms of inherited variants may be necessary. One type of inherited variant the may contribute to the heritability of psychiatric and substance use disorders are long interspersed element-1 retrotransposons (L1). Literature evidence demonstrates that L1 insertions have poor linkage disequilibrium with candidate SNPs commonly used in genotyping arrays. Therefore, it may be possible that L1s can explain at least a portion of the missing heritability associated with psychiatric and substance use disorders. However, to date, there is no literature evidence associating any specific inherited L1 retrotransposon insertion with a psychiatric or substance use disorder.

Methods: We used REBELseq to identify inherited and somatic L1s in NeuN+ gDNA from postmortem brains from individuals with SZ and controls (CT; n = 63 each). Polymorphic L1 insertions of interest were validated in DNA from SZ, BPD and CT individuals (n = 2268 each). In a preliminary study of CUD, REBELseq was also used to identify L1s in NeuN+ gDNA from postmortem brains (CUD n = 25, CT n = 26). Lists of genes containing L1s in SZ and CUD were utilized for identifying enriched gene ontologies and biological pathways.

Results: We identified inherited L1 insertions in the genes ARHGAP24 and SNTG2 that are associated with risk for SZ (ARHGAP24, chi square p = 0.029, odds ratio (OR) 1.206; SNTG2, chi square p = 0.008, OR 1.182) and BPD (ARHGAP24, chi square p = 0.021, OR 1.218; SNTG2, chi square p = 0.002, OR 1.212). Analysis identified multiple gene ontologies and pathways affected by L1 burden in SZ. Similarly, L1s putative associated with risk for CUD and the gene ontologies and biological pathways they effect were identified.

Conclusions: These data suggest that a subset of inherited L1 retrotransposon insertions are associated with risk for SZ and BPD and that, at least in part, may help explain a portion of their missing heritability. Preliminary results suggest a similar role for L1s in CUD.

Disclosure: Nothing to disclose.

25.2 Neuron-Specific Regulation of Chromosomal Megadomains Associated With Retroviral Silencing

Sandhya Chandrasekaran

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

Background: At the level of the cell nucleus, loosely organized euchromatin spatially segregates from densely packed heterochromatin, broadly delineated as 'A' (active) and 'B' (inactive) compartments on a genome-wide scale. This A/B compartmentalization is largely driven by affinity interactions among the heterochromatic segments of chromosomes, which underlie the phase separation of 'unlike' A vs. B chromatin. Further subdivisions of these compartments are defined by additional aspects of epigenomic regulation, including, but not limited to, differential histone modification landscapes. To date, however, studies on chromatin regulatory mechanisms governing the organization and function of A/B compartments in the brain, including in neurons, are lacking.

Methods: We first used in situ Hi-C to profile spatial chromatin organization in NeuN± n = 4, 4 (2M/2F/group). Subcompartments were designated by k-means clustering (k = 4, 250 kb bins) of Hi-C reads (HiC-Pro) and concordance with ENCODE histone modifications. Significant trans- were identified (HOMERv4.8), and repeat hotspot associations were performed using Fisher's 2x2 genome-wide. Trans- changes (n = 4 (2M/2F)) upon neuron-specific Setdb1 loss were determined by DESeq2 (1Mb bins, padj < 0.05) and classified by subcompartment. Transposon derepression was evaluated using ChIPseq (n = 3,3 (1M,2F/group)) and RNAseq (n = 6,6 (3M,3F/group)). Behavioral testing was performed according to published protocols. Electron microscopy (n = 4,4) was performed on cortical sections to visualize IAPs in vivo. In situ Hi-C was performed in iNeurons and astrocytes (n = 2,2 (M)) and associated with repeat hotspots. Finally, we performed Fisher's 2x2 with published GWAS loci (36 datasets) and human trans-.

Results: Here, we explored specific aspects of A/B compartmentalization in neurons of adult mouse cerebral cortex, and discovered neuron-specific features of chromatin organization. This includes a neuron-specific B compartment subtype, 'B2 Neuron', that is not shared with the surrounding non-neuronal cells (p = 4.8x10-62), and defined by increased trans-chromosomal contact frequencies encompassing clusters of phylogenetically young Endogenous Retrovirus 2 (ERV-2/intracisternal-A-particle IAP) retrotransposon elements (2.1x10-35). Importantly, neuron-specific ablation of Kmt1e/Setdb1, a histone H3K9 methyltransferase integral to the KMT1E-KAP1-Zinc finger retrotransposon suppressor complex in peripheral systems, results in the rewiring of the B2 Neuron Hi-C interactome with loss of trans- interactions within the B2 Neuron subcompartment (67%), with profound epigenomic changes and widespread transposon derepression. This was associated with increased anxiety- and depression-like behaviors, with susceptible neurons showing massive accumulation of IAP proviral particles in neuronal somata (p = 3.7x10-5), with proviruses encroaching upon dendritic processes and spines. Finally, we find conservation of this neuron-specific mode of retroviral heterochromatin organization in humans, and significant genome-wide association with disease risk loci implicated in neuropsychiatric disease including schizophrenia (p = 1.4x10-8).

Conclusions: Our findings link neuron-specific regulatory mechanisms associated with chromosomal megadomain and spatial genome organization to transposon repression which, upon escape, could lead to accumulation of proviral particles in neurons with potentially detrimental consequences for brain function and behavior.

Disclosure: Nothing to disclose.

25.3 Maternal Immune Activation Drives LINE-1 Viral-Like Mobile DNA Elements That Cause Somatic Mutations in Brain

Jennifer Erwin

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

Background: Growing evidence implicates somatic mosaicism and transposons as sensors of environmental stress in the brain. Exposure to certain environmental factors causes a long-lasting risk for neuropsychiatric disorders and also results in activation of Long Interspersed Nuclear Elements (LINE-1 or L1) retroelements. L1 is a 6kb DNA element with an RNA polymerase II promoter and encodes for the proteins required for retrotransposition. L1 creates somatic mutations during brain development.

Despite the potential for increased L1 activation to cause somatic mutations, the role of L1 in environment associated risk is poorly understood. Recent sequencing of postmortem tissue suggests altered L1-driven somatic mutation profiles occur in Rhett syndrome, schizophrenia and Ataxia-telangiectasia. Studies in mouse and macaque demonstrate that maternal immune activation results in increased L1 activity. Herein, we investigate the functional role of increased somatic retrotransposition in perturbing neuronal development and contributing to neurological disorders.

Methods: We use a combination of in vitro mouse and human neural stem cell differentiation models to interrogate the direct molecular link between Il-6 exposure and L1 activation in neural progenitor cells. We established an in vivo mouse model to manipulate levels of L1 during MIA. Mice exposed to fetal MIA, via polyI:C injection at E9.5, demonstrate impaired sensorimotor gating measured by prepulse inhibition. This parallels the sensorimotor-gating deficits observed in humans at high risk of schizophrenia. We then use a mouse maternal immune activation model of combined with inhibition of retrotransposition by nucleoside analog reverse transcriptase inhibitors to ask if inhibition of L1 reverse transcription has a behavior outcome in sensorimotor-gaiting and open field.

Results: We demonstrate that attenuating L1 activity during fetal MIA specifically ameliorates the sensorimotor gating function without altering the acute pro-inflammatory immune response ($n = 8–12$ females per group from 3 litters per group, linear mixed model with treatment as a fixed factor and a random intercept for litter, $p < 0.01$). Interestingly, MIA-related anxiety phenotypes are independent of L1 activity. Using hipocampal neural progenitor cells in vitro, we demonstrate that MIA-induced pro-inflammatory cytokine IL-6 activates transcription and retrotransposition and allows escaping of host surveillance mechanism for L1 elements. We find that exposure of in vitro neural progenitor cells to IL6 leads to a robust activation of L1 RNA ($n=5$ per group, 1.5 fold, $p < 0.001$), promoter ($n = 5$ per group, 20-fold increase $p < 0.0001$), retrotransposition by reporter assays ($n = 5$ per group, 2.5fold increase, $p < 0.005$) and increased accumulation of single-stranded cytoplasmic DNA, which is a result of L1 reverse transcription activity.

Conclusions: This suggests that IL-6 increases L1 activity in neural progenitor cells and that L1 reverse transcription specifically mediates sensory motor gating deficits related to neurodevelopmental disorders caused by maternal immune activation. While L1s remain active in both human and mouse genomes, it is particularly prevalent during neurogenesis and neural differentiation. L1 activity has been thought to contribute to the dynamic genome and expand neuronal diversity and genomic coding potential. Our in vivo experiments combining inhibition of L1 reverse transcription with MIA model during early embryonic development revealed L1 activation as a novel and unexpected regulator of animal behavior.

Disclosure: Nothing to disclose.

Mini Panel

26. Biomarkers of Neurodevelopmental Disorders in Early Infancy: Implications for Early Detection and Intervention

26.1 Pre-Symptomatic Prediction of ASD in High-Risk Infants With Scalable EEG Methods:

Abstract not included.

26.2 Toward Presymptomatic Prediction of ASD Using Eye Tracking

Abstract not included.

26.3 The Presymptomatic Prediction of Autism Spectrum Disorder Using Infant MRI

Abstract not included.

Mini Panel

27. Sex Differences in the Reward System: From Animal Models to Patients

27.1 Neurobehavioral Sex Differences in the Human Reward System: Convergence Across Levels of Analysis

Brian Mickey

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

Background: Women and men are affected differently by disorders of the reward system, including addictions and mood disorders. A comprehensive understanding of sex differences in the reward system is needed to develop more effective and more personalized interventions for both men and women. Previous studies have not systematically examined responses to both positive- and negative-valence stimuli across neurobehavioral levels of analysis. Here we report sex differences in reward- and punishment-related traits, perception, behavior, autonomic arousal, and neural activation in a large sample of young adults.

Methods: Sex differences were quantified in a normative sample of 221 adults (121 women, 100 men, age 18–22) who performed a monetary incentive task, which was designed to measure differential responses to stimulus salience (behavioral relevance) and valence (win versus loss). Participants provided self-reports of reward- and punishment-related traits and subjective ratings of task stimuli. Behavior was measured by performance accuracy and autonomic arousal was measured via skin conductance during the task. Neural activation was quantified in a sub-sample of 44 subjects who performed the task during functional MRI. This task robustly activated the mesoaccumbal pathway and the salience network, so the midbrain, bilateral nucleus accumbens (NAc), dorsal anterior cingulate cortex (dACC), and bilateral anterior insula (AI) were evaluated as anatomically-defined a priori regions of interest. Statistical analyses employed linear mixed models. Findings were considered statistically significant at $p < 0.05$ after multiple-comparison correction.

Results: Compared to women, men reported higher trait reward sensitivity (Hedges' effect size, $d = 0.61$) and fun seeking ($d = 0.49$). Women reported higher trait behavioral inhibition ($d = -0.46$). Relative to women, men rated high- versus low-salience stimuli as more arousing ($d = 0.42$) and, similarly, autonomic responses to salient stimuli were greater in men ($d = 0.46$). These

sex differences in subjective and autonomic arousal were consistent with behavior: compared to women, men exhibited greater differential accuracy to high- versus low-salience stimuli (d = 0.39). Sex differences were also evident in the mesoaccumbal pathway and salience network. Relative to women, men showed greater responsiveness to salience within the NAc, midbrain, AI, and dACC (d = 0.61–0.89). In contrast to salience sensitivity, analyses of valence sensitivity (win versus loss) revealed no significant sex differences in behavioral, autonomic, or neural responses.

Conclusions: Our findings reveal novel sex differences in the processing of positive- and negative-valence incentive stimuli. Relative to women, men exhibit a greater responsiveness to high-salience stimuli and, furthermore, this hyper-responsiveness converges across levels of analysis -- from neural activation to autonomic arousal to behavior and perception. The lack of sex differences in response to win versus loss stimuli suggests that the greater responsiveness among men pervades both positive- and negative-valence systems. These results suggest a neurobehavioral basis for sexually dimorphic disorders of the reward system.

Disclosure: LivaNova: Grant (Self); Futramed: Advisory Board (Self)

27.2 Sex Differences in Reward- and Punishment-Guided Actions

Abstract not included.

27.3 Reward Processing in Chronic Pain Varies by Sex and Opioid Use

Abstract not included.

Mini Panel

28. Emerging Role of Hypocretins/Orexins in Psychiatric Diseases

28.1 Hypocretin/Orexins and Hyperarousal

Luis de Lecea

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

Background: The hypocretins (Hcrts), also known as orexins, are two neuropeptides derived from the same precursor expressed by a few thousand neurons in the lateral hypothalamus. Activity of Hcrt neurons is essential for arousal stability. Stress has been known to induce insomnia/hyperarousal in humans and rodent models. Despite the strong evidence demonstrating a causal relationship between arousal-promoting neurons and behavioral wakefulness, whether these same cell populations are recruited during stress exposure remains unknown. A well-defined neural circuit linking stress to arousal has yet to be adequately described.

Methods: We used the EnvA-pseudotyped glycoprotein (G)-deleted rabies virus (EnvA + RVdG) in Hcrt-cre mice (n=5) to trace the monosynaptic inputs to Hcrt neurons. We then monitored the activity of CRHPVN neurons in CRH::Cre mice (n = 5) and Hcrt neurons in Hcrt::Cre mice (n = 5) by measuring Ca2+ transients during natural sleep/wake transitions using fiber photometry. We thus conducted a series of optogenetic experiments in Hcrt::Cre, CRH::Cre, CRH::Cre-ATA3 mice (N = 5) which have their Hcrt neurons ablated, and CRH::Cre-Cas9 mice (N=3) with the crh gene disrupted using CRISPR-Cas9 technology in CRHPVN neurons.

Results: -CRHPVN neurons directly innervate HcrtLH neurons

Rabies virus-mediated monosynaptic tracing revealed a major population of PVN neurons directly project to Hcrt neurons. We further performed antibody staining in the PVN and found around 60% of the RVdG-labeled PVN neurons are CRH-positive and about half of the CRHPVN neurons were labeled by the RVdG. Interestingly, arginine vasopressin (AVP) and oxytocin (OXT) neurons, another two major populations of neurons intermingled with CRH neurons in the PVN were labeled with a much lower ratio.

- Mild optogenetic stimulation of LH-projecting CRHPVN neurons leads to insomnia

We used a mild optogenetic stimulation paradigm with neglectable effects on HcrtLH neurons in changing the amount of sleep. Strikingly, this same optogenetic stimulation of CRHPVN neurons labeled with ChR2-eYFP by AAV-Retro vectors injected to LH significantly increased the amount of wakefulness, here defined as insomnia/hyperarousal. Interestingly, optogenetic stimulation of LH-projecting CRHPVN neurons of the CRH::Cre-ATA3 mice without Hcrt neurons can also trigger a robust increase of wakefulness but the effect was significantly smaller when compared with the condition with intact Hcrt neurons ($p < 0.0005$). We further investigated whether CRH release was necessary for the optogenetically-induced arousal response. We generated viruses carrying sgRNAs to selectively disrupt the crh gene in CRHPVN neurons of CRH::Cre-Cas9 mice. Optogenetic stimulation of CRHPVN neurons projecting to LH from crh gene-disrupted mice failed to increase wakefulness suggesting a critical role of CRH in activating downstream arousal promoting brain nuclei including the HcrtLH neurons ($p < 0.0005$).

Conclusions: In this study, we find that the CRHPVN-HcrtLH pathway plays a crucial role underlying stress-induced insomnia/hyperarousal. We further demonstrate that optogenetic activation of CRHPVN neurons projecting to the LH elicits long-lasting wakefulness mimicking hyperarousal/insomnia induced by stress exposure,

Disclosure: Nothing to disclose.

28.2 The Role of the Orexin/Hypocretin System in Modulating Rodent Intermale Aggressive Behavior

Meghan Flanigan

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

Background: Recent findings suggest that brain reward systems controlling the valence of social interactions are dysregulated in some neuropsychiatric patients displaying heightened aggression. Although not previously implicated in aggression, the neuropeptide orexin/hypocretin is involved in arousal, pro-social behavior, drug addiction, and a wide array of motivated behaviors. Here, we investigated whether brain-wide and circuit-specific manipulation of the orexin/hypocretin system can modulate aggression and its rewarding properties.

Methods: Male CD1 wild type mice (n = 5–12/group/experiment), CD1xGlutamate decarboxlyase 2 (GAD2)-Cre F1 hybrid mice (n = 5–12/group/experiment) or CD1xOrexin-Cre F1 hybrid mice (n = 5–12/group/experiment) were utilized in this work. First, qPCR and in-situ hybridization (ISH) were used to characterize the expression of orexin receptor mRNA in the LHb following aggressive experience in the Resident Intruder (RI) test. In-vivo GAD2 neuron-specific knockdown of orexin receptor 2 (OxR2) in the LHb was performed with AAVs encoding an OxR2-directed microRNA, and effects on aggression and aggression conditioned place preference (CPP) were measured. In-vivo activity of LH-LHb orexin neurons during the resident intruder test and aggression

CPP test was manipulated with optogenetics. Systemic antagonism of OxRs was performed during the RI test, test, open-field test, social recognition task, and object recognition task. Statistical tests employed included paired and unpaired t-tests, one-way ANOVA, non-parametric Kruskal-Wallis test, and two-way ANOVA.

Results: qPCR and ISH revealed increased OxR2 expression selectively in GAD2 LHb neurons following aggression (pPCR: $p = 0.03$, ISH: $p = 0.0002$). Optogenetic stimulation of LH orexin terminals in the LHb enhanced aggression (latency: $p = 0.04$, duration: $p = 0.04$) and aggression CPP ($p = 0.01$), while optogenetic inhibition of these neurons decreased these behaviors (latency: $p = 0.0003$, duration: $p = 0.004$, CPP: $p = 0.009$). GAD2 neuron-specific knockdown of OxR2 in the LHb reduced aggression (latency: $p = 0.03$, duration: $p = 0.004$) and aggression CPP ($p = 0.04$). Systemic antagonism of OxR2 with EMPA or seltorexant reduced aggression without altering locomotion, anxiety-like behavior, social memory, or object memory. Systemic antagonism of OxR1 or both OxR1 and OxR2 did not strongly affect aggression, locomotion, or anxiety-like behavior.

Conclusions: These findings implicate the orexin/hypocretin system in aggression and its rewarding properties and indicate that pharmacological agents targeting orexin receptors may be a viable treatment for some psychiatric patients displaying elevated aggression.

Disclosure: Patent pending for use of Orexin receptor 2 antagonists to treat aggression (Self)

28.3 Translational Evaluation of Novel Selective Orexin-1 Receptor Antagonist JNJ-61393215 in an Experimental Model for Panic in Rodents and Humans

Giacomo Salvadore

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

Background: Orexin neurons originating in the perifornical and lateral hypothalamic area project to anxiety- and panic-associated neural circuitry and are highly reactive to anxiogenic stimuli. Preclinical evidence suggests that the orexin system and particularly the orexin-1 receptor (OX1R), may be involved in the pathophysiology of panic and anxiety. Selective OX1R antagonists thus may constitute a potential new treatment strategy for panic- and anxiety-related disorders.

Methods: Here, we characterized a novel selective OX1R antagonist, JNJ-61393215, and determined its affinity and potency for human and rat OX1R in vitro. We also evaluated the safety, pharmacokinetic and pharmacodynamic properties of JNJ-61393215 in first-in-human single and multiple ascending dose studies. Finally, the potential anxiolytic effects of JNJ-61393215 were evaluated both in rats and in healthy humans using CO2 challenge to induce panic symptoms.

The single ascending dose study was a phase 1, randomized, double-blind, placebo-controlled study to assess safety, tolerability, and PK of single increasing oral doses of JNJ-61393215 in 80 healthy adult participants. The multiple ascending dose study was a randomized, double-blind, placebo-controlled study to investigate safety and tolerability, PK and PD of JNJ-61393215 in 32 healthy participants under fasted conditions. To investigate the potential anxiolytic effects of JNJ-61393215 in humans, 39 healthy male subjects sensitive to the anxiogenic effects of 35% CO2 inhalation at screening were randomized to receive JNJ-61393215 25mg, JNJ-61393215 90mg, alprazolam 1mg bid or placebo for 7 days. The study used an incomplete cross-over design and each subject was randomized to receive either placebo or one of the three active treatments. Subjects underwent a 35% CO2 inhalation challenge after 6 days of dosing with the study drug in each cross-over period and the anxiety symptoms induced by the CO2 challenge were measured using the Panic Symptom List (PSL-IV).

Results: In the rat CO2 model of panic anxiety, JNJ-61393215 demonstrated dose-dependent attenuation of CO2-induced panic-like behavior without altering baseline locomotor or autonomic activity and had minimal effect on spontaneous sleep. In phase-1 human studies, JNJ-61393215 at 90 mg demonstrated significant reduction in CO2-induced fear and anxiety symptoms compared to placebo according to the primary outcome measure PSL-IV (difference of LS Means: -2.3; $p < 0.02$); a significant anxiolytic effect was also demonstrated for a therapeutic dose of alprazolam (difference of LS Means vs. placebo: -3.4; $p < 0.03$). Somnolence and headache were the most frequently reported adverse events and all events were mild in severity.

Conclusions: These results support the safety, tolerability, and anxiolytic effects of JNJ-61393215, and validate CO2 exposure as a translational cross-species experimental model to evaluate the therapeutic potential of novel anxiolytic drugs.

Disclosure: Johnson & Johnson LLC: Employee, Stock/Equity (Self)

Mini Panel

29. Using Precision Medicine to Understand Stress in Maternal and Child Mental Health

29.1 Prenatal Stress Induces Reductions in Key Maternal Microbes and Microglial Dysfunction in Utero

Tamar Gur

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

Background: In utero exposure to maternal stress has been linked with an increased risk of psychiatric disorders, and the underlying mechanisms are currently being elucidated. Previously we have shown that microbes are required for intrauterine placental and fetal brain inflammation following prenatal stress, and that the chemokine CCL2 is required during prenatal stress for both intrauterine inflammation and reduced social behavior in adulthood. We hypothesized that fetal microglia are a key mediator of aberrant central nervous system development and are tied to key microbial changes. Here, we used a prenatal stressor in pregnant mice to examine novel relationships between prenatal stress exposure, maternal microbes, and alterations in fetal microglia, including quantity and activity.

Methods: Pregnant WT C57/BL6 and CCL2 -/- females were randomly assigned to either the stressed experimental group or non-stressed control group ($n = 10-14$/group). Mice were stressed between embryonic day (E)10-E16 for 2 h a day using a well-validated restraint stress paradigm; controls were left undisturbed. RT-PCR, Nanostring, immunohistochemistry, and multiplex ELISA were used to examine microglia cytokine production, and microglial activity (e.g phagocytosis) related gene expression. For microbiome data, DNA metagenomic libraries were generated using the KAPA Library System. Libraries were sequenced using the Illumina NovaSeq SP flow cell.

Results: Prenatal stress lead to increased number of microglia in the fetal hippocampus, as measured by IBA-1+ staining ($p < 0.05$). In addition, there was an increase in levels of the pro-inflammatory cytokines IL-1β and IL-6 in fetal microglia ($p < 0.05$) exposed to prenatal stress. In addition, microglia exposed to prenatal stress demonstrated increased expression of phagocytosis-related genes. Genome-resolved microbial metagenomic analyses revealed reductions in genes, microbial strains, and metabolic pathways primarily associated with pro-inflammatory

function. Notably, Parasutterella, a microbe associated with gut health and found to be reduced in women with high anxiety during pregnancy, was reduced in the stressed dams Parasutterella excrementihominis genome copies per million reads (Kruskal Wallis and Wilcoxon Signed Rank tests, $p = 0.006$).

Conclusions: Altogether, these data suggest a critical role for microbes in mediating the inflammatory consequences prenatal stress. Specific targeting of microbes during pregnancy may prove to be beneficial to offspring exposed to maternal stress in utero and advance our practice of personalized medicine.

Disclosure: Nothing to disclose.

29.2 Depression During Pregnancy is Associated With an Altered Gut Microbiome and Blood Metabolome

Beatriz Penalver Bernabe

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

Background: One in ten women experience depression during their pregnancy or antenatal depression (AND). AND confers significant risks to mother (e.g., suicide) and child (e.g., preterm birth, low birth weight, infant neurodevelopmental disorders), yet only 5% of women with AND receive adequate care. Despite increasing evidence linking depression to the gut microbiome, this research has not been extended to the perinatal period. Our aim was to examine gut microbial structure and composition and the blood metabolites in pregnant women with and without AND.

Methods: Sixty-four pregnant women provided fecal and blood samples at their first (<16 gestational weeks) and second trimesters (24–28 gestational weeks) and completed the Computerized Adaptive Diagnostic Test for Major Depression Disorder (MDD) diagnostic screening tool (CAD-MDD). Using DADA2, 16S rRNA amplicon sequence analysis of fecal DNA, we identified exact sequence variants (ESVs) that were correlated against AND using Generalized Linear Models (GLM). Non-targeted metabolomics was performed using LC-MS/MS in the collected plasma samples.

Results: AND rates were 15.6% (T1) and 10.6% (T2). While Shannon index was not associated with AND, the average Bray-Curtis distance was inversely associated with AND ($p = 0.02$). Several ESV were significantly different in women with AND compared with those without. For instance, Paraprevotella and Faecalibacterium were enriched and depleted respectively in women with AND overall, while Lactobacillus was only depleted at their first trimester. In randomized clinical trials with non-pregnant subjects, Lactobacillus species reduced negative thoughts associated with sad mood. Moreover, the relative abundance of 91 metabolites was distinct in women with AND versus controls. Hippurate, a human-microbial metabolite, was depleted in women with AND. In the general population, low levels of hippurate are associated with episodes of depression and with low abundance of Faecalibacterium species. Glycodeoxycholic acid, a bile acid, was enriched in women with AND. Notably, gut microbiota can dictate bile acid concentrations.

Conclusions: We provide new evidence that AND is associated with altered gut microbial composition and blood metabolic profiles that vary with gestational age. Our results confirm our current understanding of the role of the gut microbiota in mood disorders and expand it to the complex and evolving pregnancy period. Our research could serve as a future assay to detect AND in clinical settings.

Disclosure: Nothing to disclose.

29.3 The Gut-Heart-Brain Axis and Maternal Mental Health

Mary Kimmel

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

Background: Altered stress responses are implicated in perinatal mood and anxiety disorders (PMAD). Heart rate variability (HRV) measures represent activity of the autonomic nervous system (ANS), including the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The ANS and the immune system help the individual navigate the stress of the dynamic perinatal period; pregnancy, delivery, and postpartum. Microbial composition and function in relation to HRV and host-immune function is being examined in a cohort of 94 women, 78% of whom had a history of major depression or anxiety disorder as determined by the Structured Clinical Interview for DSM-V, at two time points in pregnancy and one time point postpartum. Presented here are preliminary HRV findings and cytokine changes of subsets of the cohort.

Methods: Self-assessment of symptoms included the Edinburgh Postnatal Depression Scale (EPDS), Generalized Anxiety Disorder-7 (GAD-7) and the Perceived Stress Scale (PSS); blood to measure cytokines; and fecal samples were collected from each visit. The Trier Social Stress Test (TSST) was administered at the postpartum visit with HRV metrics measured before, during, and after the stressor. Percent change in levels of each cytokine was analyzed between each visit.

Results: In subset of 38 subjects, 13% had an elevated EPDS or GAD in the postpartum and 24% had an elevated score in the 3rd trimester. In the 3rd trimester, 42% had moderate or severe scores on the PSS; 63% postpartum. EPDS score was positively correlated with HRV HF at recovery and trended towards being positively correlated at baseline and with SDNN during the stressor. In another subset of 21 subjects, the EPDS was positively associated with changes in fractalkine, IL12_p70, and IL-13. There were trends towards the EPDS positively associated with changes in GM-CSF and IL-5; GAD-7 positively associated with GM-CSF and changes in ITAC, IL-2, IL-5, IL-6, IL-7; and PSS positively associated with changes in IL-13 and IL-7. When looking at the 12 subjects where HRV and cytokine measures have both been analyzed at this time, there is a large individual variation in presence of elevated symptoms at different points, in changes in cytokines across the visits, and in responses to the TSST. For example, one subject had elevated EPDS scores in pregnancy and improved by the postpartum, and her cytokine and HRV profile postpartum may indicate treatment effects.

Conclusions: Measures of the immune system and the ANS in combination have the potential to improve understanding of maternal responses to stressors and adaptation to the perinatal period. This preliminary work indicates that SDNN, a measure of both SNS and PNS, is higher during the stressor and vagal tone, as measured by HF, tends towards higher at recovery from a social stressor in those with elevated EPDS scores. Higher vagal tone has been seen in a study by Fauholt-Jepsen et. al. comparing HRV during a manic affective state of patients with bipolar spectrum disorders. PMAD are more likely associated with bipolar spectrum presentations than at other times. Immune factors indicate that there is a dysregulation of anti-inflammatory cytokines from the pro-inflammatory transition during delivery into the postpartum period. These analyses will be repeated in the larger cohort and microbial composition and function added to group individuals in stress response profiles.

Disclosure: Abbvie Laboratories: Stock / Equity (Spouse); Sage Therapeutics: Grant (Self); Otsuka Pharmaceuticals: Honoraria (Self); Miller Communications in partnership with Sage Therapeutics: Honoraria (Self)

Mini Panel

30. Connecting Brain to Body: Intrinsic and Antipsychotic Drug-induced Systemic Disruptions in Schizophrenia

30.1 Peripheral and Central Biomarkers Associated With Inflammation in Early Psychosis

Kristin Cadenhead

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

Background: Early-life exposure to stress, infection and/or inflammation has the potential to induce systemic changes linked to metabolic abnormalities, enhanced production of pro-inflammatory cytokines and activated microglia. Elevated serum cytokines have been reported in neuropsychiatric diseases including depression, dementia, and psychosis. Pro-inflammatory cytokines inhibit neurogenesis and hippocampal function, induce apoptosis in cortical neurons and oligodendrocytes, and affect synapse formation and connectivity.

We have reported that Clinical High Risk (CHR) for psychosis participants from the North American Prodromal Longitudinal Studies Consortium demonstrate evidence of metabolic abnormalities, before the onset of psychosis or antipsychotic treatment, that are associated with symptoms and poor functioning. Additionally, early life adversity in CHR is associated with plasma biomarkers of inflammation and oxidative stress in new data from our group. In a separate sample of CHR, medicated and unmedicated FEP participants we have found evidence of elevated proinflammatory biomarkers that are greatest in the CHR sample followed by unmedicated FEP.

1H-MRS studies in psychotic illness suggest that neuroinflammation can result in elevated levels of myo-inositol (Ins) and choline-containing compounds (Cho). In the present study, we compared glutamate, Cho, Ins and N-acetylaspartate (NAA) in bilateral dorsal caudate and Medial Prefrontal Cortex (MPF) in 13 antipsychotic-naive FEP participants and 10 healthy controls (HC) ages 14–30 and explored the associations with peripheral inflammatory biomarkers.

Methods: 1H-MRS spectra were obtained using PRESS (TE =35ms) and shimmed to achieve full width at half maximum (FWHM) ≤12 Hz and analyzed using LCModel. Neuroinflammatory biomarkers (cytokines, chemokines, markers of vascular injury) were analyzed by commercial ELISA with internal controls. The association between neurometabolite levels that differed significantly between groups and neuroinflammatory biomarkers were analyzed using Pearson correlations.

Results: There were significantly higher levels of Glu in the Left (LC) and Right (RC) caudate in FEP compared to HC ($p < 0.05$) and associated with lower Brain-derived neurotrophic factor (BDNF) ($r = -0.81$; $p < 0.05$) and Thymus and activation-regulated chemokine (TARC) ($r = -0.87$; $p < 0.01$) levels in the RC, possibly indicating disruption of neuroprotective, modulatory effects of BDNF on Glu circuitries. FEP also had higher levels of Ins in the RC ($p < 0.05$) associated with lower Macrophage Derived Chemokine (MDC) ($r = -0.78$; $p < 0.05$) and in the MPF associated with lower Macrophage Inflammatory Proteins (MIP 1B) ($r = -0.77$; $p < 0.05$), possibly indicating a proinflammatory response associated with neuronal insult. Levels of Choline were higher in FEP in all three ROIs and this was associated with lower Eotaxin ($r = -0.89$; $p < 0.01$) but higher monocyte chemoattractant protein 1 (MCP1) ($r = 0.82$; $p < 0.05$) likely suggesting a neuroinflammatory response at the blood brain barrier. No group differences were found in NAA levels.

Conclusions: Our results are in line with previous studies showing neurometabolite changes present at the onset of psychotic illness. New data demonstrates an association between neurometabolites and inflammatory biomarkers, providing preliminary evidence for the interplay of neuroinflammatory and neurodegenerative processes implicated in the emergence of psychotic illness.

Disclosure: Nothing to disclose.

30.2 New Peripheral Pancreatic Dopamine Mechanisms of Antipsychotic Drug-Induced Metabolic Disturbances

Zachary Freyberg

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States

Background: Antipsychotic drugs (APDs) are used to treat highly prevalent psychiatric illnesses, making them some of the most widely prescribed psychiatric medications. However, these drugs also cause profound metabolic disturbances including weight gain, insulin resistance and increased risks of type 2 diabetes (T2D) and cardiovascular disease. All APDs cause metabolic side effects to differing degrees and treatments to reduce these metabolic symptoms are limited. The mechanisms for APD-induced metabolic disturbances are poorly understood. Nonetheless, the single unifying property of all APDs is their blockade of dopamine (DA) D2-like receptors including D2 (D2R) and D3 (D3R) receptors, suggesting a role for these receptors in APD-induced metabolic dysfunction. Importantly, we and others discovered that D2R and D3R are expressed peripherally in both human and rodent insulin-secreting pancreatic beta cells, key regulators of glucose metabolism. D2R and D3R are also expressed in glucagon-secreting pancreatic alpha cells. We thus hypothesize that APD-induced metabolic disturbances are driven by the direct actions of APDs on pancreatic alpha cell and beta cell D2-like receptors.

Methods: Human pancreatic islet transcriptome analysis: De-identified human islet alpha and beta cells (3 females, 2 males) were purified by FACS. DA secretion: Measured by HPLC as described (Farino et al., 2019). Insulin and glucagon secretion assays: De-identified cadaveric human islets and BALB/c mouse islets were cultured overnight prior to use. Islets were glucose-stimulated and supernatants collected for insulin and glucagon measurement via HTRF. All studies were IRB- and IACUC-approved and conducted on n>3 experimental days.

Results: We characterized the DA signaling and biosynthetic machinery in human pancreatic alpha and beta cells by RNAseq. We found that human alpha and beta cells express the complete DA biosynthetic, catabolic and signaling machinery. HPLC also showed that alpha cells synthesize and secrete DA and DA precursor L-DOPA. Alpha and beta cells express all five DA receptors (D1-D5), with D2R and D3R being the predominantly expressed DA receptors, suggesting that APDs target the pancreas directly.

DA potently decreased glucagon release, in addition to inhibiting glucose-stimulated insulin secretion (GSIS), suggesting that DA modulates both glucagon and insulin secretion in islets. We also found that APDs clozapine and olanzapine substantially increased alpha cell glucagon secretion relative to vehicle. Haloperidol similarly raised glucagon secretion, albeit to a lesser degree. All three APDs also significantly raised GSIS from the same islets. Our results suggest that APDs enhance insulin and glucagon release, contributing to systemic metabolic dysfunction.

Conclusions: Pancreatic alpha cells are a key source of DA which modulates insulin and glucagon secretion. APDs disrupt this pancreatic DA signaling via alpha and beta cell D2R and D3R to disturb regulated secretion of key hormonal regulators of metabolism. Our work suggests that APDs act directly on both alpha cell and beta cell DA signaling to significantly disturb insulin and glucagon secretion. Acting on these new pancreatic targets

also presents a novel therapeutic approach for mitigating or reversing APD-induced metabolic dysfunction.

Disclosure: Nothing to disclose.

30.3 Antipsychotic Drugs Inhibit Central Glucose Sensing to Result in Whole-Body Insulin Resistance

Margaret Hahn

Centre for Addiction and Mental Health, Toronto, Canada

Background: Antipsychotics (APs) remain the cornerstone treatment for schizophrenia and are widely prescribed for other conditions. However, their use presents a significant risk for adverse glycemic effects. Independent of adiposity changes, APs directly dysregulate whole body glucose metabolism, and this occurs in part through the central nervous system (CNS). To this end, we have recently demonstrated that olanzapine impairs CNS insulin-action, resulting in whole body insulin resistance. In addition to a critical role of hormones such as insulin in the CNS, glucose-sensing at the hypothalamus is also pivotal for regulation of whole-body insulin sensitivity. Glucose also represents the primary fuel for brain function, and the hypothalamus represents the key brain center (through glucose sensing neurons) to ensure maintenance of key homeostatic systems. Here, we set out to examine the effects of a first-generation AP (haloperidol) and second-generation AP (olanzapine) on CNS-glucose sensing, and subsequent regulation of peripheral glucose metabolism.

Methods: Gold-standard, pancreatic-euglycemic clamps were used to assess changes in glucose kinetics in response to a primed, continuous intracerebroventricular (ICV) infusion of glucose or vehicle solution (2 mM, 5 µL/hour, into the 3rd ventricle, approximating post-postprandial levels). Male rats were co-treated with an acute injection of olanzapine (3mg/kg, S.C.), haloperidol (10mg/kg, S.C.) or vehicle(veh). AP dosing was based on clinical D2 occupancy. Groups included (ICV–peripheral) Veh–Veh ($n = 6$), glucose (Glu)–Veh ($n = 8$), Glu–olanzapine(Ola) ($n = 6$), Veh–Ola ($n = 6$), Glu-haloperidol (Hal) ($n = 6$) and Veh-Hal ($n = 7$). The peripheral glucose infusion rate needed to maintain euglycemia during the clamp was used as a measure of whole-body insulin sensitivity. A tracer (3-H3-glucose) infusion throughout the procedure was used to assess glucose kinetics, including hepatic glucose production and peripheral glucose uptake.

Results: As expected, ICV (central) glucose infusion caused a significant increase in the peripheral glucose infusion rate (mg/kg. min) compared to veh (Veh-Veh 2.96 ± 0.72 vs Glu-Veh 9.15 ± 1.41), ($p < 0.05$). This effect was mitigated by both olanzapine (Glu-Veh 9.15 ± 1.41, Glu-Ola 0.63 ± 0.38, $p < 0.05$) and haloperidol (Glu-Veh 9.15 ± 1.41, Glu-Hal 3.00 ± 0.47, $p < 0.05$). Compared to vehicle, ICV glucose significantly suppressed hepatic glucose production (clamp relative to basal: Veh-Veh $19.4\% \pm 15.3$ vs Glu-Veh $71.2\% \pm 14.1$, $p < 0.05$) and this effect was inhibited by olanzapine (Glu-Ola$16.72\% \pm 12.62$). ICV glucose did not alter peripheral glucose utilization compared to ICV vehicle (clamp relative to basal: Veh-Veh $24.4\% \pm 17.27$ vs Glu-Veh $17.0\% \pm 18.96$, $p > 0.05$). However, glucose utilization was significantly suppressed following haloperidol (clamp relative to basal: Veh-Veh $24.4\% \pm 17.27$ vs Glu-Hal (-)$24.2\% \pm 5.12$, $p < 0.05$). In summary, olanzapine and haloperidol both impaired central glucose sensing resulting in whole body insulin resistance via alterations in glucose production (olanzapine) and glucose utilization (haloperidol).

Conclusions: This data, for the first time, demonstrates evidence that APs disrupt central glucose-mediated regulation of glucose kinetics. Perturbed glucose-sensing in the CNS is expected to have deleterious metabolic consequences and possibly disrupt other brain glucose-dependent functions such as cognition. The study unveils a novel effect of AP treatment to disrupt brain nutrient-sensing, suggesting this may be a mechanism by which these drugs increase risk of type 2 diabetes.

Disclosure: Alkermes: Advisory Board (Self)

Mini Panel

31. Aging With Bipolar Disorder: Emerging & Global Data on Brain-Age, Emotion-Regulation and Comorbidity

31.1 Aging, Attentional Biases, and Emotional Regulation Strategies in Bipolar Disorder

Caitlin Millett

Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, United States

Background: Disorder (BD) is a disease characterized by periods of manic and depressive episodes, heterogeneity in neurocognitive functioning, and abnormal emotional regulation (ER). ER refers to the ability to flexibly and dynamically respond to affectively valenced stimuli in the service of goal-directed behaviors. Determining how distinct ER strategies in such patients interact with ER trends observed in normal aging may be crucial to predicting clinically relevant functional outcomes in aging populations with BD and providing them with adequate treatments.

Methods: This is a post-hoc analysis of a cross-sectional study. Participants completed the Cambridge Neuropsychological Test Automated Battery (CANTAB) Emotion Recognition Task (ERT), which measures the ability to identify both negative (sad) and positive (happy) facial expressions. Three age cohorts were identified based on the age range of the sample. These cohorts were fixed to compare healthy controls (HCs) vs. BD patients on ERT scores in subsequent analyses. Diagnostic groups were compared by age cohort on recognition accuracy for both happy and sad words from the ERT using a multivariate ANOVA. We also tested for a diagnosis-by-age interaction. Results from the Brief Coping Orientation to Problems Experienced (B-COPE) scale allowed us to characterize the habitual use of both adaptive and maladaptive coping strategies. A series of univariate ANOVAs were performed with a fixed age cohort and diagnosis, on coping strategy type (adaptive vs. maladaptive) and an adaptive: maladaptive ratio. Finally, we conducted a multiple regression to predict social functioning, using the Social Adjustment Scale-Leisure and Activities. Predictors included age cohort; diagnosis; sex; race; measures of affective bias (ERT performance); a measure of cognitive control (Stroop); current depression (Hamilton Depression Rating Scale (HDRS) scores); current mania (Young Mania Rating Scale (YMRS) scores); and B-COPE regulation strategy ratio.

Results: 257 BD patients – whose diagnoses were verified via the structured clinical interview for the DSM-5 (SCID-5) – and 47 HCs were comprehensively characterized. The age range of the sample was 18–65 years and the mean age was 46. The sample was divided into three age cohorts to represent early (20–40 years; $n = 97$), mid- (41–50 years; $n = 71$), and late-life (51–65 years; $n = 89$). (1) In an analysis examining ER and attentional bias, there was a significant diagnosis by age interaction ($p < 0.05$); HCs reported a higher 'positivity effect' with age ($p < 0.05$) – a pattern not observed in the BD group. (2) Further, the Brief COPE scale revealed a shift toward adaptive coping styles in older adults ($F = 4.12$; $p < 0.02$), however, the age-related shift toward the use of adaptive ER strategies was not seen in BD patients ($F = 3.2$; $p < 05$). (3) Lastly, we found that emotional dysregulation predicts social disability, where performance on the SAS Social Leisure

model was significant ($F = 27.2$; $p < 0.001$), with an adjusted R-squared of 0.29. Significant predictors included: current B-COPE adaptive/maladaptive strategy use, diagnosis, ERT percent correct for sad faces, and depression.

Conclusions: Overall, these data demonstrate significant differences in ER across the lifespan for patients with BD vs. HCs. Our results support the hypothesis that both brain-based measures (negative bias) and behavioral strategies used to regulate emotion both contribute to social functioning outcomes and that several additional measures are likely to moderate these relationships (e.g. sex, symptoms).

Disclosure: Nothing to disclose.

31.2 Aging –Related Correlates of Comorbidity and Functional Status in a Global Integrated Bipolar Dataset

Martha Sajatovic

Case Western Reserve University, Cleveland, Ohio, United States

Background: The evolution of bipolar disorder (BD) symptoms and functioning across the lifespan is incompletely understood. A strategy to overcome the challenge of limited older-age bipolar disorder (OABD) studies is represented in the Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) which pools adult multi-national samples. The sample for this analysis comprised 1672 individuals (1,420 with BD), mean age 61.42 years (SD 12.53, range 18-95 years), 57% women, 80% with Type 1 BD. Data is derived from multiple sources including observational and clinical research studies. This cross-sectional analysis of baseline GAGE-BD data examined age associations with functioning and medical comorbidity. We also examined predictors of functioning and moderation by age.

Methods: In the GAGE-BD, functioning is primarily measured by the Global Assessment of Functioning (GAF) with a sample mean of 63.88 (SD 14.69). Manic symptoms are mostly measured with the Young Mania Rating Scale (YMRS), while depressive symptoms are measured with several instruments, necessitating "cross-walking" procedures to classify depression into ordinal categories of increasing severity. Manic symptom severity in this sample was low, mean total YMRS of 3.5 (SD 5.1). Categories of depression severity in BD cases that included evaluable data for this domain ($N = 784$) found no/minimal depression in 453 cases (57.8%), mild symptoms in 201 (25.6%), moderate symptoms in 114 (14.5%), and severe symptoms in 16 (2.0 %). Medical comorbidity was assessed using a variety of methods. Common comorbidities in cases that include medical information ($N = 1347$) were cardiovascular (47.2%, $N = 599$), musculoskeletal (39.1%, $N = 383$), endocrine (30.6%, $N = 412$) and gastrointestinal conditions (24%, $N = 200$).

Results: Among BD cases, older age was associated with better functioning ($p < 0.0001$) and greater medical co-morbidity, specifically for cardiovascular ($p < 0.0001$), gastrointestinal ($p = 0.0004$), musculoskeletal ($p = 0.002$) and endocrine ($p = 0.045$) when controlled for gender. The association of functioning with age was not different by gender ($p = 0.67$). Common comorbidities and sex were not associated with functional status, however increased depressive symptom severity ($p < 0.0001$) and a higher burden of mania symptoms ($p < 0.0005$) were associated with lower functional status. The strength of the relationship of mania and functioning was similar across the age spectrum ($p = 0.87$), but the relationship of depressive severity to poorer functioning was stronger in older vs. younger adults ($p = 0.002$).

Conclusions: In spite of limitations inherent to pooled data findings support preliminary conclusions regarding OABD. Medical comorbidity is highly prevalent, particularly cardiovascular disease, seen in nearly half of individuals with OABD. In spite of ongoing symptoms and medical burden, some individuals may be able to optimize functioning. Given the general demographic trend of both greater numbers and higher proportion of OABD, additional research on managing predictors of functional status and resiliency are urgently needed.

Disclosures: Nuromate, Otsuka, Alkermes: Grant (Self); Alkermes, Otsuka, Janssen, Neurocrine, Bracket, Health Analytics, Frontline Medical Communications: Consultant (Self); Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate: Royalties (Self)

31.3 Advanced Brain Age and its Clinical Correlates in Bipolar Disorder: Evidence From Global and Local Imaging Data

Lisa Eyler

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

Background: Large, multi-site studies show reduced regional brain size and increased white matter (WM) micro-structural abnormalities on MRI among bipolar disorder (BD) relative to non-mentally ill comparison (NC) participants. Some have characterized BD as a neuro-progressive disorder, predicting advanced "brain age" in BD. Brain age is calculated by applying an algorithm trained to predict chronological age from a multivariate combination of MRI features. Advanced brain age compared to actual age (brain-predicted age difference, brain-PAD) is seen in many neural disorders; single-sample study findings in BD have been mixed, however. Multi-site, global studies allow for powerful tests of advanced brain age, while single-site clinical research permits a multi-modal approach and more thorough examination of clinical correlates.

Methods: Brain-PAD was calculated for 1454 BD participants (555 men/899 women) and 1279 NC (590/689), aged 18-75, from 25 global ENIGMA Bipolar Disorder Working Group sites. A ridge regression model, trained to predict chronological age from 77 MRI-based brain size features in an independent sample of >2000 NC, was applied. Linear mixed models controlling for site, age, and sex compared BD and NC brain-PAD, and examined clinical correlations in BD. For 49 euthymic BD from one site, brain-PAD was independently estimated by applying a partial least squares regression model predictive of age in 80 NC based on measures of regional brain size, fMRI response, WM micro-structural integrity, WM hyperintensities, and resting perfusion. BD and 53 age-matched NC were compared, and demographic and clinical correlates examined, with general linear models. Brain-PAD based on brain size only was compared to multi-modal brain-PAD in this sample.

Results: Brain-PAD in the multi-site dataset was 2.16 years higher in BD than NC ($p < 0.0001$). Women had older brain-PAD ($p < 0.02$), with no differential sex ($p = 0.17$) or age ($p = 0.06$) effects by group. Among BD, factors associated with more advanced brain age were: BD-I diagnosis ($p = 0.02$), not taking Lithium ($p < 0.001$), taking anti-epileptics ($p < 0.001$), taking second generation anti-psychotics ($p = 0.004$), non-euthymic state ($p < 0.001$), and later age of onset ($p = 0.02$). In the single site data, multi-modal brain-PAD was 4.6 years higher in BD than NC ($p = 0.002$), with age as a significant covariate ($p = 0.013$). More advanced brain-PAD in younger individuals ($p < 0.001$) and in males vs females ($p = 0.003$) was seen only in BD. Among BD, advanced brain age was related to: lower education ($p = 0.04$) and premorbid IQ ($p = 0.04$) and higher lifetime number of manic ($p = 0.01$) but not depressive ($p = 0.40$) episodes. Lithium use was not associated, but few in the sample were on lithium. Brain-PAD based only on size measures (as in the global data analysis) was not different between groups (2.4 years, $p = 0.12$), but did correlate with multi-modal brain-PAD ($r(95) = 0.45$, $p < 0.01$).

Conclusions: Large-scale, single modality and small-scale multimodality studies show that MRI-based brain age is modestly advanced in BD compared to NC. Importantly, BD who are on antiepileptics and non-euthymic and those with a history of more manic episodes have older-appearing brains, while lithium use may be protective. The brain-PAD metric could be useful clinically to identify accelerated brain aging in BD patients to identify those in most need of interventions to slow neurocognitive and functional declines.

Disclosure: Nothing to disclose.

Panel

32. Circuits and Intracellular Pathways Mediating Chronic Pain and the Actions of Opioids

32.1 A Photoswitchable Opsin for Spatial and Temporal Control of GPCR Signaling

Bryan Copits

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

Background: Optical manipulations of genetically defined cell types have generated significant insights into the dynamics of neural circuits. While optogenetic activation has been relatively straightforward; rapid and reversible synaptic inhibition has been far more difficult to achieve. Instead of relying on unpredictable ion manipulations or slow photoactivatable toxins at axon terminals, we took a different approach to leverage the natural ability of inhibitory presynaptic GPCRs to silence synaptic transmission.

Methods: Live-cell imaging experiments were performed in vitro using a spinning disk confocal microscope with wide-field LED photostimulaton of opsin-expressing cells.

Calcium channel currents were recorded from cultured DRG neurons using standard protocols. Cells were perfused with choline external and barium was used as the charge carrier. Cells were voltage-clamped at -80 mV and currents were elicited by test pulses to 0 mV. LED stimulation was delivered through the microscope objective to activate opsin-expressing neurons.

Synaptic recordings were made from acute thalamocortical brain slices. EPSCs were evoked by electrical stimulation of opsin-expressing cells in the thalamus while recording postsynaptic responses in layer IV of the barrel cortex. Excitatory currents were pharmacologically isolated and optical stimulation was delivered to axon terminals through the microscope objective.

Cre-dependent opsins were injected into the ventral tegmental area of DAT-Cre mice to target dopamine neurons and fiber optics were placed above the somas or their terminals in the nucleus accumbens. Operant behaviors were performed with mice trained in fixed ratio paradigms to associate a light cue with access to a lever to receive a sucrose reward. After training, mice were tested before and during optical inhibition on VTA dopamine neurons.

Results: Here we characterize parapinopsin (PPO), a photoswitchable non-visual opsin from lamprey pineal gland that couples to Gi/o-signaling cascades. PPO can be rapidly activated by pulsed blue light, switched off with amber light, and is effective for repeated or prolonged inhibition. We developed viral vectors for cell-specific expression of PPO, which traffics very effectively in numerous neuron types. At presynaptic terminals, PPO can silence glutamate release and suppress dopamine-dependent reward and cocaine place preference behaviors in vivo.

Conclusions: PPO thus fills a large gap in the neuroscience toolkit for rapid and reversible synaptic inhibition and has broader utility for achieving spatiotemporal control of inhibitory GPCR signaling cascades in diverse biological and pharmacological applications. We are currently using this new inhibitory GPCR-based opsin to understand pain processing in the amygdala and descending circuits of the periaqueductal gray. We are also engineering new chimeric receptors to allow for photoswitchable control of other GPCRs, like opioid and dopamine receptor families, to better understand how they regulate pain and addiction behaviors.

Disclosure: Nothing to disclose.

32.2 Epigenetic and Transcriptional Mechanisms of Neuropathic Pain and Addiction Comorbidities

Venetia Zachariou

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

Background: This project investigates epigenetic and transcriptional mechanisms in the brain reward circuitry mediating long-term pain states and responses to opioid analgesics. Neuropathic pain is characterized by a range of sensory, cognitive and affective symptoms. We are using the murine spared nerve injury (SNI) model of neuropathic pain to understand gene expression adaptations in components of the reward pathway, at time points that both sensory and anxiodepressive symptoms are observed. We also applied an oxycodone misuse paradigm to gain insight on genes and pathways associated with opioid dependence in pain-free versus chronic pain states.

Methods: The expression of epigenetic modifiers, chromatic marks and transcription factors was monitored using quantitative PCR, or Fluorescent in situ hybridization (RNA Scope).

Hargreaves, Von Frey, Cold Plate, conflict avoidance assays were used to monitor sensory hypersensitivity. Novelty suppressed feeding, social interaction, light avoidance, open field, running wheel, were used to assess emotional or motivational states.

RNA Sequencing (RNASeq, Illumina HiSeq4000) and subsequent bioinformatic analysis were used to identify differentially expressed genes and upstream pathways between treatments and brain regions. Western blotting and qPCR were used for validations.

Results: Our work, identified several intracellular pathways implicated in the maintenance of chronic pain states. The epigenetic modifier HDAC5 (Histone deacetylase 5) in the nucleus accumbens (NAc) binds to chromatin complexes to suppress the expression of several genes that affect synaptic reorganization and recovery from sensory hypersensitivity, including the transcription factor MEF2C. Overexpression of MEF2C in the NAc of DBA2J mice by use of viral mediated gene transfer, did not affect the induction sensory hypersensitivity, but it disrupted the maintenance of SNI symptoms, as mice recovered from sensory ad affective behaviors within 3 weeks after the induction nerve injury ($n = 10–12$, $p < 0.05$ or $^*p < 0.01$ at 3 weeks after SNI).

We also used genomic approaches to determine if chronic pain states affect transcriptomic adaptations associated with oxycodone misuse. RNASeq analysis from NAc, ventral tegmental area and medial prefrontal cortex tissue ($n = 4$ per group) reveal that prolonged exposure to oxycodone, triggers unique transcriptional alterations in each of these brain regions in pain-free versus chronic pain states. Our bioinformatic analysis provided insights for tailored treatment strategies for the alleviation of emotional and sensory manifestations of opioid withdrawal under chronic pain states.

Conclusions: Our findings provide insight on epigenetic and transcriptional mechanisms that control the maintenance of chronic pain states and responsiveness to pain-alleviating drugs.

Interventions in transcriptional mechanisms, such as promotion of MEF2C activity in the NAc, may disrupt pain chronicity.

Using the SNI model, we discovered unique transcriptional pathways in the reward center that are associated with oxycodone physical dependence under chronic pain, providing insight on novel and tailored treatments for physical dependence.

Disclosure: Nothing to disclose.

32.3 Optogenetic Activation of Highly Opioid-Sensitive Ventrolateral PAG Inhibitory Afferents to VTA Evokes Immobility

Abstract not included.

32.4 Interactions Between PACAP and Opioid Receptors – Implications for Trigeminal Pain

Amynah Pradhan

University of Illinois At Chicago, Chicago, Illinois, United States

Background: Chronic opioid use can result in opioid induced hyperalgesia (OIH), where pain spreads beyond the initial injury and is refractory to treatment. Opioids are commonly prescribed for trigeminal pain (headache/migraine), and can worsen this disorder resulting in medication overuse headache and pain chronicity. Using a large scale peptidomic approach, our lab has recently identified pituitary adenylate cyclase activating polypeptide (PACAP) as a link between OIH and chronic trigeminal pain. The goal of these studies was to determine the effect of inhibition of PACAP PAC1 receptor in models of opioid-exacerbated trigeminal pain and aura; and to determine the expression of mu and delta opioid receptors, PAC1, and PACAP.

Methods: To model opioid exacerbated trigeminal pain, mice were injected daily with morphine (10 mg/kg) or vehicle for 11 days. On days 3,5.7.9. and 11 they also received a low dose of the known human migraine trigger nitroglycerin (NTG, 0.1 mg/kg) or vehicle. To model opioid exacerbated aura, mice were treated with vehicle or morphine twice daily for 4 days (20 mg/kg on days 1–3, 40 mg/kg on day 4), and on day 5 they were tested for cortical spreading depression (CSD), a model of migraine aura. Animals were anesthetized, the skull was thinned, CSD was induced by dripping KCl onto the dura, and both optical intrinsic imaging and local field potentials were recorded. We tested the effect of the PAC1 inhibitor, M65 (0.1 mg/kg), in these models. RNAScope in situ hybridization was used to determine expression of opioid receptors, PAC1, and PACAP in brain and peripheral regions. Significance was determined with 3-way ANOVA for behavioral experiments, unpaired *t* test and 2-way ANOVA for CSD recordings, and 1 way ANOVA for RNAScope analysis.

Results: Only mice treated with morphine and low-dose NTG combined developed chronic trigeminal allodynia ($p < 0.001$ effect of time and treatment, $n = 18$/group). Treatment with M65 on day 12 (24h after the final morphine/NTG injection) significantly reversed this hypersensitivity ($p < 0.001$, $n = 9$/group). Pre-treatment with escalating doses of morphine significantly increased the number of CSD events ($p < 0.05$, $n = 8–9$/group). In a separate experiment PAC1 inhibition decreased this exacerbation of CSD by morphine ($p < 0.01$ OIH-veh vs OIH-M65, $n = 8–12$/group). MOR and PACAP were co-expressed in the trigeminal ganglia, whereas MOR and PAC1 receptor showed high co-expression in the trigeminal nucleus caudalis. There was significant co-expression between MOR+/PACAP+ and MOR+/PAC1+ cells in the cortex. In contrast, the delta opioid receptor was generally co-expressed with PAC1 receptor in all brain regions analyzed ($p < 0.05$, $n = 4$/group).

Conclusions: These results suggest that one way that opioids facilitate the transition from episodic to chronic trigeminal pain is through induction of the PACAPergic system. PAC1 receptor antagonists may be particularly beneficial for the treatment of opioid induced hyperalgesia and medication overuse headache induced by opioids. Future experiments will focus on identifying the distinct opioid-PACAPergic circuits that regulate trigeminal pain and OIH.

Disclosure: Amgen: Grant (Self)

Study Group

33. Impact of the COVID-19 Pandemic on the Pipeline and Workforce of Physician-Scientists

M. Mercedes Perez-Rodriguez*, Matthew Kayser, Antonia New, Mark Chavez, Erika Forbes, Rene Kahn, David Kupfer, Eduardo Leonardo, Pauline Lund, Evan Noch, Carolyn Rodriguez, Alan Schatzberg, Christopher Williams

Study Group Summary: The COVID-19 pandemic has severely affected research worldwide. Physician-scientists are a particularly vulnerable group, and they are experiencing the negative effects of the COVID-19 crisis across all levels of training and career stages.

Some examples of the negative impact of COVID-19 include lab closures, disruptions in MD and MSTP training programs (e.g., clinical clerkship cancellations and delays, inability to continue PhD work), redeployment to clinical departments of faculty, residents and fellows (including those in research tracks), hiring freezes, and pay cuts.

While some institutions have offered resources or assistance to these trainees to support them during this difficult time, the COVID-19 crisis will likely have a far-reaching impact on the physician-scientist pipeline and workforce.

The overall goal of this study group is to foster a discussion around challenges related to the COVID-19 crisis and strategies to preserve the pipeline of physician-scientists. Specifically, we will discuss the following:

1. Disruption of MSTP and MD training programs, research track residencies and fellowships due to COVID-19.
2. Impact of redeployment of faculty, residents and fellows to clinical departments.
3. Career delays and tenure clock extensions due to productivity loss related to COVID-19.
4. Recruitment and retention strategies for physician-scientists in the setting of hiring freezes and financial challenges across academic institutions. This is particularly important for physician-scientists as the NIH-funded trainee stipends and faculty salary caps for physician-scientists are almost always supplemented by the institution to achieve competitive compensation.
5. Changes in research scope and focus related to COVID-19, including scaling up of remote research activities and switch to COVID-19-related research.
6. Challenges and strategies for scientific conferences, research dissemination, and networking and career development events.
7. Safe, socially distant methods to continue research and training during the COVID-19 pandemic.
8. Institutional and federal initiatives to minimize the impact of COVID-19 on physician scientists training and career development

Disclosures: Neurocrine Biosciences, AI Cure, Takeda/Millennium Pharmaceuticals: Grant (Self); Neurocrine Biosciences:

Advisory Board (Self); Merck: Grant (Self); American Foundation of Suicide Prevention: Consultant (Self)

Panel

34. Hardship, Hard Drugs and Soft Circuits: How Sex and Adversity Interact to Influence Reward Circuitry and Addiction

34.1 Adversity and Trauma Effects on Neural Stress and Craving Responses: Sex Differences and Influence on Relapse in Addiction

Rajita Sinha

Yale University, New Haven, Connecticut, United States

Background: Cumulative adversity and early life trauma significantly influence addiction in a sex-specific manner, but how adversity influences addiction risk and relapse at the neural circuit level is not clear. Chronic drug abuse disrupts neural stress responses and increases drug craving, but sex differences in these effects are unclear. This presentation will highlight novel data on how sex and drug use history interact to influence adversity effects on addiction risk and relapse.

Methods: Treatment engaged and abstinent inpatient men and women with current substance use disorders (SUD: men = 46, women = 26), outpatient treatment-entering men and women with

Alcohol Use Disorder (AUD: men = 52, women = 32), socially drinking men and women (SD: men: 50; women: 55) were studied using structured diagnostic and Cumulative Adversity (including trauma) Interview (CAI) and drug use and relapse data collection with urine and daily self-reports. Subjects also participated in a multimodal functional magnetic resonance imaging (fMRI) session utilizing a novel brief sustained stress, alcohol and neutral cue procedure using visual stimuli presented in a repeated block design. Subjective rating of stress, arousal and alcohol craving were assessed during the fMRI scan.

Results: Adversity (CAI) scores were significantly higher in AUD relative to SD ($F(1,186) = 8.43$, $p < 0.0003$), including the trauma subscale ($F = 5.7$, $p < 0.004$), as were in-scanner ratings of stress ($F = 7.97$, $p < 0.0004$), arousal ($F = 8.24$, $p < 0.0003$) and craving ($F = 29.11$, $p < 0.000001$). In the fMRI, women vs. men reported higher stress ($t = 4.03$, $p < 0.0001$) and arousal ($t = 4.01$, $p < 0.0001$). CAI scores ($F = 13.4$, $p < .00001$) and trauma ($F = 11.81$, $p < .00001$) predicted higher stress ($F = 4.29$, $p < .02$) and arousal ($F = 4.32$, $p < 0.02$) in men ($p < 0.05$), but not women in both AUD and SD groups. Life trauma interacted with sex to significantly predict craving only in AUD, and higher trauma predicted higher stress- and cue- craving in men only ($F = 3.7$, $p < 0.03$). Using whole brain voxel based analyses (whole brain threshold: $p < 0.001$, cluster corr: $p < 0.05$), CAI significantly predicted stress and alcohol cue neural responses, with blunted activation in ventromedial, dorsolateral prefrontal and anterior cingulate cortex (VmPFC, DLPFC, ACC), and greater ventral and dorsal striatum (VS/DS) activation in AUD women, but greater limbic (amygdala, hippocampus, insula) and DS responses in AUD men. Responses were higher in VmPFC, premotor cortex and VS in SD men, whereas responses in salience regions (OFC, VS, DS) occurred in SD women. In women SUD, greater drug use and relapse post-inpatient treatment were predicted prospectively by blunted VmPFC/rACC activation to stress; greater DS cue responses were predictive in men

Conclusions: Our findings indicate significant sex-dependent influences of adversity and trauma on both neural and subjective responses to cues which promote craving and relapse, and suggests specific consideration of these influences in developing new prevention and treatment targets for addiction going forth.

Disclosure: Nothing to disclose.

34.2 Sex-Dependent Consequences of Early Life Adversity on Reward Circuit Development Promote Opioid Addiction Vulnerability

Sophia Levis

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

Background: The epidemic of opioid use, addiction, and overdose is an ongoing public health problem in the U.S. Whereas opioid over-prescription and genetic predispositions play a in this epidemic, these factors alone cannot explain the exponential rise in opioid abuse. Individuals who have experienced early life adversity (ELA) such as poverty or abuse are overrepresented among opioid abusers, and addicted women report experiencing such adversity at a disproportionate rate, suggesting that they may be uniquely vulnerable to this risk factor. The mechanisms by which ELA confers increased vulnerability to opioid addiction are still poorly understood, and in humans, it is impossible to dissociate ELA from other co-existing vulnerabilities. Therefore, we employ a naturalistic ELA model in rats to examine the sex-specific impacts of ELA on reward and stress circuit development, and concomitant opioid drug seeking behaviors.

Methods: ELA was modeled in male and female Sprague Dawley rats by limiting bedding and nesting from postnatal day 2-9, whereas controls were housed in standard cages. As adults, rats were tested on intravenous heroin self-administration, extinction, and reinstatement, as well as in a measure of microeconomic demand elasticity for opioids. We assessed ELA-induced changes in reward- and stress-circuit nodes which might convey susceptibility to the addictive effects of opioids using two approaches(a) the activation of brain regions (nodes) of the circuit by heroin in naïve and in opioid-experienced animals. (b) gene expression changes in the same nodes/regions for a panel of reward- and stress-related molecules All experiments included 7+ rats per sex and rearing condition, and data were analyzed using *t* test or ANOVA with Bonferroni post-hocs.

Results: Results: ELA robustly increases opioid addiction-like behavior in female, but not male rats. Compared to controls, ELA females persisted in seeking heroin longer during extinction (e.g., number of days until extinction criterion $t12 = 2.509$; $P = 0.0274$; $n = 7$/group), showed greater cue-induced (ELA vs. CTL active lever presses: $t24 = 4.676$; $P = 0.0002$; $n = 7$/group) and heroin-primed reinstatement (ELA vs. CTL active lever presses: $t24 = 4.676$; $P = 0.0002$; $n = 7$/group), and showed less elastic opioid demand, similar to a phenotype seen in humans addicted to opioids ($t28 = 2.630$; $P = 0.0137$; $n = 15$/group). In contrast, ELA males did not exhibit opioid addiction-like behaviors. Preliminary findings suggest that ELA-induced opioid vulnerability in females may involve altered heroin-induced activity in nucleus accumbens, especially in a dorsomedial accumbens shell opioid "hedonic hotspot." Initial results also suggest sex-dependent changes in pleasure- and stress- related molecule expression in several of the nodes of the reward and stress circuits.

Conclusions: ELA produces a sex-specific pro-opioid addiction phenotype in female rats, which may be caused by disrupted neurodevelopment of reward and stress circuits, leading to aberrant neural responses to opioid drugs.

Disclosure: Nothing to disclose.

34.3 Early Life Adversity Accelerates Alcohol Intake Escalation

in Mice: Sex Specificity and Potential Role of Parasubthalamic Corticotropin Releasing Factor

Candice Contet

The Scripps Research Institute, La Jolla, California, United States

Background: Vulnerability to alcohol use disorders resulting from childhood adversity is well documented in humans. We sought to identify experimental conditions whereby early life stress facilitates excessive alcohol drinking in mice, which would enable further investigation of the underlying neurobiological mechanisms. Polymorphisms in the gene encoding corticotropin-releasing factor (CRF) type 1 receptor modulate the effect of childhood adversity on adolescent and adult alcohol use, supporting a role for the dysregulation of CRF signaling. Accordingly, we examined the potential role of a little-studied source of CRF in the brain, the parasubthalamic nucleus (PSTN), in the control of alcohol consumption

Methods: Early life adversity (ELA) was produced by rearing male and female C57BL/6J mouse pups in cages containing limited bedding and nesting materials, which results in erratic maternal care. As adults, mice underwent alcohol drinking during limited-access two-bottle choice (2BC) sessions, combined or not with chronic intermittent ethanol (CIE) vapor inhalation to induce alcohol dependence ($n = 5–8$ per sex x stress x alcohol condition). To study the role of PSTN CRF neurons in alcohol intake escalation, chemogenetic manipulations were conducted in Crh-IRES-Cre mice ($n = 6–8$) and virally mediated RNA interference was used to knock down CRF expression in C57BL/6J mice ($n = 10–12$).

Results: In males, ELA did not impact baseline alcohol consumption, but instead accelerated ethanol intake escalation upon CIE exposure (after 4 rounds of CIE/2BC:ELA, $p = 0.048$; control, $p = 0.69$). In contrast, females were insensitive to both ELA and CIE, a striking sex difference. In ELA but not control males, withdrawal from CIE reduced open arm exploration in the elevated plus-maze ($p = 0.039$) and increased immobility in the tail suspension test ($p = 0.012$). Other effects of CIE withdrawal were similar regardless of history in males, such as increased digging ($p = 0.008$) and lowered mechanical nociceptive thresholds ($p = 0.02$); whereas object recognition grooming and corticosterone levels were unaffected by CIE. Testing potential mechanisms, we found that chemogenetic stimulation of PSTN CRF neurons increased ethanol intake and digging activity in both males and females (all $p < 0.01$), while their chemogenetic inhibition reduced baseline and CIE-escalated alcohol drinking ($p = 0.0005$). Finally, CRF knockdown in PSTN delayed escalation of alcohol intake in CIE-exposed males (after 3 rounds of CIE/2BC: control, $p = 0.008$; knockdown, $p = 0.27$) and accelerated recovery from mechanical hyperalgesia during CIE withdrawal (3 days vs. 13 days: control, $p = 0.77$; knockdown, $p = 0.012$).

Conclusions: ELA accelerates the transition from moderate to excessive alcohol drinking and exacerbates emotional-like dysfunction during withdrawal in C57BL/6J males, but not females. Increased CRF expression and neuronal activity in the PSTN may be responsible for this ELA effect. The lack of effect of ELA in CIE-exposed females may represent a resilient phenotype, contrasting with the vulnerable phenotype of males. Clearly, the sex-dependent nature of ELA and other types of adversity on alcohol consumption and the role of PSTN CRF neurons in this process are worthy of further mechanistic investigation

Disclosure: Nothing to disclose.

34.4 Sex-Dependent Dopamine System Plasticity Following Adversity- Implications for Mental Illness

Abstract not included.

Study Group

35. The Mega Impact of Microaggressions: Insights and Practical Solutions

Gretchen Neigh*, Maria Oquendo, VJ Periyakoil, Catherine Njathi-Ori, Christine Moutier, Gretchen Neigh

Study Group Summary: While overt sexism, heterosexism, racism, and classism still exist, the incidence in professional settings has decreased. This is in large part due to the creation and implementation of very clearly stated policies regarding commitments to equality by universities, medical centers, and professional organizations. However, existing policies do not address micro-level interactional practices of inclusion and exclusion. While the individual contribution of any one microaggression may seem trivial, the cumulative effect is to convey a message of who belongs and who does not. Often, the undercurrent of microaggressions, fueled by everyday inequalities, is perpetuated by individuals engaging in mindless, unknowing, and habitual patterns in which they do not recognize the cost of their behaviors to the underrepresented groups with whom they interact. The negative effects of cumulative microaggressions have been documented across levels of scientific training and academic ranks. This Study Group will bring to the forefront the difficulties created by microaggressions and highlight how implicit bias can further perpetuate the cycle. In addition, particular emphasis will be placed on corrective actions that bystanders and victims can take to break the cycle. Dr. VJ Periyakoil will discuss the ways in which microaggressions can manifest in the setting of academic medicine, highlighting the ways in which privilege is invisible to those that have it, but bias and discrimination are readily apparent to those that experience it. Dr. Catherine Njathi-Ori will introduce specific actions that individuals can take to address microaggressions in the moment, focusing on using a non-accusatory manner with opportunities for both sides to reflect on the potential effects of statements and actions. Dr. Christine Moutier will then provide insight to communication mechanisms by which it is possible to change the culture through a coordinated process of climate awareness, identification, and coaching. The goal of this session is to first raise awareness and second to provide easy to remember and implementable strategies. Following the brief participant presentations, discussion will focus on types of micro-resistance which have been established to be effective and scenarios that provide illustration of how to implement such strategies. At the conclusion of this session, participants should be able to: (1) recognize microaggressions, (2) appreciate the cost of microaggressions, and (3) productively respond to microaggressions when either the direct target or a bystander. Through a reduction of microaggressions, a more inclusive culture can be established which will promote retention of a diverse workforce in the realm of academic medicine and research.

Disclosure: Nothing to disclose.

Panel

36. Role for Non-Neuronal Cells in the Brain in Neuropsychiatric Disorders

36.1 Choroid Plexus Regulates Septal Inputs to Habenula to Control Nicotine Craving

Paul Kenny

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

Background: Relapse rates are remarkably high in tobacco smokers attempting to quit, particularly during early stages of withdrawal when craving is most intense, yet mechanisms of nicotine craving and relapse remain poorly understood. The septum is a core component of the limbic system strategically positioned between the hippocampus, basal forebrain and basal ganglia to regulate memory, mood and motivation. Abstinent smokers show deficits in these same processes, suggesting that septal dysfunction could contribute to relapse vulnerability

Methods: Slice and in vivo electrophysiological recordings coupled with optogenetics, and functional magnetic resonance imaging (fMRI), were used to determine the actions of nicotine on septal activity. Cre-dependent DREADDs and diphtheria toxin expression were used to manipulate septo-habenula activity. Single cell RNA sequencing (scRNAseq) was used to characterize nicotine-induced transcriptional plasticity in the posterior septum. Intracranial injections were used to deliver compounds to targeted brain regions.

Results: We found that neurons in the septal triangular nucleus (TNS) oscillate at theta frequency, an activity pattern that optimally enhances TNS-derived excitatory signaling in the habenula. Nicotine decreased the activity of TNS neurons, the power of theta oscillations, and TNS-derived excitatory transmission in the habenula. Doses of nicotine sufficient to disrupt TNS-habenula communication triggered intense craving-like nicotine-seeking responses during the early stages of withdrawal in rats and mice. Chemogenetic stimulation of the TNS-habenula circuit attenuated withdrawal-induced nicotine-seeking, whereas lesion or chemogenetic inhibition of this circuit exacerbated this craving response. Using scRNAseq, we were surprised to find that nicotine had modest effects on gene expression in TNS neurons. By contrast, nicotine induced robust transcriptional plasticity in non-neuronal cells, most robustly in ventricular ependymal and choroid plexus (ChP) cells that surround the TNS and other periventricular components of the posterior septum. In particular, insulin-like growth factor 2 (IGF2) was downregulated in ChP cells, and local infusion of IGF2 into TNS abolished withdrawal-induced nicotine seeking.

Conclusions: These findings suggest that perturbation of septal communication with habenula plays a key role in nicotine craving and vulnerability to relapse. Remarkably, nicotine disrupts the septo-habenula circuit by decreasing levels of IGF2 released by the choroid plexus, which serves as a trophic factor for septal neurons. These findings suggest that the choroid plexus may play a previously unrecognized role in regulating drug crazing and likely other complex behaviors.

Disclosure: Eolas Therapeutics: Stock / Equity (Self); Takeda: Advisory Board, Grant (Self); AstraZeneca: Patent (Self); Eli Lilly: Grant (Self)

36.2 Sex-Specific Adaptations of the Blood-Brain Barrier Promote Vulnerability to Social Stress and Depression

Caroline Menard

Université Laval, Quebec City, Canada

Background: Major depressive disorder (MDD) will affect 20% of individuals and is now considered the leading cause of disabilities worldwide. Prevalence, symptoms, and treatment of depression all point toward major sex differences. Most studies explored biological mechanisms underlying MDD exclusively in males which may explain high rate of relapse and treatment resistance. This lack of efficacy also suggests that neuron-centric traditional treatments do not address important causal biological factors. We reported that chronic social defeat stress (CSDS) induces blood-brain barrier (BBB) leakiness through loss of tight junction protein claudin-5 (cldn5) in the nucleus accumbens (NAc), a mood regulation center, of male mice leading to passage of circulating inflammatory mediators into the brain and establishment of depression-like behaviors. Here we investigated if stress-induced loss of BBB integrity is occurring in a sex- and region-specific manner which could explain differences in MDD symptomatology.

Methods: Social defeat has been extensively studied in humans as higher prevalence of mood disorders and suicide attempts have been reported in victims of bullying. In rodents, repeated exposure to CSDS through physical encounter with a larger aggressive mouse induces a depression-like phenotype characterized by anhedonia (loss of pleasure), social avoidance, etc. Following CSDS a subpopulation of mice does not develop depressive behaviors and is considered resilient, allowing us to study not only the mechanisms of depression but also biological adaptations promoting resilience to chronic stress. We combined this behavioral paradigm to molecular, morphological, and functional studies and discovered sex-specific BBB alterations induced by chronic stress exposure.

Results: After 10-day CSDS, cldn5 gene expression is unchanged in the NAc of stress-susceptible females but decreased in the prefrontal cortex (PFC) (one-way ANOVA, $^{**}p = 0.0055$), a brain region regulating decision making and social behaviors, when compared to unstressed controls and resilient mice. Immunostaining confirmed a reduction of cldn5 proteins in the female PFC (one-way ANOVA, $^{***}p = 0.0005$) with protein levels correlated with social interactions (Pearson's correlation, $^{**}p = 0.0073$). Importantly, this sexual dimorphism of stress-induced neurovascular adaptations was confirmed in postmortem human brain samples from depressed individuals (one-way ANOVA, $^{*}p = 0.0290$), adding translational value to our findings. We are currently performing viral-mediated functional manipulation to confirm the causality of cldn5 loss in the female PFC in the establishment of depressive behaviors and possibly sex-specific MDD symptomatology.

Conclusions: Our recent data suggest that stress-induced neurovascular changes are not occurring in the same brain regions in stressed females. Traditional preclinical studies targeting males only represent an important caveat to the development of efficient treatment and may be associated with higher prevalence of depression in women. It is imperative to study mental health as whole-body maladaptive responses and not only neuron-centric and consider sex differences to develop innovative therapeutic strategies. The BBB has been a major challenge to overcome in the development of novel efficient antidepressant drugs and the possibility to modulate brain emotional responses by acting directly on the neurovasculature is intriguing and appealing.

Disclosure: Nothing to disclose.

36.3 Maturation of Hippocampal Perineuronal Nets Underlies the Ontogeny of Memory Specificity

Paul Frankland

University of Toronto/Hospital for Sick Children, Toronto, Canada

Background: Compared to memories in adults, memories in infants and young children are more prone to forgetting over time (i.e., infantile amnesia; IA) and expressed less specifically (i.e., infantile generalization; IG). While biological mechanisms have been identified for IA, the neurobiology of IG remains unknown. We hypothesized that the maturation of perineuronal nets (PNNs), late-developing extracellular matrix structures known to inhibit juvenile plasticity in sensory systems, may regulate memory specificity across development. We demonstrate here that adult-like precision of hippocampus-dependent memories emerges

during the fourth postnatal week (i.e., between P20 and P24) in parallel with the peak expression of PNN proteins and rapid accumulation of WFA+ PNNs around parvalbumin-expressing (PV+) interneurons in the CA1 subfield of the hippocampus.

Methods: In order to test whether there is a causal relationship between CA1 PNN development and memory precision, we tested (1) whether interventions that degrade CA1 PNNs, or inhibit PV+ interneuron activity, induce juvenile-like generalization in adult mice, and (2) whether interventions that accelerate CA1 PNN maturation, or activate PV+ interneurons, lead to the precocial expression of specific memories in juvenile mice. In order to manipulate PNNs, developed novel viral tools targeting hyaluronan and proteoglycan link protein 1 (HAPLN1) to interfere with or accelerate PNN maturation in adult and infant mice, respectively. Memory precision was assessed using contextual fear conditioning, and related, paradigms.

Results: Overexpression of a dominant-negative HAPLN1 in CA1 de-stabilized PNNs and re-instated infant-like generalization in adult mice. Conversely, overexpression of wild-type HAPLN1 in CA1 accelerated PNN growth and induced adult-like memory specificity in infant mice. Similar results were obtained using pharmacological manipulations of PNNs in CA1. Moreover, we establish that early-life experiences shape the trajectory of PNN maturation in the hippocampus and subsequently, the development of memory specificity. We find that adverse experiences in a model of early-life stress delay PNN and memory development such that the neural and behavioral phenotypes observed in juvenile mice resemble those of infants. In contrast, rearing pups in enriched environments during the first weeks of life led to precocial PNN growth in CA1 and memory specificity. Lastly, to address the neural circuit mechanism by which PNNs promote memory specificity, we used chemogenetics to directly manipulate the activity of PV+ cells in CA1, thus mimicking the effects of PNN manipulations on PV+ interneuron physiology. Our preliminary data show that inhibition of PV+ neurons in CA1 of adult mice during learning is sufficient re-instate infant like generalization without affecting the density of PNNs. Ongoing experiments are examining whether increasing PV+ interneuron activity promotes memory specificity in adult and infant mice lacking PNNs. Together, our findings support a role for PNNs in the development of the hippocampal memory system.

Conclusions: These data establish that the maturation of PNNs in the hippocampus, which is influenced by early-life experiences and regulates inhibition in CA1 circuits, underlies the switch from memory generalization to memory specificity during childhood.

Disclosure: Nothing to disclose.

36.4 Long-Lasting Structural and Functional Effects of Cocaine Self-Administration on Accumbens Astrocytes Contribute to the Incubation of Cocaine Craving

Kathryn Reissner

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

Background: Accumulating evidence indicates a panoply of effects of cocaine on rat nucleus accumbens astrocytes. These include impaired glutamate transport and regulation of glutamate homeostasis, and decreased structural features and synaptic colocalization. Intriguingly, these adaptations are either only observed after a period of abstinence or extinction, or are exacerbated by a prolonged period of extinction or abstinence. This raises the hypothesis that impairments in astrocyte structure and function may mediate increased propensity to relapse associated with protracted abstinence, known as incubation. Accordingly, this study is designed to measure abstinence-dependent functional impairments in astrocytes, and to test the hypothesis that stimulation of astrocytes can normalize these impairments and inhibit the incubation of cocaine craving.

Methods: For behavioral testing, Sprague-Dawley rats received intrajugular catheters and intra-accumbens microinjections of either GfaABC1D-hM3Dq(Gq)mCherry or Gfap104-mCherry. Rats were trained in cocaine self-administration (6h/day) for 10 days, followed by 45 days of forced abstinence. Rats then received 3 systemic injections of either 1xPBS or CNO in PBS (Tocris cat no 4926) at 150, 90, and 30 min prior to extinction testing. Pilot studies revealed that 3 injections yielded more significant effects than two.

For Ca2+ imaging studies, we developed a novel AAV designed to express genetically encoded calcium indicator CaMPARI2 under control of the astrocyte-specific GfaABC1D promoter. Photoconversion of CaMPARI2 from green to red is achieved by calcium stimulation in the presence of UV light in acute brain slices or in vivo.

Results: Colocalization analysis indicates decreased synaptic interaction with astrocytes following cocaine self-administration and 45 days of abstinence (WD 45) (expt 1). We then tested whether DREADD stimulation could inhibit cocaine seeking at this time point. Indeed, we observed a significant reduction in lever pressing at WD45 associated with CNO stimulation of astrocytes (expt 2). Ongoing studies are designed to extend behavioral investigations to determine whether DREADD stimulation associated with decreased lever pressing also normalizes the decreased synaptic colocalization of accumbens astrocytes observed at this time point in cocaine-abstinent rats. Lastly, we are using novel AAV5GFAP-CaMPARI2 to assess the effects of cocaine on stimulated calcium signals in rat astrocytes at WD45, and whether this is influenced by DREADD stimulation.

Conclusions: These studies are designed with the overarching goal to extend our appreciation for how drug use affects astrocyte structure and function, and how these adaptations influence motivation for cocaine. Optimization of novel AAV5GFAP-CaMPARI2 allows us to interrogate Ca2+ responsiveness of accumbens astrocytes following abstinence from cocaine self-administration, and whether astrocyte DREADD stimulation reverses the decreased synaptic colocalization and/or Ca2+ responses in accumbens astrocytes. These studies further inform how DREADD stimulation of rat accumbens astrocytes can reduce drug seeking associated with the incubation of cocaine craving, and the translational potential of accumbens astrocytes in substance use disorders.

Disclosure: Nothing to disclose.

Panel

37. Insight Into Sex Differences in Psychiatric Syndromes From Transcriptomic and Genomic Analyses

37.1 Sex- and Cell Type-Specific Role for Long Noncoding RNAs in Depression Susceptibility and Resilience

Orna Issler

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

Background: Depression is a common, chronic and debilitating disorder. Women are twice as likely to suffer from depression as men, yet the molecular mechanisms contributing to this sex difference remain poorly understood. Long non-coding RNAs (lncRNAs) are a recently discovered class of regulatory transcripts, which represent a substantial portion of the human genome. We explored the sex-specific role of lncRNAs in depression.

Methods: We bioinformatically analyzed a genome-wide profile of RNAs in six brain regions from both male and female postmortem depressed and control human subjects (n = 9–13 per group). We identified specific target lncRNAs with potential sex-specific roles in depression. Using viral tools, we expressed these lncRNAs in the prefrontal cortex (PFC) of mice from both sexes in a cell-type specific manner. Phenotyping included behavioral tests for anxiety- and depression-like behavior (n = 7–13 per group), slice electrophysiological recording (n = 3–8 per group) and RNA-sequencing (RNA-seq) (n = 3–5 per group). In parallel, we tested the effects of manipulation of target sex-specific depression-related lncRNAs in human-derived neuronal progenitor cells (NPCs) using RNA-seq (n = 3 per sex) and Chromatin Isolation by RNA Purification (ChIRP) assays. Finally, we tested the levels of circulating lncRNAs in the blood using qPCR from depressed subjects before and after treatment with ketamine.

Results: In recently published work (Issler et al., Neuron, 2020), we found that lncRNAs represent about one-third of the differentially expressed genes in depressed subjects compared to controls, and displayed complex region- and sex-specific patterns of regulation. We identified the neuronal lncRNA, LINC00473, as downregulated in PFC of depressed females, but not males. Several lines of evidence in mouse models, NPCs, and cultured neuron-like cells support the view that LINC00473 represents a natural, pro-resilient factor in the female brain the loss of which contributes to anxiety and depression.

In unpublished work, we identified an additional key lncRNA, RP11-298D21.1, which is upregulated in the PFC of depressed females only. RP11-298D21.1 is expressed in oligodendrocytes in addition to neurons. We utilized a cell type-specific viral expression system to test the role of this lncRNA in the two cell types and found that expressing it in neurons promotes behavioral stress susceptibility, an effect seen in female mice only. Such neuronal overexpression also promoted transcriptional changes that resemble the depressed human female transcriptome only. Expressing RP11-298D21.1 in oligodendrocytes also promotes behavioral stress susceptibility in female mice only, and we are currently testing its effects on gene expression and myelin sheath thickness. Finally, we identified that circulating RP11-298D21.1 levels are higher in depressed woman, not men, and that these levels are normalized following ketamine treatment.

Conclusions: Together, this work establishes that lncRNAs play a key role in depression and contribute to observed sex differences in this disorder. We identified key targets: LINC00473 as a female pro-resilient lncRNA with reduced expression in PFC of depressed females, and RP11-298D21.2 as a female pro-depressive lncRNA induced in depressed females. Our dataset identifies numerous other lncRNAs that are abnormally expressed in depression and now warrant further investigation.

Disclosure: Nothing to disclose.

37.2 Sex-Specific Effects of PTSD on Human Brain Gene Expression

Matthew Girgenti

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

Background: Posttraumatic stress disorder (PTSD) affects approximately 8% of the general population, with higher rates in extreme stress groups, including combat veterans or victims of sexual assault. Despite extensive study of the neurobiological correlates of PTSD, little is known about its molecular determinants. We report the first trasncriptome-wide analysis of gene expression changes in postmortem brain of a large cohort of PTSD subjects. Our results demonstrate extensive transcriptional changes in 4 discrete prefrontal cortex (PFC) subregions of PTSD subjects, with both combined sex as well as unique, sex-specific molecular signatures.

Methods: RNA sequencing (RNA-seq) was used to characterize the differentially expressed genes (DEGs) of four PFC subregions (dorsolateral PFC (dlPFC; BA9/46)), medial orbitofrontal cortex (OFC; BA11), dorsal anterior cingulate cortex (dACC; BA24), and subgenual prefrontal cortex (sgPFC; BA25) from postmortem tissue of subjects diagnosed with PTSD, a matched non-PTSD psychiatric control (major depressive disorder(MDD)) and matched neurotypical controls. For each brain region, we examined 52 PTSD subjects (26 males, 26 females), 45 MDD (18 females, 27 males), and 46 controls (20 females, 26 males). We evaluated the transcriptomic organization of the PTSD PFC by Weighted Gene Correlation Network Analysis (WGCNA). We integrated genotype data from the largest PTSD GWAS (n=186,689) with human prefrontal cortical eQTLs to perform the first PTSD transcriptome-wide association study (TWAS).

Results: We observed large numbers of DEGs across all regions (FDR <0.05). Additionally, significant differential regulation of individual exons and exon-exon junction usage were observed (FDR<0.05). We explored the possibility of sex-specific gene expression changes in the PTSD brain and identified marked differences between males and females. We identified a transcript co-expression module containing a GABA-signaling network that included interneuron genes SST and ELFN1 as significant key drivers for the module. TWAS allowed us to match DEGs with cis-regulated expression changes to genetic risk loci for PTSD, linking heritability with specific illness effects on the transcriptome. Seven cortical TWAS hits were also significant DEGs including the key driver ELFN1. We also examined convergent and divergent molecular signatures of PTSD with other psychiatric disorders. Consistent with recent genetic studies of PTSD, the global transcriptomic signatures for PTSD more closely resemble schizophrenia and bipolar disorder but not major depression.

Conclusions: These results demonstrate sex-specific transcriptomic signatures across the PTSD PFC. Sex-specific, co-expression modules with only modest homology between females and males were also identified. One female-specific module includes the key driver DEG ELFN1 that was also identified as one the top cortical TWAS hits linking observed expression changes from illness with genetic heritability. These results indicate that sex plays an important role in the molecular pathology of PTSD.

Disclosure: Nothing to disclose.

37.3 Sex and Disease Differences in Circadian Rhythms of Gene Expression in the Human Brain

Abstract not included.

37.4 Sex Differences in Shared and Non-Shared Genetic Architecture Among Mood and Psychotic Disorders: Genomics as a Spotlight for Transcriptomics

Jill Goldstein

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

Background: Sex differences are pervasive in psychiatric disorders, including major depressive disorder (MDD), schizophrenia (SCZ), and bipolar disorder (BIP). Previous studies of cross-disorder genetic risk identified by the PGC and shared sex differences in brain abnormalities suggest possible shared sex-dependent genetic risk. Here, we capitalized on a unique opportunity to utilize cohorts from the PGC and iPSYCH (N = 232,405) to assess

interactions between sex and genetic risk of MDD, SCZ and BIP individually and shared across disorders.

Methods: Samples included 65,537 cases (30,917 SCZ, 18,988 BIP, 15,732 MDD) and 93,699 controls (65%, 42%, 32%, 49% male, respectively) (96.7% European; 3.3% East Asian, from SCZ only). Samples were filtered for relatedness and duplications at Pi-Hat>0.1; related samples were resolved by excluding one. SNPs with <0.6 imputation quality and/or <0.01 minor allele frequency were excluded. Cohort-specific logistic regression analyses were performed, with main effect and SNP-by-sex interaction terms for each SNP (10 ancestry covariates). Inverse variance-weighted meta-analysis with genomic control was performed within or across disorders, plus across disorders using ASSET in R. Brain expression and eQTL databases were used to evaluate functional relevance of significant loci. MAGMA pathway analysis tested for enrichment of genotype–by–sex (GxS) interaction in CNS, immune, synapse, and histone methylation pathways specifically, and hypothesis-free in MSigDB pathways.

Results: SNP associations showed substantial overlap across sex. However, across disorders genome-wide significant SNP-by-sex interaction was detected for a locus encompassing the NKAIN2 gene (rs117780815; $p = 3.2 \times 10-8$) that interacts with sodium/potassium-transporting ATPase enzymes important for neuronal excitability. Three additional loci showed evidence ($p < 1 \times 10-6$) for cross-disorder GxS interaction (rs7302529, $p = 1.6 \times 10-7$; rs73033497, $p = 8.8 \times 10-7$; rs7914279, $p = 6.4 \times 10-7$). Gene-based analyses across disorders identified GxS interaction ($p = 9.6 \times 10-7$) with transcriptional inhibitor SLTM. Most significant SNP in SCZ was in the MOCOS gene (rs11665282; $p = 1.1 \times 10-7$), implicating vascular endothelial cells. Secondary analysis of SCZ PGC detected near-significant interaction (rs13265509; $p = 1.1 \times 10-7$) in a locus containing IDO2, a kynurenine pathway enzyme with immunoregulatory functions previously implicated in SCZ, BIP, and MDD. Pathway enrichment analysis detected significant GxS of calcium channel complexes in SCZ and genes regulating vascular endothelial growth factor (VEGF) receptor signaling in MDD (both pFDR<0.05).

Conclusions: In the largest genome-wide GxS analysis of mood and psychotic disorders to date, there was substantial genetic overlap between the sexes. However, significant sex-dependent effects were enriched for genes related to neuronal development, immune and vascular functions across and within SCZ, BIP, and MDD at the variant, gene, and pathway enrichment levels. These analyses will contribute to understanding sex-influenced brain mechanisms through further transcriptomics and proteomics research.

Disclosure: Cala Health: Advisory Board (Self); Cala Health: Stock / Equity (Self)

Panel

38. Variability in Neurodevelopmental Trajectories in Childhood and Adolescence is Associated With Diverse Affective, Cognitive, and Behavioral Outcomes Through Adulthood

38.1 Youth Exposed to Maltreatment Show Age-Related Alterations in Hippocampal-Frontoamygdala Function During Extinction Recall

Dylan Gee

Yale University, New Haven, Connecticut, United States

Background: Exposure to childhood trauma is a major risk factor for psychiatric disorders. Delineating the neurodevelopmental mechanisms linking early-life trauma to psychopathology is critical for the early identification of risk and optimizing interventions to promote resilience following trauma. Youth exposed to maltreatment show alterations in fear conditioning and related hippocampal-frontoamygdala circuitry, yet much remains unknown about extinction and extinction recall, processes that are central to discriminating threat from safety following trauma.

Methods: Children and adolescents ages 8–17 years old ($N = 161$; 77 female, 84 male) with ($n = 87$) or without ($n = 71$) exposure to maltreatment (physical abuse, sexual abuse, domestic violence) completed a fear conditioning and extinction task, which used blue and yellow bells as conditioned stimuli (CS+/CS−) and an aversive alarm noise as the unconditioned stimulus, across two separate days. At the first session participants completed acquisition and extinction during measurement of skin conductance response. Within one week, participants completed extinction recall and re-extinction during fMRI scanning. Analyses focused on the amygdala, hippocampus, and subgenual anterior cingulate cortex (sgACC) as a priori regions of interest defined using the Harvard Oxford probabilistic atlas. Given hypotheses about the impact of maltreatment on hippocampal and frontoamygdala development, we tested whether maltreatment was associated with altered age-related patterns of activation during extinction recall and re-extinction.

Results: Youth with maltreatment exposure showed altered age-related patterns of activation in the amygdala (maltreatment x age interaction: $F(1,125) = 5.40$, $p = 0.022$) and hippocampus (maltreatment x age interaction: $F(1,125) = 4.58$, $p = 0.034$) during extinction recall. Specifically, whereas youth without a history of maltreatment showed stable activation with age, youth with maltreatment exposure showed age-related increases in amygdala and hippocampus activation to the CS- (vs. CS+) during recall. Findings also revealed an interaction between maltreatment, age, and sex ($F(1,125) = 4.86$, $p = 0.029$), such that females (but not males) with maltreatment exposure showed an altered age-related pattern of sgACC activation during re-extinction. Whereas females without a history of maltreatment showed an age-related decrease in sgACC activation to the CS+ (vs. CS-) during re-extinction, females with maltreatment exposure did not show an age-related change in sgACC activation.

Conclusions: Childhood maltreatment may alter the typical developmental course of fear extinction and related brain activation. In particular, youth exposed to maltreatment showed exaggerated amygdala and hippocampus activation to safety with age, suggesting a possible failure to discriminate between threat and safety in an age-expected manner at the neural level. Altered hippocampal and frontoamygdala function may underlie difficulties learning or integrating environmental cues signaling safety that could increase risk for maltreatment-related psychopathology during development.

Disclosure: Nothing to disclose.

38.2 Longitudinal Functional Brain Correlates of Persistence and Remission in Pediatric PTSD

Ryan Herringa

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

Background: Previous studies have identified functional brain abnormalities in pediatric PTSD suggesting altered frontoparietal-subcortical function during emotion processing. However, little is known about functional brain substrates underlying recovery versus persistence of PTSD in the context of the developing brain. Here, we examine functional neural correlates of PTSD persistence and remission over time in youth while undergoing a threat processing task.

Methods: This naturalistic longitudinal study included 23 youth with PTSD and 28 typically developing (TD) youth group-matched for sex and age at baseline and one-year follow-up. Average age at baseline was 14 years old, with a range of 8–18 years. Of the PTSD group, 9 remitted at one-year while 14 had persistent PTSD. At each time, youth completed an emotional appraisal task in which they viewed threat and neutral images during fMRI. Voxelwise linear mixed effects analyses of activation were conducted using a 3 group*time*valence design, covaried for sex and baseline age, with whole-brain or small volume (amygdala/hippocampus) correction pFWE<.05. Based on activation findings, a subsequent analysis of right hippocampal functional connectivity was performed under a similar group model with whole brain correction at pFWE < 0.05.

Results: Youth PTSD remitters had lower maltreatment exposure and depression and anxiety severity at baseline compared to nonremitters ($p < 0.05$), but did not differ on baseline PTSD severity, IQ, or interval treatment ($p > 0.3$). Brain activation analyses revealed a group*time*valence interaction in the right hippocampus. Here, both TD youth and PTSD remitters showed evidence of decreased activation to threat vs. neutral over time, while youth with persistent PTSD showed increased activation to threat vs. neutral over time ($p = 0.03$). In a group*-time interaction, remitters also showed increased activation in left occipital cortex (V4, BA 18) over time. Next, functional connectivity analysis using the right hippocampal seed showed significant group*time interactions with the right ($p = 0.01$) and left ($p = 0.02$) posterior parietal cortex (BA 39/40). Here, TD youth and remitters showed increased or stable connectivity over time, while youth with persistent PTSD showed decreased connectivity over time. Finally, PTSD remitters also demonstrated increased hippocampus connectivity over time with left V4 and middle temporal gyrus (BA 22) compared to TD and persistent PTSD.

Conclusions: To our knowledge, these findings represent the first report of functional brain substrates of persistence and remission in pediatric PTSD, suggesting unique processes to both. Notably, activation and connectivity in the hippocampal-parietal mnemonic network appears to diverge markedly over time in youth with persistent versus remitted PTSD. Increased hippocampal activation to threat and reduced connectivity in the hippocampal-parietal network over time may contribute to heightened threat memory encoding and persistence of PTSD. While further study in expanded samples and correlation with emotional memory encoding will be needed to explore these possibilities, these findings suggest potential biomarkers and treatment targets which could be utilized to advance treatment of youth suffering from PTSD.

Disclosure: Nothing to disclose.

38.3 Elucidating Attention Neural Markers as Predictors of Future Vulnerability to Mood Disorders Across Infancy, Adolescence and Young Adulthood a Multimodal Approach

Michele Bertocci

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: In ongoing studies, using multimodal neuroimaging, we are examining prefrontal cortical-striatal-amygdala emotional regulation circuitry in infants, and youth at familial risk for mood disorders, to identify neural predictors of future risk for mood disorders from infancy to adolescence. Our goal is to determine the extent to which functional and structural abnormalities in neural regions and white matter tracts supporting directed attention during emotional regulation can predict future emotional regulation behaviors and affective symptoms.

Methods: We used measurements of white matter quantitative anisotropy and volume derived using tractography from the cingulum, uncinate fasciculus and forceps minor along with laboratory tasks and penalized regression, in 3-month old infants to prospectively predict emotional regulation capacity at 9-months. Using negative binomial regression, we examined associations among prefrontal-cortical-striatal-amygdala emotional regulation circuitry activity during a task measuring emotional regulation, a 2-back-working memory-emotional face distracter versus 0-back with no face distracter tasks, in familial at-risk 9 to 17 year-olds and: mood and anxiety symptom changes over 4 years after scan.

Results: To date, in $n = 20$, 3-month old infants (65–126 days; 6 female), lower uncinate fasciculus and cingulum quantitative anisotropy, greater uncinate fasciculus volume, age, being female, lower SES and higher maternal postnatal depression predicted negative emotionality at 9-months (253–331 days). Lower cingulum and uncinate fasciculus quantitative anisotropy and greater uncinate fasciculus volume were associated with greater negative emotionality at 9-months. Infant gender, age, socioeconomic status and maternal postnatal depression accounted for 69.9%, and neural measures 17.3%, of 9-month negative emotionality variance.

In ongoing data analyses in $n = 15$ at-risk youth with a parent with Bipolar Disorder (6 female; 14.14 (2.34) years) and $n = 19$ at-risk youth with a parent with another psychiatric disorder (11 female; 13.78 (2.22) years), lower right midcingulate cortical deactivation and baseline subsyndromal depression severity, predicted greater increase in subsyndromal depression after scan 1 $Chisq(3) = 8.44$, $p = 0.0377$. Right midcingulate cortex activity $Chisq = 6.19$, $p = 0.0128$, rate ratio = 3.49 (95%CI: 1.30 −9.34); for every 1 SD decrease in right mid cingulate deactivation, there was a 3.49 increase in syndromal depression scores after controlling for other covariates.

Conclusions: We show abnormal infant white matter structural integrity in tracts connecting cortical regions important for emotional regulation predict greater future negative emotionality in infants. In parallel, the relationship between lower deactivation in a mid cingulate cortical region implicated in error monitoring during an emotional working memory task and greater future depression severity in at-risk adolescents suggests that elevated monitoring of distracting error monitoring information during the task might interfere with cognitive function in everyday life, and predispose to depression. Together, findings from both studies indicate white matter and cingulate cortical activity during emotional regulation are potential objective markers of future mood disorder vulnerability in infants and youth at familial risk for mood disorders.

Disclosure: Nothing to disclose.

38.4 Variable Neurobehavioral Outcomes in Youth at Familial Risk for Mood Disorders

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

Background: Youth at familial risk for mood disorders have aberrant emotion and reward regulatory networks. However, the differential inter- and intra-network connectivity that lead to variability in resilient or emergent mood symptom outcomes is poorly understood.

Methods: We examined activation and connectivity profiles (resting state and emotion processing/reward tasks) that distinguish healthy offspring of parents with bipolar disorder (BD-risk, $n = 43$), healthy offspring of parents with major depressive disorder (MDD-risk, $n = 46$), and healthy controls (HCLs, $n = 50$). Regression modeling was used to examine whether differential

activation and connectivity predicted psychopathology. Baseline connectivity among 24 HCLs, 23 high-risk who developed psychopathology (CVT), and 27 high-risk who remained resilient (RES) at an average of 3-year follow-up were also compared.

Results: Intrinsic connectivity between amygdala, striatum and medial frontal cortex distinguished BD-Risk from MDD-Risk and HCLs ($p < 0.001$ voxel-level and $p < 0.05$ cluster-level, FDR-correction), and predicted mood/anxiety disorders at follow-up (ß = −11.0, $p = 0.026$). BD-risk youth had reduced putamen activation and decreased left putamen connectivity with the left anterior cingulate cortex and right posterior cingulate cortex (PCC) while processing positive emotions compared to MDD-risk and HCLs ($Z > 2.3$; $p < 0.001$). Decreased left putamen-right PCC connectivity was associated with a higher risk of conversion at follow-up in BD-risk (Hazard Ratio = 8.28, $p < 0.01$). BD-risk youth exhibited reduced lingual gyrus and occipital fusiform cortex activation while anticipating monetary gain and increased superior temporal gyrus activation while anticipating monetary loss compared to MDD-risk and HCLs. RES youth had reduced activation in the right supramarginal gyrus during processing of happy facial expressions, and in the right precuneus and inferior frontal gyrus during processing of fearful facial expressions compared to CVTs ($Z > 2.3$; $p < 0.05$, corrected). In RES youth, stronger baseline IPL-precuneus connectivity correlated with more prosocial behaviors on the strengths and difficulties questionnaire ($r(16) = 0.654$, $p = 0.004$) and improved global functioning ($r(18) = 0.580$, $p = 0.005$) at follow-up.

Conclusions: Striatolimbic intrinsic connectivity may be an early and specific predictor of psychopathology in high-risk youth. In contrast, inferior parietal, caudate, and precuneus activation and connectivity during emotion processing may represent markers of resilience and thus useful targets for novel intervention approaches for at-risk youth.

Disclosure: NIH, Brain and Behavior Research Foundation, PCori, Johnson & Johnson, Stanford Department of Psychiatry: Grant (Self); Sunovion, Google X, Limbix: Advisory Board (Self); American Psychiatric Association Publishing: Royalties (Self)

Panel

39. Adolescence as a Heterogeneous Stage With Discrete Windows for Vulnerability and Treatment in Anxiety and Drug Abuse: Translational Perspectives

39.1 The Vulnerability to Stimulant Drugs in Adolescence is Sexually Dimorphic

Cecilia Flores

McGill University, Montreal, Canada

Background: Initiating drug use in adolescence associates with increased lifetime risk to psychopathology, including drug abuse. This is thought to result from the impact that drugs could have on the developmental events that are ongoing in the medial prefrontal cortex (mPFC) during this time, most notably alterations to the gradual ingrowth of dopamine (DA) axons, which is controlled by the Netrin-1/DCC guidance cue pathway. Our work in male mice shows that amphetamine (AMPH) in adolescence downregulates the Netrin-1/DCC system, via microRNA (miRNA) mechanisms, inducing aberrant mPFC mesocortical DA connectivity and deficits in behavioral inhibition in adulthood. These effects are restricted to early adolescent period, as they are no longer observed upon mid-adolescent or adult exposure. Whether AMPH in adolescence induces similar changes in female mice remains unknown.

Methods: Male and female C57BL6 mice were treated with AMPH (4 mg/kg, i.p.) or saline in early adolescence (postnatal day 22 to 31) or mid-adolescence (postnatal day 35 to 45), 1 injection every other day. This AMPH regimen induces conditioned place preference in males and females and reaches peak drug plasma levels similar to those seen in recreational use in humans (Cuesta et al., Addiction Biology, 2019). Via quantitative analysis of gene and protein expression, Dcc mRNA and Netrin-1 levels in pre- and postsynaptic components of DA neurons we measured, 1 week after treatment termination. In the same samples levels of miR-218, a repressor of Dcc expression, were assessed. The extent and organization of mPFC DA connectivity and behavioral inhibition in adulthood was investigated using unbiased stereology methods and the Go/No-Go task

Results: In contrast to males, AMPH in early adolescence does not downregulate Dcc in DA neurons or Netrin-1 in the nucleus accumbens in female mice. In turn, females are insensitive to the deleterious effects of early adolescent AMPH on adult mPFC DA innervation and cognitive deficits observed in males. This sexually dimorphic effects appear to result from male-specific upregulation of miR-218 by AMPH at this early age.

In mid-adolescence, male mice are no longer sensitive to the effects of AMPH on miR-218, Dcc and Netrin-1 expression and are protected against disruption of mesocortical DA development and behavioral deficits. Instead, mid-adolescent females are now sensitive to AMPH-induced upregulation of miR-218 and therefore downregulation of Dcc mRNA expression in DA neurons. Notably, mid-adolescent females also show upregulation of Netrin-1 expression in the nucleus accumbens, presumably offsetting the effects of reduced Dcc expression. Indeed, mid-adolescent females continue to be resilient against disruption of mPFC DA development and cognitive deficits

Conclusions: There are striking sex differences in sensitivity to the impact of AMPH on the Netrin-1/DCC pathway and consequently on mPFC and cognitive development. The female brain appears to be "actively" protected against deleterious effects across the adolescent period. This resilience seems to involve a lack of drug-induced regulation of Dcc expression or compensatory changes in Netrin-1 levels, depending on the adolescent stage. The disruption of the maturing brain by drugs of abuse in adolescence may be sex-specific as well as the molecular mechanisms underlying drug-induced vulnerability to developing specific psychiatric conditions.

Disclosure: Nothing to disclose.

39.2 Safety Signal Induced Elevations in Ventral Hippocampal Activity During Adolescence Can Improve Extinction Learning

Heidi Meyer

Weill Cornell Medicine, New York, New York, United States

Background: A peak in diagnoses for anxiety disorders occurs during adolescence and earlier onset of psychiatric symptoms is associated with increased symptom severity. Making matters worse, conventional behavioral treatments based on principles of fear extinction have limited long-term efficacy for a notable percentage of the adolescent patient population. Thus, generating a framework for clinical treatments that integrates an understanding of the typical and atypical development of fear circuitry and behavior is crucial to enhancing both the immediate and long-term benefits of treatment during adolescence. To address this, my research investigates processes underlying the acquisition and application of safety signal learning, a form of fear inhibition with high clinical relevance.

Methods: Adolescent (postnatal day, P29) and adult (P70) mice underwent discriminative conditioning during which they were

repeatedly presented with fear cues (a tone paired with a footshock) and safety cues (a second tone, no footshock). After acquiring an explicit "safety signal" with conditioned inhibitor properties, mice underwent extinction with a safety signal intermixed (n = 15 Adults/16 Adolescents), presented simultaneously (n = 13/15) or absent (n = 15/15). Rates of extinction and the retention of extinction gains 2 weeks later were quantified. To investigate how the brain uses safety signals to inhibit fear, in-vivo calcium imaging (fiber photometry) was used to record neural activity in prelimbic-projecting ventral hippocampal neurons (VH-PL) alongside behavior (n = 14/7).

Results: Rates of extinction differed by group in adolescents ($p < 0.001$; driven by delayed extinction following intermixed safety exposure) but not adults. Two weeks later, extinction retention differed by group in both adolescents ($p < 0.001$) and adults ($p < 0.03$). While exposure to intermixed safety cues during extinction improved retention in both ages, the magnitude of retained extinction was significantly stronger for adolescents ($p < 0.01$) than adults ($p < 0.07$). Simultaneous fear and safety pairings during extinction did not impact retention for either age. Fiber photometry recordings revealed increases in VH-PL activity across extinction trials, but no age differences. Conversely, while VH-PL also exhibited higher responding to safety cues than fear cues in both ages, the elevation was greater for adolescents ($p < 0.04$).

Conclusions: These findings inform the parameters for when and how safety signals can be used effectively. Notably, mice in the 'intermixed' groups are exposed to half as many fear cues as mice in other groups. Yet, while constant inhibition of fear via a safety signal is not beneficial, alternating presentations of fear and safety cues during extinction can augment fear regulation. This research also addresses a gap in the literature regarding the mechanisms underlying adolescent fear inhibition. Replicating our recently published findings in adults (Meyer et al. PNAS, 2019), using safety signals to inhibit fear during adolescence similarly recruits VH-PL neurons. However, safety signal induced elevations in VH-PL activity apparent specifically during adolescence may confer an advantage for using safety signals to facilitate extinction. Together, these findings have great translational potential for optimizing treatments for pediatric anxiety disorders.

Disclosure: Nothing to disclose.

39.3 Attenuated Pavlovian Bias Supports Better Reinforcement Learning of Approach and Inhibitory Action in Adolescence When Learning From Reward, but Not Loss or Threat

Juliet Davidow

Northeastern University, Boston, Massachusetts, United States

Background: Adolescence is a time when newfound autonomy exercised during novel experiences can present opposing options for how to act when signals in the environment conflict with strongly felt urges, e.g. studying instead of streaming on a Monday night. Operant learning systems support building associations between cues (Monday) that signal what actions (study) lead to desired outcomes (good grades). But, "Pavlovian bias" describes evolutionary links between particular actions and outcomes (approach-positive, avoid-negative) facilitating learning, while hindering learning of contingency violations (e.g. avoid-positive). Recent work in adults and patients posit that the effect of Pavlovian bias on operant learning relates to psychiatric disorders that emerge during adolescence, but this has not been studied in adolescence. We used novel computational models to assess the influence of Pavlovian bias on learning from monetary gains (positive), monetary losses (negative), and loud aversive noise (threat) in typically developing humans (N = 218, 11–22 years old).

Methods: Two cross-sectional studies investigate operant learning under Pavlovian bias using a probabilistic reinforcement learning task. Study 1 (N = 94, Female (F) = 48, Male (M) = 46) assessed learning differences in approach and inhibitory behavior from positive vs. negative outcomes, and Study 2 (N = 124, F = 81, M = 40, Nonbinary (NB) = 3) from threat. We fit a hierarchical reinforcement learning model to estimate the contributions of Learning Rate, Pavlovian Bias, and other psychology processes hypothesized to give rise to decisions. We use mixed-effect logistic regression to investigate for linear and non-linear age-related patterns in observed decision behaviors and estimated parameters from the computational model.

Results: Results showed a significant non-linear effect of age for approach-positive ($\chi = 0.64$, SE = 0.18, $p = 0.010$) and for avoid-positive ($\chi = 0.79$, SE = 0.07, $p = 0.001$) conditions, suggesting that when learning to act optimally from monetary gains for both approach and inhibitory action-responses, mid-to-late adolescents learned to a greater extent than early-adolescents and young-adults. In contrast, learning from monetary loss and threat was captured by a linear improvement with increasing age. Computational model results suggest that better learning in mid-to-late adolescents emerged from reduction of Pavlovian biases ($\chi = 0.22$, SE = 0.07, $p = .003$).

Conclusions: When learning from positive outcomes, mid-to-late adolescents outperform younger and older individuals, in part from reduced interference of Pavlovian bias. But when learning from threat or negative outcomes, better performance was related to increasing age, paralleled by decreases in Pavlovian bias. Collectively, this suggests different mechanisms for decision processes supported by learning from positive vs. negative or threatening outcomes with implications for clinical interventions and treatments.

Disclosure: Nothing to disclose.

39.4 Treatment-Related Increase in Harm Avoidance in Adolescents With Co-Occurring Substance Use and Psychiatric Diagnoses

Marisa Silveri

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

Background: Adolescence is a developmental period characterized by rapid changes in the brain, placing teens at high risk for initiation and escalation of substance use. Many adolescents seeking substance use treatment have co-occurring psychiatric diagnoses, including high rates of anxiety disorders. However, little research has investigated the co-occurrence of anxiety and substance use disorders. Specifically, little is known about how anxiety may present differently in adolescents with and without substance use disorders and whether anxiety symptoms are differentially affected by treatment in these groups. This study described sought to examine changes across domains of anxiety symptoms (physical symptoms, social anxiety, harm avoidance and separation anxiety) in adolescents with and without substance use disorders.

Methods: Participants were adolescents (N = 486, ages 13–19, mean age = 17.0 ± 1.4 years) enrolled in a two-week residential treatment program completed the Multidimensional Anxiety Scale for Children (MASC) at intake and discharge. The MASC measure domains of physical symptoms, social anxiety, harm avoidance, and separation anxiety. Psychiatric and substance use diagnoses were established using the MINI-KID Structured Clinical Interview, administered at intake. Participants were stratified into those with a substance use disorder (SUD+) and those without (SUD-).

Results: A repeated-measures ANOVA showed an overall reduction in total anxiety, physical symptoms, social anxiety, and separation anxiety scores at discharge compared to baseline ($p < 0.001$), but an increase in harm avoidance ($p < 0.005$). The SUD- group reported a significant decrease in total anxiety ($p < 0.005$) and separation anxiety ($p < 0.005$) from baseline to discharge, whereas the SUD+ group reported decreases in all MASC domains ($p < 0.001$) except harm avoidance, which was significantly higher at discharge compared to baseline ($p < 0.005$). An independent samples ANOVA showed a significant substance use by symptom change interaction, with substance users exhibiting greater social and total anxiety reductions and greater increases in harm avoidance after treatment ($p < 0.005$). There were no gender differences in harm avoidance scores and no correlations with age. At time of intake, lower harm avoidance scores were correlated with greater impulse control and emotion regulation difficulties, higher impulsivity measures (including negative urgency, positive urgency, and sensation seeking), and more frequent risky behaviors (substance use and rule breaking).

Conclusions: These results indicate that acute residential treatment for adolescents with dual diagnoses, co-occurring SUD and psychiatric diagnoses, differentially influences anxiety levels and reduction of symptoms by discharge. Namely, SUD+ adolescents show increased harm avoidance after treatment. Further research should investigate whether increased harm avoidance after treatment is related to less risk-taking and lower rates of relapse in substance-using adolescents. Identifying heterogeneity in anxiety across youth with and without substance use disorders can help to identify treatment needs, including the potential need for personalized treatment.

Disclosure: Nothing to disclose.

Study Group

40. Examining Social Behavior in a Time of Social Distancing

Larry Young*, Amanda Kentner, Brian Trainor, Alexa Veenema, Rosemary Bagot, Sam Golden, Carmen Sandi, Joshua Neunuebel

Study Group Summary: During this time of social distancing, our intuitive understanding of an instinct or 'need' that drives us to be together has become even more apparent. Undeniably, social behaviors are fundamental to the survival of animals, including humans. Guided by social interactions, such as those that are affiliative, aggressive, and cooperative in nature, individuals gain reproductive opportunities and develop the parental behaviors that propagate our species. Moreover, social attachments are critical to healthy psychological development and well-being. Interruptions in the ability to engage in these behaviors, whether mediated by neural circuits, environmental experiences (e.g. social isolation), or a combination of both, can lead to impairments in mental health and species typical functioning. Given the ongoing situation, it is expected that emerging research questions will focus on the implications of COVID19 on mental health, as measured in part by the establishment and maintenance of social behaviors in our new world. In the laboratory, a diversity of social behaviors and model organisms are used to understand the neurobiology of neuropsychiatric and neurodevelopmental disorders. While investigators use different models/tasks with distinct advantages/drawbacks, there are very few opportunities to consult and establish a consensus on the appropriate design, implementation, and translational perspectives for this work. During this session, we will review several sociability metrics and discuss their strengths and weaknesses, in addition to the translation use/purpose of each, and the underlying neural circuits engaged. Some metrics to be covered include social interaction, social preference, social discrimination, social propinquity and vigilance, aggression, play behavior, reproductive behaviors, social communication (including USVs), social odor discrimination, social rejection/aversion and social defeat. The presenters will address the importance of standardizing the general designs within and across laboratories. Major questions to be addressed include: What can social behavior tests teach us regarding the causes and treatments of mental disorders and their underlying neural circuits? Are these sociability measures well validated? Do each of these tests apply across species, age, and sex? We will also explore considerations of the social dynamics between focal animals and their conspecifics in addition to the appropriateness of methodological designs. Our study group discussions will facilitate the development of best practices for standardized social behavior metrics to improve the rigor, reproducibility, and relevance of this work to mental health research and our new socially distanced reality.

Disclosure: Nothing to disclose.

Panel

41. Insights Into Mechanisms Regulating Pathological Alcohol Consumption Arising From Studies of Reward-Related Neuroplasticity

41.1 Investigating the Development of Compulsive Alcohol Drinking From First Exposure to Compulsion Using Longitudinal Calcium Imaging

Kay Tye

Salk Institute for Biological Studies, La Jolla, California, United States

Background: The majority of Americans are exposed to alcohol, yet only 15–20% of U.S. adults have an alcohol use disorder (AUD) 1,2. Why are some individuals capable of moderate alcohol consumption while others become compulsive drinkers? AUD is a chronic relapsing mental disorder, in which alcohol use becomes compulsive, even in the face of negative consequences, and is the leading risk factor for disability and premature death among people between 15 and 49 (3,4).

Plasticity in the medial prefrontal cortex (mPFC) has long been thought to mediate pathological drug-seeking behaviors, including compulsive alcohol drinking. Humans at high-risk for AUDs display aberrant PFC activity, even prior to their first exposure to alcohol (5–7) and activity in this region can predict the severity of future substance abuse (8). However, we still need a mechanistic understanding of what biological underpinnings lead to this correlation (9).

Methods: We used cellular resolution calcium imaging to assess the activity of mPFC-dPAG projectors ($n = 300–400$ neurons per day, N=animals, across 14 days) during a novel Pavlovian alcohol conditioning task. Using this task, we tested for compulsive alcohol consumption before and after two weeks of binge alcohol exposure. Binge drinking produced wide individual differences in compulsive alcohol drinking, whereby approximately 50% of animals continued to consume high levels of alcohol, despite adulteration with the bitter tastant quinine, after binge exposure.

By using advanced computational techniques for visualizing the ensemble dynamics across many days we can now visualize the progression and pinpoint changes in response profiles across single neurons and population ensembles of PFC-PAG projecting neurons over multiple days from the initial exposure to alcohol through the development of compulsive drinking behaviors.

Results: Surprisingly, the magnitude of inhibitory responses in mPFC-dPAG projectors during the first alcohol drinking session

was positively correlated with the expression of binge drinking-induced compulsive alcohol consumption three weeks after the initial exposure session ($N = 8$, $p < 0.01$). To test causality of mPFC-dPAG inhibition during drinking in inducing compulsive drinking, we used a closed-loop optogenetic approach to photoinhibit mPFC-dPAG projectors during licking for alcohol with quinine. Inhibition of this pathway conferred a compulsive phenotype, even in animals with minimal prior alcohol exposure ($N = 13$, $p < 0.001$), but did not alter licking for water. Conversely, we found that closed-loop optogenetic activation of mPFC-dPAG projectors paired with licking for alcohol decreased consumption ($N = 16$, $p < 0.01$), demonstrating that activation of this pathway is sufficient to recapitulate some of the effects of quinine on alcohol intake.

Conclusions: Together, our results support a model where inhibition or activation of the mPFC-dPAG circuit attributes positive or negative valence to unconditioned stimuli, respectively. The activity of mPFC-dPAG neurons can decode the animal's behavior (drink or no drink) on the subsequent trial, using a support vector machine classifier. Binge drinking reduces the sensitivity of this cortico-brainstem pathway to punishment in the context of alcohol-drinking, thereby driving compulsive drinking in a subset of animals.

Disclosure: Nothing to disclose.

41.2 Molecular and Neurodevelopmental Mechanisms Contributing to Drug-Taking Behaviors

Stephanie Groman

Yale University, New Haven, Connecticut, United States

Background: Although most people will use a drug of abuse within their lifetime, only a subset of individuals will ever develop an addiction. This suggests that some individuals are more susceptible to developing an addiction than others. We hypothesized that decision making could serve as a biomarker for assessing addiction risk in individuals and could provide a unique approach for interrogating the neurobiological determinants of addiction susceptibility.

Methods: Decision-making was assessed in separate cohorts of male rats ($N = 70$) and mice ($N = 10$) using a probabilistic reversal learning (PRL) task before and after cocaine ($N = 50$), methamphetamine ($N = 20$), or alcohol ($N=10$) self-administration. Choice behavior in the PRL task was analyzed with a reinforcement-learning model to quantify select reinforcement-learning processes and identify predictors of drug-taking behavior. Individual differences in positive-outcome updating was found to predict drug-taking behaviors and we hypothesized that these differences would be linked to neurodevelopment changes that occur during adolescence. To investigate this, decision making was assessed in male and female rats ($N=60$) across adolescent development and into adulthood (PND30 – PND150) and proteomic analyses performed in ventral striatum, amygdala, and orbitofrontal cortex tissue to identify the signaling mechanisms that underlie age-related changes in decision making.

Results: Individual differences in the ability of adult rodents to make adaptive choices in PRL task prior to drug self-administration predicted drug-taking behaviors, such that rodents with poorer performance in the PRL task had greater drug-taking behaviors than those with better performance. The computational analyses revealed that individual differences in value updating based on positive-outcome, but not negative-outcome predicted drug-taking behaviors across different drug classes. We hypothesized that differences in positive-outcome updating observed in adult animals might emerge during adolescence and found evidence supporting this hypothesis. Notably, the rate of improvement in positive value-updating during adolescence predicted individual differences in adulthood, suggesting that the molecular changes that occur during this developmental period may be involved in addiction susceptibility. Proteomic analyses found that adolescent-related improvements in decision-making were associated with signaling pathways known to be involved in the stabilization of neural circuits.

Conclusions: By combining sophisticated behavioral and computational approaches across critical developmental periods with discovery-based proteomic analyses, our translational framework provides novel insights into the reinforcement-learning and neurodevelopmental mechanisms mediating addiction susceptibility and identifies a unique target for preventing addiction.

Disclosure: Nothing to disclose.

41.3 Molecular Mechanisms Regulating Craving, Reward Circuit Dysfunction, and Alcohol Consumption

Abstract not included.

41.4 Interference With the Reconsolidation of Alcohol-Related Reward Memories as a Novel Method to Reduce Drinking

Ravi Das

University College London, London, United Kingdom

Background: Maladaptive reward memories (MRMs) are involved in the development and maintenance of harmful alcohol use. The process of memory reconsolidation - where stored memories become briefly labile upon retrieval – may offer a means to disrupt MRMs and prevent relapse. Rodent research has shown that drug-seeking behavior can be abolished by N-methyl D-aspartate (NMDA) receptor antagonists following reactivation of conditioned drug seeking memories. Human work has suggested that reconsolidation interference may be achievable through purely behavioral means. However, reliable means for pharmacologically weakening and behaviorally rewriting MRMs in humans remain elusive.

Methods: A randomized experimental study was used to to test whether ketamine could weaken alcohol MRMs and reduce drinking in a reconsolidation-dependent manner. Ninety hazardous/harmful alcohol drinkers were randomized to one of three groups: (1) MRM Retrieval + ketamine (active group) (2) MRM Retrieval + placebo (placebo control) (3) No MRM retrieval +ketamine (memory reactivation control). Retrieval groups underwent a brief alcohol memory reactivation procedure intended to destabilize alcohol MRMs. Outcomes were acute alcohol reactivity pre-post manipulation and drinking levels up to 9 months following manipulation.

Results: The MRM+retrieval (active) group evidenced highly significant reductions in reward responses to alcohol from pre to post manipulation (alcohol wanting, anticipation and enjoyment). They also showed significantly greater reductions in short and long-term drinking levels, compared to ketamine-alone or MRM retrieval-alone control groups. Blood concentrations of ketamine and its metabolites during the critical 'reconsolidation window' predicted beneficial changes only following MRM retrieval, indicating a reconsolidation-dependent mechanism for the observed effects.

Conclusions: This is the first demonstration that the NMDAR antagonist ketamine is able to disrupt MRMs in hazardous drinkers when administered immediately after MRM retrieval. Such disruption of MRMs produced a broad reduction in reward responses to alcohol and drinking, following a single, brief manipulation. This translation of therapeutic memory

reconsolidation manipulation in human heavy drinkers provides a key first step in developing new approaches to reducing harmful drinking.

Disclosure: Nothing to disclose.

Panel

42. Let the Brain Data Speak! Data-Driven Approaches to Characterizing Mental Illness

42.1 A Focus on the Homogeneous: Enhancing Sensitivity to Mental Illness and Brain Changes by Leveraging Homogeneity in Space, Time and Subjects in High Dimensional Brain Imaging Data

Vince Calhoun

Georgia State, Georgia Tech, Emory, Atlanta, Georgia, United States

Background: The use of brain imaging to study mental illness has shown to be a powerful tool to capture information on the underlying brain changes. However diagnostic heterogeneity is a major issue as the field struggles to learn from the brain imaging data. One important aspect which has not been well explored is the use of rich, high-dimensional brain data to guide us through this complex territory. We show that by focusing on more similar subsets of data, identified via advanced algorithmic strategies, we can facilitate an apples-to-apples comparison, enhance sensitivity to mental illness, and provide a framework for improved stratification.

Methods: We focus on several examples using multiple large N data sets of individuals on the psychosis and mood spectrum. Our first approach highlights a novel approach which identified 'statelets' or homogeneous temporal primitives of transient connectivity patterns in fMRI data. The second approach captures homogeneous subsets of individuals within data driven subspaces in multimodal brain imaging data. And finally, we show that we can leverage this information to refine grouping of individuals, essentially showing where the biological data is pushing against a pre-defined category.

Results: Results show that leveraging advanced 'clustering' like approaches to identify subsets of data which are more homogeneous within and between subjects groupings enhances our ability to capture neural data which is linked to unique patterns of symptoms. We can also capture new information about how mental illness impacts brain dynamics, for example showing that patients with schizophrenia show much shorter statelet behavior than do controls. And finally, we show that such strategies, perhaps counter-intuitively, enhance our sensitivity to uncover changes in brain that may inform our approach to nosology as well as prove useful targets for future treatment studies.

Conclusions: The brain imaging field has largely focused on group studies, or more recently on individual subject classification using existing categories. We show that a focus on identifying unique subsets of data and subjects which exhibit homogeneity can leverage the benefits of both approaches, increase sensitivity to unique clusters of symptoms, and help potentially refine our understanding of diagnostic categories.

Disclosure: Nothing to disclose.

42.2 Dynamic Functional Neural Connectivity Across the Psychiatric Spectrum: The Case of Autism and Schizophrenia

Abstract not included.

42.3 The Need for Decentralized Data-Driven Approaches in Markers of Symptom Severity

Jessica Turner

Georgia State University, Atlanta, Georgia, United States

Background: Within large-scale aggregation and analyses of neuroimaging data, the ENIGMA Consortium (Enhancing Neuroimaging Genetics through Meta-Analysis) has produced many findings in psychiatric imaging, and imaging genetics more broadly. These studies with tens of thousands of subjects' data involve large scale international collaboration, with combinations of methods including data aggregation for mega-analysis, and decentralized, distributed analyses for prospective meta-analyses without data sharing. The data-driven projects within ENIGMA, however, using multivariate or machine learning approaches, have required explicit imaging data transfer between the participating data sources and the analysis team, limiting participation and sample sizes. The COINSTAC project (Collaborative Informatics and Neuroimaging Suite Toolkit for Anonymous Computation) is a platform for decentralized analyses, which allows both prospective meta-analyses and data-driven algorithms to be implemented without requiring transferring data to a central repository. We are integrating ENIGMA and COINSTAC in a project examining negative symptoms and structural and functional measures in datasets including individuals with schizophrenia.

Methods: ENIGMA analyses to date have predominantly used regression models. We have a network of 8 sites and a total sample of ~700–900 participants (depending on the region analyzed), with structural imaging data and the Scale for the Assessment of Negative Symptoms (SANS) item-level data. The structural imaging data has been processed and segmented into standard cortical and subcortical regions; each dataset is analyzed locally, and summary data is returned to the central site for meta-analysis. Using COINSTAC, the analysis runs automatically across sites, rather than depending on individual sites to perform the analysis. As an initial analysis we use COINSTAC to perform an automated meta-analysis of negative symptom factor scores vs subcortical volumes and cortical thickness.

Results: Total symptom severity was related to lower nucleus accumbens volume ($r(912) = -0.09$, $p < 0.02$), and larger lateral ventricle volume ($r(948) = 0.065$, $p < 0.05$). Symptom factor scores, such as anhedonia and avolition, also showed significant associations with cortical thickness in frontal and temporal lobe regions. Using COINSTAC, the analysis these analyses can be conducted without the need to run statistical analysis code locally and sending results to a central location manually. The platform also allows for iterative statistical analyses employed in many data driven approaches such as ICA and machine learning.

Conclusions: These results indicate the feasibility of using COINSTAC as an automated platform for decentralized analyses. These meta-analyses, however, are model-driven, examining each brain region independently; they can be done in a single communication step among sites, unlike methods which using iterative processes across all the data sets to identify the patterns of gray matter differences. Balancing the growing need for multivariate and other iterative analyses in examining brain/disorder relationships with the need to let data stay where they are, this project is supporting the need for decentralized data-driven applications in clinical neuroimaging research.

Disclosure: Nothing to disclose.

42.4 Prediction of Short- and Long-Term Clinical Response in Initially Antipsychotic-Naïve Schizophrenia Patients Based on Multimodal Neuropsychiatric Data: A Machine Learning Framework

Bjørn Ebdrup

Center for Neuropsychiatric Schizophrenia Research, Mental Health Center Glostrup, University of Copenhagen, Glostrup, Denmark

Background: Approximately one-third of patients with schizophrenia fail to respond to antipsychotic treatment, but markers of clinical response are missing. Machine learning approaches have shown promise in prediction of clinical outcome, but the reproducibility of machine learning analyses in computational psychiatry is a growing concern.

This presentation will discuss a workflow aiming at reducing bias and overfitting in a multimodal neuropsychiatric dataset of antipsychotic-naïve, first-episode schizophrenia patients. As a novel feature in psychiatric research, simulated data were included in the design process. Moreover, analyses were conducted in two independent machine learning (ML) approaches, one based on a single algorithm and the other incorporating an ensemble of algorithms.

The aims were to (1) classify patients from controls, (2) predict short- and long-term treatment response, and (3) validate the methodological framework.

Methods: Data included 138 antipsychotic-naïve, first-episode schizophrenia patients (44 females /94 males), who had undergone assessments of psychopathology, cognition, electrophysiology, structural magnetic resonance imaging (MRI), before and after their first antipsychotic treatment period. Perinatal data and long-term outcome measures were obtained from Danish registers. Baseline diagnostic classification algorithms also included data from 151 matched controls (52 females/99 males).

Short-term treatment response in patients was defined as change in PANSS score after initial treatment. Long-term response was a binary outcome (good vs. poor) based on data from Danish registers.

Results: The two ML approaches both significantly classified patients from healthy controls. The single algorithm approach yielded a balanced accuracy (BACC) of 64.2% (confidence interval (CI): [51.7, 76.7]), and the ensemble approach yielded a BACC of 63.8% (CI: [50.8, 76.7]).

Post hoc analyses showed that the classification primarily was driven by the cognitive data.

Neither approach predicted short- nor long-term treatment response. Validation of the framework showed that choice of algorithm and parameter settings in the real data was successfully guided by results from the simulated data.

Conclusions: This rigorous modeling framework involving simulated data and two parallel ML approaches significantly discriminated patients from controls. However, the extensive neuropsychiatric data from antipsychotic-naïve patients were not predictive of treatment response. Validation of the framework showed that the ranking of the algorithms and parameter settings in the simulated was maintained in the real data.

Disclosure: Nothing to disclose.

Panel

43. C4, Microglia, Synaptic Pruning, Schizophrenia: Real or Lost in Translation?

43.1 The Synaptic Hypothesis of Schizophrenia and Effects of Drugs: An in Vivo Imaging Study and Complementary Preclinical Study

Abstract not included.

43.2 Synaptic Density in Schizophrenia and the Effect of Antipsychotic on Synaptic Density and Microglial Activation: Clues to Pathomechanism

Rajiv Radhakrishnan

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

Background: Decreased synaptic spine density has been the most consistently reported postmortem finding in schizophrenia (SCZ). Preclinical studies suggest that the decrease in synaptic spine density may be mediated by complement C4 and microglial activation. We examined in-vivo synaptic vesicle density in SCZ using positron emission tomography (PET) and [11C]UCB-J, a ligand that binds to synaptic vesicle protein, SV2A. Furthermore, to inform whether decreased synaptic density in SCZ is disease-related and/or an effect of antipsychotic medications, we examined the effects of chronic antipsychotic exposure on synaptic density (using [11C]UCB-J PET) and on microglial activation (using [11C]PBR28 PET) in non-human primates.

Methods: SCZ patients ($n = 13$) and age-matched healthy controls (HCs) ($n = 15$) underwent PET imaging using [11C]UCB-J and High Resolution Research Tomography (HRRT). [11C]UCB-J availability (binding potential, BPND) was estimated using a 1T model with centrum-semiovale as the reference region. In a within-subject preclinical study, NHPs ($n = 2$) NHPs underwent PET imaging with [11C]UCB-J and [11C]PBR28 before- and –after receiving 8 weeks of haloperidol decanoate (in a dose-escalation schedule to a target dose of 2mg/kg intramuscular, administered every 2 weeks).

Results: Relative to HCs, SCZ patients, showed lower synaptic density (BPND) with significant differences in the dorsolateral prefrontal cortex (DLPFC) (-9%, $p = 0.03$), anterior cingulate (-11%, $p = 0.003$), and hippocampus (-15%, $p = 0.002$). In the preclinical study in NHPs, following 8 weeks of haloperidol exposure, there was decrease in synaptic vesicle density (4–15% across regions; cingulate (-9%), hippocampus (-6%) and frontal cortex (-8%)) and a simultaneous increase in brain microglial activation (9–88% across regions; cingulate (40%), hippocampus (9%) and frontal cortex (35%)).

Conclusions: Consistent with the postmortem literature, synaptic vesicle density is lower in SCZ across several brain regions including the DLPFC, anterior cingulate, and hippocampus. Antipsychotic exposure in NHPs resulted in a reduction in synaptic density and a simultaneous increase in microglial activation.

Disclosure: Neurocrine Biosciences: Grant (Self)

43.3 Overexpression of Complement Component C4A Promotes Excessive Synaptic Loss and Alteration in Behavior

Yingying Zhang

Boston Children's Hospital, Boston, Massachusetts, United States

Background: The complement component 4 (C4) gene is linked to schizophrenia and synaptic refinement. In humans, greater expression of C4A in the brain, but not its closely related gene C4B, associates with increased schizophrenia risk. Schizophrenia involves impaired cognition, perception, and motivation and tends to become clinically apparent in late adolescence and early adulthood. This is concurrent with an excessive loss of gray matter and reduced dendritic spine density, which suggests that the loss of synaptic connections might contribute to the behavioral and cognitive deficits. Studies have shown that the classical complement cascade, including C1q, C3, and C4, is critical for regulating

developmental synapse elimination. Therefore, we hypothesize that increased C4A could cause schizophrenia by induce excessive synapse elimination via microglia engulfment of synaptic material during development.

Methods: Unlike humans, mice only have one single gene for C4. To properly model the function of C4A and C4B, we generated BAC transgenic mouse model that has variable numbers of copies of human C4A and C4B genes on a C4 deficient background. We performed eye-specific segregation assay in P10 hC4A/- and hC4A/A littermates (n=6). We compared synapse density in the pre-frontal cortex (PFC) of P60 hC4A/- and hC4A/A mice by quantifying SV2 and Homer1 colocalized puncta (4–8 fields of view per mouse from 8 hC4A/- and 9 hC4A/A mice). We did Golgi staining to measure the spine density of pyramidal neurons in the PFC of 6-month-old hC4A/- and hC4A/A mice (5–6 neurons per mouse, n=5 mice per genotype). We measured microglia engulfment of synaptic material in the frontal cortex of P40 hC4A/- and hC4A/A mice via flow cytometry ($n = 6$ hC4A/- and $n = 8$ hC4A/A). We performed mouse behavioral tests, including three-chambers test for social interaction, novelty-Y-maze test for short-term memory and light-dark box test for anxiety-like behavior (littermates from 2 cohorts were used, $n = 8$ WT, $n = 15$ C4-/-, and $n = 10$ C4-/-, $n = 16$ hC4A/-, $n = 10$–12 hC4A/A). For all studies, both sexes were used.

Results: Mice with higher C4A copy number had excessive synaptic pruning as measured by percentage overlap of ipsilateral and contralateral region in an eye-segregation analysis in P10 dLGN ($p < 0.01$ by Student's *t* test).Over expression of C4A also caused reduced synaptic density in the PFC of P60 mice ($p < 0.01$ by Mann–Whitney test) and reduced spine density of PFC pyramidal neurons from 6-month old mice ($p < 0.0001$by Mann–Whitney test). Microglia purified from the PFC of P40 hC4A/A mice engulfed more synaptic material compared to hC4A/- littermates ($p < 0.01$ by Mann–Whitney test). C4A over-expression also caused behavioral changes. Unlike other control groups, hC4A/A mice showed no preference for mouse vs. object in a three-chamber test, suggesting deficits in social interaction ($p < 0.05$ by Student's *t* test). Novelty-Y-maze test suggested hC4A/A mice had impaired short-term memory. hC4A/A mice also exhibited more anxiety-like behavior in light-dark box assay ($p < 0.01$ by One-way ANOVA with Tukey test).

Conclusions: Our study provide the first evidence that increasing C4A expression enhanced microglia uptake of synaptic particles, reduced synapse density and caused behavioral changes. Such changes were not observed in C4 deficient mice, suggesting that C4 is not needed, or has compensatory pathways for normal brain development. Therefore, the use of therapeutic strategies targeting C4 downregulation are likely not to affect developmental pruning.

Disclosure: Nothing to disclose.

43.4 Association Between Brain Complement Component 4 Expression and Brain Microglial Biomarker, Translocator Protein 18Kd (TSPO)

Romina Mizrahi

University of Toronto, Toronto, Canada

Background: Alterations in the immune system, particularly the major histocompatibility complex (MHC) have been implicated in the pathophysiology of schizophrenia. Complement 4 (C4A), a major component of the MHC, increased risk of schizophrenia and was elevated in post-mortem schizophrenia brains. C4 promotes synapse elimination by microglia in preclinical models, however, it is unknown whether this process is also present in humans. Given the role of complement proteins, particularly C4, in mediating microglial engulfment of synaptic material, it is possible that C4A expression relates to microglial activation.

Methods: We scanned with high resolution [18F]FEPPA positron emission tomography to quantify TSPO and obtained brain C4A brain expression (as per Sekar 2016) in 110 individuals, including 32 psychosis patients, 37 clinical high risk for psychosis (CHR) and 41 healthy controls.

Results: We show that higher brain C4A expression is associated with higher brain microglial marker, TSPO (n=110, main effect of C4A expression: $F(1,110) = 7.85$, $p = 0.006$). Further, brain C4A expression was significantly different between groups, lower in CHR as compared to healthy controls (main effect of group: $F(2,124) = 4.25$, $p = 0.016$). We also show a robust effect of sex on brain C4A expression, and an effect of both sex and cannabis on brain TSPO.

Conclusions: This study shows, for the first time, the relation between C4A expression and microglial function in living human brain, which supports the immune-activation/synaptic-elimination hypothesis of schizophrenia involving complement gene gain of function and microglia-driven synaptic pruning.

Disclosure: Nothing to disclose.

Study Group

44. From Computation to Clinic: Identifying and Overcoming Barriers to Clinical Translation of Computational Models of Cognition and Affect

Sarah Yip*, Deanna Barch, Henry Chase, Shelly Flagel, Quentin Huys, Anna Konova, Read Montague, Martin Paulus

Study Group Summary: Effective translation of basic research findings to clinical settings is a primary challenge of modern psychiatry. Theory-driven computational psychiatry approaches have enormous potential for elucidation of mechanism via the provision of translational links across basic and clinical domains. These approaches have already demonstrated utility in providing clinically relevant understanding (e.g., disorder classification, risk for return to substance-use during treatment, and antidepressant efficacy). Despite this potential, translation of computational psychiatry approaches to real-world clinical settings remains exceedingly rare, and consensus regarding specific barriers to implementation—and on the best strategies to overcome these barriers—is limited. This study group brings together computationally trained researchers and clinicians to provide an interactive forum for (i) identification of the challenges specific to clinical application of computational models of cognition and affect and (ii) discussion of novel approaches to overcome these challenges.

Our panel of experts will first briefly highlight recent, promising work from several domains of psychopathology (e.g., addiction, mood disorders), including examples of how computational approaches may be used to: effectively translate preclinical to clinical mechanisms of reward learning; probe neuromodulatory systems in humans; identify changes in learning and decision making processes that foreshadow relapse; and address issues of translation from animal to human and lab to clinic, with an eye toward issues of implementation and informing policy. Emphasis will be placed on examples of both successful translation and on roadblocks to translation.

Following this, primary mechanistic and pragmatic challenges for computational translation of preclinical and clinical research will be introduced as a basis for discussion with the ACNP audience, with a specific focus on basic science challenges (cross-species paradigm translation, modeling individual difference factors), human neuroimaging challenges (reliability, interpretability of

individual data points, analysis considerations), operational challenges (infrastructure for multisite data collection across integrated levels of analysis and expertise), and real-world clinical challenges (cost, robustness to clinical setting, stakeholder adoption).

The primary goal of this study group is to generate novel solutions for overcoming barriers to translation of computational psychiatry approaches via discourse between panel members and attendees. By attending this session, participants will both learn about cutting edge computational findings and actively contribute to moving the field forward.

Disclosure: Nothing to disclose.

Panel

45. Biochemical Modulation of Psychomotor Mechanisms in Psychiatric Disorders

45.1 All Roads Lead to the Motor Cortex – Psychomotor Mechanisms in Psychiatric Disorders

Georg Northoff

University of Ottawa Faculty of Medicine, Ottawa, Canada

Background: Psychomotor abnormalities apart from catatonia have been abundantly observed in psychiatric disorders like major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCH). While early psychopathological descriptions highlighted the truly psycho-motor nature of these abnormalities, more recent investigations conceive them rather in purely motor terms. This has led to an emphasis of dopamine-based abnormalities in subcortical-cortical circuits including substantia nigra, basal ganglia, thalamus, and motor cortex.

Methods: I present data from various resting state fMRI studies on schizophrenia ($n = 70$) (SCH), bipolar disorder (BD) ($n = 45$), and major depressive disorder (MDD) (N=30). Specifically, I present resting state data that focus on functional connectivity (FC) from subcortical regions like raphe nucleus and substantia nigra over basal ganglia and basal ganglia to motor cortex.

Results: The results show the following ($p < 0.001$, FDE-corrected): (i) significantly reduced FC from substantia nigra to motor cortex in SCH and MDD independent of their psychomotor status; (ii) significantly reduced FC from raphe nucleus to thalamus and motor cortex in psychomotor retardation in SCH, BD, and MDD; (iii) significantly enhanced FC from substantia nigra to thalamus and motor cortex in psychomotor agitated subjects with SCH, BD, and MDD.

Conclusions: Together, our findings show that psychomotor retardation and agitation show neuronal substrates in a trans-nosological way across SCH, BD, and MDD. This suggests dimensional rather than categorical interpretation of our findings along the RDoC lines. Further, our findings show psycho-motor mechanisms as the motor loop can be down- or up-modulated by the primarily non-motor raphe nucleus and its transmitter serotonin. Finally, our findings clearly show the relevance of balances, i.e., domain-based substantia nigra and serotonin raphe nucleus in mediating psychomotor phenomena in a trans-nosological way. We conclude that psychomotor mechanisms operate in a dimensional and cross-nosological way and may thus be considered paradigmatic examples of a dimensional approach as suggested in RDoC and the recently introduced Spatiotemporal Psychopathology (Northoff 2016, 2017, 2018).

Disclosure: Nothing to disclose.

45.2 Multiparametric Structural and Functional Neuroimaging of Catatonia and Parkinsonism

Dusan Hirjak

The Central Institute of Mental Health, Mannheim, Germany

Background: Catatonia and Parkinsonism are psychomotor and trans-nosological syndromes characterised by distinct and overlapping motor phenomena, affective symptoms and behavioral anomalies. However, the question whether the two psychomotor syndromes exhibit common or specific neural correlates of the characteristic symptoms remains unresolved. Therefore, the primary goal of this presentation is to shed light on common and distinct structural and functional neuroimaging biomarkers of catatonia and parkinsonism in schizophrenia spectrum disorders (SSD).

Methods: This presentation reports a total of four MRI studies: The first study examined the brainstem regions volumes in catatonic SSD patients (Northoff Catatonia Rating Scale (NCRS) total score≥3; $n = 30$) compared to non-catatonic SSD patients (NCRS total score = 0; $n = 29$). The second study examined the brainstem regions volumes in SSD patients with (Simpson and Angus Scale (SAS) total score of ≥4; $n = 36$) and without (SAS total score <4; $n = 64$) parkinsonism. The segmentation of the brainstem structures was carried out using FreeSurfer vers. 6.0. Third, we used TBSS, tractometry (along tract statistics using TractSeg) and graph analytics (clustering coefficient—CCO, local betweenness centrality) to examine specific white matter (WM) microstructural differences between SSD patients with ($n = 35$) and without ($n = 62$) parkinsonism and healthy controls ($n = 16$). Finally, we calculated the functional connectivity (FC) between thalamus and sensorimotor network (SMN) and between substantia nigra (SN) or raphe nucleus (RN) and basal ganglia (BG) in the entire sample of right-handed SSD patients ($n = 111$) and correlate it with NCRS and SAS scores.

Results: The results showed that: (1) Catatonic patients had smaller midbrain volumes ($p = 0.004$, Bonferroni corr.) when compared to non-catatonic patients. In the catatonic patients' group, correlations were detected between NCRS motor scores and midbrain ($p = 0.023$) and whole brainstem ($p = 0.015$, Bonferroni corr.) volumes. (2) Patients with parkinsonism had smaller medulla oblongata ($p = 0.017$), midbrain ($p = 0.008$, Bonferroni corr.) and whole brainstem ($p = 0.033$) volumes when compared to patients without parkinsonism. In the combined sample of SSD patients with and without parkinsonism (dimensional approach; $n = 100$), we identified a correlation between SAS total score and medulla ($p = 0.041$) and midbrain ($p = 0.043$) volumes. (3) Patients with parkinsonism showed reduced fractional anisotrophy (FA) measured via tractometry in the corpus callosum, corticospinal tract, striato-fronto-orbital, and striato-premotor tract as well as increased CCO in the supplementary motor area ($p < 0.05$). (4) FC between thalamus and SMN was associated with the severity of catatonia in SSD ($p < 0.05$). FC between SN and basal ganglia was associated with parkinsonism in SSD ($p < 0.05$).

Conclusions: Our data demonstrate that brainstem structures involved in dopaminergic-based motor circuits such as medulla and midbrain play an important role in the pathogenesis of catatonia and parkinsonism in SSD. These results further support the notion that structural and functional connectivity alterations of fronto-parietal and cortico-subcortical networks contribute to parkinsonism and catatonia in SSD patients.

Disclosure: Nothing to disclose.

45.3 Psychomotor Neurocircuits and Negative Affect in Serious Mental Illness

Stephan Taylor, University of Michigan, Ann Arbor, Michigan, United States

Background: The concept of 'psychomotor' has received renewed attention in recognition of neurobiological findings implicating motor networks in multiple psychiatric conditions. For example, the clinical syndrome of catatonia – occurring across different diagnostic groups – is defined in the DSM5 as primarily a motoric disturbance, and yet affective features are also prominent. In this presentation, two experiments will examine: (1) negative affect in patients with histories of catatonia, and (2) connectivity of the amygdaloid nuclei, which code social-emotional salience, across two disorders.

Methods: In experiment 1, we conducted data mining of more than 2 million electronic health records in a large academic center to test the hypothesis that catatonia in schizophrenia is more likely to occur with co-morbid diagnoses of an anxiety disorder than patients diagnosed with schizophrenia without episodes of catatonia. In experiment 2, we examined resting state connectivity of the amygdala, using functional magnetic resonance imaging, in cohorts of patients with schizophrenia (SCZ, $n = 37$), obsessive-compulsive disorder (OCD, $n = 54$) and healthy comparison subjects (HC, $n = 61$). We also sought to replicate findings of hyperactivity of thalamo-motor connectivity previously reported in schizophrenia.

Results: Experiment 1: Of 5474 patients with chart diagnoses of schizophrenia spectrum disorders (295.xx DSM codes), 7.9% also had a recorded episode of catatonia. Of those patients with catatonia, 49.9% had a co-morbid diagnosis of anxiety disorder and 62.4% had a co-morbid diagnosis of depressive disorder. Of those patients without recorded episodes of catatonia, only 32.6% had co-morbid anxiety diagnoses (CHI-sq=53.2, $p < 0.000$) and 41.4% had co-morbid depressive disorder diagnoses (CHI-sq = 71.3, $p < 0.000$). Experiment 2: A left ventral amygdala seed showed a significant focus of differential connectivity in the right pre-central region (less connectivity in both patient groups). There were additional regions in left pre-central gyrus and bilateral superior temporal gyrus where SCZ<HC. The left thalamic seed showed less connectivity in the adjacent right thalamus for SCZ and OCD patients, relative to controls, but greater connectivity SCZ>HC in the right pre-central gyrus.

Conclusions: The results identify two aspects of psychomotor psychopathology. A tendency to experience catatonia, as predicted, is associated with negative affect (anxiety and depression) in patients with schizophrenia spectrum diagnoses. Considering neurocircuitry of a paradigmatic emotional nucleus in the brain, the amygdala, results demonstrate abnormal connectivity between amygdala and motor networks in both schizophrenia and OCD. The findings in schizophrenia, with more abnormal amygdala connectivity in several cortical networks, as well as thalamo-cortical hyperconnectivity with the motor networks, may reflect greater functional impairment in this disorder.

Disclosure: Boehringer-Ingelheim: Grant (Self)

45.4 Neurodevelopmental Patterns of Parkinsonism in Schizophrenia

Abstract not included.

Panel

46. Targeting Brain Circuits for Reward and Affect With Deep Brain Stimulation

46.1 Deep-Brain Stimulation in a Mouse Model for Compulsive Behavior Reveals Distinct Effects on Neuronal Activity in Different Nodes of Cortico-Striatal Circuits

Ingo Willuhn

Netherlands Institute for Neuroscience, Amsterdam, Netherlands

Background: Deep-brain stimulation (DBS) of the internal capsule (IC) is an effective therapy for otherwise treatment-resistant patients suffering from obsessive-compulsive disorder (OCD). However, it often requires long periods of time to determine optimal DBS parameters, and even after optimization, not all patients respond to DBS. Here, we used an animal model for compulsive behavior, SAPAP3 knockout mice (SAPAP3-/-), to better understand DBS effects. SAPAP3 is expressed predominantly in cortico-striatal projections and its genetic deletion induces aberrant activity in these circuits, considered a neural correlate of OCD. Moreover, SAPAP3-/- display an anxious phenotype with behavioral inflexibility and excessive self-grooming that can lead to skin lesions, if left untreated, and can be rescued with SSRI, the first-line pharmacological OCD therapy. Here, we (1) investigated brain mechanisms underlying IC-DBS by monitoring relevant behavior and activity in OCD-relevant brain regions, (2) systematically varied several typically optimized DBS parameters, and (3) introduced novel intermittent DBS.

Methods: Using implantable, miniaturized fluorescence microscopes in freely behaving male and female SAPAP3-/-, we measured DBS-induced changes in single-cell calcium dynamics. The calcium indicator GCaMP6s was delivered via virus injection into the secondary motor cortex ($n = 5$), prelimbic cortex ($n = 5$), medial ($n = 4$) and lateral ($n = 4$) orbitofrontal cortex, and ventral ($n = 5$) and dorsal ($n = 5$) striatum. GCaMP6s fluorescence, indicative of neuronal activity, was captured via a GRIN relay lens implanted above the target region. We used a machine-learning classifier to quantify grooming. Standard DBS parameters were 120Hz, 80 µs pulse-width, and 200 µA. We systematically varied all three of these parameters.

Results: Our findings demonstrate that IC-DBS rapidly reduced excessive grooming ($R2 = 0.67$) and, similar to OCD patients, 'symptoms' quickly returned after discontinuation of DBS ($R2 = 0.33$). (1) This therapeutic effect was accompanied by instantly altered neuronal activity in all brain regions monitored (R2 range = 0.23–0.43). However, this effect was not uniform across regions and revealed subsets of imaged neurons that were either excited, inhibited, or not affected by DBS, as well as differences in transient DBS-onset responses and subsequent sustained responses (R2 range = 0.13–0.39). (2) Variation of DBS parameters yielded overall that the greater the applied pulse-width or current, the more effectively DBS recruited neurons (increasing size of both excited and inhibited subsets; R2 range = 0.05–0.53) and suppressed grooming (R2 range = 0.12–0.42). (3) Intermittent DBS was as effective as continuous DBS in grooming suppression, irrespective of DBS pause duration (1, 5, or 10 s every 10 s; $R2 = 0.41$).

Conclusions: Our results support the idea that IC-DBS effectively reduces excessive grooming in SAPAP3-/- via recruitment of cortico-striatal circuits. Furthermore, our findings demonstrate brain-wide recruitment of neurons and complex, differentiated effects across brain regions that are at odds with an idea of a uniform DBS effect. Intermittent DBS may be a future treatment option for OCD patients that could preserve DBS battery life. Together, we report animal-model data furthering our knowledge on brain mechanisms of IC-DBS in several capsule-connected brain regions. Detailed future analysis will determine which aspects of DBS-induced neuronal activity are most correlated with specific behavioral outcomes.

Disclosure: Nothing to disclose.

46.2 Circuit-Selective Deep Brain Stimulation for Obsessive-Compulsive Disorder

Martijn Figee

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

Background: Deep brain stimulation of the anterior limb of the internal capsule (ALIC DBS) is an effective treatment for refractory obsessive-compulsive disorder (OCD). However, precision targeting and optimization of DBS parameter selection remains a hit-or-miss endeavor, with some evidence that ill-targeted stimulation in the ALIC may actually work against therapeutic benefit. Animal tracing studies and human tractography suggest that the putative ALIC target for OCD impacts brain circuits for reward, affect and inhibitory control, including projections to orbitofrontal (OFC) and ventromedial (vmPFC) cortex, ventrolateral cortex (vlPFC), dorsal anterior cingulate cortex (dACC), dorsal medial cortex (dmPFC) and dorsolateral prefrontal cortex (dlPFC). The recent development of directional segmented DBS leads may allow for selective stimulation of these ALIC-projections. Here, we developed directional white matter tractography stimulation models in OCD patients with ALIC DBS to identify which projections are most therapeutic.

Methods: We developed structural connectivity maps of therapeutic stimulation by performing probabilistic tractography analysis on OCD patients with ALIC DBS. We built patient-specific volume of tissue activation (VTA) models using postoperative CT images fused to preoperative structural T1 and diffusion-weighted MRI scans. We estimated proportional probability of connections between the VTA and each projection cortical target region (vmPFC/OFC, vlPFC, dlPFC, dmPFC, and dACC) for DBS responders and non-responders. Response was defined as a minimal 35% improvement in Yale Brown Obsessive-Compulsive (YBOCS) score after routine clinical parameter optimization. To further explore where connectivity would be able to best explain clinical improvement, we correlated connectivity values from stimulation sites to cortical regions to the percentage of change in YBOCS score from baseline to optimization using Spearman correlation. Finally, we developed directional tractography activation models and explored personalized circuit-specific targeting and stimulation for patients with directional DBS-leads.

Results: All patients with ALIC DBS displayed stimulation of OFC/vmPFC and dmPFC connections. However, non-responders had incomplete stimulation of vlPFC, dACC and dlPFC compared to responders. Correlation analysis revealed that fibers from the dorsolateral ALIC to vlPFC were positively associated with improvement in Y-BOCS scores, while connections from ventral ALIC to vmPFC were negatively associated. We were able to successfully construct a stimulation tractography model of directional segmented lead configurations along the medial-lateral axis, which we used for personalized DBS targeting and programming in our most recent patients. Early observations suggest that this directional precision-strategy allows for fast improvement in patient-specific symptom domains for reward, affect and inhibitory control.

Conclusions: Our findings suggest that the therapeutic benefit of ALIC DBS for OCD depends on stimulation of a subset of specific ALIC connections, which can be selectively targeted using directional DBS-systems. These directional circuit-response maps can be used to guide clinical programming decisions and enhance the precision of surgical targeting for ALIC DBS in OCD and other disorders of motivation and emotions.

Disclosure: Nothing to disclose.

46.3 Deconstructing the Subthalamic Physiology of Affect, Reward and Risk: Identifying Stimulation-Responsive Biomarkers Using a Dimensional Approach With Deep Brain Stimulation

Valerie Voon

University of Cambridge, Cambridge, United Kingdom

Background: Deep brain stimulation (DBS) is effective for Parkinson's disease (PD) and obsessive-compulsive disorder (OCD) targeting the subthalamic nucleus (STN), a critical integrative node for motor, limbic and cognitive pathways. PD is a neuropsychiatric disorder with core impairments in depressive, apathy and impulse control symptoms. Previous STN local field potential (LFP) studies highlight a role for theta in conflict and alpha and gamma in affective processing. Here we focus on core cognitive processes underlying PD and STN function examining the underlying neurophysiology and capacity for modification with stimulation.

Methods: We assessed 15–23 PD patients with STN LFP and prefrontal EEG recordings and acute stimulation effects in the perioperative period time-locked to cognitive tasks. The tasks included the Monetary Incentive Delay (MID) task designed to dissociate reward and loss anticipation from outcomes, Affect task to assess the role of stimulation frequency on negative valence and arousal; and Risk taking and stimulation dissociating the effects of uncertainty and loss aversion. We used time-frequency analyses and two-way or mixed models ANOVA and paired-tests where indicated cluster corrected FDR $P < 0.05$ as the threshold.

Results: We show in the MID task that the anticipation of loss aversion is characterised by greater gamma and delta power whereas the consummatory phase of reward outcome is characterised by robust theta-delta power in STN and prefrontal EEG along with greater STN-prefrontal coherence (all findings ANOVA cluster corrected FDR $p < 0.05$). In the Affect task, using a support vector machine approach, combined early theta and late alpha power categorizes negative from neutral affective stimuli during subjective evaluation (cluster corrected FDR $p < 0.05$). Targeting the late alpha difference, stimulation at 10 Hz frequency time-locked to the negative stimulus enhances positive valence bias whereas high 130 Hz clinical frequency decreases arousal (frequency x stimulation x valence-arousal interaction: $p < 0.05$). Critically, depressed PD patients showed greater improvements in positive bias at low rather than high frequency. Finally, in the Risk task, we show that risk aversion is associated with greater delta and greater gamma activity, which can be decomposed with linear effects: gamma was associated with loss aversion and delta with uncertainty effects (all cluster-corrected FDR $p < 0.05$) convergent with the MID findings. Using drift diffusion models, we show that high frequency stimulation time-locked to the decision phase increased risk aversion by enhancing caution by shifting thresholds and the starting bias towards the cautious choice.

Conclusions: These findings converge to decompose specific frequencies in the STN as a function of cognitive processes suggesting differential cognitive frequencies for loss aversion, certainty and negative affective evaluation. We further highlight a potential role for specific frequency effects on depressive symptoms in PD. The identification of stimulation-responsive biomarkers of cognitive processes provides a critical step towards the development of precise responsive neuromodulation. These findings highlight a dimensional approach towards the neuromodulation of psychiatric disorders.

Disclosure: Nothing to disclose.

46.4 A Personalized Approach to Deep Brain Stimulation for Treatment Resistant Depression

Katherine Scangos

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

Background: Major depression is a common and debilitating disorder worldwide. While medication, psychotherapy and electroconvulsive therapies (ECT) are effective for many patients, a substantial subset remain refractory to all available treatments. Deep brain stimulation (DBS) emerged in 2003 as a highly promising new treatment option. While initial approaches targeted the subgenual cingulate (SGC) or ventral capsule/ventral striatum (VC/VS), the question of where to stimulate remains unresolved. We present a strategy for personalized DBS where we deliver brain stimulation over a multi-day period across 10 affect and reward brain regions in order to select a personalized target site for implantation of a chronic DBS device.

Methods: We are conducting a clinical trial of personalized closed-loop DBS for treatment resistant MDD. This trial was approved by the institutional review board and food and drug administration (FDA)(Presidio: https://clinicaltrials.gov/ct2/show/NCT04004169). In the first stage, 12 patients are surgically implanted with ten stereoelectroencephalography electrodes within the most promising sites bilaterally for modulating depression based on published literature. Depression symptoms are assessed serially multiple times a day using Likert scales of patient response and physician rated affect, and the HAM-D6 subscale of the HAMD-17. We then tested the clinical effects of a preselected set of stimulation parameters through a systematic bipolar stimulation survey. From this survey, we selected a reduced set of parameters for further testing with blinded, sham-controlled stimulation and prolonged stimulation periods.

Results: We present results from our first patient in this trial as proof-of-concept that a personalized approach is possible. We elicited an elaborate repertoire of emotions across different sites and stimulation parameters across reward and affect circuitry. Experiences were dependent on brain region, location within that region, and stimulation frequency. Through sham controlled stimulation, we found that there were in fact three stimulation paradigms - in the SGC, orbitofrontal cortex, and VC/VS - that led to a positive mood changes with differing effects on level of arousal. We found that responses to repeated trials of stimulation were reproducible as a function of context/state at time of stimulation, dose dependent, and sustained beyond the stimulation period.

Conclusions: We present a novel approach to DBS that includes a 10-day inpatient interval where multi-day, multi-site recordings are performed prior to implantation of a chronic neuromodulation device. Future work will be needed to determine the extent to which there is variability among individuals in stimulus-response relationships, identify neurophysiological correlates of these relationships, and test their application in a closed-loop design. We show that by leveraging the ability to record and stimulate from affect and reward circuits from multiple locations simultaneously we can identify personalized brain targets that inform a highly innovative DBS approach.

Disclosure: Genentech: Employee (Spouse)

Panel

47. Towards a Better Understanding of the Mechanism of Action of Psychedelics: Bridging the Gap Between Molecular, Systems-Level, and Clinical Findings

47.1 Engineering a Safer Psychoplastogen

David Olson

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

Background: The long-lasting therapeutic effects of psychedelics can possibly be explained by their ability to promote neural plasticity in key circuits relevant to the treatment of neuropsychiatric diseases. Recently, we demonstrated that the psychoplastogenic properties of psychedelics can be decoupled from their hallucinogenic effects through rational chemical design. However, it is currently unclear if these non-hallucinogenic psychoplastogens can produce positive effects on rodent behaviors relevant to the treatment of neuropsychiatric disorders.

Methods: By applying the principles of function-oriented synthesis (FOS), we engineered a non-hallucinogenic, non-cardiotoxic psychedelic analog that we call tabernanthalog (TBG). The improved safety of TBG was established using a combination of receptor profiling as well as zebrafish toxicity and rodent head-twitch response assays. To determine the therapeutic potential of TBG, we measured TBG-induced neuronal growth in cell culture and also in vivo using two-photon microscopy. Antidepressant-like behavioral effects of TBG were assessed following unpredictable mild stress. The anti-addictive properties of TBG were measured using the two-bottle choice paradigm for alcohol consumption in mice and heroin self-administration in rats.

Results: We found that TBG is capable of promoting cortical neuron structural plasticity, reducing alcohol and heroin consumption, and producing antidepressant-like effects in rodents despite the fact that it does not elicit a mouse head-twitch response.

Conclusions: The hallucinogenic properties of psychedelic compounds do not appear to be necessary for their effects on structural neural plasticity or several rodent behaviors relevant to treating depression and substance use disorders. The advent of non-hallucinogenic psychoplastogens could provide a solution to the safety concerns that have prevented the widespread use of psychedelics in medicine.

Disclosure: Delix Therapeutics: Board Member (Self); Delix Therapeutics: Stock / Equity (Self)

47.2 Using Brain-Behavior Relationships and Psychedelic Pharmacological Imaging to Inform Personalized Treatment Decisions in Psychosis Spectrum Disorders

Jie Lisa Ji

Yale University, New Haven, Connecticut, United States

Background: A major challenge in psychiatry is matching patients to treatments. Patients with the same diagnosis often exhibit neural and behavioral heterogeneity and different treatment responses. Mapping specific symptoms to neural circuits and molecular targets is key to developing personalized treatments. Critically, pharmacological neuroimaging can inform howa specific mechanisms underlie psychiatric symptoms. For example, though both lysergic acid diethylamide (LSD) and ketamine induce core psychosis spectrum disorder (PSD) symptoms and target implicated mechanisms, their behavioral effects and mechanisms of action differ, suggesting they may relate to different dimensions of PSD. Understanding how the mechanisms of these drugs map to PSD characteristics could provide insight into the different mechanisms, and optimal treatment targets, for individual patients.

Methods: We defined a brain-behavioral space (BBS) in PSD (N = 436) with resting state fMRI data and psychosis/cognition measures. Controls (CON N = 202) were used for comparison. Principal component analysis (PCA) was used to find principal components (PC) of maximal symptom variation; a general linear model was used to relate variation along these PCs to global brain connectivity (GBC) across PSD, using PC3 as an exemplar. The subset of PC3 neural features for which the symptom-to-neural mapping is maximized was then selected via a step-down process. Next we selected PC3-optimized patients based on their PC3 score

and neural similarity to the PC3 map. We tested if mechanisms underlying the PC3 BBS could be informed using NMDA (via ketamine) or serotonin 5-HT (via LSD) receptor manipulation in two independent within-subject drug infusion datasets (N = 39, N = 24 respectively). We computed maps of the effect of ketamine or LSD on GBC vs. placebo and the ρ of these maps vs. the PC3 BBS map. We use these maps to inform treatment decisions for PC3 patients. Both sexes were included in all data.

Results: We identified 5 significant PCs of PSD symptom variation. PC3 loaded positively on a number of positive symptoms (e.g. hallucinations) and negatively on negative symptoms (e.g. anhedonia). Despite differences in traditional symptom scores between PSD and CON, no neural regions survived type I error correction (p<.05); however, we found robust relationships between PC3 score and specific neural circuits. The PC3 map was highly similar to the ketamine map ($\rho = 0.76$, $p < 0.05$), suggesting that the neural circuits affected by ketamine may overlap with those that covary with PC3 symptoms. We show that, for negatively-scoring PC3-optimized patients, ketamine may modulate their symptom-relevant circuits such that their similarity with the PC3 map is reduced, and thus their (negative) PC3 symptoms may also be reduced. Of note, ketamine has shown efficacy in treating depression. Contrarily, PC3 and LSD maps were not similar ($\rho = -0.01$, $p > 0.05$), suggesting that 5HT receptor-acting drugs are ineffective in treating PC3-optimized patients.

Conclusions: We describe a framework for identifying putative molecular targets for different PSD presentations by combining BBS mapping with pharmacological neuroimaging. Here, we show how ketamine and LSD data can be leveraged to differentially select between NMDA and 5HT-receptor modulating drugs for exemplar PSD patients, based on their specific symptoms. These results highlight the potential of psychedelic agents in developing targeted and effective treatments for PSD.

Disclosure: Patent application: Patent (Self); BlackThorn Therapeutics: Consultant (Self)

47.3 Altered Prediction-Error Processing May Underlie Psilocybin-Induced Changes in Bodily Self-Processing

Katrin Preller

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

Background: Psychedelic substances induce subjective alterations in our sense of body and sense of self. Despite the importance of altered bodily self-perception in disorders such as anorexia nervosa or depression, the neural mechanisms underlying these changes are poorly understood. We therefore conducted a pharmacological imaging study combining the administration of the classic psychedelic Psilocybin with a Roving Somatosensory Oddball Task while participants underwent simultaneous EEG/fMRI imaging.

Methods: Fifteen healthy humans (n = 10 male and n = 5 female; mean age = 26.86 years) participated in a double-blind, randomized, placebo-controlled, within-subject study. Participants received Placebo or Psilocybin (0.2 mg/kg body weight, orally) on two different occasions at least two weeks apart. The Roving Somatosensory Oddball Task was conducted 85 min after Psilocybin/Placebo administration while participants underwent simultaneous EEG/fMRI scanning. Stimuli consisted of somatosensory electrical stimulation (50 ms pulse duration) on the median nerve of the left forearm at about twice the individual perceptual threshold. To induce tactile mismatch responses, trains of stimuli switched randomly between high and low intensity after a variable number of 3 to 7 repetitions. The first stimulus of each new train was modeled as the "Deviant" and each third repetition in a train as "Standard". FMRI images were analyzed using a general linear model implemented in SPM12. The contrast Deviant > Standard was computed for each participant. Stimulus-locked EEG segments were created based on the marker position of the Deviant and Standard stimuli per condition. Global field power and event-related potentials were analyzed. The study was registered at clinicaltrials.gov (NCT03736980).

Results: Psilocybin reduced the BOLD signal in the Deviant > Standard contrast in the ventromedial prefrontal cortex and the dorsomedial prefrontal cortex ($p < 0.05$, FWE corrected). Psilocybin induced a stronger global field potential comparted to Placebo across both stimulus types ($p < 0.05$). In line with the fMRI results, a significant interaction between treatment condition and stimulus type was revealed for the frontal electrode AF2 ($F(1, 14) = 5.129$, $p < 0.05$) at the time interval 216–414 ms after stimulus with a significant difference between Standard and Deviant in the Placebo condition, but not in the Psilocybin condition. A significant positive correlation was found between Psilocybin-induced "Disembodiment" and the mean amplitude of the EEG difference wave (Deviant - Standard) for the time interval 216–414 ms at the AF2 electrode in the Psilocybin condition ($r = 0.630$, $p = 0.012$).

Conclusions: These results show that disruption of tactile prediction error processing in the medial prefrontal cortex may underlie changes in bodily self-perception. This seems to be driven by increased salience attribution to non-salient stimuli and dependent on serotonin 2A/1A receptor stimulation by Psilocybin. Together these results shed light on the pharmacological and mechanistic underpinnings of altered bodily self-perception and may therefore highlight important therapeutic targets for psychiatric disorders characterized by altered bodily self-perception body perception such as anorexia nervosa and depression.

Disclosure: Nothing to disclose.

47.4 Sustained Reductions in Headache Burden After the Limited Administration of low Dose Psilocybin in Migraine and Cluster Headache: Results From Two Preliminary Studies

Emmanuelle Schindler

Yale School of Medicine, West Haven, Connecticut, United States

Background: Headache disorders maintain top worldwide disability ratings, urging the continued investigation of novel targets and mechanisms of treatment. Anecdotal evidence suggests that psilocybin, lysergic acid diethylamide (LSD), and other select indoleamine 5-hydroxytryptamine 2A (5-HT2A) receptor ligands confer sustained therapeutic benefit in cluster and migraine headache, though controlled studies are lacking. We sought to carry out the first controlled investigations of the effects and safety of psilocybin in these headache disorders.

Methods: Two exploratory clinical trials were carried out in adult males and females with migraine or cluster headache (twelve each). The migraine design was a double-blind, placebo-controlled, cross-over study and the cluster design was a randomized, double-blind, placebo-controlled study. Migraine subjects received single administrations of oral placebo (microcrystalline cellulose) and psilocybin (0.143 mg/kg) two weeks apart. Cluster subjects were randomized to receive a pulse regimen of three administrations of either psilocybin (0.143 mg/kg) or placebo, each administration separated by approximately 5 days. Headache diaries, in which subjects documented headache attacks, began two weeks before the first test day and ended two weeks after the second test day for migraine subjects and two months after the last test day for cluster subjects. Physiological and psychological drug effects were monitored during sessions

and several follow-up contacts with subjects were carried out to assure safety of study procedures. Ten subjects in each the migraine and cluster studies were included in the final analysis.

Results: Over the 2-week period after single drug administration, the reduction in weekly migraine days from baseline was significantly greater after psilocybin [−1.65 (95% CI: −2.53 to −0.77) days/week] than after placebo [−0.15 (−1.13 to 0.83) days/week; $p = 0.003$, $t(9) = 4.11$; effect size −1.15]. Over the 3-week period after initiating the pulse regimen, the reduction in weekly cluster attacks from baseline was greater with psilocybin [−6.03 (−9.96 to −2.10)] than with placebo [+1.17 (−2.76 to 5.10); $p = 0.017$, $t(8) = 2.99$; effect size −1.89]. In neither study did the rating of psychedelic effects during acute psilocybin exposure correlate with the change in headache burden. Psilocybin was well-tolerated in both studies and there were no unexpected or serious adverse events.

Conclusions: These two exploratory controlled trials showed that limited administration of a low oral dose of psilocybin has sustained therapeutic effects in migraine and cluster headache. These findings validate the potential value of psilocybin in headache research and medicine. That the reductions in headache burden were not correlated with acute psychedelic effects in these studies urges the consideration of the several neurobiological functions common to both headache pathology and the known actions of select 5-HT2A receptor ligands as potential sources of therapeutic effects in headache.

Disclosure: CH-TAC, LLC: Grant (Self)

Panel

48. New Approaches to Modulate Forebrain Interneurons for the Treatment of Psychiatric Disease

48.1 Interneurons in the Cortical Working Memory Network in Schizophrenia

Abstract not included.

48.2 mGlu1 and mGlu5 Receptors Modulate Prefrontal Cortex Somatostatin Interneurons Through Distinct Mechanisms of Action

Max Joffe

Vanderbilt University, Nashville, Tennessee, United States

Background: The prefrontal cortex (PFC) is an essential hub for the regulation of affective, motivational, and cognitive behaviors. Excitatory projection neurons convey the primary output from the PFC, but local inhibitory interneurons are essential in regulating PFC circuit function. One interneuron subtype, characterized by the expression of the neuropeptide somatostatin (SST), filters incoming information by inhibiting the apical dendrites of nearby pyramidal cells. While SST interneurons are implicated in the pathophysiology of several psychiatric diseases, our understanding of the mechanisms that regulate their physiology remains limited.

Methods: We interrogated PFC interneuron physiology using a combination of ex vivo whole-cell electrophysiology, in vivo fiber photometry, and mouse behavior. We employed novel, selective, and systemically active pharmacological tools to examine how metabotropic glutamate receptor subtypes 1 (mGlu1) and 5 (mGlu5) regulate PFC interneurons. Furthermore, we evaluated causative relationships between SST interneuron physiology and animal behavior using optogenetics and cell type-specific knockout mice.

Results: mGlu1 activation rapidly increased excitatory transmission onto SST interneurons and thereby facilitated inhibitory transmission onto pyramidal cells. Systemic delivery of an mGlu1 positive allosteric modulator recruited this circuitry to reverse cortical hyperexcitability and working memory deficits induced by MK-801 administration. By contrast, mGlu5 activation mediates long-term potentiation on SST interneurons. Acute restraint stress hijacked this plasticity to enhance amygdala-driven feedforward inhibition and impair PFC-dependent cognitive processing.

Conclusions: These findings reveal novel mechanisms through which endogenous signaling events regulate synaptic physiology and plasticity on SST interneurons. Small molecule mGlu receptor modulators have great potential to ameliorate disease-related deficits in PFC microcircuit function. Specifically, potentiating mGlu1 receptor function may improve cognitive symptoms in schizophrenia and mGlu5 negative allosteric modulators may induce their well-known anxiolytic effects by inhibiting synaptic plasticity on SST interneurons. These findings are especially interesting in light of the genetic associations between Grm1 and schizophrenia and between Grm5 and major depressive disorder.

Disclosure: Nothing to disclose.

48.3 Cell-Specific Pharmacological Dissection of Microcircuit Mechanisms by Which Striatal Fast-Spiking Interneurons Regulate Striatal Output

Nicole Calakos

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

Background: Striatal fast-spiking interneurons (FSI) are critical for the adaptive behavioral transition from goal-directed to habitual responding. Mouse studies show that striatal circuitry in habitual mice is characterized by increased gain in striatal output and increased FSI excitability. However, increased striatal output and increased activity of a GABA-ergic interneuron thought to mediate feed-forward inhibition presents a paradox. To understand this paradox, we have examined synaptic contributions to the FSI-striatal projection neuron circuitry. Our studies take a 3-pronged approach employing empirical measurements, cell-specific synaptic manipulations and computational modeling.

Methods: In acute brain slices, evoked synaptic currents using whole-cell patch clamp methods and evoked population dynamics using GCaMPs with multiphoton microscopy were measured (as in O'Hare et al., Neuron 2016). GABA contributions were manipulated using cell-specific pharmacology made possible by the DART technique (Drugs Acutely Restricted by Tethering; Shields et al., Science 2018). Computational models were developed from published and unpublished empirical measurements of synaptic properties to develop a predictive model for the transformation of synaptic inputs to action potential firing in striatal projection neurons.

Results: Habitual behavior is associated with modulation of GABA synaptic strength on striatal fast-spiking interneurons (goal, $n = 16$; habit, $n = 18$; $p = 0.0212$). Although ostensibly either an increase of Glu strength or decrease in GABA strength would increase FSI excitably, computational modeling indicates that IPSC timing is a critical variable for predicting effects on striatal output, i.e. projection neuron firing. Global and cell-specific pharmacological manipulations of Glu and GABA synapses in the striatal circuitry support this model by revealing microcircuit sites whose manipulation promotes or inhibits output ($n = 60$–300 cells from 3–5 slices per condition).

Conclusions: We find that FSI GABA synaptic strength is a site of plasticity in habit formation and that GABA-ergic modulation of

fast-spiking interneurons is a potent site to influence striatal output. Non-canonical FSI effects on striatal output are observed in subsets of cells. Computational models of FSI-SPN microcircuit can predict which subsets of projection neurons are inhibited and which are promoted.

Disclosure: Nothing to disclose.

48.4 Neuroactive Steroids Influence Affective Switching Through Parvalbumin Interneuron-Driven Modulation of Oscillatory States in the Basolateral Amygdala

Jamie Maguire

Tufts University School of Medicine, Boston, Massachusetts, United States

Background: The episodic nature of depression implies transitions between healthy and pathological brain states. Studies are beginning to elucidate the relationship between network and behavioral states. For example, oscillations within and between the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) are associated with behavioral states relevant to valence and emotional processing. However, the mechanisms mediating transitions between network and behavioral states are unknown. Interestingly, the neuroactive steroid, allopregnanolone, has demonstrated clinical success for the treatment of depression and has been implicated in mediating affective switching. Here we examine the ability of neuroactive steroids, allopregnanolone and SGE-516, to facilitate transitions between network and behavioral states.

Methods: Optogenetic techniques were employed to examine the role of parvalbumin (PV) interneurons in oscillation generation in the BLA. Immunohistochemistry and electrophysiology were used to determine the cell types mediating sensitivity to allopregnanolone in the BLA. The impact of allopregnanolone on oscillations in the BLA was measured using local field potential (LFP) recording. Allopregnanolone was infused into the BLA and the impact on behavioral states was compared to mice lacking the GABAAR δ subunit on PV interneurons in the BLA. Oscillations in the BLA were recorded pre- and post- subjection to chronic unpredictable stress (CUS) in mice treated with SGE-516 or vehicle.

Results: PV interneurons in the BLA are critical for oscillation generation and they express a high level of the neurosteroid-sensitive GABAAR δ subunit. Allopregnanolone through actions on PV interneurons in the BLA is capable of modulating oscillations in the BLA and altering behavioral states. Allopregnanolone levels and GABAAR δ subunit expression are decreased in the BLA following CUS. Oscillations recorded within and between the mPFC-BLA are perturbed following CUS and SGE-516 treatment restores the healthy network and behavioral state.

Conclusions: These findings demonstrate that PV interneurons in the BLA are critical mediators of oscillations in the BLA and are sensitive to modulation by neurosteroids. Allopregnanolone is capable of modulating oscillations in the BLA and influencing behavioral states, through actions on GABAAR δ subunit-containing receptors on PV interneurons. Chronic stress is capable of perturbing the mPFC-BLA network, by impairing local neurosteroid signaling in the BLA, biasing the network towards the pathological state. Whereas, neurosteroids are capable to restoring the healthy network and behavioral state. These findings may explain the durability of effect of neurosteroid-based treatments in clinical trials for the treatment of both postpartum depression and major depressive disorder.

Disclosure: SAGE Therapeutics: Advisory Board (Self)

Panel

49. Sleep, Circadian Rhythms and Substance Use Disorders

49.1 Investigations Into the Behavioral and Molecular Consequences of Chronic Opioids and the Relationship to Disrupted Sleep

Julie Blendy

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: Opioid use often progresses into a vicious cycle of abuse and withdrawal, resulting in very high rates of relapse. While the physical and psychological symptoms of opioid withdrawal are well documented, sleep disturbances caused by chronic opioid exposure and withdrawal are less well understood. Opioids can significantly disrupt sleep acutely and long-term. Further, poor sleep may influence opioid use, suggesting a reciprocal feed-forward interaction between poor sleep and opioid use. Disrupted sleep impairs cognitive performance, mood, and pain tolerance, demonstrating that sleep dysfunction may contribute to the difficulty in staying abstinent from opioids. Improving sleep disturbances associated with morphine could halt the pathophysiological feedback cycle between opioids and poor sleep. To understand the underlying mechanisms associated with this bidirectional relationship, we used an oral morphine administration paradigm to characterize sleep patterns and assess associated molecular changes at different timepoints of the addiction cycle.

Methods: Oral administration aligns with misuse of prescription opioids and allows for chronic administration of opioids while recording sleep stages. Mice received 2 mg/mL saccharin dissolved in water for 2 days prior to morphine exposure. Morphine was dissolved at a 0.3 mg/mL concentration and increased to 0.5 mg/mL the next day and remained at 0.5 mg/mL for the duration of the experiment. Mice (N = 14, both sexes) had 11 days of 0.5 mg/ml morphine. 24 h after removal of morphine, mice were tested for somatic signs of spontaneous withdrawal for 30 min to confirm dependence. Sleep EEG was recorded at specific timepoints before, during and after morphine exposure, and scored for wakefulness, total sleep time, rapid eye movement (REM) and non-REM episodes. A subset of mice were used for molecular analysis. For these studies, 4 aged matched controls never received morphine, 4 received morphine and 4 received morphine and underwent 24 h withdrawal.

Results: We found morphine increased wakefulness and decreased sleep time during the active period. Acute, but not protracted withdrawal, increased wakefulness and decreased NREM during the inactive period. This increase in wakefulness during morphine was accompanied by changes in inflammatory and metabolic gene expression in prefrontal cortex. Cyclooxygenase 2 and nitric oxide synthase 2 were increased during morphine exposure but reduced to control levels during withdrawal. TNFα remained increased during withdrawal. To assess the behavioral consequences we tested mice in anxiety- and depressive-related behaviors 2 weeks following morphine exposure. Mice displayed decreased grooming in the sucrose splash test, a measure of grooming and self-care, but paradoxically, a decrease in time spent immobile in the tail suspension test, a response typically associated with anti-depressant or active coping behaviors.

Conclusions: We found significant alterations in sleep parameters during morphine exposure and withdrawal. Increases in wakefulness during morphine accompanied a cortical gene expression profile that is reminiscent of an inflammatory sleep deprivation state. Ongoing studies are focused on identifying molecular mechanisms underlying these changes and how to

intervene with treatments during withdrawal to improve sleep disturbances and reduce withdrawal symptoms.

Disclosure: Nothing to disclose.

49.2 Chemogenetic Retinal Stimulation Activates Locus Coeruleus Neurons and Counters Depression- and Addiction-Associated Behaviors

Gary Aston-Jones

Brain Health Institute, Rutgers University, Piscataway, New Jersey, United States

Background: Decades of research indicate mood and addiction disorders are associated with disrupted circadian rhythms. Chronic light deprivation compromises locus coeruleus (LC) neurons and induces behaviors linked with depression (Gonzalez & Aston-Jones, PNAS 2008). Suprachiasmatic nucleus (SCN) provides an indirect circadian input onto LC via a relay in dorsomedial hypothalamus (DMH) (Aston-Jones et al., Nat. Neurosci. 2001). SCN is therefore in a key position to integrate light information with LC, via a circuit we denote as the Photic Regulation of Arousal and Mood (PRAM) pathway: retina→SCN→DMH→LC (Bowrey & Aston-Jones, Anxiety Depress. 2017).

Methods: Experiment 1. Sprague Dawley rats received intravitreal (IVI) injections of an AAV encoding a Gq DREADD: AAV2-hSyn-hM3D(Gq)-mCherry; (n = 12) or control virus (AAV2-hSyn-EGFP; n = 10). Rats were subjected to continuous darkness for 8 wk during which daily ip injections of the DREADD agonist clozapine-N-oxide (CNO) were given. Rats were then subjected to assays of mood (saccharin preference, elevated plus maze and forced swim). LC tissue was stained for apoptosis (Poly ADP ribose polymerase, PARP) and tyrosine hydroxylase (TH).

Experiment 2. We tested LC response to chemogenetic retinal activation. We dark-adapted two groups of rats (hM3Dq, n = 6 or EGFP, n = 10) for 12 h before recording activity of LC neurons in anesthetized rats. We also stained for the activity marker Fos in SCN, DMH and LC, to determine whether PRAM structures were stimulated during chemogenetic retinal activation.

Experiment 3. To confirm the retinal cell-type responsible for depression-linked behaviors, intrinsically photosensitive retinal ganglion cells (ipRGCs; melanopsin cells) of rats in 12:12 light:dark conditions were ablated using a saporin toxin that selectively eliminated melanopsin-expressing cells (Mel-SAP; n = 10). Ten weeks later, rats were subjected to behavioral analyses as in Experiment 1.

Experiment 4. Rats expressed retinal hM3Dq or EGFP as above and were trained to self-administer iv cocaine for 3-8wk. During subsequent 2wk of abstinence, rats received daily CNO and were then tested for cocaine demand using a within-session behavioral economics procedure (Bentzley et al., PNAS 2014; James et al., Biol. Psychiatr. 2018).

Results: Experiment 1. ERG and Fos analysis showed that Gq DREADD retinal stimulation increased RGC activity. Constant darkness (8 wk) induced a depression-like phenotype in control animals, which was prevented by daily activation of retinal Gq DREADDs.

Experiment 2. Gq DREADD stimulation of RGCs increased the tonic firing rate of LC by 60% and was associated with increased Fos expression in RGCs, SCN, DMH and LC.

Experiment 3. Mel-SAP lesions of melanopsin RGCs induced a depression-like phenotype. This was also associated with increased apoptosis in noradrenergic LC cells as seen with increased PARP staining.

Experiment 4. Rats with stimulation of retinal Gq DREADDs during abstinence had less incubation of cocaine demand than EGFP control rats.

Conclusions: Dysregulation of the PRAM pathway may induce neural damage in LC neurons associated with behaviors linked to depression and addiction, which can be prevented by PRAM activation of LC. The PRAM pathway presents a novel circuit for a relatively non-invasive way to treat depression and addiction.

Disclosure: Merck Pharmaceuticals: Consultant (Self)

49.3 Cocaine-Induced Neural Adaptations in the Lateral Hypothalamic Melanin-Concentrating Hormone Neurons

Yanhua Huang

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Sleep abnormalities often accompany withdrawal from chronic use of a variety of drugs, including cocaine, opioid, cannabis, and nicotine. Chronic cocaine users often experience reduced total sleep time and increased sleep fragmentation resembling chronic insomnia, which have been recapitulated in the rat cocaine self-administration model. The persistent sleep problems are not only a comorbidity but may drive the vicious cycle by fostering drug use and relapse. In particular, rapid eye movement (REM) sleep regulates the formation and modulation of emotional memories, and cocaine-induced long-term REM (but not non-REM) sleep impairment negatively impacts relapse-like behaviors in rats after withdrawal. However, it is not understood whether and how cocaine experience imposes persistent changes to REM sleep regulatory machinery, and what may serve as effective means to improve REM sleep after withdrawal. Here, we focus on the melanin-concentrating hormone (MCH) neurons in the lateral hypothalamus (LH), which respond to REM sleep loss and regulate REM sleep initiation and maintenance.

Methods: Adult male Sprague Dawley rats were trained to self-administer intravenous cocaine. Three weeks after withdrawal, LH MCH neuron transcriptome was profiled using laser-microdissection followed by RNA sequencing. MCH neuron functional properties were assessed using slice electrophysiology. Finally, using chemogenetic and optogenetic approaches, it was tested whether counteracting cocaine-induced MCH neural adaptations may positively impact REM sleep after withdrawal.

Results: Three weeks after cocaine withdrawal, LH MCH neurons exhibit a wide range of gene expression changes tapping into cell membrane signaling, intracellular signaling, and transcriptional regulations. Functionally, they show reduced membrane excitability and decreased glutamate receptor activity, consistent with increased expression of voltage-gated potassium channel gene Kcna1 and decreased expression of metabotropic glutamate receptor gene Grm5. Finally, chemogenetic as well as optogenetic stimulations of LH MCH neural activity increase REM sleep after long-term withdrawal with important differences. Whereas chemogenetic stimulation promotes both wakefulness and REM sleep, optogenetic stimulation of these neurons in sleep selectively promotes REM sleep.

Conclusions: Cocaine exposure persistently alters gene expression profiles and electrophysiological properties of LH MCH neurons. Counteracting cocaine-induced hypoactivity of these neurons selectively in sleep enhances REM sleep quality and quantity after long-term withdrawal. Thus, LH MCH neuronal stimulation may help alleviate cocaine-induced REM sleep impairment after withdrawal, and may be explored for potential benefits for reducing relapse-like behaviors.

Disclosure: Nothing to disclose.

49.4 Transcriptional Signatures in the Human Postmortem Brain Reveal Molecular Links Between Circadian Rhythms and Opioid Use Disorder

Ryan Logan

University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, United States

Background: More than 90% of patients with opioid dependence relapse within the first year of treatment. Vulnerability to relapse is associated with severe and persistent disruptions to sleep and circadian rhythms, leading to the possibility that interventions which improve sleep and/or target circadian rhythms could mitigate cravings and reduce relapse. However, the neurobiological mechanisms underlying these relationships between opioid dependence, circadian rhythms, and sleep are largely unknown. Few studies have examined the cellular and molecular alterations associated with opioid dependence in human postmortem brains. We investigated the molecular alterations in both the dorsolateral prefrontal cortex (DLPFC) and nucleus accumbens (NAc), key nodes of reward, from subjects with OUD. Our studies discovered novel circadian-dependent pathways in DLPFC and NAc associated with OUD. Manipulating these pathways in the mouse brain revealed novel mechanisms of opioid relapse and tolerance.

Methods: Both DLPFC and NAc were collected from postmortem brains of subjects with OUD and unaffected controls (n=40). RNAseq assays were completed, followed by a computational pipeline based on differential expression (DE) analyses, including rank-rank hypergeometric overlap (RRHO), Gene Ontology (GO), and Weighted Gene Co-expression Network Analysis (WGCNA). We also used time of death (TOD) analyses to reconstruct molecular rhythms in the human brain. Using findings from the human, we manipulated similar pathways in NAc of male and female mice using intersectional genetics (n=8-16 per sex), followed by opioid conditioned place preference (CPP), self-administration (SA), and tolerance and withdrawal behavioral assays.

Results: In OUD, we found 567 and 1,306 DE genes in DLPFC and NAc, respectively (corrected $p < 0.01$ and log-fold-change of less than −0.26 and greater than 0.26). RRHO revealed robust overlap of transcriptional signatures in DLPFC and NAc of OUD subjects, suggesting similar patterns of gene changes associated with opioid dependence. WGCNA uncovered changes in gene correlations across multiple modules derived from DLPFC and NAc and gene networks specific to OUD. Pathways enriched in the DLPFC of OUD subjects included metabolism, glutamate, immune, and inflammation, while NAc pathways included metabolism, immune, oxidative stress, and circadian rhythms. TOD analysis found striking differences in molecular rhythms between OUD and unaffected subjects in both DLPFC and NAc. Further analyses predicted upstream regulators related to immune and circadian rhythm pathways, including the circadian transcription factor NPAS2. Deletion of NPAS2 function in the mouse NAc lead to increased fentanyl CPP and SA ($p < 0.05$), reflecting enhanced conditioned reward, seeking and relapse behaviors. NPAS2-deficiency also altered tolerance and withdrawal in a sex-specific manner with females developing tolerance significantly faster their male counterparts.

Conclusions: Our studies begin to uncover the molecular and cellular pathways associated with OUD, including marked disruption in molecular rhythms in human DLPFC and NAc. Our results also indicate that opioid-induced disruptions to molecular rhythms in these brain regions may be involved opioid craving, relapse, and tolerance. Therefore, circadian-dependent modulation of transcriptional signaling in corticostriatal circuitry may be a critical pathway involved in the pathophysiology of OUD.

Disclosure: Nothing to disclose.

Study Group

50. COVID-19 and Substance Use Disorders: Intertwined Epidemics

Nora Volkow*, Susan Weiss, Susan Tapert, Linda Chang, Sharon Walsh, Gail D'Onofrio, Elena Koustova, Peter Friedmann

Study Group Summary: The COVID-19 pandemic has rapidly created enormous challenges for individuals, healthcare and judicial systems, and wider social and economic structures. Science is urgently needed to address these challenges. Among the most vulnerable populations are those with substance use disorders (SUD), although currently there is very limited information about the interactions of drug use and SUD with COVID-19. We can anticipate that drug use might affect COVID-19 incidence and exacerbate adverse consequences, based on known factors related to the acute pharmacological effects of drugs (e.g., nicotine and methamphetamine might affect viral entry into cells) and their chronic effects (e.g., methamphetamine increases the risk for pulmonary hypertension, cardiomyopathy and neuroinflammation; opioids increase the risk for hypoxemia); route of administration (i.e., smoking or vaping tobacco or cannabis adversely affect pulmonary function); as well as the multiple social and economic factors that impact substance-using populations, including stigma, homelessness, and incarceration.

In the United States, the opioid epidemic continues to drive overdose fatalities and may exacerbate the COVID-19 crisis, and vice versa. The COVID-19 pandemic jeopardizes the deployment of evidence-based interventions to prevent and reverse opioid overdoses and to treat opioid use disorders (OUD). Of necessity, restrictions on the dispensing of methadone and on the need for in-person visits for prescribing buprenorphine have been relaxed, which may improve treatment access. Greater access to virtual environments, whether for telehealth or for virtual support groups, potentially increases the reach of treatment approaches. However, the efficacy of these interventions long term and the proportion of those who benefit need to be evaluated. Similarly, we need to examine the potential neuropsychiatric direct consequences of COVID-19 if it enters the brain (including the fetal brain during pregnancy), which is currently unknown, or indirect effects via immune system changes or from stress associated with the pandemic. These could be further exacerbated by drug use; conversely, the stress from COVID-19 could also contribute to drug use, its escalation and to relapse. Hence there is a need for research to assess the impact of COVID-19 on people with OUD and other SUD, including those with limited access to healthcare and other resources.

This study group will focus on critical areas to identify priorities for further research and opportunities for innovation. Gail D'Onofrio will discuss how COVID-19 is affecting the treatment of OUD and overdose in emergency departments. Sharon Walsh will discuss community-based strategies during COVID-19 to help people in treatment and recovery, including use of telehealth or virtual recovery groups in rural and urban settings. Peter Friedmann will discuss issues affecting those with SUD in the criminal justice system, including those released from jails or prisons to decrease the census during the pandemic. Linda Chang will discuss how COVID-19 may affect neurodevelopment in babies born to pregnant women with SUD. Susan Tapert will discuss COVID-19 effects on routines, family, peer relations, substance use among teens, and implications for brain development. And Elena Koustova will discuss the translational opportunities to expand screening and treatment of COVID-19 in patients with SUD.

Disclosure: Nothing to disclose.

Panel

51. Transmission of Trauma: Biological Influences on the Maternal and Fetal Brain in Highly Vulnerable Populations

51.1 The Biological Embedding of Chronic Stress Related to Racial Discrimination and Trauma Experiences Within African American Communities

Sierra Carter

Georgia State University, Atlanta, Georgia, United States

Background: Research 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 Americans (AA). Researchers have suggested that early life exposure to psychosocial stressors, such as racial discrimination and trauma, may influence negative affective states (e.g., depression) and other adjustment related factors (e.g., self-control and self-confidence) across the lifespan and intergenerationally. These experiences also have effects on poor physical health through physiological dysregulation and increased wear and tear on body systems over time. Although a growing literature has examined the effects of early life stress related to racial discrimination and trauma exposure on adulthood health, very limited research has examined the intergenerational effects of these stressors. Furthermore, there is a paucity of research has examining how socioeconomic status (SES)/contextual factors could influence this process. This presentation will discuss study findings among AA mothers and children that examined how experiences of racial discrimination and trauma are linked to stress-related disorders as well as biomarkers of accelerated aging and allostatic load with a focus on context.

Methods: Data was collected from two separate research studies. One sample included 368 AA participants from the longitudinal Family and Community Health Study. A second sample included 230 AA pregnant women who were recruited as part of the Grady Trauma Project. Self-report interviews included demographic characteristics, trauma exposure, and report of racial discrimination and general well-being/functional impairments. Blood pressure was assessed at AA pregnant women's medical visits and biomarkers were extracted from blood collected during separate interviews for both studies.

Results: Results from one study revealed that among AA pregnant women, racial discrimination experiences were related to more PTSD symptoms ($r = 0.35$, $p < 0.01$). Further, racial discrimination that was reportedly experienced getting medical care was significantly related to prenatal systolic and diastolic blood pressure ($r = 0.23$ and 0.23, $p < 0.01$). A second study found a significant indirect effect of racial discrimination (age 10-15) on accelerated aging through adult maladjustment (depression, self-esteem, self-confidence; age 20–29; $\beta = 0.021[0.001, 0.057]$) for African youth across the lifespan, accounting for 32% of the total variance. SES significantly moderated the association between racial discrimination and adult adjustment. This led to a greater indirect effect of discrimination on aging among those raised in higher SES households. The significant buffering effect of parental support/racial socialization will also be discussed.

Conclusions: These findings support research that chronic stress due to racial discrimination and trauma can confer independent and intergenerational risk for accelerated aging, stress-related disorders, and possibly premature disease and mortality in AAs.

Disclosure: Nothing to disclose.

51.2 Pregnancy Alters the Structure of Mothers' Brains: Prior Childhood Abuse and Reflective Parenting Skills are Associated With Gray Matter Volume 2-8 Years Post Birth

Catherine Monk

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

Background: New data demonstrate the profound influence pregnancy and the associated surges in sex steroid hormones exert on the human maternal brain, specifically reduced gray matter (GM) in regions subserving social cognition. These structural alterations are often interpreted as the consequence of adaptive pruning because greater reductions are associated with more optimal self-reported attachment behaviors. GM reductions are shown to endure to 2-years postpartum yet to date have not been examined more distal to the pregnancy period. Moreover, this emerging research has not included women at psychosocial disadvantage based on minority status or considered the moderating roles of childhood trauma and parenting qualities on later maternal brain structures. This enhanced perspective has the potential to identify contextual factors influencing maternal neurobiology, which in turn affect child outcomes.

Methods: Two samples of healthy, primarily Latina (67 and 75%, respectively), pregnant women were studied at Columbia University Medical Center in New York (A) $N = 120$, ages 18–42 and (B) $N = 23$, ages 15–45. During the 3rd trimester, both cohorts self-reported Childhood Maltreatment (CM) using the Childhood Trauma Questionnaire; group A underwent social cognition assessment focused on parenting sensitivity at 4 months post-partum as well as MRI session and group B completed an MRI session when children were 6-8 years old; both MRI protocols used on a GE Signa Premier 3T scanner including T1-weighted structural data that were processed and analyzed using Freesurfer 6.0. By December, we expect to have analyzed MRI data from 30 more mothers based on n=15 previously aquired sessions and $n = 15$ enrolled and not yet scanned.

Results: In both samples, women endorsed high levels of childhood trauma versus no trauma: 56 and 43%, respectively. In sample A at 4 months postpartum, trauma exposed women did not differ from unexposed women on any subscale of the Parental Reflective Functioning index: Pre-mentalizing modes subscale ($F = 0.32$, $p = 0.85$), certainly about infant mental states ($F = 0.44$, $p = 0.51$), and interest and curiosity in infant mental states ($F = 0.44$, $p = 0.51$). MRI findings from sample B revealed larger bilateral putamen volumes in those with older children, as well as increased thickness in inferior frontal and precentral cortices. A significant interaction between childhood trauma in the women and child age in bilateral putamen volume was also detected (p's < 0.05).

Conclusions: Childhood trauma may not consistently adversely impact parenting abilities; the further out from birth, women who experienced childhood trauma showed increased putaminal volumes, and increased thickness in regions that support control processes, potentially reflective of ongoing plasticity related to caregiving, which might benefit them and their caretaking abilities of their future child.

Disclosure: Nothing to disclose.

51.3 Developmental Timing of Interpersonal Trauma Determines the Unique and Lasting Impact on Biomarkers of Neuropsychiatric Disease in Humans and Mice

Kathleen Morrison

West Virginia University, Elkridge, Maryland, United States

Background: Interpersonal trauma is associated with a variety of negative outcomes in adulthood, including mood disorders and poor autonomic nervous system functioning. However, the biological underpinnings of these lasting outcomes are not well

understood. One difficulty in identifying the biological mechanisms is that interpersonal trauma often occurs in the context of a high level of overall trauma. We set out to determine if sexual trauma, an extremely salient and discrete interpersonal trauma, (1) produced a unique biological signature and (2) whether experiencing the sexual trauma at particular ages differentiated this signature. Further, we developed a mouse model in order to determine the mechanisms underlying the lasting consequences of early life stressful experiences.

Methods: 101 African-American women ages 18 to 45 were recruited from a larger study of risk factors for PTSD. Lifetime trauma history and PTSD symptoms were measured via the Traumatic Events Inventory (TEI) and the Modified PTSD Symptom Scale, respectively. The TEI is a 14-item screen for history of traumatic events. Participants reported whether they had experienced sexual assault or abuse before age 13, between the ages of 14-17, or at age 18 or later. Women were further assessed for anthropometric measurements, blood pressure, fear-potentiated startle, skin conductance response, and blood was drawn. Extracellular vesicles from blood plasma were assessed by proteomics and small RNA sequencing. Circulating cell free mitochondrial DNA (ccf-mtDNA) and relevant cytokines were measured in blood plasma. A mouse model was developed and assessed for translational potential. Female mice were subject to chronic stress during one of three periods: 3-5 weeks old, 5-7 weeks old, or 7-9 weeks old. During adulthood, mice were tested for outcomes similar to those in humans ($n = 8$ per group): biomarkers in blood plasma and indicators of autonomic nervous system function.

Results: For measures associated with metabolic state, sexual trauma was broadly associated with negative outcomes regardless of the age of trauma. This includes increased body weight, hip circumference, and hypertension. For measures related to the autonomic nervous system, there was a specific signal associated only with sexual trauma experienced between ages 14–17. Women who experienced sexual trauma during this age range had increased autonomic reactivity, as indicated by fear potentiated startle and skin conductance. Further, women who experienced sexual trauma between ages 14–17 had 7-fold higher copy numbers of ccf-mtDNA in blood plasma and a distinct extracellular vesicle proteome. Findings from the mouse model show that chronic stress during the early adolescent period closely recapitulated the findings from humans.

Conclusions: Even in the context of high levels of overall trauma, sexual trauma produced a distinct signature at the metabolic, autonomic, and inflammatory levels in adult women. Importantly, this signature was not related to current PTSD symptoms. Developmental timing of the sexual trauma determined the magnitude of impact on previously identified biomarkers of neuropsychiatric disease, such as increased inflammation and ccf-mtDNA. Additionally, novel biomarkers in the proteome of extracellular vesicles were identified as dramatically altered by exposure to sexual trauma. The mouse model recapitulated key metabolic, autonomic, and inflammatory findings, thus providing a valid approach to address mechanistic questions relevant to the results from the human studies.

Disclosure: Nothing to disclose.

51.4 Unraveling Health Disparities in Infant Mortality and Altered Development in a Humanized Mouse Model

Eldin Jasarevic

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

Background: Profound disparities exist in maternal-child health outcomes between racial and ethnic groups that have lasting health outcomes. Africa-American in the United States are significantly more likely to experience preterm birth and maternal and infant mortality than white women. Indeed, the causes and consequences of these health disparities are complex, heterogenous, and remain clinically ill-defined. Moreover, maternal risk factors, such as diet, infections and lifetime trauma typically co-occur and contribute to poor health outcomes in offspring. In addition, a more recently identified maternal-fetal interaction occurs at birth, with the maternal vaginal microbiota providing a source of microbiota that colonize the neonate gut. Maternal vaginal microbiota can harbor potential pathogenic bacteria, such as Gardnerella vaginalis (Gv), that stimulate the neonate's naïve immune system, a response that may turn pathological in a newborn already primed from a inflammatory prenatal environment. In this talk, we will discuss development of a novel mouse model of multi-layered compounding of insults to the fetus: (1) a 'vulnerable programming' that occurs in the prenatal inflammatory environment, (2) a 'vulnerable state' that occurs by being born premature, and (3) a major insult that triggers a host of systemic responses in the neonate that, collectively, contributes to life-long susceptibility to disease.

Methods: We used a combination of genomic, flow cytometric, mass cytometric and pharmacological manipulations. Further, we model these compounding risk factors as a 'triple hit' where: (1) pregnant mice on a high fat, low fiber diet with high glucose are vaginally lavaged at mid-gestation with Gv to model the insult of the prenatal inflammatory environment, (2) pups are then delivered by c-section at E18.5 to model prematurity, and (3) pups are orally gavaged with a human CST-IV microbiome to model the postnatal insult.

Results: Administration of a high fat – low fiber (HFt-LFb) diet resulted in significant differences in pre-pregnancy body weight gain, glucose intolerance, and gut microbiota composition relative to females consuming a low fat – high fiber (LFt-HFb) diet. Using 16S rRNA sequencing and qPCR, we validated the human inoculation procedure and recovery of human-associated microbiota from the neonate gut. The combinatorial effects of maternal diet, infection and microbiome influenced the survival of newborn mice, an observation consistent with clinical reports on infant mortality. Indeed, triple hit offspring showed a rate of 60% mortality relative to the 100% survival among LFt-HFb offspring. Of the triple hit offspring that survived, single-cell mass cytometry showed a significant expansion of neutrophils in the periphery, with neutrophils accounting for almost 80% of all immune cell in circulation. Tracking of offspring body weight revealed significant acceleration in the rate of body weight gain and increased body weight in the triple hit offspring that survived, suggesting lasting programming of metabolic syndrome in these offspring.

Conclusions: This translational approach demonstrates novel contributions of compounding and multi-layered maternal risk factors on infant mortality, immune programming and lasting metabolic outcomes in mice. Through the use of this mouse model and application of known maternal risk factors, including human cervicovaginal microbiota, we may come closer to estimating combined risks and to identifying causal mechanisms that may yield novel therapies and biomarkers to be further examined in clinical trials.

Disclosure: Nothing to disclose.

Panel

52. Innovative Approaches to Uncover Cellular and Circuit Mechanisms Underlying Psychiatric Disorders

52.1 Circuit Mechanisms Underlying Fear Memory Discrimination and Generalization

Abstract not included.

52.2 Neural Adaptation Mediated by Ventral Pallidum Dopamine Receptor 3 Drives Cocaine Seeking by Potentiating Inhibitory Inputs to Lateral Habenula

Byungkook Lim

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

Background: The ventral pallidum (VP) is an important convergent point at the interface of the motivational and reward circuitry implicated in drug addiction and depression. Indeed, VP lesions cause strong reductions in hedonic response and motivation for reward. The VP receives dense inputs from the nucleus accumbens (NAc), a major component of the mesolimbic reward pathway, and transmits this information to downstream targets such as the ventral tegmental area (VTA), lateral hypothalamus (LH), amygdala and the lateral habenula (LHb). While cellular and molecular changes in the NAc, LHb, and VTA have been identified as hallmarks of drug addiction, identifying a link between these areas has remained elusive. Given its efferent and afferent connections to these regions, the VP is a likely putative target, capable of integrating and transmitting reward-relevant signals throughout the brain. However, it is still unknown how the VP circuitry contributes to drug addiction, and whether specific cell types within the VP are responsible for these effects.

Methods: In this study, we used the Drd3-Cre transgenic animals to selectively monitor and manipulation dopamine receptor 3 (Drd3)-expressing neurons in VP with calcium imaging and optogenetic stimulation, respectively. Statistical significance will be mainly assessed using analysis of variance (ANOVA) and t-tests followed by appropriate post-hoc tests. Both male and female animals are used in all of our experiments.

Results: We found the selective up-regulation of Drd3 in VP during the withdrawal after the cocaine self-administration, and knockdown of Drd3 suppressed the cocaine seeking after the withdrawal. In addition to that, the increased Drd3 signal elevated the activity of VP neurons and inhibiting this enhanced neuronal activity can also suppressed the cocaine seeking after the withdrawal.

Conclusions: We demonstrate that dopamine receptor D3 (Drd3)-dependent plasticity in VP drives potentiation of dopamine release in the nucleus accumbens during relapse to cocaine seeking and contributes to the development of relapse behavior in cocaine self-administration paradigm. Especially, suppressing elevated activity of VP Drd3-expresssing neurons projecting to the lateral habenula (LHb) potently reduces drug seeking following abstinence from cocaine self-administration. Our results describe a novel role of Drd3-mediated plasticity in modulating VP-to-LHb circuitry for cocaine seeking after withdrawal.

Disclosure: Nothing to disclose.

52.3 Unraveling Neural Coding Mechanisms in Freely Behaving Mice Using miniScope

Da-Ting Lin

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

Background: The neural ensemble concept originates from the cell assembly hypothesis proposed by Donald Hebb in 1949, which posits that behavior relevant information is not stored in individual neurons but rather within a subset of neurons termed cell assemblies (nowadays referred to as neural ensembles). Hebb further proposed that sequential activation of cell assemblies leads to the formation of phase sequences to represent behaviors and cognitive processes. Currently, assays for immediate early gene activation such as c-fos have been used extensively to identify neural ensembles. This approach does not offer temporal resolution allowing one to distinguish neural ensembles coding behavior variables separated by only a few seconds. Therefore, it does not allow one to study sequential activation of neural ensembles and the formation of phase sequences. In vivo single unit recording technique offers mini-second temporal resolution, but it does not allow comparison of behaviorally tuned neural ensembles and phase sequences longitudinally. The advent of in vivo calcium imaging using miniature fluorescence microscopes has made it possible to track activity of hundreds of neurons with single cell resolution in freely moving animals, which could open the door for detecting sequential activation of neural ensembles and the formation of phase sequences in reward seeking and consumption.

Methods: In the present study, we employed our custom miniScope system to simultaneously track calcium activities from hundreds of neurons during operant food self-administration training across several weeks, prior to the start of learning through stable behavior performance. To study operant conditioning behavior in greater detail, we first used DeepLabCut to track mouse body parts. We then developed a "Deep Behavior Mapping" method to extract behavioral features that we then grouped into "behavioral microstates". We combined longitudinal miniScope imaging with "Deep Behavior Mapping" to examine how sequential activation of neural ensembles form phase sequences to code behavior streams in operant reward seeking.

Results: We observed stereotyped behavior stream in operant conditioning from lever press to pellet consumption in well-learned mice. We identified neural ensembles by clustering the behavioral tuning of all neurons to the identified behavioral microstates from Deep Behavior Mapping. Interestingly, we found that behaviorally tuned neural ensembles form phase sequence to represent the stereotyped operant conditioning behavior stream in well-learned mice. We further showed that neural ensembles and phase sequences emerge through learning to code specific behavior stream. Our study offers an innovative approach to study neural representation of operant conditioning and opens a new avenue for elucidating neural representation of behavior streams by integration of in vivo miniScope imaging with deep behavior mapping.

Conclusions: Sequential activation of neural ensembles form phase sequences to code behavior stream in operant reward seeking

Disclosure: Nothing to disclose.

52.4 Understanding the Role of SETD1A, a Risk for Schizophrenia and Developmental Brain Disorders, in Neural Development Using Human iPSC and Mouse Models

Hongjun Song

University of Pennsylvania, Philadelphia, Pennsylvania, United States

Background: The recent advances in human genetic studies have led to a much better understanding of genetic underpinning of major psychiatric disorders. The identification of high confidence genetic risk factors provides an entry point to understand how dysregulation of specific molecular and cellular pathways and biological processes can lead to major psychiatric disorders. SETD1A, encoding a subunit of the histone lysine methyltransferase, has been identified as a high confidence risk factor for

schizophrenia. Many loss-of-function variants of SETD1A have been associated with schizophrenia and developmental brain disorders. The role of SETD1A in the development and function of the nervous system is not well understood.

Methods: We have developed complimentary experimental models to investigate the role and mechanism of SETD1A in regulating neural development and synaptic functions. First, using CRIPSR-based genome editing, we have generated multiple pairs of isogenic iPSC lines with heterozygous loss-of-function mutations of SETD1A under different genetic backgrounds. Second, we have developed approaches to differentiate isogenic iPSC lines into 3D forebrain cortical organoids to examine the impact on cortical neurogenesis and into monolayer forebrain cortical neurons to examine the impact on synapse formation and function. Third, we have generated conditional knockout mice of Setd1a in the nervous system to examine the in vivo impact on neurogenesis and neuronal function.

Results: We have identified critical roles of SETD1A in regulating cortical neurogenesis and synaptic functions. First, we have found cortical neurogenesis deficits in both heterozygous SETD1A loss-of-function mutant cortical organoids and in the forebrain of Setd1A conditional knockout mice. Second, we have found synaptic deficits in forebrain cortical neurons derived from iPSCs with heterozygous SETD1A loss-of-function mutations. Specifically, we found both reduction in the density of synaptic puncta by immunocytochemistry and reduced frequency of spontaneous glutamatergic synaptic transmission by electrophysiology. Third, we found that heterozygous SETD1A loss-of-function mutations in iPSC-derived forebrain cortical neurons leads to transcriptional dysregulation. The dysregulated genes are enriched in GO terms related to both presynaptic and postsynaptic functions as well as to risk genes for schizophrenia. Interestingly, few dysregulated genes were identified in the cortex of heterozygous Setd1A conditional knockout mice, suggesting human specific transcriptional dysregulation.

Conclusions: Taken together, our study identifies critical roles of a prominent genetic risk factor for schizophrenia in regulating neural development and synaptic functions and provides platforms to understanding underlying mechanisms.

Disclosure: Nothing to disclose.

Study Group

53. Strategies and Pitfalls in Advancing Novel Analgesic Drugs From the Academic Bench to the Clinic

Smriti Iyengar*, Christopher Flores, James Campbell, Amy Chappell, Theresa Branchek, Scott Dax, Theodore Price

Study Group Summary: New, non-opioid and non-addictive therapeutics for treatment of chronic pain are desperately needed. NIH has led new investment in enhancing pain management through the HEAL Initiative, creating an excellent opportunity for translating innovative ideas into new therapeutics. However, a chasm still exists in terms of commercializing this innovation that is difficult for most academics to bridge. The primary content of this session will be the sharing of information, experiences and opportunities with the goal of helping researchers better understand how to move their projects toward the clinic.

We will focus on 3 major areas:

1. HOW TO START:

develop a project from a target to a drug
validate a target for drug development
optimize a drug to move towards clinical development
plan for an IND application

2. HOW TO TRANSITION:

When does a project transition from early stage to Investor/ Pharma interest?
How does one protect intellectual property?
How does one get to a licensing deal?
How does one transition from being an early drug development startup to a later stage clinical development company>?

3. HOW TO FINANCE/FUND:

When do you raise money?
Who are the people that are needed to make this happen?
What is the right time to do so?
What are market rates for licensing deals?
How much does developing IP cost?

Disclosure: Electrical Engineering, Delphi: Employee (Spouse), Eli Lilly Retiree: Stock / Equity (Self)

Panel

54. Mitochondria in Psychopathology: New Research Opportunities

54.1 Mitochondria Activity is Constrained by Genomic Variants in the Cortex of Schizophrenia and Bipolar Disorder Subjects

Marquis Vawter

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

Background: The mitochondria genome is composed of mitochondria DNA (mtDNA) encoded genes (MEGs, n = 37), and nuclear-encoded mitochondria genes (NEMGs, n ~ 1,722). Mitochondria are a plausible biological pathway in the pathogeneses of schizophrenia (SZ) and bipolar disorder (BD). Recent genetic and functional activity studies support the theory of mitochondria dysfunction in these disorders. The genetic studies coalesce around three areas, (i) risk loci for SZ and BD are enriched with common NEMG variants, (ii) NEMG and MEG gene burden tests for SZ and BD show association with Complex I genes and (iii) interactions between NEMG and MEG loci increases the risk burden for SZ and BD. We extend these findings by asking if mitochondria traits in the brain are risk factors for SZ or BD by genome-wide association (GWA) testing of quantitative traits and Mendelian Randomization (MR) testing. Two traits shown to be altered in the brain were selected for further study, common deletion of mitochondria DNA (4977 bp deletion), and the complex I activity, the first component in the electron transport chain.

Methods: Postmortem brain samples from 94 subjects (dorsolateral prefrontal, superior temporal gyrus, V1 visual) cortices' were obtained from the UCI Pritzker Brain Bank. The mitochondria common deletion and Complex I activity traits were measured using published methods (PMID: 29594135). GWA of exome sequencing variants for the quantitative traits using MAF >2.5% in this sample.

Results: After correction for diagnosis, age, and population stratification, we found multiple loci that passed the genome-wide significance threshold ($p < 5E{-}08$) for the common deletion (CD) trait and Complex I (CI) activity. Seventeen loci were associated

with the CD in the dorsolateral prefrontal cortex, which included four NEMGs (ATAD3A, MTG1, TRABD, SELO). There was a highly significant GWA result with Complex I activity levels in the V1 visual cortex to a broad region that contained multiple NEMGs (CYBA, NT5DB2, SMIM4, ALAS1, GLYCTK) related to Complex I function on chr3:51990646-52518786.

The MR inverse variance weighted method was applied for the GWA of the mitochondria CD and CI activity levels as the exposure and SZ GWAS (n = 82315, PMID: 25056061) as the outcome. The CD showed a significant MR association (beta = 0.0559, se = 0.020, p value = 0.0052). The MR results for self-reported BD (β = −0.0004, se = 0.0001, p value = 0.0205, UK Biobank b:6906), showed a smaller beta compared to SZ, the betas show a reverse direction. For the CI levels in the V1 visual cortex and SZ there is a significant negative MR association (boot-strapped β = −0.0003, p value = 2.8E–04). This MR result provides preliminary evidence that Complex I trait is a risk factor for SZ, the same SNPs are associated with both SZ and a decrease in Complex I level. Horizontal pleiotropy was not significant for either quantitative exposures of CI or CD.

Conclusions: This new approach to the study of neuropsychiatric disorders showed the mitochondria activity traits, Complex I and the mtDNA common deletion levels, as risk factors for SZ. The results show a highly significant genome-wide association with Complex I and mtDNA common deletion levels for NEMG loci. This proof of principle demonstrates the feasibility of studying quantitative mitochondria postmortem brain traits in an exome-wide manner. These preliminary analyses require replication in proposed larger samples to replicate these exploratory and exciting observations.

Disclosure: Nothing to disclose.

54.2 MRS Studies of Bioenergetics in Psychotic Disorders

Dost Ongur

McLean Hospital, Belmont, Massachusetts, United States

Background: Multiple lines of evidence from genetic, cellular, imaging, and clinical studies implicate abnormalities in mitochondrial function and brain energy availability in psychotic disorders. These abnormalities are of interest because they may lead to novel treatment interventions. Our group has been conducting a series of 31P Magnetic Resonance Spectroscopy (31P MRS) studies to probe relevant processes in the brain in individuals with schizophrenia and bipolar disorder.

Methods: In a series of studies, we have recruited patients with chronic and stable schizophrenia and bipolar disorder with matched healthy controls, as well as with patients experiencing a first episode of schizophrenia and bipolar disorder (maximum 1 year of symptoms and 1 hospitalization) with matched healthy controls. We conduct clinical evaluations including full SCID as well as PANSS, YMRS, and MADRS at the time of visit. In our unpublished study we collected data from 16 patients with first episode schizophrenia (Mean age 21.9) and 34 matched controls (mean age 22.1).

We collect 31P MRS data on a 4 Tesla Varian scanner using a dual-tuned surface coil. The region of interest is a 6x6x4cm voxel including the medial and anterior prefrontal cortex. 31P MRS data are frequency/phase corrected and analyzed using homegrown software to quantify: ATP & PCr concentrations, creatine kinase forward reaction rate (CK Kf) and flux, pH, NAD+ and NADH concentrations. We conduct statistical evaluations using Chi-square and ANOVA as appropriate.

Results: In previous studies, we have reported significant reductions in CK Kf and acidic pH, consistent with a slowing down of ATP synthesis and compensatory shift to glycolysis and lactate build-up in chronic schizophrenia patients. This is accompanied by redox imbalance as reflected in the NAD+/NADH ratio, indicating downstream effects of metabolic distress.

We now report results from first episode schizophrenia where we find evidence for reduced CK Kf (0.26 ± 0.06 in controls vs. 0.22 ± 0.05 in patients; F = 4.47, p = 0.04) but with normal pH values (7.02 in both groups). This CK Kf reduction is accompanied by a reduction in NAD+/NADH (4.76 ± 1.50 in controls vs. 3.64 ± 1.37 in patients; F = 5.68, p = 0.02). This NAD+/NADH reduction corresponds to a Cohen's d effect size of 0.78 and is greater than that seen in our previous work with chronic schizophrenia patients.

Conclusions: In this work, we extend our results from chronic schizophrenia to first episode. In young people experiencing a first episode of schizophrenia, we see evidence for impaired ATP synthesis through the CK enzyme as well as redox dysregulation; the latter is even greater here than in chronic patients. By contrast, pH is not acidic in first episode as it is in chronic patients, suggesting that the slowing of ATP synthesis and accompanying redox imbalance has not yet led to a compensatory shift towards glycolysis in the first episode. Our results provide new insights into the unfolding cascade of mitochondrial function and bioenergetic abnormalities in psychotic disorders.

Disclosure: Nothing to disclose.

54.3 Cell Type-Specific Transcriptional and Ultrastructural Analyses of Mitochondria in the Prefrontal Cortex of Schizophrenia and Bipolar Disorder Subjects

Jill Glausier

University of Pittsburgh, Pittsburgh, Pennsylvania, United States

Background: Schizophrenia (SZ) and bipolar disorder (BD) share some genetic and environmental risk factors, as well as certain clinical features. These shared factors and features in SZ and BP may be linked via similar functional and morphological brain alterations, many of which have been associated with evidence of mitochondrial dysfunction. However, the severity of mitochondrial dysfunction, and/or the specific mitochondrial functional pathways affected, might differ between diagnoses, and these differences may be influenced by the anatomical resolution of analysis.

Methods: To address this issue, we analyzed in SZ and BP subjects transcriptomic data that index different mitochondrial functional pathways in samples of DLPFC total gray matter, layer 3 pyramidal neurons (L3PNs) and L5PNs using a dual strategy: (1) identification of differentially-expressed genes (DEGs) and assessment of their enrichment for functional pathways, and (2) application of weighted gene co-expression network analysis (WGCNA) for an unbiased examination of how disease-related differences in gene expression affect higher-order gene co-expression relationships.

Results: In DLPFC gray matter, 41% of mitochondrial-related genes were differentially expressed in SZ whereas only 8% were differentially expressed in BP. In SZ, 83% of DEGs showed lower expression, and these DEGs were significantly enriched for functional pathways that index energy production. The DEGs in BP were not enriched for functional pathways. This disease-related pattern of findings was also identified in pyramidal neurons from SZ and BP subjects.

Because the greatest mitochondrial-related transcriptomic alterations were present in SZ subjects, we next investigated whether mitochondria located within PN axon terminals exhibit an impaired morphology that is reflective of mitochondrial dysfunction in the disease state. Preliminary quantitative electron microscopic analyses demonstrate that mitochondria

ultrastructural integrity is not impaired in DLPFC PNs in SZ subjects relative to unaffected comparison subjects.

Conclusions: Together, these findings support the idea that mitochondrial perturbations are present in the DLPFC in both SZ and BP, but that the severity and nature of these alterations, and their apparent cell type-specificity, differ across diagnoses. The selective and coordinated down-regulation of energy production genes, along with morphologically preserved mitochondria, in SZ is most consistent with the effects of chronic reductions in pyramidal neuron firing. This interpretation that lower neuronal demand for energy production due to less firing, and not defective mitochondrial function, is operative in the DLPFC in SZ is consistent with existing anatomical and genetic data which implicate impaired synaptic processes in the etiology of SZ, and not primary insults to mitochondria.

Disclosure: Nothing to disclose.

54.4 Mitochondrial Recalibrations and Signaling in Response to Stress in Mice and Humans

Abstract not included.

Study Group

55. New Nosological Approaches: Competing or Complementary

Leanne Williams*, Carlos Blanco, Antonia Kaczkurkin, Roman Kotov, Bob Krueger,

Bruce Cuthbert

Study Group Summary: There is widespread agreement that classification based on DSM/ICD is a bottleneck to advancing understanding of the neurobiological basis of psychiatric disorders and development of new treatments. Several theory- and data-driven approaches have been articulated as alternatives to DSM/ICD phenotypes, but their relative merits have not been systematically evaluated. This fractured state of the field impedes application of new nosologies in research and discourages investment from agencies and private foundations.

This study group will outline the theory underlying the leading alternatives to DSM/ICD and supporting data. The goal is to engage the panelists and the audience in a discussion of the strengths and weaknesses of each approach. There will be a particular emphasis on whether the models compete or complement each other, whether certain models are preferable for specific applications (e.g., understanding etiological pathways, target identification), and whether and how these models can be integrated.

Specific models that will be presented and discussed include Hierarchical Taxonomy of Psychopathology (HiTOP), which is a system of empirically-identified dimensions of abnormal behavior; circuit-based taxonomies, which characterize dimensions of neural function and describe their links to psychopathology; the Research Domain Criteria (RDoC), which includes constructs thought to cut across neural functions and behavior, manifesting in both units of analysis.

We will present data from extensive literature reviews and new seminal papers evaluating dimensionality of behavioral, neural function, and links between them. Specifically, we will present new findings from the ABCD Study, the Philadelphia Neurodevelopmental Cohort, Minnesota Twin registry, the Adolescent Development of Emotions and Personality Traits (ADEPT) project and the Stanford RDoC Anxiety and Depression (RAD) project. Data were analyzed using structural equation modeling, canonical correlation analysis, principal component analysis and machine learning to evaluate links between biology and behavior.

The discussions of this study group are expected to encourage adoption of empirical models of psychopathology that can help advance etiological research, facilitate discovery of new treatment approaches, and attract the interest of funding agencies and private foundations.

Disclosure: One Mind Psyberguide: Advisory Board (Self)