MPA Molecular Psychiatry Association

9TH BIENNIAL MOLECULAR PSYCHIATRY MEETING

POSTER ABSTRACTS

Thursday, March 7, 2024

T1. The Relationship Between Plasma Erythropoietin Levels and Symptoms of Attention Deficit Hyperactivity Disorder

Young Joon Kwon, Soonchunhyang University Hospital Chunan

Objective: There are animal models associating dopamine dysfunction with behavioral impairments that model attention deficit hyperactivity disorder (ADHD). Erythropoietin (EPO) has trophic effects on dopaminergic neurons. The aim of this study was to examine the EPO plasma levels and determine whether there was any correlation between plasma EPO levels and clinical characteristics of ADHD.

Methods: Plasma EPO levels were measured in 78 drug-naïve children with ADHD and in 81 healthy children. The severity of ADHD symptoms was determined by scores on the Korean ADHD Rating Scale (K-ARS) in ADHD children and healthy controls.

Results: The difference between median plasma EPO levels in ADHD children and in healthy controls was not statistically significant. Adjusting for age and sex, a linear regression analysis showed that inattention score was significantly higher in the second highest tertile of plasma EPO compared to those in the lowest tertile. Hyperactivity-impulsivity score was significantly higher in the highest tertile of plasma EPO compared to those in the lowest tertile. Moreover, total K-ARS scores were significantly higher in the second highest tertile of plasma EPO compared to those in the lowest tertile.

Conclusion: These findings suggest that plasma EPO levels were related to some ADHD symptoms, which could be used in the monitoring of the disorder.

T2. Exploring Genomic Commonalities in ADHD and Multisite Chronic Pain

Victor de Oliveira, University of Sao Paulo

Background: Attention Deficit Hyperactivity Disorder is associated with pain. The treatment for pain involves analgesics, such as paracetamol. Epidemiological evidence has suggested a potential risk factor for ADHD in the offspring of pregnant women who use paracetamol. Our primary goal is to pinpoint genomic regions contributing to the genetic overlap between ADHD and multisite chronic pain (MSP). Furthermore, we explored whether any of the identified genes or pathways intersect with the known pharmacological properties of paracetamol.

Methods: We utilized genome-wide summary statistics for ADHD and MSP. We estimated global and local genetic correlations (rg) between the phenotypes. Moreover, we performed an enrichment analysis of genes within identified regions and investigated whether they or their associated functions overlap with the pharmacokinetics or pharmacodynamics of paracetamol.

Results: Global rg between ADHD and MSP was positive and significant while the local analysis yielded 12 distinct loci. The enrichment analysis of the genes within these regions revealed a diversity of functions. There was no presence of paracetamol-metabolizing genes, and it did not overlap with known paracetamol pathways. However, after a "drug enrichment analysis" that suggests other possible pathways affected by paracetamol, the ADHD vs chronic pain-related pathways overlapped with “Neuron Projection Morphogenesis (GO:0048812)”, “Cell Morphogenesis Involved In Neuron Differentiation (GO:0048667)” and “NCAM1 Interactions (R-HSA-419037)”.

Conclusion: Our data contribute to the hypothesis that the connection between paracetamol use and ADHD may be mediated by the presence of pain and their shared underlying genetic background.

T3. The Relation Between the Congenital Zika Infection and Autism Spectrum Disorder Outcome

Patricia Beltrao-Braga, University of São Paulo (USP)

Background: In 2015, Zika virus (ZIKV) infection was first reported in Brazil as causing microcephaly and other developmental abnormalities in newborns, leading to the identification of the Congenital Zika Syndrome (CZS), which is marked by prejudice in the neurodevelopment even after birth. Viral infections have been considered as an environmental risk factor for neurodevelopmental disorders outcome, such as Autism Spectrum Disorder (ASD).

Methods: To investigate the impact of ZIKV vertical infection on brain development of children born with CZS, we produced 2D central nervous system (CNS) cells, like neurons and astrocytes, all derived from induced pluripotent stem cells (iPSC) from these patients. Besides CZS, some patients were also diagnosed with ASD.

Results: Comparing iPSC-derived neurons from CZS with a control group, we found lower levels of pre and postsynaptic proteins and a reduced number of functional synapses. Glutamate levels were also decreased. Additionally, the CZS group exhibited elevated levels of cytokine production, one of them, IL-6, already associated with ASD phenotype.

Conclusion: These findings suggest that ZIKV vertical infection may cause long-lasting disruptions in brain development during fetal stages, even without the virus after birth. These disruptions could contribute to the manifestation of neurodevelopmental disorders like ASD. Further studies are necessary to fully comprehend the mechanisms underlying these effects and develop potential interventions to mitigate the impact of ZIKV vertical infection on neurodevelopment.

T4. Maternal Immune Activation Alters Neurodevelopment in Offspring Prefrontal-Amygdala Circuitry in a Non-Human Primate Model

Erin Carlson, MIND Institute, University of California Davis School of Medicine

Background: Epidemiological research has shown that maternal infection during pregnancy is associated with an increased risk of offspring neurodevelopmental disorders, including autism and schizophrenia. The nonhuman primate (NHP) model of maternal immune activation (MIA) in pregnancy provides a critical translational bridge for understanding the impact of MIA exposure on highly derived circuitry in the primate brain. Previous research in our Poly-IC-based rhesus macaque model has shown altered development of the prefrontal cortex in MIA-exposed NHPs, including reduced prefrontal cortical volumes, aberrant morphology of pyramidal neurons, and altered expression of synaptic genes.

Methods: We applied precision sampling techniques to isolate fresh frozen tissue from temporal lobe blocks in a pilot sample (N=4 MIA-exposed vs. 4 saline controls). Samples from the lateral and central nucleus of the amygdala were processed into single nuclei suspensions and analyzed using single-nuclei RNA-seq (snRNA-seq). We additionally analyzed neuroimmune protein concentrations using multiplexed bead assays in the same cohort across a broader distribution of anatomical regions in the temporal lobe.

Results: We identified unique cellular population profiles and region-specific patterns of differential gene expression (DGE). Specifically, genes associated with synaptic architecture and function were most strongly affected in MIA-exposed offspring. We additionally found altered distribution of neuroimmune proteins, including TGF-a, in the basolateral amygdala, as well as the entorhinal cortex and white matter.

Conclusions: These results support the hypothesis that prenatal MIA exposure results in lifelong changes in amygdala development in primates that contributes to aberrant social behavior observed in the MIA-exposed NHP.

T5. Autism Risk Genes Converge on Cilia

Elina Kostyanovskaya, UCSF

Background: Autism spectrum disorder (ASD) is highly comorbid with cilia-related disorders like congenital heart disease, hydrocephalus, blindness, and asthma. However, the role of ASD risk genes at the cilium has not been systematically investigated. Cilia are small membrane-bound organelles present in almost all cells of the body, including neurons, and are critical for neurogenesis, neuron activity, and many more processes that have been implicated in ASD. Our group has previously shown that two high-confidence ASD risk genes, DYRK1A and KATNAL2, are required for cilia formation in vivo. Therefore, we hypothesize that ASD risk genes may converge at the cilium.

Methods: Here we use the high-throughput diploid frog model X. tropicalis for genetic analysis of many ASD risk genes in live, intact embryos, and validate our results in human iPSC-derived neurons.

Results: Here we show that numerous high-confidence, large-effect autism risk proteins of diverse annotated function localize to cilia in vivo, and that ASD-associated patient variants disrupt this localization. Loss of function causes convergent defects in ciliogenesis, which can be rescued by supplying the human version of the gene. Building on these findings, we test for broader evidence of convergence among the top 255 strongest associated ASD risk genes and find compelling enrichment for cilia-related biology.

Conclusion: These results add to mounting evidence that ASD risk genes converge on the cilium, and that the abundance of comorbid cilia-related disorders may stem from common pathobiology.

T6. Quantifying the Developmental Trajectory of Autism Associated Brain Overgrowth Using MRI and 3D Cellular Resolution Imaging

Felix Kyere, University of North Carolina at Chapel Hill

Heterozygous Chd8 loss of function mutations are associated with macrocephaly in both humans and mouse models, and autism in humans. Our goal is to quantify cells across the entire neocortex in both Chd8V986*/+ mice and wildtype (WT) littermate pairs to determine the cell types that drive ASD-associated macrocephaly using whole-brain MRI and light-sheet imaging.
Nine littermate pairs of brains per sex per genotype (P4 and P14, total N=72) were imaged at 60μm isotropic resolution using MRI to quantify volume differences. Additionally, we generated 3D cellular resolution (0.75μm x 0.75μm x 4μm) images from the same brains at P4 using iDISCO+ tissue-clearing and labeled them with nuclear markers for all nuclei (TOPRO), deep- (CTIP2), and upper-layer neurons (BRN2).

Cortical volumetric differences, measured from MRI, were not detected across genotypes at P4 (P=0.62; N=36); however we observed 3.23% increase in brain volume across genotypes at P14 (P=0.00028; N=36), suggesting a temporal dependence of Chd8 haploinsufficiency on brain structure. We quantified all the nuclei in the P4 cortex using a trained machine learning algorithm (precision=0.963; recall=0.899; 3D training data =25,000 nuclei). We did not detect significant cell count or density differences across genotypes in the P4 isocortex (P=0.66; N=20). However, we detected sex differences in cell counts (13% more cells in female hippocampus and basal ganglia compared to males, P=0.039, N=20), but not density.

Our results suggest that the effects of Chd8V986*/+ on brain development may be time-dependent. We are now focusing on assessing cell- and region-specific effects of Chd8V986*/+ mutation.

T7. Multi-Dimensional Characterization of Chd8 Haploinsufficiency on Mouse Cerebellar Development
Nicolas Seban, UC Davis Center for Neuroscience
Background: The role of the cerebellum (CB) in proprioception and motor control is well-established, however recent studies strongly implicate this structure in higher order cognitive functions that are tightly related to Intellectual Disability and Autism Spectrum Disorder (ASD). Nevertheless, its role in non-motor contributions is often overlooked in ASD research. Mutations in the chromatin-remodeling factor CHD8 are strongly associated with ASD. Studies in haploinsufficient Chd8 mice have focused on the forebrain, mostly cerebral cortex, exhibiting ASD-relevant genomic, neuroanatomical, and behavioral pathology.
Methods: We are analyzing differential gene expression, chromatin accessibility, and developmental trajectory in the CB via paired snRNA-seq and snATAC-seq from Chd8 gender-balanced cohorts of heterozygous mutants and wild-type littermates. We examined gross neuroanatomy via immunohistochemistry (IHC) and are validating cell-type specific differential expression (DE) via RNA fluorescence in situ hybridization (FISH). Electrophysiological properties of key CB neurons were examined via patch clamp recordings.

Results: We found no gross changes in CB anatomy or major cell populations via IHC, but extensive cell-type specific DE and linked differential accessibility (DA) in mutant Chd8 mice. These results suggest a broad developmental asynchrony phenotype, most prevalent in Purkinje cell neurons and molecular layer interneurons, raising the possibility of altered circuit assembly or function. Electrophysiology and RNA FISH validation experiments are ongoing.

Conclusions: Our preliminary findings generate a foundation for future expanded studies towards the ultimate goal of understanding how the Chd8 mutation impacts the development of specific cerebellar cell-types and circuits, and how aberrant CB signaling is associated with ASD-relevant neuropathology.

T8. Sustained Rescue of Social Deficits in a Mouse Model for ASD
Pierre Llorach, UNC Chapel Hill
Background: Dysfunction of the serotonin (5-HT) system has long been associated with sociability deficits in psychiatric and neurodevelopmental disorders, notably autism spectrum disorder (ASD). Therapeutics targeting the 5-HT system (SSRIs) are often ineffective in treating social impairments, thus new treatments are needed. Mice with heterozygous Arid1b deletion selectively in 5-HT neurons (SertCre+/-;Arid1bflx+/-) display impaired social behavior, providing a mouse model for ASD. Previous publications demonstrate that a 5-HT1b receptor agonist or MDMA acutely reverses social deficits present in multiple mouse models for ASD. Here we investigate the neural mechanisms underlying the long-lasting rescue of a two-dose MDMA regimen.
Methods: We utilize mouse models of social behavior (3-chamber sociability assay) in combination with pharmacology, optogenetics, fiber photometry and slice electrophysiology.

Results: We find that a two-dose regimen of MDMA induces a long-lasting rescue of social deficits independently of the 5-HT1b receptor. c-Fos analysis revealed the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc) have altered activity following two doses of MDMA. We show that optogenetic modulation of mPFC-to-NAc terminals is sufficient to induce this sustained reversal of social deficits. Dual-site fiber photometric recordings show changes in Ca2+ dynamics between experimental groups and across behavioral sessions. Electrophysiological data suggests modifications in synaptic strength of mPFC-to-NAc neurons in this phenotype.

Conclusion: Our work identifies a neural circuit and synaptic adaptations underlying the long-lasting rescue of social deficits induced by a two-dose MDMA regimen. These findings provide a target for future investigation, to identify a molecular locus for therapeutic intervention.

T9. Deciphering Molecular Link Between Hypoxia, Circadian Dysregulation, and Autism Spectrum Disorder (ASD)
Li Li, Stanford University
Background: Human brain development involves fine sculpture of the neuronal network through eliminating redundant synapses by astrocytes; malfunction of this process is associated with ASD. Neonates experienced hypoxic episodes have higher risk of developing ASD. The mechanistic link between hypoxia exposure and ASD development has not been revealed. We developed human cortical organoids (hCOs) from induced pluripotent stem cells (iPSCs) to recapitulate human brain development and applied it to study hypoxia effects on astrocytes at neonatal-equivalent stages. Methods: We generated hCOs from 4 iPSC lines and cultured them till 10 months, a timepoint resembling neonatal stage of development. We exposed astrocytes isolated from hCOs to hypoxia conditions performed RNA-sequencing. To evaluate their capability of eliminating synapses in vitro we performed synaptosome engulfment assays. We validated the in vitro findings in a mouse model. Results: We identified hypoxia decreases astrocyte engulfment of synaptosomes. Transcriptome analyses revealed circadian rhythm pathway dysregulation under hypoxia, which we confirmed using PER2::LUCIFERASE assay. Knocking-down a key clock gene up-regulated by hypoxia, REV-ERBα rescued synaptosome elimination defect in hypoxic astrocytes. Increased REV-ERBα activity using agonists was sufficient to decrease synaptosome engulfment by astrocytes, which was replicated in vivo in adult mouse hippocampus.
Conclusion: Our study identified a novel mechanistic link between hypoxia, circadian rhythm disruptions, and synapse elimination by astrocytes. These findings uncover previously unknown role of circadian rhythm in neuropsychiatric disorders development.

T10. Measuring Neuronal and Glial Contribution to Brain Overgrowth in an Autism-Associated Mutation
Ian Curtin, Univ. of North Carolina at Chapel Hill
Background: De novo mutations within the Chd8 gene are strongly linked to ASD and macrocephaly in both clinical and preclinical studies. Using a Chd8V986*/+ mouse model, we aim to identify the brain regions and specific neural cell types contributing to the increase in brain size.
Methods: We collected Chd8V986*/+ mice and their WT littermates at P14 (9 per sex per genotype; total N = 36) and measured brain volume using MR imaging across all brains collected. The same brains are undergoing cellular resolution imaging using tissue clearing (iDISCO+) followed by light-sheet microscopy (resolution = 0.75um x 0.75um x 4um). Brains are being labeled with markers for all nuclei (TOPRO), neuronal (NEUN) and glial cell nuclei (SOX9). We are finalizing acquisition of cellular resolution images (28 of 36 collected).

Results: We detected significant increases in brain volume for Chd8V986*/+ at P14, including whole brain volume (~3%, $p < 0.05$), cortex (2.5%, $p < 0.05$), hippocampus (~1.2%, $p < 0.05$) and fiber tracts (~1.6%, $p < 0.05$). These differences are consistent when stratified by sex (N = 18 per sex) and provide clear evidence for Chd8V986*/+ mediated brain overgrowth. We have optimized and validated the iDISCO+ protocol using neural nuclear-specific antibodies. We will use these combined datasets to assess the cellular basis of macrocephaly.

Conclusions: Our results replicate previous reports of significant increases in brain volume in Chd8V986*/+ mouse models. We will test whether volume increase is driven by increased numbers of neurons or glia, and in what brain regions.

T11. Autism Risk Genes are Required for Enteric Nervous System Development
Kate McCluskey, University of California, San Francisco

Background: People with autism spectrum disorder (ASD) are 3-4 times more likely to experience gastrointestinal (GI), but the underlying biology is unknown. The gastrointestinal tract is innervated by the enteric nervous system (ENS), which controls gastric motility. Many large-effect risk genes have been identified for ASD and work in our lab has shown that these top ASD genes are required for neuron development in the brain. Here we develop Xenopus tropicalis as a powerful model to study the effect of autism risk gene mutations on ENS development.
Methods: Our lab leverages the frog model Xenopus tropicalis to perturb multiple autism risk genes in parallel to investigate convergent mechanisms. Here we targeted 2 high-confidence, large-effect ASD risk genes of differing cellular annotations and assayed development of the neural crest and ENS progenitors.

Results: We show that disruptions in DYRK1A (kinase) or CHD2 (chromatin modifier) cause defects in the migration of neural crest cells into the gut. We determined that the migration defects can be independent of crest specification defects by inhibiting Dyrk1a pharmacologically after specification was complete. Then we profiled GI symptoms from patient clinical records for many top ASD risk genes and observed high incidence of GI dysmotility issues.

Conclusions: Our results suggest that ASD risk genes of disparate known biological function converge to affect ENS progenitor migration. We are planning to knockdown these ASD risk genes to model constipation in tadpoles and use drug screening to rescue these defects to uncover mechanisms that will be clinically translatable.

T12. Alterations to Inhibitory Synapse Distribution and Synaptic Gene Expression in the Amygdala in Autism Spectrum Disorder

Kari Hanson, University of California-Davis

Background: Alterations to the balance between excitatory and inhibitory (E/I) neuronal activity has been hypothesized to underlie local and systems-level dysfunction in neurodevelopmental disorders, including autism spectrum disorder (ASD). Aberrant structure or function of the amygdala in ASD has been associated with deficits in social behavior and cognition. We hypothesized that neuron loss with age in the amygdala may disproportionately affect inhibitory GABAergic neurons, contributing to E/I imbalance.
Methods: We utilized design-based stereological methods to estimate the total numbers of immunohistochemically stained GAD65/67 (GAD) and parvalbumin-positive (PV) interneurons in the lateral, basal, and accessory basal nuclei in a sample of ASD and neurotypical cases. We additionally examined a subset of cases to measure the density of excitatory and inhibitory synapses using immunolabeling for Synapsin 1 and PSD95 or GAD65/67. Further, we quantified gene expression in bulk tissue samples from the lateral and basal nucleus and paralaminar region using Quantigene Plex gene expression assays.

Results: Preliminary analyses indicate no significant differences in total GAD or PV neuron numbers or their density between ASD and neurotypical cases in the basolateral nuclei. However, we found a significantly higher density of GAD+ synapses in both the basal and lateral nuclei. We further found a significant increase in the expression of SLC17A7 (VGLUT1) in the lateral nucleus, suggesting altered excitatory gene expression, with no significant differences in GAD1 expression.

Conclusion: Together, these data support the hypothesis that E/I imbalance is a feature of the pathophysiology of ASD that may contribute to progressive socioemotional impairments.

T13. Network Analysis Temporally Linking Causal ADHD and Autism Genes to Co-Occurring Traits and Biomarkers

Catriona Miller, University of Auckland

Attention-deficit/hyperactivity disorder (ADHD) and autism are neurodevelopmental conditions with substantial variation in long-term outcomes between individuals. Epidemiological and clinical studies have identified many co-occurring conditions of autism and ADHD; however, the genetic links have not been fully resolved.
In this study, we integrated different levels of biological information (genetic variants, gene expression, and protein-protein interactions) to investigate the genetic relationships between both autism and ADHD and co-occurring traits. We also conducted a two-sample Mendelian Randomization analysis to identify putatively causal genes.

Our network analysis highlighted clusters of genes linked to the intersection between autism and ADHD and their co-occurring traits. For example, the 17q21.31 locus associated with neurological traits, the 3p21.1 locus associated with cognition and worry, and FADS1/FADS2 associated with metabolic traits. Four non-coding genes (i.e. LINC02210

LRRC37A4P, RP11-259G18.1, RP11-798G7.6) and four coding genes (i.e. ST3GAL3, TIE1, PIDD1, and PTPRF) were identified in cortical tissue as putatively causal for autism and ADHD, respectively. Downstream causal gene network analysis identified biological pathways linking the ADHD putatively causal genes with eye conditions, rheumatoid arthritis, and potential biomarkers, including lymphocyte count and lipoprotein (a) levels.

Our results support the hypothesis that an individual's phenotype is partially determined by their genetic risk for co-occurring conditions. Overall, this study provides insights into the tissue dependent, temporal relationship between both ADHD and autism with co-occurring traits and highlights potential biomarkers. These findings could be used to develop predictive models for improved clinical management and personalization of diagnosis.

T14. A New NLGN4X Variant Cluster in Autism Spectrum Disorder

Eunhye Hong, National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH)

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties in social interactions, deficits in communication, and repetitive behaviors. Numerous genes have been identified as potential contributors to ASD based on both human genetics and etiological evidence. Among these genes, neuroligins (NLGN1-3, NLGN4X, and NLGN4Y) have emerged as strongly linked to ASD. NLGNs are postsynaptic cell adhesion molecules that interact with presynaptic neurexins (NRXNs) and play a crucial role in neuronal development, synaptic transmission, and synaptic plasticity. Within the NLGN family, NLGN4X stands out with the highest number of variants associated with ASD. Most of these rare variants are located within the extracellular esterase homology domain, and these mutations lead to issues with surface expression and impaired neuronal function. Notably, multiple variants within the first 100 amino acids of NLGN4X (Nguyen et al., Neuron, 2020) display trafficking defects. We have now identified a new cluster of variants slightly downstream (aa 235-245) from the previously characterized cluster. These new variants are linked to severe trafficking defects in NLGN4X. Analysis of the crystal structure has revealed that each of these variants is likely to disrupt the overall structure, leading to significant steric clashes with surrounding residues. Through extensive biochemical and imaging studies, we have revealed that these variants exhibit impairments in maturation, surface expression, and synaptogenesis. This discovery sheds light on the structure/function relationship of ASD variants and provides valuable insights into potential therapeutic targets for individuals affected by this condition.

T15. Understanding Social and Attachment Deficits in ASD

Gina Williams, University of California - San Francisco

Background: Interrogating the neurobiology underlying the pathogenesis of ASD in traditional animal models is hampered by limited social behaviors in these species. Prairie voles are highly social rodents which display diverse, robust social behaviors and long-term relationships. Comparative studies suggest that the neural and genetic mechanisms mediating such attachments may be conserved across mammals that display such behaviors, making this species a powerful system to understand the biology of neuropsychiatric conditions characterized by the disruption of social behaviors.

Methods: We generated prairie vole mutant lines bearing a loss of functional allele of Scn2a, a high-confidence ASD-associated gene, and characterized the social behaviors of juvenile and adult heterozygous mutants. We assessed the social dynamics of heterozygous male and female Scn2a mutant prairie voles as compared to wildtype siblings through a battery of behavioral assays to investigate social behavior of these animals at multiple timepoints and throughout pair bonding.

Results: We found that mutants heterozygous for Scn2a display distinct, sex-specific, and context-specific differences in social dynamics across the lifespan. Specifically, Scn2a-/+ juvenile females show a decrease in play fighting as compared to wildtype siblings. Scn2a-/+ adult female prairie voles show increased aggression when introduced a novel conspecific and delayed partner preference. Scn2a-/+ adult male prairie voles display atypical prosocial behavior with a novel stranger as compared to wildtypes.

Conclusion: These experiments lay the groundwork to uncover potential biological mechanisms underlying social deficits in genetic models of ASD and determine if the neural or genetic differences observed in mutants persist throughout the lifespan.

T16. Recent Studies on Bipolar Disorder and ADHD

Alagu Thiruvengadam, School of Medicine University of Maryland

State of the art diagnosis of mental illness is controversial. There are no biological markers for diagnosing any mental illness. The Membrane Potential Ratio (MPR) offers hope to be the first biological marker that could be used for both diagnosis and monitoring the treatment response. The Membrane Potential Ratio (MPR) is the ratio of the membrane potential of whole blood cells in a test buffer to that in a reference buffer. MPR is lower for bipolar disorder (BD) patients when compared to that of a group of ADHD patients. Others with and without mental illness are classified as Negatives. The MPR values for Negatives fall between BDs and ADHDs. The MPR responds readily to successful treatments. This result could be used to monitor the progress of treated patients. In addition, the medication response characteristics of the MPR serve as a self-validation for the MPR test itself. The cause of these effects observed in RBCs is explained by the diacylglycerol (DAG) pathway modulating human small conductance potassium channels (hSK). Since the hSK family is widely distributed in neurons, the differences observed in RBCs among BDs, ADHDs and Negatives are explained by this finding. Knowledge of this signaling pathway elucidates how lithium treats bipolar disorder. Additionally, the mechanism of induced switching associated with certain antidepressants given to patients who are bipolar can also be explained by this pathway. Further research on this pathway would lead to new drug development for these illnesses.

T17. Breath Biopsy in Psychiatry: A Systematic Review

Ayse Irem Sonmez, The University of Minnesota

Non-invasive exhaled breath analysis identifies biomarkers that are indicative of health conditions by analyzing the chemical composition of exhaled breath. In this study, we examined exhaled breath methods and the results of studies in relation to psychiatric and neurocognitive disorders.

PRISMA guidelines were used to conduct a systematic review of the literature. Our search in March 2023 included PubMed, Scopus, and Web of Science. Inclusion criteria included: enrollment of individuals 18 years or older; use of any version of exhaled breath analysis with quantitative results; discussion of findings in relation to the brain or psychiatric disorders; and availability of full-text in English. Participants 17 years of age or younger, animal studies, conference abstracts, systematic reviews, and case studies were excluded.

We identified 954 papers after removing duplicates. Title and abstracts were reviewed and full text was retrieved for 38 studies, 17 of which met the inclusion criteria. In four studies, electronic noses were used, whereas in the remaining studies, exhaled breath samples were collected with Tedlar bags and analyzed with gas chromatography mass spectrometry. Seven studies investigated the effects of smoking, one study examined sleep stages on exhaled breath. Diagnoses included MS, schizophrenia, Alzheimer's, Parkinson's, complex regional pain syndrome, Major Depressive Disorder, methadone use, and Amyotrophic Lateral Sclerosis. These diagnoses were distinguished from healthy control subjects by breath analysis, which also identified multiple metabolic markers.

Breath biopsy is a feasible and promising method to investigate biomarkers in psychiatric disorders. Further clinical and translational research is needed in this field.

T18. Precision Medicine for Psychotic Disorders: Objective Assessment, Risk Prediction, and Pharmacogenomics

Alexander Niculescu, Indiana University School of Medicine

Background: Psychosis occurs inside the brain, but may have external manifestations (peripheral molecular biomarkers, behaviors) that can be objectively and quantitatively measured. Blood biomarkers that track core psychotic manifestations such as hallucinations and delusions could provide a window into the biology of psychosis, as well as help with diagnosis and treatment.

Methods: We endeavored to identify objective blood gene expression biomarkers for hallucinations and delusions, using a stepwise discovery, prioritization, validation, and testing in independent cohorts design.

Results: We were successful in identifying biomarkers that were predictive of high hallucinations and of high delusions states, and of future psychiatric hospitalizations related to them, more so when personalized by gender and diagnosis. The top biological pathways uncovered by our work are glutamatergic synapse for hallucinations, as well as Rap1 signaling for delusions. Some of the biomarkers are targets of existing drugs, of potential utility in pharmacogenomics approaches (matching patients to medications, monitoring response to treatment). The top biomarkers gene expression signatures through bioinformatic analyses suggested a prioritization of existing medications and nutraceuticals, such as valproate, clozapine, lithium, fluoxetine, and omega-3 fatty acids. Finally, we provide an example of how a personalized laboratory report for doctors would look.

Conclusions: Overall, our work provides advances for the improved diagnosis and treatment for schizophrenia and other psychotic disorders.

T19. Neurodevelopmental Centiles and Regional Vulnerability to Schizophrenia and Autism Spectrum Disorder in 22q11.2 Deletion Syndrome

Zachary Trevorrow, University of Washington

Background: 22q11.2 deletion syndrome (22q11DS) is associated with neuroanatomic changes and elevated risk for schizophrenia (SCZ) and autism spectrum disorder (ASD). However, neuroanatomic metrics change across development and similarity of psychosis- or ASD-related brain alterations in 22q11DS versus idiopathic SCZ and ASD is unclear. We examined age-normalized differences in cortical surface area (SA) and thickness (CT) in 22q11DS with or without psychosis (22qPsy+/22qPsy-) and with or without ASD (22qASD+/22qASD-), and similarity of differences across regions to those observed in idiopathic schizophrenia and ASD.

Methods: SA and CT metrics were derived from T1-weighted MRI for 412 controls and 437 22q11DS patients (50 22qPsy+/387 22qPsy-; 77 22qASD+/78 22qASD-) using FreeSurfer, and normalized for age and sex using the BrainChart reference dataset. Regional vulnerability/similarity (RVI) across regions to idiopathic SCZ and ASD were calculated using effect size maps from ENIGMA TOOLBOX.

Results: All 22q11DS groups had lower age-normalized SA than controls (p's < .005), with no significant differences between 22q11DS groups. 22qPsy- had thicker age-normalized CT than 22qPsy+ and controls (p's < .05); 22qPsy+ and controls were similar. CT was higher for both 22qASD+ and 22qASD- than controls (p's < .005), and did not differ from one-another. 22qPsy+ had higher SCZ-RVI for CT and SA than 22qPsy- and controls, with 22qPsy- showing lower SCZ-RVI CT than controls (p's < .05). 22qASD+ and 22qASD- did not differ in ASD-RVI but were both higher than controls (p's < .05).

Conclusions: Findings suggest that ASD does not significantly impact brain changes already present in 22q11DS, while psychosis is associated with neuroanatomic differences aligned with idiopathic schizophrenia.

T20. Excitatory Dysfunction Drives Network Deficits in a Schizophrenia 16p11.2 Duplication iPSC Derived Neuronal Model

Euan Parnell, Northwestern University

The 16p11.2 locus is a highly penetrant copy number variant (CNV) linked to autism spectrum disorders (ASD), intellectual disability (ID) and schizophrenia (SCZ). Whereas both duplication and deletion at the 16p11.2 locus are risk factors for numerous neurodevelopmental disorders, only duplications are linked to schizophrenia. There appears therefore, to be a unique role of 16p11.2 duplication in schizophrenia risk, suggesting a distinct etiological role for 16p11.2 duplication. Using induced iPSC-derived cortical neurons from crispr-cas9 isogenic 16p11.2 duplication lines and SCZ patient lines, penetrant 16p11.2 duplication phenotypes that may contribute to SCZ susceptibility were identified. Transcriptomic analyses identified deficits in neurite outgrowth, calcium handling and cell-cell junction gene expression. Consistent with this, iPSC from both isogenic and patient lines showed robust alterations in morphology calcium handling. Moreover, these deficits converged on a penetrant alteration in network activity, revealed by multi-electrode array and network calcium imaging. Interestingly, network dynamics deficits were unchanged in the presence of iPSC-derived inhibitory neurons, supporting 16p11.2 duplication as a causative factor in excitatory cortical neuronal network dysfunction. These factors may contribute to excitatory neuron dysfunction in 16p11.2 duplication carriers early in development and promote cortical dysfunction and, thus, SCZ risk.

T21. Mitochondrial Dysfunction in 22q11.2 Deletion Syndrome Neuropathology

Dhriti Nagar, School of Medicine, Stanford University

Background: The 22q11.2 microdeletion syndrome (22q11.2DS) is the most common microdeletion, with a prevalence of approximately 1-in-1,000 fetuses and 1-in-4,000 live births. This syndrome is clinically characterized by congenital heart defects, immune system dysfunction, and a 20-fold increase in susceptibility to psychosis. This deletion impacts genes essential for mitochondrial function, affecting energy production and synaptic function in neurons. Studies on rodent models and organoids from affected individuals highlight anomalies like abnormal mitochondrial structures and hyperexcitability in excitatory neurons.

Methods and Results: We utilized the innovative human brain organoid model to investigate mitochondrial morphology and metabolism within excitatory neural progenitor cells specific to 22q11.2DS. We also found imbalances in the

glutamate/glutamine ratios in excitatory neurons. Delving further with human forebrain assembloids derived from 22q11.2DS iPSCs, we discerned compromised migration patterns in inhibitory neurons coupled with mitochondrial fragmentation. Comprehensive metabolic analysis of 22q11.2DS organoids indicates reduction in mitochondrial metabolic capacity. At the molecular level, an abnormal phosphorylation pattern of the mitochondrial protein DRP1 was noted, but treatment with the inhibitor Mdivi-1 showed promise in addressing these anomalies. Our future endeavors will leverage multielectrode array recordings, multi-omic profiling, and scRNA sequencing.

Conclusion: Overall, our research seeks to unpack the mitochondrial aspects of 22q11.2DS using human brain organoids and explore potential interventions. By performing in-depth investigation of the contribution of mitochondrial dysfunction to the excitation-inhibition balance in 22q11.2DS, the scientific insights from this project will fill a critical gap in current knowledge and foster the development of targeted therapies using novel in-vitro screening strategies.

T22. Glyoxalase I as an Alternative Molecular Target for Novel Fast-Acting Antidepressant Drugs Following Chronic Mild Stress

Martina Ulivieri, University of California - San Diego

Background: Depression is a complex mood disorder affecting millions of people of all ages worldwide. Current medications require weeks of treatments and are inefficient in a wide range of patients (30-40%). Ketamine remains the only fast-acting antidepressant compound clinically approved, but still lacks the effectiveness in ≈30% of patients and possesses abuse liability. We recently demonstrated that subchronic Glyoxalase I (Glo1) inhibition induces antidepressant effects following chronic mild stress (CMS). Glo1, is a key enzyme mediating the catabolism of methylglyoxal (MG), an endogenous GABAA partial agonist. Our study aims to investigate the fast-acting antidepressant properties of methylgerfylin (MeGFN), a Glo1 inhibitor, after acute systemic administration.

Methods: Male and female Balb/c mice will be exposed to 6-weeks of CMS and tested in a battery of behavioral tasks resembling depressive behaviors: sucrose preference, reward seeking following reward omission, effort-related choice (ERC), social interaction, coat-state, open field, forced swim test (FST). Animals will receive MeGFN, ketamine (fast-acting antidepressant control group) or their respective vehicles.

Results: A single MeGFN injection is able to relieve depressive behavior assessed both in the coat-state and FST, and restoring social interaction dysfunction without affecting locomotor activity within 24/48 hours. Moreover, through our studies we clarify the impact of CMS and acute effects on reward seeking after disappointment, and ERC and elucidate gender differences present in the protocol and in the antidepressant effect of MeGFN.

Conclusions: Through our data we demonstrated that glyoxalase system, and particularly Glo1 enzyme is a novel suitable molecular target for novel fast-acting antidepressant drugs.

T23. Sex Differences in a Stress Induced Depressive Phenotype: A Time Course of Behavioural and Central Effects

Maja Ramljak, Carleton University

Background: Females show a two-fold increase in the prevalence of mood and anxiety disorders. Similarly, there are sex differences in cognitive, depressive, and anxiety behaviours following exposure to acute and chronic stressors in rodents. We have previously shown that astroglial cells respond to five weeks of chronic stress by upregulating perineuronal net (PNN) components, leading to an upregulation of PNNs themselves surrounding interneurons in the mPFC. However, the timing of the onset of these changes in response to chronic stress is unknown in addition to whether there are sex differences in their onset or trajectory.

Methods: We employed a rodent model of chronic variable stress (CVS) whereby male and female mice were exposed to a time course of chronic stress ranging from one to five weeks in duration followed by a battery of behavioural testing to assess depressive/anxiety-like behaviours and histopathological analysis of their brains.

Results: We found sex differences in depressive and anxiety-like behaviours over time whereby males and females show baseline differences and males respond to stress earlier. There was a significant effect of stress on emotive behaviours as early as one-week post-stress onset in males and by two weeks both sexes showed similar stress-induced phenotypes compared to controls. Cell-specific differences in both the timing and nature of chronic stress were also observed. For example, microglial cells show an activated state as early as one week post-stress.

Conclusion: Altogether, these data show sex differences in behavioural and cellular patterns of response to chronic stress over time.

T24. SARS-CoV-2 Vaccination in Pregnancy and Postpartum Depression

M. Mercedes Perez-Rodriguez, Icahn School of Medicine at Mount Sinai

Background: The SARS-CoV-2 vaccine protects against severe COVID-19 disease during pregnancy. As the brief inflammatory reaction after vaccination may impact depressive symptoms per the neuroinflammatory hypothesis of depression, we aimed to explore a potential association between SARS-CoV-2 vaccination during pregnancy and postpartum depression.

Methods: Sample: Pregnant individuals (n=627) from Generation C (n=564) and Generation C-SF (n=63) cohorts at Mount Sinai Health System, NY (04/2020-09/2023). Assessments: Edinburgh Perinatal Depression Scale (EPDS) at 1-9 months postpartum. SARS-CoV-2 vaccination status/timing were determined from vaccination records. Quantile regression examined the relationship between SARS-CoV-2 vaccination timing (categorical predictor) and EPDS scores (continuous outcome), adjusting for relevant covariates. Groups based on vaccination timing: 1) vaccinated, at least one dose during pregnancy, 2) vaccinated, all doses before pregnancy, 3) vaccinated, at least one postpartum dose before EPDS assessment but none during pregnancy, 4) no history of SARS-CoV-2 vaccination (reference group).

Results: 100 (16%) participants were vaccinated during pregnancy, 94 (15%) before pregnancy, 57 (9%) postpartum, and 376 (60%) were not vaccinated. Among participants vaccinated during or prior to pregnancy, there were no significant associations between vaccination and EPDS scores in any quantile. Those vaccinated postpartum but before EPDS only showed a significant negative association at the 75% quantile (Coefficient=-1.41,CI=-2.46;-0.48) but not in other quantiles.

Conclusions: SARS-CoV-2 vaccination before/during pregnancy was not significantly associated with postpartum depression. Postpartum SARS-CoV-2 vaccination was associated with slightly lower EPDS scores in those with more depressive symptoms. Those with less severe depression may be more likely to seek medical care including vaccination.

T25. Pan-UK-Biobank Trans-Ancestry GWAS of Major Depression: Genomic Discovery and Portability

Roseann Peterson, State University of New York Downstate Medical Center

Most genome-wide association studies (GWAS) in the UK Biobank (UKB) have been restricted to ~360,000 “White-British” unrelated individuals, excluding 27% of the participants (either related or non-White-British). Recent studies show that combining relatively small cohorts of non-European ancestries with a larger European-ancestry sample can enhance the power of GWAS, the fine-mapping of genome-wide significant loci, and the predictive performance of polygenic risk scores (PRSs) across populations. To realize these benefits in the UKB, we present a workflow for trans-ancestry GWAS, leveraging the genetic diversity in the UKB and including the related individuals to maximize sample size. We first statistically assigned the UKB samples to the closest-matching ancestry group, while examining the impact of using different reference panels. Through our approach, we incorporated ~35,000 non-European-ancestry (African, Admixed-American, Central/South-Asian, East-Asian, Middle-Eastern) and ~455,000 European-ancestry samples in GWAS. With depression as an example phenotype, we performed pan-UKB GWAS using two distinct approaches: 1) ancestry-stratified mixed-effects GWAS followed by cross-ancestry meta-analysis, and 2) joint trans-ancestry mixed-effects GWAS. In both approaches, mixed-effects models allow inclusion of related samples and traditionally determined ancestry outliers. We performed sensitivity analyses examining the robustness of mixed-effects GWAS to ancestry outliers. Compared to European-ancestry GWAS, diverse-ancestry analyses yielded more genome-wide significant loci, with the trans-ancestry mixed-effects GWAS having the highest power. Although the skewed ancestry distribution in the UKB prohibits differentiating population-specific genetic associations, the presented protocols can help improve inclusiveness in the near-term. Long-term, expanded recruitment of diverse populations remains imperative to achieve sample-size parity in genomic studies.

T26. Uncovering Genetics of Anorexia and Bulimia Nervosa Through Large Scale Sequencing

Franjo Ivankovic, Analytic and Translational Genetics Unit, Massachusetts General Hospital

Introduction: Both anorexia (AN) and bulimia (BN) nervosa are marked by a substantial genetic component, with family study heritability estimates of 0.58-0.76 for AN and 0.30-0.83 for BN. Despite the heritability estimates, discovery of genetic risk factors for AN and BN remain limited. Genome-wide association studies are limited in power and resolution,

and discoverability of genetic risk factors is hindered by study-design limitations such as potential confounding of BMI due to current AN nosology.
Method: We are conducting a blended genome exome (BGE) sequencing of an initial 10,000 AN/BN cases and 10,000 controls over the next 3 years. BGE is the most cost-efficient comprehensive genome profiling currently available, and it combines the whole genome of medium depth (4x) and the protein-coding exomes at high depth (30x) to capture critical, ultra-rare protein-coding variants.

Results: Preliminary imputation results showed that BGE generated 13.8 million imputed variants (INFO > 0.8) at a higher per-sample genotype concordance (mean=99.1%), compared to a genotype array with 7.8 million imputed variants and lower concordance (mean=98.2%).

Conclusion: BGE captures additional variants without enriching false positives and is a feasible method for cost-effectively capturing a spectrum of genetic variance ranging from common to ultra-rare. Our long-term goal is to use BGE to elucidate genetic architecture of AN/BN and identify ultra-rare variants and their impact on the disease risk.

T27. Decoding Neuropeptidergic Control of Stress-Induced Binge Eating in Claustrum
Jingyi Chen, University of Washington School of Medicine
The experience of stress promotes the development and persistence of binge eating behaviors. However, how and where stress-induced binge-eating behaviors happen is still largely unknown. Dynorphin (dyn)/kappa opioid receptor (KOR) neuropeptide system is well known for playing a crucial role in mediating the dysphoric and anhedonic aspects of stress. Recent studies show reduced binge eating behavior while maintaining normal hunger states when treated with opioid receptor antagonists. Given these findings, we aimed to explore the neural circuit basis of dynorphinergic control of stress-induced binge-like eating behavior in a mouse model. We found mice experienced 15 mins of the forced swim will significantly increase their food intake of familiar palatable food (high fat, high sugar, HPD) compared to non-stressed mice. We also found increased cFos-positive cells in the claustrum (CLS), a subcortical structure with highly abundant expression of KORs. When targeting CLSKOR cells through viral-mediated knockout, we have found intact KOR signaling in CLS is necessary for elevated binge-like eating in stressed mice. When infusing norBNI (KOR-antagonist) locally in CLS, we were able to block stress-induced binge eating, which indicates dynorphin release is critical for this behavior. We further characterize and dissect the dynorphinergic components of this behavior using dynorphin biosensors and in vivo imaging in CLS. We identify the anterior insular cortex as the dynorphinergic input to CLS for this behavior through tracing and optogenetic manipulation. By characterizing the neural circuit mechanisms involved and cell activity dynamics within the CLS, we aim to understand how neuropeptides regulate stress-induced binge eating.

T28. Adipose Tissue-Brain Interactions Modulate Activity Based Anorexia in Mice
Stephanie Dulawa, UCSD
Background: Anorexia nervosa (AN) is characterized by hypophagia, low body weight, and compulsive exercise. The activity-based anorexia (ABA) paradigm induces aspects of AN in rodents. We tested whether transplanting white adipose tissue (WAT) from high fat diet-fed obese mice into normal weight recipient mice would attenuate ABA in recipients. We also assessed whether the effects of transplanted obese WAT depends upon agouti-related peptide (AgRP) neurons.
Methods: Adult female C57BL6/J mice received a WAT transplant harvested from normal or obese mice (n=21/group). Four weeks later, recipient mice were tested for ABA. During baseline, food and running wheels were available. During restriction, running wheels were available, but food was only available 3 hours daily. Mice were removed from the study after losing 25% of their initial bodyweight. Next, an identical study was performed, except half of the mice in each transplant group underwent early life AgRP neuron ablation (n=12/group).

Results: Obese WAT recipients remained in the ABA paradigm longer than control WAT recipients ($X2=7.61$, $p < .01$). An AgRP ablation x transplant interaction was found ($X2=5.18$, $p < .05$). Post-hoc tests showed that AgRP ablation reduced survival in obese WAT recipients, but not control WAT recipients ($p < .05$). Furthermore, AgRP-ablated obese WAT recipients showed reduced survival compared AgRP-ablated control WAT recipients ($p < .05$).

Conclusion: Our results indicate that transplanting WAT from obese mice into normal weight recipients extends body weight maintenance in the ABA paradigm. This effect depends upon AgRP neurons, suggesting cross-talk between WAT and the brain in the regulation of an anorexia-related phenotype.

T29. Differences in Circadian Transcript Expression Rhythms in the Prefrontal Cortex Across Psychiatric Illnesses

Madeline Scott, University of Pittsburgh

Background: The importance of circadian rhythms in health and disease has become increasingly apparent, especially in psychiatry where sleep and circadian behavior disruptions are a common feature across many disorders. Our lab and others have identified differences in gene expression rhythms in Major Depression (MDD) and Schizophrenia (SCZ) using human postmortem brain tissue. Additionally, in the striatum of subjects with a history of psychosis, with either SZ or Bipolar Disorder (BD), we observed far fewer rhythms than in non-psychiatric comparison (NPC) subjects, suggesting that differences in gene expression rhythms may be more related to symptom presentation than specific diagnoses. The current study seeks to examine these differences across multiple disorders in two regions of the prefrontal cortex (PFC).
Methods: We performed RNA-sequencing on the dorsolateral PFC (DLFPC) and subgenual anterior cingulate (sgACC) of 249 subjects diagnosed with either MDD (n = 83), BD (n = 33), or SCZ (n = 50) and 83 NPC subjects. Rhythmicity analyses were performed on and compared between each diagnosis group, and then for groups determined by various demographic and clinical features including sex, psychosis, mood symptoms, death from suicide, nicotine use, and other medication statuses.

Results: Many differences in gene rhythmicity were observed, including pathway enrichment differences between sgACC and DLPFC that were specific to SCZ. An additional striking observation was that the MDD cohort had many more rhythmic genes than NPC subjects, which were specifically associated with mitochondria.

Conclusion: Across diagnoses we see differences in timing and identity of gene expression rhythms.

T30. Wnt Activity Reveals Context-Specific Genetic Effects on Gene Regulation in Neural Progenitors

Jordan Valone, University of North Carolina at Chapel Hill

Background: Gene regulatory effects in bulk-post mortem brain tissues are undetected at many non-coding brain trait-associated loci, perhaps because some genetic variants have distinct functions in specific contexts, like during stimulation of a developmental signaling pathway. Wnt signaling influences development of the cerebral cortex, so we measured the effects of common genetic variants on regulatory activity during Wnt stimulation.
Methods: We evaluated context-specific effects of genetic variation in a population of primary human neural progenitor cells (hNPCs; nmax= 82), by measuring chromatin accessibility (caQTLs) and gene expression (eQTLs) following stimulation of the canonical Wnt pathway (CHIR, WNT3A) or vehicle.

Results: Wnt-responsive regulatory elements (WREs) were enriched for variants associated with brain structure and neuropsychiatric disorders. Over 43,000 caQTLs regulating over 36,000 unique caPeaks were identified alongside over 3,000 unique eQTL-eGene pairs. Stimulation of the Wnt pathway increased the detection of genetically influenced REs/genes by 66.2%/52.7%, and led to the identification of 397 REs primed for effects on gene expression. Genetically influenced REs were enriched in regions under positive selection along the human lineage, including a previously validated enhancer of the Wnt receptor gene FZD8. We also found over 1,800 response-caQTLs and 102 response-eQTLs, where a significant genotype-by-condition interaction was detected. Context-specific molecular quantitative trait loci increased brain-trait colocalizations by up to 70%.

Conclusion: Our results characterize context-specific genetic effects in hNPCs that provide novel insights into neurodevelopmental gene regulatory mechanisms underlying brain trait-associated loci.

T31. Ultrastructural Markers of Glutamate Synaptic Function in Postmortem Human Prefrontal Cortex

Jill Glausier, University of Pittsburgh School of Medicine

Background: Investigations of individually-resolved synapses in human brain can provide unprecedented insight into the basis of normal and abnormal brain function. Analysis at this level of resolution requires a volume electron microscopic (VEM) approach to directly visualize synapses in three-dimensions (3D) within human brain tissue. Indeed, in vivo synaptic activity and function can be indexed by quantifiable synaptic and sub-synaptic ultrastructural measures in preserved ex vivo brain samples.
Methods: Dorsolateral prefrontal cortex (DLPFC) from a 62-year-old male decedent with no neuropsychiatric disorders was aldehyde-fixed and sectioned at 50um. Sections underwent high-contrast staining followed by resin embedding. DLPFC layer 3 was excised and imaged via focused ion beam-scanning electron microscopy (FIB-SEM). Synaptic bouton, active zone, spine and postsynaptic density (PSD) volumes were quantified in 50 DLPFC layer 3 glutamatergic synapses.

Results: All cortical neuropil components were readily identifiable in 3D, including Type 1 glutamatergic synapses. Analyses show the expected strong correlation between presynaptic active zone and PSD volumes (r=0.76), moderate correlation between postsynaptic dendritic spine and PSD volumes (r=0.36), and a mean synaptic vesicle diameter of 40.4nm and volume of 5.3e4 ± 2.1e4 nm3.

Conclusions: Our preliminary studies demonstrate DLPFC L3 samples of excellent fixation and staining for VEM by FIB-SEM. Quantitative analysis of sub-synaptic measures showed mean values and correlations consistent with prior ultrastructural studies. Overall, our study supports the compatibility of postmortem human brain tissue research with FIB-SEM. Future applications of this workflow can directly inform the basis of cellular and synaptic dysfunction in individuals with psychiatric disorders.

T32. Spatial and Multi-Omics Characterization of Spiny Projection Neuron Heterogeneity in the Adult Striatum

Jenesis Kozel, University of Pittsburgh

Background: Striatal dopamine (DA) neurotransmission is implicated in a wide variety of behaviors, particularly in addiction. The striatum is primarily composed of spiny projection neurons (SPNs) that historically have been segregated into two subpopulations based on the expression of stimulatory D1-like receptors versus inhibitory D2-like receptors. Increasing evidence supports the existence of SPNs that co-express multiple DA receptors, yet it remains unclear whether these co-expressing cells represent a population distinct from cells that express only D1-like or D2-like receptors alone. To address this, we definitively identified and then characterized these different SPN subpopulations in striatum using a combination of imaging and multi-omics approaches.

Methods: We used multiplex RNAscope to define the precise spatial localization of the predominantly expressed striatal DA D1 (D1R), D2 (D2R) and D3 (D3R) receptors across dorsal-ventral and rostral-caudal axes. Additionally, we employed complementary single-nuclei multi-omics analyses across multiple species to create a merged atlas of striatal cell subtypes.

Results: We reveal heterogeneous subpopulations of SPNs that are uniquely distributed along dorsal-ventral and rostral-caudal axes in the adult mouse striatum. These SPNs co-express multiple DA receptors, including D1R/D2R and D1R/D3R, and display sex differences. We standardized the D1/2R-co-expressing neurons as "eccentric SPNS", which contain discrete subtypes based on spatial distribution and conserved marker genes. We also find that these striatal cellular subtypes have unique correlations to human genetic risk for psychiatric disease.

Conclusion: Our data demonstrates the existence of several distinct DA receptor-expressing SPN subpopulations that display anatomical, transcriptomic, and functional diversity.

T33. A Study on the Effects of Sirtuin 1 on Dendritic Outgrowth and Spine Formation and Mechanism in Neuronal Cells

Bo-Hyun Yoon, Naju National Hospital

Background: Increasing evidence suggests that depression is associated with impairments in neural plasticity. Sirtuin 1 plays an important role in neural plasticity, and the activation of mechanistic target of rapamycin complex 1 (mTORC1) signaling is known to improve neural plasticity. In this study, we aimed to determine whether sirtuin 1 affects dendrite outgrowth and spine formation through mTORC1 signaling.

Methods: Resveratrol (sirtuin 1 activator; 1 and 10 μM) and sirtinol (sirtuin 1 inhibitor; 1 and 10 μM) were treated in primary cortical culture with and without dexamethasone (500 μM). Levels of sirtuin 1, phospho-extracellular signal regulated protein kinase 1/2 (ERK1/2), phospho-mTORC1, and phospho-p70 ribosomal protein S6 kinase (p70S6K) were evaluated using Western blot analysis. Dendritic outgrowth and spine density were assessed using immunostaining.

Results: Resveratrol significantly increased levels of sirtuin 1 expression and phosphorylation of ERK1/2 (a downstream target of sirtuin 1), mTORC1, and p70S6K (a downstream target of mTORC1) in a concentration-dependent manner under dexamethasone conditions. Resveratrol also significantly increased dendritic outgrowth and spine density. Conversely, sirtinol significantly decreased levels of sirtuin 1 expression and phosphorylation of ERK1/2, mTORC1, and p70S6K in a concentration-dependent manner under normal conditions. Moreover, sirtinol significantly decreased dendritic outgrowth and spine density.

Conclusion: Consistent with the results of sirtinol, sirtuin 1 knockdown using sirtuin 1 siRNA transfection significantly decreased dendritic outgrowth and spine density as well as phosphorylation levels of ERK1/2 and mTORC1. These data suggest that sirtuin 1 enhances dendritic outgrowth and spine density by activating mTORC1 signaling.

T34. Clinical Evidence of Antidepressant Effects of Insulin and Anti-Hyperglycemic Agents and Implications for the Pathophysiology of Depression—A Literature Review

Sang-Yeol Lee, Wonkwang University Hospital and School of Medicine

Close connections between depression and type 2 diabetes (T2DM) have been suggested by many epidemiological and experimental studies. Disturbances in insulin sensitivity due to the disruption of various molecular pathways cause insulin resistance, which underpins many metabolic disorders, including diabetes, as well as depression. Several anti-hyperglycemic agents have demonstrated antidepressant properties in clinical trials, probably due to their action on brain targets based on the shared pathophysiology of depression and T2DM. In this article, we review reports of clinical trials examining the antidepressant effect of these medications, including insulin, metformin, glucagon like peptide-1 receptor agonists (GLP-1RA), and peroxisome proliferator-activated receptor (PPAR)-γ agonists, and briefly consider possible molecular mechanisms underlying the associations between amelioration of insulin resistance and improvement of depressive symptoms. In doing so, we intend to suggest an integrative perspective for understanding the pathophysiology of depression.

T35. Diabetes Alters the Transcriptional Signature of Cholinergic Neurons in the Brain Reward Circuitry

Jessica Ables, Icahn School of Medicine At Mount Sinai

Background: Diabetes is associated with an increased risk for depression and anxiety, and glycemic control correlates with depression scores and suicidality. Diabetes has been found to impair cognitive processing, but little is known about reward processing. Postmortem studies indicate that areas within the reward circuitry demonstrate the largest number of changes in gene expression. Here we present work focused on characterizing the molecular and behavioral signatures of cholinergic neurons within the reward circuitry of several mouse models of diabetes.

Methods: Adult male and female C57BL6J or ChAT-NuTRAP mice were treated with STZ or given high fat diet to model aspect of Type 1 and Type 2 diabetes respectively. Behavior was assessed at 6w after diabetes onset using translational operant tasks such as progressive ratio and probabilistic reversal learning. Cholinergic neurons from the NAc and habenula were transcriptionally profiled 6 and 12w after onset of diabetes.

Results: Diabetic mice acquire operant tasks slightly faster than control mice, but breakpoints on progressive ratio are not altered. Diabetic mice are slightly more impulsive, with more lever presses than control mice. Reducing hyperglycemia normalizes lever pressing. On a neuroeconomics task, diabetic mice earn fewer total rewards because they perseverate on their most preferred flavor. Transcriptionally, fat and dopamine metabolic pathways are upregulated in STZ-treated mice, while synaptic plasticity and electron transport are upregulated in high fat diet mice.

Conclusion: Diabetes alters both gene expression and behavior in mouse models. These results reveal direct effects of hyperglycemia on reward circuitry.

T36. Modeling Lithium's Effect on Neurogenesis Using Induced Pluripotent Stem Cell-Derived Brain Organoids

Martin Lundberg, Karolinska Institute

Background: Lithium is one of the most effective treatments of bipolar disorder in terms of preventing both manic and depressive episodes. Moreover, several lines of evidence have indicated both neuroprotective and neurogenic effects of lithium. However, the mechanism behind these effects remains poorly understood. The aim of this study is to investigate lithium's effect on human neuro- and gliogenesis in vitro using iPSC-derived brain organoids. Methods: We reprogrammed fibroblasts from four healthy controls into iPSCs and differentiated these into dorsal forebrain organoids. The organoids were treated with either 1 mM lithium chloride or vehicle for 2 months and then processed for subsequent characterization. Results: Using immunohistochemistry and single-cell RNA sequencing, we have verified the generation of both excitatory and inhibitory neurons, astroglial and oligodendroglial cells at various stages of development, intermediate progenitor cells, as well as several subtypes of radial glia in our organoid model. Preliminary analysis indicates an increased proportion of intermediate progenitor cells in lithium treated organoids. Using the generated single-cell RNA sequencing data set we are further analyzing the effect of lithium on cellular composition, developmental trajectories, and transcriptional regulation of different cell populations. Seahorse analysis does not indicate a significant difference in mitochondrial metabolism between lithium-treated and untreated organoids. Conclusion: The described organoid model

constitutes a suitable platform for investigating the effects of lithium on human neuro- and gliogenesis. With the use of single cell transcriptomics, we are utilizing this model to improve our understanding of the various neurobiological effects of lithium.

T37. Association Between Polygenic Scores for Lithium Response and Response to Lithium Augmentation in Unipolar Depression

Julia Kraft, Charité – Universitätsmedizin Berlin

Recent studies indicate that Polygenic Scores (PS) constructed on Genome-Wide Association Studies (GWAS) for lithium response in Bipolar Disorder (BD) could be useful to predict lithium responsiveness. However, it is unclear whether PS for lithium response (LIR-PS) predict response to lithium augmentation in individuals with major depression (MD). Based on GWAS for lithium response in Bipolar Disorder (ConLi+Gen) we calculated LIR-PS in a cohort of MD patients who underwent LA (N=286) after AD non-response. Depressive symptom severity was measured weekly using the Hamilton Depression Rating Scale (HAMD). Continuous change in severity (ΔHAMD) and response (50% reduction in HAMD scores), were tested for association with LIR-PS in regression models respectively using demographic and ancestry components as covariates. A subgroup analysis was conducted by retaining only individuals with sufficient lithium serum levels (≥ 0.5 mmol/l for ≥ 2 weeks; N=224). We observed an association between LIR-PS and ΔHAMD (beta=-1.04 , CI=[-1.86,-0.23], p=0.012, R2=2.24%) but not between LIR-PS and categorical response (OR=1.11, CI=[0.87,1.41], p=0.414, NKR2 =0.32%) at a p-value threshold of PT=0.05. In the subgroup, LIR-PS remains associated with symptom improvement during LA (beta=-1.23, CI=[-2.14,-0.32], p=0.008 at PT=0.05) explaining up to 3.16 % of variation in ΔHAMD. Our preliminary results suggest that lithium response in mood disorder may underlie similar genetic variation and that LIR-PS may also be useful in the prediction of LA response in MD.

T38. Antidepressant Augmentation Strategies Targeting Signal Transduction Proof of Concept in Animal Models

Eleni Tzavara, CNRS

Background: Antidepressant (AD) resistant depression is a major cause of disability. We recently identified a novel AD target, the transcription factor ELK-1 operating inside the cell rather than the synapse where « classical » ADs act. We propose that an augmentation strategy (classical + ELK-1 modulator) leads to rapid AD action and/or better efficacy.

Methods: After social defeat (SD, males) or vicarious social defeat (VSD, females) susceptible animals screened in the social interaction test (SI, score < 1) were used in two different sets of experiments. (i) To determine the augmentation effect in the delay of onset-of-action, they were treated for 6days with either desipramine (DES; 15mg/kg), fluoxetine (FLX; 10mg/kg), the ELK-1 modulator (TDE; 2 mg/kg) or combination (DES + TDE; FLX + TDE).

(ii) To determine the augmentation effect on treatment response, they were treated for 14 days with DES; then stratified into responders (R) and non-responders (NR) in the SI. NR were divided into two groups, one treated for an additional week with DES alone (n=10) and one treated with DES+TDE (n=9), all rescreened at 21 days.

Results: DES+TDE resulted in (i) faster action onset (6 days instead of 14 days) and (ii) greater proportion of AD-R (6/9) than DES alone (2/10). However, this effect was not found with FLX+TDE. The TDE effect was prevented by the mGluR5 antagonist MPEP.

Conclusion: ELK-1 modulation represents a promising novel augmentation strategy, most likely via glutamate modulation. However, this does not apply to all AD classes, in particular not to SSRIs.

T39. GABA-Ghoul: A Case of Major Depression With New-Onset of Psychotic Features That Resolved With Cessation of Pregabalin and Tolerated Gabapentin

Hajira Chaudhry, Henry Ford Hospital

Background: In 2020, approximately 9 million people were prescribed pregabalin in the United States. Pregabalin decreases the concentration of various neurotransmitters, including glutamate, dopamine, and serotonin, via binding to the alpha-2-delta subunit of voltage-gated calcium channels in presynaptic neurons. It is generally well tolerated. However, in rare cases it associated with psychosis, typically in withdrawal, via an unclear mechanism. To educate providers, a case of depression with psychotic features on pregabalin will be presented.

Methods: Literature search via PubMed, Web of Science, APA PsychNet for the terms: “pregabalin + induced + depression”, "pregabalin + psychosis”, " pregabalin + delirium”, 19 articles were found, 4 discussed neurotoxic, 7 discussed delirium, the remainder were case reports.

Case/Results: 36-year-old female history of 1 prior episode of depression with no risk factors for psychosis presented to the psychiatric unit with latency, disorganization, psychomotor retardation, and persecutory delusions. Patient on discharge continued to have psychomotor retardation, slow speech, and disorganization on risperidone 2mg and sertraline 100mg. Outpatient, she stopped pregablin 300mg with near resolution of symptoms within 1 week with no reoccurrence of symptoms when titrated to gabapentin 300mg tid and reduction in risperidone to 1mg.

Discussion: Given timing of rapid improvement, history, and presentation, pregabalin likely contributed to the patient's new-onset psychotic symptoms. Pregabalin is 2.4-2.8 times more potent than gabapentin. Gabapentin has non-linear pharmacokinetics and is saturable, which may have contributed to its tolerability. This case highlights the importance of monitoring of potential side effects of pregabalin in atypical presentations of psychosis.

T40. Fluvoxamine and COVID: How an OCD Drug Was Repurposed for Treatment of COVID-19

Angela Reiersen, Washington University School of Medicine

Background: Fluvoxamine, an approved psychiatric medication, has been tested in multiple clinical trials as a treatment for acute Coronavirus Disease 2019 (COVID-19), and is now also being evaluated for treatment of post-COVID-19 sequelae (long COVID).

Methods: Review of fluvoxamine's mechanisms of action and the evidence for fluvoxamine as a treatment for COVID-19, including meta-analysis of completed clinical trials.

Results: Fluvoxamine mechanisms that may help in treating COVID-19 and its sequelae include inhibition of the serotonin transporter, anti-inflammatory effects through activation of sigma1 receptors (S1R), functional inhibition of acid sphingomyelinase (FIASMA), and inhibition of platelet and mast cell activity. Multiple clinical trials support the efficacy early fluvoxamine treatment in preventing clinical deterioration In patients with acute COVID-19 illness, with about one third reduction in hospitalization. Real-world studies conducted in multiple countries support fluvoxamine's benefit alone and in combination with other drugs. Follow-up data from acute COVID trials suggest that fluvoxamine may reduce the risk for long COVID. Fluvoxamine has shown promise in animal models of long COVID, and a long COVID trial in humans should be completed soon.

Conclusions: Fluvoxamine has been successfully repurposed for treatment of COVID-19 and is an important option, which may compliment other available treatments. More studies are needed to clarify its mechanism(s), but there is compelling evidence that fluvoxamine's S1R agonist effect and other actions are important. More studies are needed to determine whether fluvoxamine is helpful in treating long COVID.

T41. Serotonergic Modulation of Prefrontal Circuits During Set Shifting Task

Kenneth Johnson, Weill Cornell

Deficits in cognitive flexibility are a common unresolved symptom in neuropsychiatric disease. While standard treatments mitigate many other symptoms, cognitive deficits commonly remain. Utilizing a custom head fixed set shifting task and multi-photon imaging, we investigate serotonergic modulation of prefrontal circuits. These techniques allow for single cell resolution of serotonergic input and pyramidal cell activity during intradimensional and extradimensional set shifts.

T42. Effects of Polygenic Burden for Autistic Traits on Emotion Recognition in Schizophrenia

Alice Braun, Charité – Universitätsmedizin Berlin

Background: Schizophrenia patients commonly exhibit cognitive impairments, performing one standard deviation below the population mean on average. Milder socio-cognitive deficits are observed in unaffected first-degree relatives, suggesting a genetic component. Genome-wide association studies have revealed genetic overlap between psychiatric disorders, including autism spectrum disorder (ASD)-like symptoms in some schizophrenia patients. These symptoms include difficulties in social interaction, emotion recognition, and motor function. While facial emotion recognition (FER) is considered an intermediate phenotype in schizophrenia, the genetic basis of socio-cognitive deficits remains unclear. This study aims to investigate the association of polygenic scores for ASD and related traits on FER in schizophrenia patients.

Methods: The sample comprises N≈250 cases from the Berlin Research Initiative for Diagnostics, Genetics, and Environmental Factors in Schizophrenia (BRIDGE-S) and N≈1,500 cases from the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI). FER is assessed using the CANTAB Emotion Recognition Task measuring the identification of six basic emotions in BRIDGE-S and the Degraded Facial Affect

Recognition Task (DFAR) in EUGEI. Polygenic risk scores (PRS) for ASD, self-reported empathy, and cognitive empathy calculated via PLINK and PRS-CS are tested for their association with FER.

Results: Preliminary analyses in the BRIDGE-S cohort show that a higher ASD-PRS is associated with worse standardized ERT accuracy (R2=0.021, β=-0.040, SE=0.019, p=0.035).

Conclusion: Future research will explore additional genotype-phenotype associations in a larger cohort, contributing to the characterization of autistic traits in schizophrenia and enhancing our understanding of the biological underpinnings of psychiatric symptom clusters across diagnostic boundaries.

T43. Regional- and Cell Type-Specific Alterations in a Unique Subtype of Somatostatin-Expressing Neurons in Schizophrenia

Kenneth Fish, University of Pittsburgh

Background**:** In schizophrenia, GABA neurons expressing the neuropeptide somatostatin (SST) are markedly affected in the dorsolateral prefrontal cortex (DLPFC). Cortical SST neurons comprise a heterogenous group of neurons, and the subtype(s) that are affected in schizophrenia are unknown. One SST subtype, distinguished by the expression of chondrolectin (CHODL), resides primarily in the subcortical white matter (sWM), contains high levels of neuropeptide Y (NPY) and nitric oxide synthase 1 (NOS1) and regulates neurovascular coupling (NVC). In addition, CHODL-SST neurons are the near-exclusive subtype of SST neuron found in the striatum. Here, we investigated this SST neuron subtype in these two brain regions in schizophrenia.

Methods: Multiplex fluorescent in situ hybridization was used to label SST, CHODL, NPY, and NOS1 mRNAs in postmortem DLPFC and dorsal caudate sections from 18 matched pairs of schizophrenia and unaffected comparison subjects. Transcript levels were quantified in CHODL-SST neurons.

Results: In schizophrenia, CHODL-SST neurons in the sWM of the DLPFC exhibited deficits in NOS1 (effect size (ES)=–0.86, p=0.015) and NPY (ES=–0.55, p=0.18) mRNAs, but normal levels of SST (ES=–0.33, p=0.62). In contrast, CHODL-SST neurons in the caudate exhibited normal levels of SST, NPY, and NOS1 mRNAs (all $p > 0.85$) in schizophrenia.

Conclusion: The findings here show that CHODL-SST neurons are differentially affected in schizophrenia at both the transcript and region level. Through release of NOS1 and NPY, CHODL-SST neurons play a critical role in NVC. Lower expression of these transcripts in CHODL-SST neurons might contribute to altered task-related BOLD signal observed in the DLPFC of subjects with schizophrenia.

T44. Complement C4 Gene Association With Schizophrenia Clinical Profiles

Kosar Teymouri, Center for Addiction and Mental Health

Background: The most recent GWAS identified 287 loci associated with schizophrenia, and the C4 gene is the strongest genetic biomarker for schizophrenia risk. Studies showed that the brain expression of C4 depends on its structural forms and C4L is associated with higher C4A brain expression. We aimed to investigate the association between C4 and treatment-resistant schizophrenia (TRS), the number of hospitalizations (NOH), GAF score, symptom severity and age of onset.

Methods: The total of 613 subjects, over the age of 18 were included in this study. The data were retrospectively extracted from the Toronto Schizophrenia study. Patients prescribed clozapine were considered TRS.

Results: Our results showed that patients hospitalized for 2 or more times, had significantly lower copy numbers of C4S ($p = 0.023$) and C4AS ($p=0.007$). In sex-stratified analysis only, there was a significant negative association between C4S and TRS in males ($p= 0.047$). We found that age of onset was associated with higher C4AS ($p = 0.050$), and symptom severity was associated with higher copy numbers of C4B ($p = 0.010$) and C4B expression ($p = 0.011$). Also, C4A ($p = 0.015$) and C4A expression ($p = 0.012$) had a significant positive association with GAF scores.

Conclusion: Our results support the sex effect of C4 risk in schizophrenia and suggest that C4S may have a protective effect and that C4B might be involved in the more severe forms of schizophrenia. Future investigations exploring the role of C4 in other schizophrenia-related characteristics such as antipsychotic response are encouraged.

T45. Identification of Causal Genes and Putative Drug Targets for Schizophrenia Using Statistical Genetics Techniques

Karl Heilbron, Charite University Medical Center Berlin

Background: Many drugs show promise in animal models but fail in human clinical trials due to lack of efficacy. Retrospective studies have found that proteins are more likely to make successful drug targets if they have been linked to the relevant disease by human genetic studies. Genome-wide association studies (GWASes) have identified genomic regions associated with schizophrenia (SCZ) risk, but the causal genes in many of these regions remain unknown.

Methods: We used a novel statistical genetics tool, PoPS, to identify these causal genes and explore their potential as drug targets. Previous validation work has shown that genes that have the top PoP score in a GWAS locus and are also the nearest gene to the lead GWAS variant successfully predict the causal gene in the locus 79% of the time. We applied these criteria to all loci from the most recently-published SCZ GWAS.

Results: We prioritized a putative causal gene in 39/159 GWAS loci (25%). The genes with the top PoP scores included DRD2 (the target of several SCZ medications), GRIN2A (heterozygous KO mice display several abnormal features that resemble human SCZ), and CACNA1C and CACNB2 (both calcium channel subunits involved in synaptic transmission).

Conclusion: We used PoPS to identify causal genes in GWAS loci for SCZ. Our findings may help identify novel drug targets for these diseases and may lead to the development of new pharmacological approaches.

T46. Insights Offered by Hla and C4 Type Imputation in Schizophrenia

Georgia Panagiotaropoulou, Charite University Medical Center Berlin

Background: A long line of evidence points to the involvement of the Major Histocompatibility Complex (MHC) in the genetic predisposition for schizophrenia. Its implication is supported by strong hits in genome-wide association studies (GWAS). Here we take a detailed look by imputing HLA and C4 gene-types and examining them in tandem with common SNPs. We also perform conditional analysis to reveal genetic associations between them.

Methods: For the HLA genes we constructed a reference panel including HLA types merged with 1000 Genomes and we imputed into cohorts from the Psychiatric Genetics Consortium. For C4 (panel from Kamitaki et al.) we followed the analysis of Sekar et al. (2016) on this larger set of data. GWAS was performed on a cohort level, followed by meta-analysis. We merged HLA and C4 results post-imputation to reveal shared signals. Finally, we ran conditional analysis to investigate the interplay between variants.

Results: GWAS revealed a strong association of the 8.1-Ancestral-Haplotype (8.1-AH) with schizophrenia, with the most associated HLA gene-type being HLA_B*08 (OR=1.2, p=5.1e-29). After conditioning on the strongest SNP (rs13195636, OR=1.2, p=1.7e-38), the signal drops substantially but does not vanish (p=6.7e-07). Imputation of the C4 gene-types replicated previous results with smaller standard errors.

Conclusion: We integrate HLA and C4 imputation with common SNPs in the MHC. We identify new associations with schizophrenia pointing to the 8.1-AH, found to have a protective effect on the disorder. HLA and C4 types provide insights into the underlying biology and screening for them can prove useful in stratifying patients.

T47. Genome-Wide Versus Pathway-Based Schizophrenia Polygenic Risk Scores and NIH Toolbox Cognitive Measures Across Time in the Adolescent Brain Cognitive Development Study

Jinhan Zhu, University of Washington

Background: Cognitive impairment is an early sign of schizophrenia (SCZ). In Adolescent Brain Cognitive Development Study (ABCD), genome-wide SCZ polygenic risk score (PRS) has been negatively correlated with NIH-Toolbox (NIHTB) cognition measures in European ancestry studies. We examined SCZ liability in biological pathways by comparing associations of genome-wide versus pathway-specific SCZ PRS, generated for previously derived and validated neurodevelopmental co-expression gene-sets, and NIHTB scores.

Methods: Genome-wide and pathway-based SCZ-PRS were generated for 18 neurodevelopmental gene-sets using PRScsx for European ancestry youth in ABCD assessed at baseline (N=5895, mean age=9.92 yrs) and 2-year follow-up (N=4166, mean age=11.97 yrs). We examined PRS associations with NIHTB Crystallized composite (NIHTB-CC) and Total composite (NIHTB-TC) scores using linear mixed models, controlling for sex, age, ancestry principal components, and genetic relatedness.

Results: Genome-wide SCZ-PRS was significantly associated with baseline NIHTB-CC (p = 0.008), and NIHTB-TC (p=0.003). SCZ-PRS for modules M11 (Glia-Immune Signaling), M17 (Olfactory-Perception), and M18 (Sensory-Perception) were nominally associated with NIHTB-CC and NIHTB-TC, but didn't withstand pathway size correction. At

2-year follow-up, M18 was nominally associated with NIHTB-CC (competitive-p=0.033), while genome-wide PRS was insignificant.

Conclusion: Our results indicate varying associations between genome-wide and pathway-specific SCZ-PRS with neurocognition across development in ABCD. At baseline, genome-wide PRS showed strongest association with NIHTB scores, while nominal pathway-specific SCZ-PRS associations appeared attributable to larger pathway size capturing a greater proportion of overall risk. Nominal association between the Sensory-Perception pathway SCZ-PRS and early adolescent NIHTB-CC suggests that pathway-PRS may better capture genetic risk effects on cognition during this period.

T48. A Population-Driven Family-Based Genetic Study of Schizophrenia

Katherine Keller, Icahn School of Medicine at Mount Sinai

Background: Two landmark genetic studies of SCZ, the severe and highly heritable psychotic illness, recently established that some SCZ cases are caused by a rare protein-truncating variant (PTV) in one of 12 genes including GRIA3, an X chromosome gene that codes for an AMPA glutamate receptor component. Presented here is a process developed to identify individuals affected by rare PTVs in these 12 genes, followed by a case series of a family with seven members affected by a rare PTV in GRIA3.

Methods: Carriers of rare PTVs in the 12 known causal SCZ genes were identified by mining whole-exome sequencing data from the diverse population of New York City. Identified carriers were re-contacted to undergo comprehensive neuropsychiatric assessments and biospecimen collection. Seven members of this family were enrolled in the study.

Results: Six affected family members are carriers of the rare PTV, and 1 unaffected family member is a non-carrier. No affected non-carriers have been identified. The primary psychiatric diagnoses for the carriers were SCZ and neurodevelopmental disorder (NDD). Affected males in the family exhibited more severe forms of illness than affected females in the family, but having two X chromosomes was not entirely protective.

Conclusion: An X-linked pattern of inheritance was identified between the rare PTV and severe neuropsychiatric diseases, providing evidence for causality. Population-driven family-based genetic studies such as the one presented here are a new way to investigate the mechanisms of disease in individual patients, and lead to the development of novel gene-based therapeutics.

T49. Investigating Cell Types Changes in Schizophrenia With Spatially-Resolved Transcriptomics

Milda Valiukonyte, Karolinska Institute

Background: Schizophrenia is a mental disorder which affects person's cognition, perception, and emotions, and it affects around 1% of the population. Genetic studies have shown that the disease is hereditary and genetically complex, but its etiology is still widely unknown. Several line of evidence, ranging from behavior, imaging, and transcriptomics implicate prefrontal circuits. Different classes of cells have been shown to be affected in postmortem tissue using individual markers, but detailed information on transcriptomically defined cell type composition is lacking from patients. The current study builds on findings from single cell RNA-sequencing to further investigate cell type changes in brain tissues of patients affected by schizophrenia.

Methods: We used the spatial transcriptomic technique HybISS (Gyllborg et al., Nucleic Acids Research, 2020) using 156 cell type-specific and disease-related probes, combined with probabilistic cell typing (pciSeq; Qian et al., Nature Methods, 2019) to reveal cell types and their location in postmortem tissue of schizophrenia patients (n=9) to controls (n=9).

Results: While we were not powered enough to identify cell type change in terms of abundance, our preliminary findings reveal disease-specific changes in cellular interactions of neurons and non-neuronal cells.

Conclusions: Detailed understanding of cellular composition and precise changes in cellular location provides insight into new disease phenotypes and can help guide future endeavors to reveal disease biology.

T50. Regional Specificity of Morphometric Similarity Network Alterations and Cortical Transcript Patterns in Youth at Clinical High Risk for Psychosis

Gil Hoftman, UCLA

Background: Efforts are focused on understanding the pathophysiology of early psychosis. Here we characterize baseline brain morphometric similarity networks (MSNs) using structural MRI in subjects at clinical high-risk (CHR) who converted (CHRc) or did not convert (CHRnc) to psychosis, relative to control (HC) subjects and subjects who did not convert but

remained symptomatic (CHRncs) or remitted (CHRncr). We incorporate postmortem transcriptomic data from the Allen Human Brain Atlas (AHBA).
Methods: MRI data were available for 71 CHRc, 467 CHRnc, and 219 HC subjects from the NAPLS2 cohort (Age (Mean/SD): 19.2 +/- 4.4 years old; Sex: M=58%, F=42%). To increase the sample of symptomatic CHR subjects, CHRc and CHRncs were combined into a CHRcs group (N=291). MSNs were constructed from multiple structural MRI measures. Microarray data (AHBA) were related to MSNs using partial least squares (PLS) regression.

Results: Difference maps between CHR-vs-HC indicated significant increases in MSN degree in 17 visual areas, with decreases in 14 frontotemporal areas in CHR youth (all FDR $p < 0.05$). CHRcs showed significant increases in 3 visual areas and decreases in 4 frontotemporal areas relative to HCs. PLS component 1 (PLS1) for the MSN model explained 13.5% of the covariance between CHR-vs-HC MSN effect sizes and gene expression. Key markers of synaptic neurotransmission including parvalbumin and GABAA receptor subunit delta were in the top 2% of PLS1 loadings.

Conclusion: Differences in MSN topology between CHR-vs-HC subjects cluster in specific cortical areas, are identifiable at the baseline MRI scan, and associate with markers of synaptic transmission-related pathways.

T51. Oxytocin Receptor Signaling Differentially Regulates Pair Bond Behavior in Prairie Voles With Age
Kristen Berendzen, University of California, San Francisco
Background: Social attachments are essential to human social behavior and are significantly disrupted in many neuropsychiatric disorders, including those associated with age, like dementia. Mechanistic understanding of attachment behavior has been limited by the lack of genetic model species that display long term adult attachments. We used genetic loss of the oxytocin receptor (OxtR) in the prairie vole (M. ochrogaster), a species that forms long term adult pair bonds, to examine age-dependent changes in attachment behavior and gene expression.
Methods: We tested adult (2-3 mo) and aged (24 mo) male and female prairie voles bearing mutations in OxtR, a known neuroendocrine mediator of social attachment, in a battery of behavioral assays examining components of pair bond behavior. We also performed RNA- sequencing from the nucleus accumbens in wild type (WT) and OxtR mutant voles of both sexes at adult and aged timepoints.

Results: We found that genetic loss of OxtR signaling sex-specifically disrupts the formation and maintenance of pair bonds. Furthermore, female WT voles show age-dependent changes in social approach and bonding behavior that is regulated by OxtR signaling. Finally, using RNA-sequencing we identified OxtR-dependent changes in gene expression with bonding and with age.

Conclusion: Loss of OxtR signaling alters the age-dependent temporal dynamics and behavioral repertoire displayed in distinct phases of attachment. A mechanistic understanding of how genetic, endocrine, and neural pathways regulate attachment behavior with age will be highly impactful given the central role of social behavior in influencing health across the lifespan.

T52. Intracellular Mechanisms Regulating Oxytocin Receptor Activity in Neurons
Mohiuddin Ahmad, University of Oklahoma Health Sciences Center
Background: It is critical to decipher the neuronal mechanisms underlying social behavior and their impairment in psychiatric disorders with prominent social deficits. Oxytocin serves an important role as a neuromodulator regulating social behavior. Recent work has begun to clarify how oxytocin acts on neuronal circuits to modify inter-neuronal communication and circuit properties. However, the intracellular mechanisms that control oxytocin receptor (OXTR) signaling in neurons remain unexplored and need to be determined.
Methods: We performed whole-cell patch-clamp recordings in ex vivo brain slices to investigate agonist-induced desensitization of OXTR response in the mouse brain. Bioluminescence Resonance Energy Transfer (BRET) assays were applied for the first time in primary neuronal cultures to define the molecular locus of desensitization.

Results: We identified robust and rapid-onset desensitization of OXTR response in multiple regions of the mouse brain. Both postsynaptic spiking responses and presynaptic activation undergo similar desensitization. Using BRET assays, we identified the GRK isoforms that are recruited to the activated OXTR in neurons followed by the recruitment of beta-arrestin-1 and -2. Interestingly, recordings in beta-arrestin-1 and -2 knockout mice and in CRISPR/Cas9-based beta-arrestin double knockout reveal that beta-arrestins are redundant for neuronal OXTR desensitization. In contrast, inhibition of GRK kinase activity leads to suppression of the desensitization of OXTR response and receptor internalization.

Conclusions: This work provides insights into the regulatory mechanisms governing an important G protein-coupled receptor in the brain, which may lead to future development of therapeutic agents that alleviate social deficits in neuropsychiatric disorders.

T53. Trauma Exposure Impacts Prospective Relationships Between Reward-Related Ventral Striatal Activity and 6-Month Depression Trajectory

Kristen Eckstrand, University of Pittsburgh School of Medicine

Background: Trauma exposure is associated with a more severe course of depression and anhedonia. Neural reward function is impacted by trauma and influences the development of affective symptoms. The purpose of this naturalistic, 6-month follow-up study was to examine how trauma exposure impacts relationships between neural reward function and the development of affective symptoms in adolescents.

Methods: 82 participants ages 13-19yrs (52% female sex, 48% racially diverse) were included in this 6-month follow-up study. Participants reported lifetime trauma exposure, depression, and anhedonia and underwent a monetary reward fMRI task. Significant reward activity to reward > neutral outcome (pFWE < 0.05) was measured within the Neurosynth "reward" mask using SPM12. A multivariate linear model, corrected for multiple comparisons, examined the interaction between trauma and neural reward activity in predicting changes in depression and anhedonia over 6 months.

Results: More trauma exposure was associated with higher baseline depression (β=1.676,p=0.019) and anhedonia (β=1.547,p < 0.001), and higher anhedonia at 6-month follow-up (β=2.050,p < 0.001), but not symptom change over 6 months. Significant neural activity to reward was observed in the bilateral ventral striatum (VS), medial prefrontal cortex, and right ventrolateral prefrontal cortex at baseline. Trauma exposure moderated prospective relationships between right VS and depression trajectory (β=-4.427,p=0.009), where worsening depression was associated with a combination of more lifetime trauma exposure and lower right VS reward activity.

Discussion: More trauma exposure was associated with worsening depression in those with blunted reward function. Targeting reward circuitry function may be an important strategy to address depression, particularly among adolescents with histories of trauma exposure.

T54. A Proteome-Wide, Multi-Omics Analysis Implicates Novel Protein Dysregulation in Post-Traumatic Stress Disorder

Jiawei Wang, Yale School of Medicine

Post-traumatic stress disorder (PTSD) is a common and disabling psychiatric disorder. Here we present findings from the first proteome-wide study of the postmortem PTSD brain. We performed tandem mass spectrometry on large cohort of donors (N = 66) in two prefrontal cortical areas and found differentially expressed proteins and co-expression modules disturbed in PTSD. Integrative analysis pointed to hsa-mir-589 as a regulatory miRNA responsible for disruptions in neuronal protein networks for PTSD, including the GABA vesicular transporter, SLC32A1. In addition, we identified significant enrichment of risk genes for Alzheimers Disease (N= 94,403), major depression (N = 807,553), and schizophrenia (N = 35,802) within PTSD co-expression protein modules, suggesting shared molecular pathology. Our findings highlight the altered proteomic landscape of postmortem PTSD brain and provide a novel framework for future studies integrating proteomic profiling with transcriptomics in postmortem human brain tissue.

T55. Accelerated Aging After Early Life Adversity Evidenced by Behavioral Pattern Separation Deficits in Mice

Wei-li Chang, Columbia University and New York State Psychiatric Institute

Background: Early life adversity (ELA) can lead to accelerated maturation and senescence of the hippocampus, and is associated with increased risk for psychiatric illness. In many psychiatric conditions, overgeneralization of negative emotional responses is thought to be related to impairments in pattern separation, a cognitive process performed by the dentate gyrus (DG). The DG is the cite of adult hippocampal neurogenesis (AHN), which has been shown to support behavioral pattern separation and decreases dramatically with age.

Methods: ELA was induced using the limited bedding and nesting paradigm (P4-11). Male and female young-adult (YA, 11-12 wks) and middle-aged (MA, 11-12 mos) mice were then tested across several days in a contextual fear discrimination task with two similar contexts, one paired with foot shock. After behavioral testing, brains were perfused for immunohistochemical staining of neurogenesis markers.

Results: In YA mice, there was no effect of ELA or sex on fear discrimination. However, in MA mice, fear discrimination was impaired by ELA in both males and females. Histological analysis of doublecortin (DCX) staining did not find any differences in YA mice after ELA. Analysis of DCX in MA mice will also be presented.

Conclusion: After ELA, YA mice show no impairment in behavioral pattern separation. However, in middle age, ELA mice appear to have an accelerated decline in behavioral pattern separation. We also evaluated the relationship between behavioral pattern separation differences and markers of AHN in the dentate gyrus. These findings support compounding effects of ELA on neuropsychiatric risk over the life span.

T56. Delirium and a History of Alcohol Dependence – What is the Diagnosis?

Andrew Trinh, TTUHSC

Background: Delirium is a clinical syndrome that is described as a disturbed state of consciousness that is acute, transient and associated with multiple causes. One factor that can cause delirium is medication-induced.

Methods: A 56-year-old male presented to the emergency department for altered mental status. He endorsed visual hallucinations. Vitals were stable with hypertension, tachycardia, tachypnea, and fever. Patient was placed on CIWA protocol. The patient's mentation and vitals improved throughout hospitalization. The patient denied any recent alcohol or drug use. He mentioned a recent discharge from an inpatient treatment program and noted that 2 hours prior to his discharge, he received "an injection to stay away from alcohol." The facility that the patient was discharged from was contacted where it was confirmed he received Vivitrol injection.

Results: Vivitrol was likely the culprit that caused delirium, as the patient had been abstinent from alcohol and opioids. There was no clear explanation as to what caused him to exhibit delirium, as labs were unremarkable for infection, hepatic encephalopathy, electrolyte abnormalities, or intoxication. Furthermore, the patient denied initiating any other medications prior to his presentation, aside from Vivitrol.

Conclusion: Delirium is not a well-known adverse effect of Vivitrol. This report describes a rare case of delirium involving visual hallucinations and grandiose delusions associated with Vivitrol use that resolved after about 72 hours of being stabilized with lorazepam. Although the mechanism by which Vivitrol induces delirium remains unclear, it is important to understand the potential emergence of delirium associated with Vivitrol.

T57. Gating of Opioid Withdrawal Aversion by a Unique Class of Neurons in the Nucleus Accumbens

Jason Tucciarone, Stanford University

Background: The aversion of opioid withdrawal can drive relapse and increases risk of future overdose. More detailed understandings of circuit mechanisms underlying opioid withdrawal aversion are needed. We identified found two major populations of D1 neurons in the nucleus accumbens (NAc) that express mu opioid receptor (MOR) and either gene Pdyn or Tshz1.

Methods/Results: Optogenetic real time place preference testing of Tshz1 neurons led to avoidance of the stimulation-paired chamber, whereas stimulation of Pdyn neurons led to a preference. We hypothesized that these behavioral effects are mediated through cell-type specific modulation of dopamine (DA) release in the NAc. We stimulated Tshz1 or Pdyn cells with ChRmine while performing photometry recordings with GRAB DA. Stimulation of Tshz1 neurons led to a rapid suppression of DA release in the NAc, whereas stimulation of Pdyn neurons increased DA release. DA levels rose substantially after morphine administration but were significantly suppressed below baseline during precipitated withdrawal. Photometry recordings revealed morphine intoxication reduced activity in both cell-types yet precipitated withdrawal triggered a large rebound in activity selectively in Tshz1 cells. Reducing activity of Tshz1 neurons with hM4Di disrupted morphine withdrawal conditioned place aversion (CPA), while inhibition of Pdyn neurons had no effect on withdrawal CPA but reduced morphine conditioned place (CPP). Conclusion: Ongoing studies are examining the discrete mechanism by which Tshz1 neurons modulate DA release in the NAc. Together, these data demonstrate a unique population of NAc neurons that mediate the aversion learning of acute opioid withdrawal through strong modulation of mesolimbic DA release.

T58. Single Cell Analysis of the VTA Following Morphine Treatment in a Mouse Model of Resilience to Opioid Use Disorder

Ethan Fenton, UC Davis

Background: 80,000+ opioid overdose deaths in the United States in 2021 indicate a critical need to understand cellular/molecular mechanisms of opioid use disorder (OUD). Toward the goal of identifying OUD-driving transcriptional responses to morphine, we utilized a mouse model carrying a mutant mu opioid receptor (RMOR, for recycling-mu-opioid-receptor) that displays intact antinociceptive responses to morphine, but do not show tolerance and dependence in paradigms where wild type (WT) mice do. We investigated the transcriptional response to morphine in the ventral tegmental area (VTA) of WT and RMOR mice.

Methods: Male and female WT and RMOR mice were treated for 5-days with 10mg/kg subcutaneous morphine (or saline), which we have previously shown produces dependence in WT but not RMOR mice. On day-6, VTA was dissected and prepared for snRNAseq and differential-expression (DE) analysis.

Results: 24,799 cells passed QC and were assigned to a defined cell-cluster, giving power to identify moderate to strong cell-type specific DE. Expected neuronal and non-neuronal cells were identified, including corelease/cotransmission clusters, and were responsive to morphine. Glucocorticoid pathway genes (e.g. Sgk1) were upregulated in response to morphine in WT oligodendrocyte cells, and, notably, this dysregulation was reduced in RMOR mice. Genes involved in modulation of cellular excitability, and mediation of pain affect were differentially dysregulated across genotypes. Ongoing experiments include increasing replicates and validation via RNA-FISH.

Conclusion: Here, we uncover transcriptional programs that may underlie the transition to dependence. Our results further elucidate the molecular mechanisms of morphine response and could offer novel criteria for safer analgesics.

T59. Genetic Evidence for Cannabis Use Disorder Severity in Multi-Ethnic High-Risk Populations

Qian Peng, The Scripps Research Institute

Background: Large disparities exist in cannabis use disorder (CUD) prevalence among different ethnic groups in the U.S. This work is part of a larger study exploring risk factors for substance use disorders in high-risk populations, and aimed to conduct genome-wide association analysis, rare and low-frequency variant analysis on a CUD-severity phenotype in an American Indian (AI), a Mexican American (MA), and a European American (EA) population cohorts.

Methods: Approximately 3000 participants were deep phenotyped. AI and EA participants had low-coverage whole genome sequence, while MA participants had exome data. Association analyses, gene-based, and pathway-based burden tests were performed on a CUD-severity phenotype. Linear mixed model (LMM) was used to control for population structures and familial relatedness. We further investigated whether top-ranked pathways were distinct or shared among the population cohorts.

Results: 10 variants were found significantly associated with CUD severity in AI ($p < 5E-8$). Gene ARSA that encodes for enzyme arylsulfatase A was found significant in MA. Rare and low-frequency variants in three pathways were significantly associated with CUD severity in MA. These pathways are related to activation of arylsulfatases, integrin1, and an inflammatory condition. A pathway related to the synthesis of heparan sulfate (HS)—a type of glycosaminoglycan (GAG)—is significantly associated with CUD severity in EA.

Conclusion: While each population has distinct variants and pathways associated with CUD severity, a few small networks emerged when top pathways from different cohorts are connected through overlapping genes, implying shared genetic factors across populations for CUD.

T60. In Vivo Imaging Evidence of Neuroinflammation in Opioid Use Disorder

Eric Woodcock, Wayne State University

Background: Preclinical experimental studies, and postmortem analyses of deceased opioid users, show elevated glial markers in the brain. However, in vivo evidence of neuroinflammation among opioid use disorder (OUD) patients has yet to be published to date. Here, we applied positron emission tomography (PET) imaging with the radiotracer, α-[11C]methyl-L-tryptophan ([11C]AMT), to quantify brain kynurenine metabolic rate, a marker sensitive to pro-inflammatory signaling, among OUD patients and matched comparators.

Methods: OUD patients (n=20) enrolled in outpatient methadone maintenance therapy (MMT) and controls (n=23) underwent an afternoon 60-minute PET [11C]AMT scan (0.2 mCi/kg) under fasted conditions. Unidirectional uptake rate constant, K-complex, was quantified via Patlak plot using a left ventricular and venous input function. Group differences

in whole-brain [11C]AMT K-complex were evaluated using an one-way analysis of covariance (ANCOVA) with age as a covariate (sex, BMI, BDI-II, and FTND were non-significant covariates).

Results: Groups were well-matched for age, gender, BDI-II, FTND, and BMI (ps > 0.20). Overall, subjects were 42.9±12.6yrs old, 67.4% male, and 45.2% African-American. Mean methadone dose was 96.1±51.4mg/day. OUD patients exhibited significantly higher [11C]AMT K-complex than controls by 17%, $F(1,38)=5.16$, $p=.029$ (partial $\eta 2=0.13$; 'large' effect). Plasma kynurenine, kynurenine/tryptophan ratio, IFNγ, IL-6, GM-CSF, and CRP were elevated in OUD (ps < .05), whereas plasma tryptophan was higher in controls ($p=.01$)

Conclusions: Our findings show the first in vivo evidence of neuroinflammation among OUD patients in outpatient MMT, as evidenced by elevated brain kynurenine metabolic rate; a novel potential therapeutic target. Plasma markers show dysregulated kynurenine pathway metabolism and elevated pro-inflammatory markers among OUD patients.

T61. Investigating the Role of Inflammatory Signaling in Opioid-Induced Sleep Disruption

Mackenzie Gamble, UMass Chan Medical School

Background: Opioid use disorder (OUD) remains a public health burden driven largely by fentanyl. OUD is associated with persistent sleep disruption and is a major risk factor for relapse. snRNA-seq of OUD human postmortem brain tissue suggests that opioid use induces a pro-inflammatory state. Moreover, many cytokines are also sleep regulatory substances. It remains unclear, however, whether changes in inflammatory signaling are associated with fentanyl-induced sleep disruption and which may be responsible.

Methods: Male and female mice underwent fentanyl exposure (n = 6 per group/sex) while sleep-wake behavior was recorded simultaneously. Changes in sleep architecture were quantified. Cytokines were measured in the suprachiasmatic nucleus, thalamic reticular nucleus, and dorsal medial medulla (n= 72 total samples) to understand how inflammatory signaling changes in sleep-related brain regions during fentanyl exposure.

Results: Both NREMS and REMS were elevated during the inactive phase and remained elevated for the entire seven days of exposure ($p < 0.05$). While the same direction of effect was observed in both males and females the effect was stronger in males with wake decreased by ~55% compared to a decrease of ~45% in females ($p < 0.05$) across the seven days. Within in each brain region we found broad changes in pro-inflammatory cytokines.

Conclusions: Our findings show sex-specific effects on sleep-wake behavior due to fentanyl exposure and begin to identify inflammatory changes in brain circuitry relevant to sleep that may be important for fentanyl-induced sleep disruption.

Friday, March 8, 2024

F1. Cross-Sectional and Longitudinal Structural Network Alterations in Panic Disorder Related to Treatment Outcomes and Application of Connectome-Based Prediction Modeling: 2-Year Follow-Up

Hyun Ju Kim, CHA Bundang Medical Center

Background: A structural network-based understanding is lacking in panic disorder (PD). This study aims to explore the structural connectivity of PD via diffusion MRI (dMRI) at the cross-sectional and longitudinal connectivity levels, using connectome-based predictive modeling (CPM) to predict individual treatment outcomes.

Methods: A total of 80 participants (A total of 160 MRIs), comprising 53 PD patients and 27 healthy controls (HCs), underwent T1 structural and dMRI scans at baseline and after two years. They were assessed using the Panic Disorder Severity Scale. White-matter tractography mapped the whole-brain structural networks, and their alterations over time were observed by network-based statistics. The CPM was used to predict symptom alterations based on brain connectivity.

Results: This study revealed there were connectivity alterations in the cortico-thalamo-limbic circuitry in PD at the cross-sectional and longitudinal connectivity levels. Initial over-connectivity in the amygdala and insula and in the insula and parieto-occipital cortex were associated with non-response and non-remission to treatment. Over the two years, increased connectivity in the amygdala, hippocampus, and insula was associated with positive treatment response, and increased connectivity in the putamen, cingulate, inferior parietal lobule, and precuneus related to remission. Using CPM, these distinctive connectivity patterns emerged as a notable predictor of individual symptom modifications in PD.

Conclusion: This study highlights cross-sectional and longitudinal connectivity alterations in the extended fear network and their association with treatment response and remission in PD, emphasizing the prospective value of personalized biomarkers and suggesting the possibility of personalized treatment strategies for PD.

F2. Norepinephrine Represents Prediction Error Under Temporal Uncertainty

Aakash Basu, Yale University

Background: Individuals must learn to predict levels of threat in uncertain environments. Neuromodulators represent components of predictive learning models such as prediction errors. Despite the demonstrated role of norepinephrine in aversion, sensitive investigations of NE within computational models of threat learning have been limited by the lack of high-resolution measurements of NE.

Methods: To measure norepinephrine during aversive learning, we expressed the fluorescent NE sensor GRABNE in the mouse frontal cortex and measured its fluorescence using fiber photometry during aversive learning. To manipulate norepinephrine release during aversive learning we expressed the optogenetic actuator channelrhodopsin in the locus coeruleus.

Results: Predictive cue-evoked norepinephrine scales with threat association (adj. $R^2=0.6869$ for Association) and scales with threat imminence ($F(2,31)=6.188$, $p=0.0055$), but release decreases during delays between cue and shock ($F(1,10)=7.270$, $p=0.0225$), characteristic of prediction error. Optogenetic augmentation of shock NE also increases threat memory late in predictive cues ($F(1,13)=5.736$, $p=0.0324$), consistent with a teaching signal. However, norepinephrine release shows novel features such as release at the offset of cues and sustained release throughout a predictive cue that cannot be explained by simple prediction error. These can only be explained by learning models incorporating temporal uncertainty. Accordingly, cue offset NE was increased by increasing temporal uncertainty during the cue ($F(2,29)=13.56$, $p < 0.0001$).

Conclusions: NE release is consistent with a threat prediction error that also encodes perceived temporal uncertainty. Ongoing work will identify the contribution of these prediction errors to aversive behavior as well as to second messenger and ensemble dynamics in cortex.

F3. Resting State Cortical Network and Subcortical Hyperconnectivity in Youth With Generalized Anxiety Disorder in the ABCD Study

Sam Sievertsen, University of Washington

Background: Generalized anxiety disorder (GAD) commonly emerges during childhood, yet few studies have examined functional connectivity (FC) differences in youth, and adult findings often conflict due to small samples and targeted brain region analysis. We utilized resting-state fMRI data from the Adolescent Brain Cognitive Development study to investigate GAD-related FC differences in cortical/subcortical regions implicated in adult GAD, considering diagnosis and symptom changes across two assessment periods.

Methods: Within- and between-network FC in 164 GAD youth and 3158 healthy controls for 6 cortical networks and 6 bilateral subcortical regions was assessed via ANCOVA. Change scores in GAD-associated FC metrics between baseline and 2-year follow-up were compared for subjects with: continuous GAD, GAD at baseline and not follow-up (GAD-remitters), GAD at follow-up and not baseline (GAD-converters), and healthy controls. Associations between GAD-associated FC metrics and Child Behavior Checklist (CBCL) symptom severity were assessed using linear regression.

Results: GAD youth showed greater FC within-Ventral Attention Network (VAN) and between the Cingulo-Opercular Network (CON), Default Mode Network (DMN), Salience Network (SN), and multiple subcortical structures (FDR $p < 0.05$). Compared to continuous-GAD and control youth, within-VAN FC decreased for GAD-remitters and increased for GAD-converters between baseline and follow-up assessment. FC was not associated with CBCL symptom severity.

Conclusion: Hyperconnectivity between multiple cortical networks and subcortical regions may reflect aberrant threat sensitivity and regulation in GAD, while shifts in within-VAN hyperconnectivity as youth develop or remit from GAD may reflect changes in hypervigilance to environmental stimuli. VAN hyperconnectivity may be a marker of clinically-significant GAD symptoms.

F4. Inflammatory Cytokines During Pregnancy Predict Postpartum Anxiety: A Prospective Pregnancy Cohort

Carly Kaplan, Icahn School of Medicine At Mount Sinai

Background: Studies have linked inflammation with both depression and anxiety disorders. Pregnancy confers large-scale immune changes, and elevated inflammatory cytokines (particularly IL-1β and IL-6) during pregnancy have been associated with postpartum depression. However, the relationship between pregnancy cytokines and postpartum anxiety has not been thoroughly explored.

Methods: We included 716 participants from Generation C, a prospective pregnancy cohort (recruited from April 2020-February 2022). Anxiety symptoms were assessed 1-8 months postpartum via the Generalized Anxiety Disorder (GAD) questionnaire. Cytokine levels were measured in blood from routine draws throughout pregnancy. Using quantile regressions, the relationship between mean cytokine levels (log-transformed) and continuously measured postpartum anxiety symptoms was investigated separately for 4 cytokines (IL-6, IL-17A, IL-1β, and CRP) adjusting for maternal age, race/ethnicity, education, parity, SARS-CoV-2 infection status during pregnancy, time since April 2020 and GAD assessment timing.

Results: Mean GAD score was 2.89 (SD=3.64), and 43 (6%) participants scored above the clinical cutoff (≥10). After adjustment, IL-17A was significantly associated with increased GAD score at the 75% quantile (b=0.70, SE=0.24, p=0.004). IL-6 exhibited a positively trending correlation at the 75% quantile (b=0.22, SE=0.12, p=0.077), while IL-1β trended towards significance at the 50% quantile (b= 0.18, SE=0.10, p=0.074).

Conclusion: These findings suggest a significant link between pregnancy inflammation and postpartum anxiety, particularly among those experiencing the most significant anxiety symptoms. While specific mechanisms require further exploration, this relationship not only advances our understanding of postpartum mental health, but may also encourage investigation into novel applications of anti-inflammatory biologics in the field of psychiatry.

F5. Investigating Neurodevelopmental Mechanisms of Cullin 3 (Cul3) Haploinsufficiency Using Brain Organoid Models

Luca Trovò, University of California San Diego

Background: The Cullin3 ubiquitin ligase (Cul3) is one of the genes most confidently implicated in Neurodevelopmental Disorders (NDDs) with genome-wide significance (FDR < 0.001). At least 20 different missense and loss-of-function Cul3 mutations have been identified in patients with various NDDs. Although mouse models targeting Cul3 are available, the investigation of this gene in human-derived models is still lacking.

Methods: To investigate the molecular and cellular mechanisms behind Cul3 mutations in human-derived models, we engineered iPSCs with Cul3 haploinsufficiency (Cul3+/-) using CRISPR-Cas9 technology. One of these mutations (E246X stop-gain) replicated the mutation observed in the patient with autism. We then generated brain cortical organoids from several different haploinsufficient Cul3+/- clones, and the organoids were used to investigate size, neuron migration, protein quantification, and other relevant phenotypes.

Results: Our initial characterization revealed that Cul3+/- organoids exhibit smaller size at DIV15. We also observed impaired neuronal migration, marked by a lower number of neurons migrating out of mutant organoids and a shorter migration distance compared to control organoids. Finally, we found an upregulation of RhoA in DIV10 Cul3+/- organoids, consistent with the results from the mouse model.

Conclusion: The Cul3+/- organoids exhibit smaller size and impaired neuronal migration, possibly reflecting defects seen in the fetal brain. Finally, the RhoA upregulation provides a potential molecular mechanism for the observed migration defects, given its role in cytoskeletal dynamics, neurite outgrowth, and cell migration. Future studies will include in-depth analyses through single-cell transcriptomics, proteomics, and electrophysiological studies, as well as validation in patient-derived organoid models.

F6. Investigating the Effects of Autism-Linked Mutations in Glial KCNQ Channels on Glia-Neuron Functional Interaction

Bianca Graziano, Miller School of Medicine, University of Miami

Background: Autism Spectrum Disorder (ASD) is a genetically heterogeneous condition that has been linked to over 100 high risk genes. Mutations in the voltage-gated K+ channel called KCNQ have been associated with ASD, epilepsy, and neurodevelopmental disability. KCNQs are expressed in neurons, where they regulate neuronal excitability. KCNQs are

also expressed in glia, but their role in these cells remains unknown. In this study, we used the model organism C. elegans to investigate how mutations in glial KCNQ channels can affect behavior, glial and neuronal function.
Methods: To answer this question, we used a global knockout strain of kqt-2, a homolog of KCNQ channels. We characterized sensory behavior, glial and neuronal function of the kqt-2 mutant using olfaction avoidance assays, Ca2+ and voltage imaging. In addition, using genetic manipulation, we investigated the role of glial KCNQ channels in GABAergic inhibition. We then tested how the glial expression of different types of ASD-associated mutations affected sensory behavior and cellular function.

Results: kqt-2 knockout nematodes displayed reduced avoidance to olfactory stimulation, and decreased and increased Ca2+ in glia and neurons respectively. These behavioral and cellular phenotypes were rescued by potentiation of GABAergic signaling, and they were reproduced by its inhibition. Introduction of different types of KCNQ mutations led to distinct behavioral and cellular phenotypes.

Conclusions: glial KCNQ channels regulate neuronal function, and therefore sensory behavior, by mediating GABA release from glia in C. elegans. ASD-linked mutations in glia impair this function; thus, glial KCNQs should be considered novel targets for therapy.

F7. Cell-Type Specific and Activity-Dependent Characterization of Non-Coding Autism De Novo Variants in Human Stem Cell-Derived Neurons

Sarah Williams, Icahn School of Medicine At Mount Sinai

Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with a complex genetic architecture. Thousands of non-coding de novo variants (DNVs) have been identified (An et al. 2018), but the functional contribution of these DNVs to ASD etiology remains uncertain. Regulatory activity is highly context-dependent, so to determine whether non-coding DNVs may impact gene regulation in a cell type relevant to ASD, our lab annotated the enhancers present in human stem cell-derived excitatory and inhibitory neurons, at baseline and depolarized states, and intersected these results with the 255k ASD DNVs.
Methods: Using a massively parallel reporter assay (MPRA), we will determine whether these non-coding DNVs found in neuronal enhancers alter cis-regulatory activity in glutamatergic or GABAergic human neurons in baseline or activated states. Further, we performed the activity-by-contact model to identify the genes regulated by DNV-containing enhancers. To validate cis-regulatory activity and to compare trans-effects on downstream gene networks, a CRISPR inhibition screen will be performed targeting a subset of ASD DNV-containing enhancers and their predicted gene targets.

Results: We identified 2,495 ASD DNVs within neuronal enhancers, hundreds being cell-type specific or activity-dependent. Gene-enhancer mapping revealed that a subset of DNV-containing enhancers is predicted to regulate high-confidence ASD genes.

Conclusions: I hypothesize that ASD DNVs will have context-specific effects on enhancer activity and subsequent gene expression in human neurons, with a modulatory impact on genes and gene networks associated with ASD. These results would indicate a functional role for non-coding de novo variation in autism etiology.

F8. Pharmacotherapeutic Effects of Cannabidiol in Autism Spectrum Disorders

Mike Parkhill, Carleton University

Background: Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by social deficits and restrictive/repetitive behaviour. ASD is diagnosed in 1-2% of the global population. Cannabidiol (CBD), a compound from the Cannabis plant, has shown promise in ameliorating ASD-associated symptoms. We evaluated the efficacy of CBD in treating ASD-like behaviours in Fmr1 and Shank3 knockout mice, two monogenetic models of ASD. Methods: To establish baseline behaviours, male and female mice from each genotype were tested in the social novelty (SN)/sociability or open field/self-grooming tests. Then, they received five daily injections (subcutaneous) of vehicle or CBD (5mg/kg in males, 50mg/kg in females). After the last injection, mice were tested again. Results: At baseline, knockout mice displayed deficits in social novelty (but not sociability). SN increased significantly in both KO groups following CBD administration. Among Fmr1 KO males, the SN index among CBD-treated mice (0.71 +/-0.04) was > vehicle-treated mice (0.39+/-0.04) post-treatment. Similarly, among Shank3 KO mice, CBD-treated mice (0.72+/-0.06) had greater SN scores than vehicle-treated Shank3 mice (0.43+/-0.07). CBD-treated KO groups had comparable scores to WT mice at baseline (0.75+/-0.03). The same effect was found among females wherein Fmr1 KO mice given CBD (0.70 +/-0.04) had greater SN scores than their vehicle-treated counterparts (0.55+/-0.05). Shank3 KO females given CBD (0.80+/-0.06) and vehicle (0.40+/-0.05)

also differed. CBD-treated KO mice had scores comparable to WT mice at baseline (0.69+/-0.06). CBD did not affect sociability, grooming, or locomotion. Conclusion: These findings suggest CBD exerts specific therapeutic effects on social behaviour.

F9. Facial Expression Recognition is Linked to Clinical and Neurofunctional Differences in Autism

Hannah Meyer-Lindenberg, University Clinic Heidelberg

Background: Difficulties in social communication are a defining clinical feature of autism. However, underlying neurobiological heterogeneity impedes targeted therapies, and requires new approaches to identifying clinically relevant bio-behavioural subgroups. In the largest autism cohort to date, we examined difficulties in facial expression recognition, a key process in social communication, as a stratification biomarker, and validated them against clinical features and neurofunctional responses.

Methods: Between 255 and 488 participants aged 6-30 years with autism/typical development completed the Karolinska Directed Emotional Faces task, the Reading the Mind in the Eyes Task and/or the Films Expression Task. We examined mean-group differences on each test. Then we compared two centroid and connectivity-based clustering methods to derive subgroups based on combined performance across three tasks. Measures and subgroups were then related to clinical features and neurofunctional differences measured using fMRI during a fearful face-matching task.

Results: We found significant mean-group differences on each expression recognition test. However, cluster analyses showed that these were driven by a low-performing autistic subgroup (~30% of autistic individuals), while a larger subgroup (~70%) performed within 1SD on at least 2 tests. The low-performing subgroup had on average significantly more social-communication difficulties and lower activation in the amygdala and fusiform gyrus than the high-performing subgroup.

Conclusions: We identified a subgroup of autistic individuals with expression recognition difficulties and showed that this related to clinical and neurobiological characteristics. If replicated, expression recognition may serve as bio-behavioural stratification biomarker and aid in the development of targeted interventions for a subgroup of autistic individuals.

F10. The Loss of ZC3H14, a Polyadenosine RNA-Binding Protein, Inhibits Hippocampal Long-Term Depression and Working Memory

Kenneth Myers, Emory University

Background: The polyadenosine (poly(A)) RNA-binding protein ZC3H14 is associated with a heritable form of non-syndromic autosomal recessive intellectual disability. ZC3H14 primarily localizes to nuclear speckles, where it regulates the processing of neuronal RNA transcripts. However, ZC3H14 can also be found throughout dendrites and in dendritic spines. Using a loss-of-function mouse model (Zc3h14Δex13/Δex13), ZC3H14 was previously shown to control poly(A) tail length and working memory. The Drosophila ortholog of ZC3H14, dNab2, also regulates poly(A) tail length and short-term memory, and it is required for repression of a CaMKII translational reporter. The processing, transport, and translation of RNAs is critical for long-term synaptic plasticity. Consequently, disruptions of these mechanisms have been linked to a wide array of neurologic disorders. However, the role of ZC3H14 in neuronal development and synaptic plasticity remains unclear.

Methods: We used a combination of fluorescence microscopy and electrophysiological methods to analyze neuronal morphology, basal synaptic transmission, and synaptic plasticity in hippocampal slices.

Results: We found that dendritic morphology, basal synaptic transmission, and long-term potentiation (LTP) are normal in Zc3h14Δex13/Δex13 mice. However, we found that long-term depression (LTD) is blocked by the loss of ZC3H14.

Conclusion: To determine the underlying molecular mechanisms, we are currently investigating how the loss of ZC3H14 affects the synthesis of synaptic “LTD proteins”, and dissecting which functions of ZC3H14 are required for normal LTD. These findings may provide new insights into how a ubiquitously expressed RNA binding protein leads to neuronal-specific defects, and improve our understanding of intellectual disability.

F11. Unveiling Cell-Specific Transcriptional Dysregulation in Adult Chd8 Haploinsufficient Mouse Cortex

Stephanie Lozano, UC Davis Center for Neuroscience

Background: Mutations in CHD8 are thought to play a causal role in neurodevelopmental disorders (NDDs), including autism spectrum disorder and intellectual disability. Mice with a heterozygous mutation to Chd8 exhibit genomic,

neuroanatomical, and behavioral pathology that aligns with NDD features. We sought to identify cell type-specific transcriptomic impacts of Chd8 haploinsufficiency in the adult cortex towards understanding the lasting impact of Chd8 haploinsufficiency in the mature brain.
Methods: We leveraged snRNA-seq on adult male and female cortex from a previously characterized Chd8 mutant mouse line. We used a pseudo-bulk differential expression analysis approach to resolve cell type-specific changes in gene expression in Chd8 mutant cortex. We performed high-definition weighted gene correlation network analysis within each cell population to detect highly correlated modules of genes that change in expression as a function of Chd8 genotype.

Results: We observed cell type-specific changes in gene expression at both the single-gene and gene network levels. Layer-specific glutamatergic neurons were among the most impacted cell types, exhibiting a strong upregulated transcriptomic signature associated with neuronal maturation and axon guidance. Glial and microglial populations also showed perturbations. RNA-FISH validation of differential expression is ongoing.

Conclusions: Heterozygous Chd8 mutation leads to intricate, widespread alterations in gene expression within the adult mouse cortex. These changes are not uniform across all cell types, but rather manifest with striking specificity, particularly within layer-specific excitatory neurons. Our findings reveal a nuanced understanding of how Chd8 haploinsufficiency affects the transcriptomic landscape of the brain, illuminating its unique impact on distinct cell populations.

F12. KANSL1 Localizes to Cilia and is Required for Ciliogenesis During Embryonic Development
James Schmidt, Weill Institute of Neurosciences, UCSF
Background: Koolen-de Vries Syndrome (KdVS) is a neurodevelopmental disorder without therapeutics and with a range of clinical presentations, including hypersociability, characteristic facial features, epilepsy, respiratory defects, congenital heart defects, and hypotonia. KdVS is a genetic variant affecting the KANSL1 (KAT8 regulatory NSL complex subunit 1) gene. KANSL1 is a chromatin modifier that regulates histone acetylation, but also stabilizes microtubules. Microtubules are a structural component of cilia, membrane-bound projections present on almost all cells. Cilia defects in humans cause all of the clinical presentations observed in KdVS; therefore, we have the hypothesis that KANSL1 is involved in cilia form and/or function. Consistently, KANSL1 has a WDR5-binding domain, and WDR5 is known to play a direct role in ciliogenesis.
Methods: To test whether KANSL1 has a role in cilia formation, we used the diploid frog model Xenopus tropicalis. In this model, we are able to localize proteins on cilia and perform both gain and loss of function experiments in vivo in intact vertebrate embryos.

Results: Here we show that KANSL1 localizes to motile ciliary axonemes on multiciliated cells of the Xenopus embryonic epidermis, as well as to the actin cortical network that docks the base of cilia, named basal bodies. Loss of function experiments show the requirement of KANSL1 in cilia formation in vivo, while gain of function experiments show the effect of gene dosage on gene function.

Conclusion: These results have extended the known roles of KANSL1 to cilia formation and provide potential hypotheses about the mechanisms of pathobiology for KdVs.

F13. Premature Birth Disrupts the Function of Top-Down Circuits for Visual Processing
Adema Ribic, University of Virginia
Background: The process of birth transitions the fetus to extrauterine environment, altering the trajectory of multiple neurodevelopmental processes. Premature birth can hence disrupt brain development and, in agreement, over 50% of preterm born infants show cognitive deficits, particularly in the visual processing domain. Previous studies in infants suggest that preterm birth disrupts the function of top-down circuits for visual processing, but this has not yet been mechanistically addressed.
Methods and Results: We used preterm born mice to mechanistically address preterm birth-driven changes in the function of top-down visual processing circuits. Mice born a day early show normal physical development and intact basic visual function in adulthood. However, preterm mice fail to achieve high levels of performance in a visual discrimination task that is modulated by visual cortex (V1)-projecting anterior cingulate cortex (ACC) neurons. Preterm mice have slower reaction times at the onset of training, and decreased response inhibition even in the trained stage. To determine the potential circuit mechanisms of these deficits, we used in vivo electrophysiology and intersectional optogenetics to probe the function of top-down circuits in preterm mice. While V1-projecting ACC neurons in trained term mice develop robust

selectivity for task-relevant stimuli in the prefrontal cortex, ACC→V1 neurons in term mice show disinhibition and low to no selectivity for the task-relevant stimuli.

Conclusion: our results demonstrate that preterm birth disrupts the function of top-down circuits for visual processing and suggest that the perinatal period is a critical window for the development of both local and long-range prefrontal circuits.

F14. PTEN Activity Affected by Subcellular Localization

Nicole Desmet, Dartmouth College

Autism Spectrum Disorder (ASD) is a prevalent neurodevelopmental disorder affecting 1 in 36 children in America. While most cases are idiopathic, a growing number have been linked to genetic mutations. Recent genomic sequencing reports indicate that Phosphatase and Tensin Homolog (PTEN) is the 6th most commonly mutated gene in patients with ASD. When PTEN is mutated, unregulated activation of the AKT/mTOR pathway drives neuronal hypertrophy. While some PTEN mutations result in nuclear enrichment/exclusion of PTEN, how the localization of PTEN regulates its function is unknown.

PTEN broadly localizes throughout the cell and subpopulations may have distinct functional impacts. Using PTENflx/flx/Ai14 mice and retroviral-mediated genetic manipulation, endogenous Pten can be knocked out and simultaneously reconstituted with PTEN fused to localization motifs. By localizing PTEN to the filopodia, post-synaptic density, nucleus, or nuclear-exclusion, we analyzed the importance of subcellular location in regulating neuronal hypertrophy and protrusion formation.

In developing hippocampal neurons, Pten loss results in increased soma area, and increased spine density, length, and head area. PTEN localized to the filopodia, the post-synaptic density, and nuclear-exclusion rescue each of the phenotypes observed. These results suggest that PTEN is needed at the membrane to control neuronal growth and spine density. However, nuclear-localized PTEN can rescue the increase in dendritic spine head area. This may imply a mechanism through which PTEN-regulated transcription controls spine head area, a crucial characteristic of synapse strength and function.

Understanding how PTEN subcellular localization regulates dendritic growth, filopodial motility, and synaptic physiology will help better understand PTEN loss-associated ASD.

F15. Gene Dosage and Age Effects on Subcortical Nuclei Volumes in Individuals With 22q11.2 Copy Number Variations

Charles Schleifer, David Geffen School of Medicine at UCLA

Background: Copy Number Variations (CNVs) at the 22q11.2 locus impact neurodevelopment and elevate risk of neuropsychiatric disorders. Individuals with the deletion (22qDel) have increased rates of schizophrenia and autism, while the duplication (22qDup) increases autism risk but may protect against schizophrenia. One prior cross-sectional study of cortical structure found that cortical thickness negatively relates to gene dosage (22qDel > control > 22qDup), with the opposite for surface area.

Methods: We collected longitudinal MRI data in individuals with 22qDel (n=96 baseline, 53% female), 22qDup (n=37 baseline, 46% female), and typically developing (TD) controls (n=80 baseline, 51% female), aged 5.5-49.5 years. Volumes for the whole thalamus, hippocampus, amygdala, and 40 anatomical subregions per hemisphere were estimated with FreeSurfer. Gene dosages were approximated based on CNV status, and cross-sectional gene dosage effects were tested in linear mixed models. Developmental trajectories were mapped with nonlinear mixed models.

Results: Significant gene dosage effects were observed in the whole hippocampus but not the entire thalamus or amygdala. Among 80 subregions, 31 exhibited significant (False Discovery Rate corrected) positive or negative gene dosage effects. Specific subregions of the amygdala and thalamus (e.g., mediodorsal thalamus) showed effects not detectable at the whole-structure level. Non-linear developmental trajectories showed distinct age-related subregion volume changes in each group.

Conclusion: Gene dosage at the 22q11.2 locus predicts subregion volumes and altered subcortical development, offering insights into the genetic influences on brain development and neuropsychiatric conditions. In future studies we will explore genetic mechanisms and cell-specific effects relevant to neurodevelopmental disorders.

F16. An IGFBP2-Derived Peptide Promotes Neuroplasticity and Rescues Deficits in a Mouse Model of Phelan-Mcdermid Syndrome

Sehyoun Yoon, Northwestern University

Background: Therapeutically targeting synaptic plasticity may yield novel treatments for neurodevelopmental disorders. However, our toolbox for modulating synaptic plasticity is limited, and there is a great unmet need to develop novel classes of modulators of synaptic plasticity with therapeutic potential.

Method: We developed an IGFBP2-mimetic peptide fragment, JB2, and showed that it promotes basal synaptic structural and functional plasticity in cultured neurons and mice.

Results: We demonstrate that JB2 directly binds to dendrites and synapses, and its biological activity involves NMDA receptor activation, gene transcription and translation, and IGF2 receptors. In neurons, JB2 induced extensive remodeling of the membrane phosphoproteome. Synapse and cytoskeletal regulation, autism spectrum disorder (ASD) risk factors, and a Shank3-associated protein network were significantly enriched among phosphorylated and dephosphorylated proteins. Haploinsufficiency of the SHANK3 gene on chromosome 22q13.3 often causes Phelan-McDermid Syndrome (PMS), a genetically defined form of autism with profound deficits in motor behavior, sensory processing, language, and cognitive function. We identified multiple disease-relevant phenotypes in a Shank3 heterozygous mouse and showed that JB2 rescued deficits in synaptic function and plasticity, learning and memory, ultrasonic vocalizations, and motor function; it also normalized neuronal excitability and seizure susceptibility. Notably, JB2 rescued deficits in the auditory evoked response latency, alpha peak frequency, and steady-state electroencephalography response, measures with direct translational value to human subjects.

Conclusion: JB2 is a potent modulator of neuroplasticity with therapeutic potential for the treatment of PMS and ASD.

F17. Molecular Signatures of Hyperexcitability and Lithium Responsiveness in Bipolar Disorder Patient Neurons Provide Alternative Therapeutic Strategies

Malak Abuzgaya, McGill University, Montreal Neurological Institute

Bipolar disorder (BD) is a progressive psychiatric disorder characterized by recurrent mania and depression, often comorbid with psychosis and suicide. Paralleled with other treatments, the mood stabilizer lithium (Li) is the most effective medication to prevent manic and depressive episodes. However, the pathophysiology of bipolar disorder and lithium's mode of action is not yet fully characterized and understood. Some patients react well to Li treatment for undetermined reasons, while others are entirely non-responsive. Three major questions stand out: i) how Li is effective, ii) why for only a subset of patients, and iii) could we find a treatment for the Li non-responders? Our previous studies showed that lithium dampens neuronal excitability and the activity of the glutamatergic network in mouse cortical neurons. Here, we have developed a human induced pluripotent stem cell (hiPSC) model for bipolar disorder and investigated the cellular phenotypes of glutamatergic cortical-like neurons derived from iPSCs of patients with bipolar disorder. Our results corroborate the literature discerning a hyperexcitability phenotype of young neurons, reversible by lithium treatment in neurons derived from patients who clinically responded to lithium treatment. In this study, we combined cell imaging, electrophysiology, transcriptomic, phosphoproteomic, calcium imaging and pharmacological treatments to provide a molecular signature of disease and lithium responsiveness. From this study, we have identified alternative potential therapeutic candidates for both patient populations.

F18. Bipex 2.0: Large-Scale Exome Sequencing of over 100,000 Individuals Identifies Novel Genetic Insights into Bipolar Disorder

Cal Liao, Broad Institute of MIT and Harvard

Bipolar disorder (BD) is a complex psychiatric disorder characterized by recurrent mood disturbances with significant variations in disease severity and treatment response. Despite its substantial impact on individuals, the genetic factors contributing to BD remain incompletely understood. Exome sequencing has emerged as a powerful tool for elucidating the genetic architecture of various diseases. Here, we provide updates from the Bipolar Exome (BipEx) consortia, where we leverage large-scale exome sequencing to investigate the role of protein-truncating variants (PTVs), copy number variants (CNVs), and damaging missense variants in the pathogenesis of BD.

Our study cohort comprised of over 100,000 individuals of BD and controls, with an ancestrally diverse population. Whole exome sequencing was conducted to capture protein-coding regions, followed by robust variant calling and stringent filtering. We filtered to ultra-rare genetic variants for PTVs and damaging missense variants. Additionally, we used GATK-gCNV to call rare exonic duplications and deletions.

The initial PTV analyses revealed that the top significant associations were for AKAP11, DOP1A, KDM5B and SP4. There are additionally significant enrichments in highly constrained loss-of-function genes across PTVs (OR:1.20,P=3.18x10-29), missense (OR:1.07,P=5.95x10-11), deletions (OR:1.94,P=2.47x10-24) and duplications (OR:1.09,P=0.01). Furthermore, we see significant enrichment of schizophrenia, autism, and neurodevelopmental disorder associated genes across these genetic variant types.

By leveraging a large cohort of over 100,000 individuals, BipEx provides comprehensive insights into the genetic landscape of BD. We demonstrate the importance of PTVs, CNVs and damaging missense variants in the genetic architecture of BD, shedding light on the biological mechanisms underlying this complex disorder.

F19. The Relationship Between the Polygenic Risk Score (PRS) and the Usage of Hypnotics in Patients With Bipolar I Disorder

Moon-Doo Kim, Jeju National University Hospital

Objective: Sleep disturbance is one of the most common features among bipolar patients. This study aims to assess the correlation between Bipolar disorder-polygenic risk scores (BD-PRS) and the use of hypnotics in bipolar I disorder(BID) patients.

Methods: Sample data was collected from Genome-wide association study (GWAS) from the multicenter Bipolar Genomic Study (BiGS). From this cohort, 1,394 bipolar I patients with medication information were selected. Participants were categorized into two groups based on the presence or absence of hypnotics. Diagnostic Interview for Genetic studies (DIGS) score was used to assess clinical manifestations and life functioning of participants. Statistical analysis was conducted to analyze the correlation of the psychopathology, BD-PRS and hypnotics.

Results: 556 of 1,394 total participants (40%) were prescribed with hypnotics. Benzodiazepines were the most commonly prescribed type of hypnotics. Between groups prescribed with and without hypnotics, DIGS score was significantly higher in categories of ‘mixed symptoms’, ‘suicidality’, and ‘general impact of illness on life functioning’ in the group prescribed with hypnotics. BD-PRS was significantly higher according to four p-value thresholds ($p < 0.3$, $p < 0.2$, $p < 0.1$, $p < 0.05$) in the group prescribed with hypnotics (BZDs and/or Z-drugs). In the results of the logistic regression analysis controlling for confounding variables, a significant association between BD-PRS and the usage of hypnotics was also confirmed.

Conclusion: Presence of sleep disturbances among the participants were assumed by the prescription status of hypnotics of bipolar patients in this study. This result supports that sleep disturbance may be associated with genetic/biological factors in bipolar I disorder.

F20. Neuromolecular Etiology of Bipolar Disorder: Possible Therapeutic Targets of Mood Stabilizers

Kwanghun LEE, Dongguk University Gyeongju Hospital

Bipolar disorder is a mental illness that causes extreme mood swings and has a chronic course. However, the mechanism by which mood episodes with completely opposite characteristics appear repeatedly, or a mixture of symptoms appears, in patients with bipolar disorder remains unknown. Therefore, mood stabilizers are indicated only for single mood episodes, such as manic episodes and depressive episodes, and no true mood-stabilizing drugs effective for treat_x0002_ing both manic and depressive episodes currently exist. Therefore, in this review, therapeutic targets that facilitate the development of mood stabilizers were examined by reviewing the current understanding of the neuromolecular etiology of bipolar disorder.

F21. Landscape of Copy Number Variation in Cooperative Studies Program (CSP) #572 and the Million Veteran Program (MVP)

Tim Bigdeli, VA New York Harbor Healthcare System

Large rare copy number variants (CNVs) have established relevance for psychiatric and neurodevelopmental disorders, but recurrent deletion and duplication events account for a small fraction of affected persons with diagnosed schizophrenia or autism. With the advent of large-scale biobanks linking genomic data with electronic health records (EHRs), the broader phenotypic consequences of CNVs can be explored. Building on this literature, we undertook a comprehensive survey of large CNVs in 660,000 participants in the Million Veteran Program (MVP) and Cooperative Studies Program (CSP) #572 studies. We observe comparable prevalences of many well-studied CNVs in the MVP and UK Biobanks, including highly penetrant deletions of 22q11.2 and 3q29. Specific CNVs (e.g. 16p11.2 duplications, Klinefelter's) and total CNV burden (e.g. events spanning haploinsufficient or triplosensitive genes) were associated with schizophrenia, affective disorders,

autism, and higher body mass index. Phenome-wide association studies highlighted associations with laboratory tests, antipsychotic and antidepressant treatment, as well as self-reported personality traits. Among 9,300 participants with confirmed schizophrenia or bipolar I disorder with performance-based neurocognitive testing data, we observed carriers of deletions of 22q11.2 and 16p12.1, and duplications of 15q11.2 and 13q12.12, whose performance was 1.5 standard deviation below the mean of the aggregated sample of veterans. Ongoing analyses compare carriers of deleterious CNV and individuals in the top strata of multivariate polygenic risk, and highlight benefits of jointly modeling common and rare variants in large scale genetic studies.

F22. Genome-Wide Molecular Effects of the Neuropsychiatric 16p11 CNVs in an iPSC-To-In Neuronal Model
Pingping Qu, Stanford University

Background: Copy number variants (CNVs), either deletions or duplications, at the 16p11.2 locus in the human genome are known to increase the risk for autism spectrum disorders (ASD), schizophrenia, and several other developmental conditions. Here, we investigate the global effects on gene expression and DNA methylation using a 16p11.2 CNV patient-derived induced pluripotent stem cell (iPSC) to induced neuron (iN) cell model system.

Methods: All iPSC cell lines were differentiated to induced neurons (iNs). RNA-Seq data were used to profile gene expression. Knockdown experiments of the serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) were carried out in zebrafish. CpG-Capture bisulfite sequencing and analysis were conducted to profile DNA methylation pattern.

Results: 16p11.2 CNV patient-derived iPSCs form the basis of induced neurons (iNs). Gene expression is altered within the CNV region and genome wide. Most of the overlapping DEGs between deletions and duplications outside the 16p11.2 region show same direction of change in iPSCs and iNs. PCSK9 knockdown leads to altered developmental phenotypes in zebrafish. DNA methylation regulation is altered genome-wide.

Conclusions: Our study revealed genome-wide and cell-type specific alterations to both gene expression and DNA methylation patterns and also yielded specific leads on genes potentially contributing to some of the known 16p11.2 patient phenotypes. PCSK9 is identified as a possible contributing factor to the symptoms seen in carriers of the 16p11.2 CNVs.

F23. Behavioral Phenotypes and Comorbidity in 3q29 Deletion Syndrome: Results From the 3q29 Registry
Rebecca Pollak, Center for Advanced Biotechnology and Medicine, Rutgers University

Background: 3q29 deletion syndrome (3q29del) is associated with a significantly increased risk for neurodevelopmental and neuropsychiatric disorders. However, the full spectrum of behavioral phenotypes associated with 3q29del is still evolving.

Methods: Individuals with 3q29del (n=96, 60.42% male) or their guardian completed the Achenbach Child or Adult Behavior Checklist (CBCL/ABCL) via the online 3q29 registry (3q29deletion.org). Typically developing controls (n=57, 49.12% male) were ascertained as a comparison group. We analyzed mean performance on the CBCL/ABCL for individuals with 3q29del and controls across composite, DSM-keyed, and developmental scales; and the relationship between CBCL/ABCL performance and clinical and developmental phenotypes for individuals with 3q29del.

Results: Individuals with 3q29del showed significant behavioral impairment relative to controls across CBCL/ABCL domains. We found that the DSM-keyed CBCL/ABCL scales are potential screening tools for autism spectrum disorder (ASD), anxiety disorder, and attention-deficit/hyperactivity disorder (ADHD) for individuals with 3q29del. We identified a high degree of psychiatric comorbidity in individuals with 3q29del, with 60.42% (n=58) of individuals with 3q29del scoring in the Borderline or Clinical range on two or more DSM-keyed CBCL/ABCL scales. Finally, we found that the degree of developmental delay in participants with 3q29del does not explain the increased behavioral problems observed on the CBCL/ABCL.

Conclusions: The CBCL/ABCL can be used as screening tools in populations such as 3q29del, even in the presence of substantial psychiatric comorbidity. These results expand our understanding of the phenotypic spectrum of 3q29del and demonstrate an effective method for recruiting and phenotyping a large sample of individuals with a rare genetic disorder.

F24. Gestational SARS-CoV-2 Infection, Placental Gene Expression and Postpartum Depression
M. Mercedes Perez-Rodriguez, Icahn School of Medicine at Mount Sinai

Background: Around 30% of women suffered postpartum depression during the COVID-19 pandemic, a two-fold increase compared to pre-pandemic. The immune system is a potential mechanism underlying depression. The placenta is a driver of gestational immune changes and can modulate the maternal immune response to infections.
We aimed to investigate whether gestational SARS-CoV2 infection is associated with placental expression of immune/inflammation genes which may be in turn associated with postpartum depression.

Methods: Placental samples (n=141) were collected from the Generation C pregnancy cohort (4/2020-2/2022) at the Mount Sinai Health System, NY. Assessments: Gestational SARS-CoV-2 infection status and Edinburgh Postnatal Depression Scale scores (EPDS) at 6-weeks postpartum. RNA-sequencing provided expression profiles of 347 immune/inflammation genes. First, we conducted differential gene expression analysis by gestational SARS-CoV-2 status using the Limma R package to fit linear regression models adjusted for covariates. Next, we interrogated the relationship between these differentially-expressed genes (predictor) and postpartum EPDS scores (outcome) with linear regression analysis adjusted for covariates.

Results: Gestational SARS-CoV-2 infection was associated with downregulated placental expression of 38 genes ($p < 0.05$). Linear regression analysis of these 38 differentially expressed genes revealed negative associations between expression and postpartum EPDS scores ($p < 0.05$) in 4 genes (FZD5,CXCR6,BANK1,MET).

Conclusions: Gestational SARS-CoV-2 infection was associated with placental down-regulation of four genes (FZD5,CXCR6,BANK1,MET), whose expression was inversely associated with EPDS scores. SARS-CoV-2 infection was previously associated with lower CXCR6 expression in lung, and lower MET expression was linked to depression. These preliminary results suggest the need to explore the potential role of these immune-related genes in postpartum depression.

F25. A Toxic Work Environment: A Case of Major Depression Confounded by Reported Polybrominated Biphenyl Exposure

Jennifer Lenchner, Henry Ford Jackson Hospital

Background: In 1973 Polybrominated biphenyl (PBB) contamination of farm animal feed led to the largest environmental contamination crisis in Michigan history. The proposed pathomechanism of PBB-induced depression is disruption of dopamine metabolism, tyrosine hydroxylase activity, thyroid hormone receptors and serum thyroid hormone binding proteins. It also affects aromatase and steroid 17α-monooxygenase activities, involved in estrogen and androgen synthesis. To highlight the need for further studies and education, we present a case of a patient with major depressive disorder and PTSD raised in an area deemed hazardous due to PBB.
Methods: Literature search in PubMed, Web of Science, APA PsychNet for the terms: “PBB + depression”, "PBB + mood", "PBB + neuropsychiatric”, 17 discussed neurotoxic and neurodevelopmental effects of PBB, 7 discussed PBB exposure in adults.

Case/Results: 24-year-old assigned-female-at-birth with major depressive disorder, PTSD, family history of cancer presented outpatient with irritability, low mood, and PTSD symptoms. They declined serum PBB level but reported their sister’s PBB level was elevated. Patient achieved stability on lamotrigine 200 mg daily and prazosin 1 mg nightly.

Discussion/Conclusion: PBB neurotoxic effects or relayed neurotoxicity require additional investigation as studies in animals have varying proposed mechanisms. PBB was a significant confounder to patient's presentation and prognosis. Lamotrigine was initiated as its mechanism of action avoided pathways with potential to be altered in PBB exposure. However, limited studies have shown neuropsychiatric symptoms and neurodevelopmental deficits in people exposed, and no studies were found regarding treatment. This case highlights the complexities of treatment of people with PBB exposure.

F26. Functional Brain Networks and Depressive Symptoms in Psychotic Depression

Nicholas Neufeld, Centre for Addiction and Mental Health

Background: Major depressive disorder with psychotic features is among the most severe mental disorders and has a high risk of relapse. Identifying neural circuitry related to depressive symptoms may provide neural targets for preventative interventions. We previously found that cortical thickness in a data-driven network incorporating cingulate cortex was associated with depression symptoms. In this study, we aimed to examine whole brain resting state functional connectivity (rsFC) in established brain networks incorporating cingulate cortex and hypothesized that rsFC related to the cingulo-opercular (CiOp) and default mode (DMN) networks would be associated with depression scores.

Methods: All patients (N= 58) participated in the Study of Pharmacotherapy of Psychotic Depression (STOP-PD II) and were treated with sertraline and olanzapine. Depression was rated using the Hamilton Depression Rating Scale (HDRS). Whole brain functional connectivity was examined in established networks defined by the Multimodal Parcellation Atlas and the Melbourne Subcortex Atlas. Linear models were employed to examine associations between rsFC and depression scores while controlling for age and sex.

Results: Consistent with our hypotheses, lower within-CiOp rsFC was associated with higher depression scores (t=-3.22, p=.002). Contrary to our hypotheses, depression scores were not associated with rsFC within the DMN (t=.16, p=0.872) nor rsFC between the rest of the brain and the CiOp network (t=-1.64, p=.107) or DMN (t=.28, p=.782).

Conclusion: rsFC within the CiOp network is associated with depression scores and may provide a neural target for patients with psychotic depression.

F27. Identification of Sex-Specific Vascular and Immune Blood Biomarkers of Mood Disorders

Laurence Dion-Albert, Université Laval (CERVO Brain Research Center)

Background: Major depressive disorder (MDD) is the leading cause of disability worldwide and women have a roughly twofold higher risk than men. Only 30% of patients completely remit from MDD, suggesting that neuron-centric traditional treatments do not address important causal biological factors. Clinical studies report higher prevalence of MDD in individuals suffering from cardiovascular diseases or stroke, highlighting that inflammation and vascular dysfunction may contribute to depression pathogenesis. Indeed, circulating inflammation is elevated in treatment-resistant individuals and neurovascular adaptations modulate cognition, mood, and stress responses. We reported that loss of blood-brain barrier (BBB) integrity is implicated in MDD, in animal models and human postmortem brain samples. We propose that identification of biomarkers related to BBB hyperpermeability and inflammation could help guide diagnosis and choice of treatment in MDD.

Methods: Serum samples of 40 women and 62 men from the Signature Biobank (CIUSSS Montreal-Est) were analyzed, including individuals with a diagnosis of MDD or no mental health conditions (controls). The Patient Health Questionnaire (PHQ-9, depression state) was performed during sample collection and used to evaluate correlational relationships between biomarkers and severity of depressive symptoms.

Results: Blood levels of E-selectin and Platelet-derived growth factor BB (PDGF-BB), two vascular biomarkers providing indirect measurement of BBB integrity are altered in MDD, in a sex-specific manner. Interestingly, baseline sex differences in blood levels of both E-selectin and PDGF-BB were observed.

Conclusion: Considering that MDD is associated with sex-specific symptomatology, prevalence, and treatment responses, these results provide novel insights into vascular blood signatures of mood disorders.

F28. Automatic Detection of Complex Structural Genome Variation Across Human Populations and in PsychENCODE Brains

Alexander Urban, Stanford University

Background: Complex structural variants (cxSVs) exist in all human genomes but are effectively excluded from genome analyses due to the technical difficulties associated with their accurate detection. At the same time there are now multiple candidate loci from GWAS for conditions such as schizophrenia and bipolar disorder, raising the question of the functional sequence variants underlying these loci.

Methods: We developed Automated Reconstruction of Complex Structural Variation (ARC-SV), a graph-based probabilistic based method with a machine learning filter, that permits the characterization of cxSVs on a population-scale at highest accuracy. And we generated whole-genome sequencing data and single-cell RNA-Seq data for 119 PsychENCODE brains (controls, schizophrenia, or bipolar disorder), and matched single-cell ATAC-Seq data for 39 of these 119 brains.

Results: From 4,262 genomes spanning all continental populations, we identify 8,493 cxSVs belonging to more than 12 subclasses. Rare cxSVs in the human population are especially enriched for neural genes and loci undergoing rapid evolution, including those that regulate human-specific corticogenesis. We then show that in the PsychENCODE cohort, there is an enrichment for cxSVs that overlap with GWAS loci for schizophrenia or bipolar disorder and for which the risk allele is present. Further, we demonstrate association in the PsychENCODE patient brains, between cxSVs that overlap with expressed genes or open chromatin, and changes in gene expression and chromatin states.

Conclusion: Our results show that it is possible to detect cxSVs in standard whole-genome sequencing data and implicate cxSVs as a contributing factor in neuropsychiatric disorders.

F29. Limited Overlap of MPRA Activity With Chromatin Accessibility

Nana Matoba, University of North Carolina at Chapel Hill

Background: Massively parallel reporter assay (MPRA) is a high-throughput experiment designed to measure the regulatory activity of short DNA sequences using barcoded expression constructs. Chromatin accessibility, measured through ATAC-seq, allows inference of transcription factor (TF) binding and marks active regulatory regions. Genetic variants altering chromatin accessibility (caQTLs) are thought to disrupt TF binding.

Methods: We used MPRA in primary human neural progenitors (N=14 replicates) to measure the exogenous regulatory activity and allelic differences for 661 regions (150 bp) containing progenitor caQTLs, 5 highly active positive controls, and 100 scrambled sequences as negative controls.

Results: Replicate correlations were high and positive controls showed significantly higher MPRA activity than scrambled sequences. Only 5.98% of regions defined by accessible chromatin showed MPRA activity. 13.7% of caQTLs showed significant allelic effects in MPRA, significantly more of which were active, but there was no correlation between MPRA allelic fold change and caQTL effect size (r=-0.056). Active elements exhibit higher chromatin accessibility, GC-content, CTCF binding sites, and motifs of previously classified accessibility-independent TFs as compared to inactive elements. We did not observe any differences in previous functional annotations between active and inactive elements (chromHMM, ENCODE cRE).

Conclusion: The low validation rate for chromatin accessibility or caQTLs by MPRA was consistent with previous reports and may reflect missing chromatin structure in MPRA. In future work, we will test allelic differences in regulatory activity for 9,000 SNPs from brain structure GWAS, where those SNPs are not necessarily located in chromatin accessible peaks.

F30. Genome-Wide Association Study of Delay Discounting in 134,935 23andMe Participants

Sandra Sanchez-Roige, University of California - San Diego

Background: Delay discounting (DD) is a heritable transdiagnostic trait, or endophenotype, that has been implicated in multiple psychiatric diseases. A prior genome-wide association study (GWAS) of DD identified genetic correlations with these and other traits but was underpowered for genome-wide discovery.

Methods: We collected responses to a 30-item delay discounting questionnaire from 134,945 research participants and performed a GWAS. We explored the genetic architecture of DD and the pleiotropic mechanisms with other outcomes using an array of genomic tools.

Results: We identified 14 significant loci associated with DD, with a significant SNP-heritability estimated (9.86±0.57%). Most of these loci (e.g., rs34645063, p=3.20E-13; rs3020805, p=6.50E-10) have been previously associated with various other behavioral traits, including risk-taking, alcohol consumption, educational variables and cognitive ability, and psychiatric disorders, as well as obesity and BMI. Genetic correlation analyses revealed significant associations with 27 traits, such as educational variables (e.g., years of education rg=-0.57; intelligence rg=-0.39), smoking behaviors (e.g., smoking initiation rg=0.32; tobacco use disorder (TUD) rg=0.33), risky behaviors (e.g., externalizing rg=0.30), and health-related outcomes (BMI rg=0.28). Local genetic correlation analysis revealed 20 significant bivariate loci between DD and these 27 other traits. The locus comprising the NCAM1-TTC12-ANKK1-DRD2 gene cluster was positively correlated with 12 traits. Polygenic analyses in a hospital-based cohort (N=69,447) showed that DD polygenic risk score was associated with 127 medical traits across 16 categories.

Discussion: Our results support the polygenic architecture of DD, identifying novel significant loci and highlighting common genetic factors between DD and other psychiatric and somatic health outcomes.

F31. Psychiatric Genome-Wide Association Study Enrichment Shows Promise for Future Psychopharmaceutical Discoveries

Alexander Hatoum, Washington University in St. Louis

Background: Genome-wide association studies (GWASs) have begun to identify hundreds of genome-wide significant (GWS) loci for psychiatric disorders. These data have rapidly advanced our understanding of disease etiology, but their ability to inform clinical treatment remains largely unexplored.

Methods: As a test of validation, we examined whether GWAS signals for psychiatric disorders are enriched for current medication targets in Schizophrenia [SCZ]; n=320,404; Bipolar Disorder [BiP], n=413,466; Major Depressive Disorder [MDD], n=1,004,980) Substance Use Disorder [SUD]; n=1,025,550; Attention Deficit Hyperactivity Disorder [ADHD], n=225,534; Post-traumatic Stress Disorder [PTSD], n=174,659; Generalized Anxiety Disorder [GAD, n=241,541) and insomnia (n=386,533). We also tested if sample size, effect size of single nucleotide polymorphism (SNP) associations, or functional genomic annotation improved enrichment.

Results: We found that large psychiatric GWASs (schizophrenia, bipolar disorder, major depressive disorder, substance use disorder) are enriched (OR: 2.776-27.629) for current treatments specific to that disorder. The effect size of individual loci and the number of variants identified in the GWAS drove enrichment of current treatments. Functional annotation was enriched, but not to the extent as closest gene-mapped.

Conclusion: These results suggest that psychiatric GWAS may assist in drug repurposing and novel treatment target identification in psychiatry. Large genetic sample sizes are needed to improve discovery and gain precision in SNP effect sizes.

F32. Mpra Investigates Shared Genetic Variants of Eight Psychiatric Disorders

Jessica McAfee, UNC Chapel Hill

Background: A meta-genome-wide association study encompassing eight psychiatric disorders has shed light on the genetic architecture of pleiotropy. However, mechanisms underlying pleiotropic effects of these variants remain to be investigated.

Methods: We conducted a massively parallel reporter assay to decipher the regulatory logic of variants with disease-specific and pleiotropic effects.

Results: Pleiotropic variants differ from disease-specific variants by manifesting chromatin accessibility that extends across diverse cell types in the neuronal lineage, and altering motifs for transcription factors with higher connectivity in protein-protein interaction (PPI) networks. Next, we mapped pleiotropic and disease-specific variants to putative target genes, which may offer insights into potential mechanisms of pleiotropy. Compared with disease-specific genes, pleiotropic genes demonstrate associations with generic biological pathways, widespread temporal dynamics during neuronal lineage, and higher connectivity in PPI networks.

Conclusions: Collectively, variants exert pleiotropic effects by regulating genes involved in global biological functions.

F33. Uncovering Novel WNT Signaling Regulation During Dopaminergic Neuron Development

Alena Salasova, Aarhus University

Brain development is orchestrated by fine but complex spatiotemporal cell-to-cell communication, one of the most important being Wnt signaling. Besides other functions, Wnt/Planar Cell Polarity pathway (Wnt/PCP) is crucial for midbrain morphogenesis and cell fate decisions of midbrain dopaminergic (mDA) neurons. This lineage is affected in patients with neurodevelopmental psychiatric disorders such as Attention deficit hyperactivity disorder (ADHD), Autism spectrum disorder, or Tourette's syndrome. Nevertheless, Wnt/PCP signaling and its physiological consequences are still poorly understood. We previously showed that proneurotrophin receptor SorCS2 is required for dopaminergic innervation and wiring, while SorCS2 loss-of-function causes an ADHD-like phenotype in mice (Neuron 2014; Transl Psychiatry 2021). Indeed, SorCS2 was recently identified as a risk gene for ADHD. By combining proteomics, RNA sequencing, biochemical approaches, high-resolution imaging, and functional experiments in frogs, fish, and mice, this comprehensive study identifies novel signaling crosstalk where SorCS2 interacts with the core Wnt/PCP receptor Ror2 to regulate its correct activity during mDA lineage development. Moreover, we formulate a molecular mechanism of how the Ror2-SorCS2 signaling complex directs embryogenesis across vertebrates emphasizing its conserved function. These observations are highly relevant for future clinical applications for patients with abnormal Wnt or SorCS2 signaling activity.

F34. Developmental Patterns of Alternative Splicing in Layer 3 Pyramidal Neuron Subtypes of the Primate Dorsolateral Prefrontal Cortex: Implications for Schizophrenia

Kevin Dowling, University of Pittsburgh School of Medicine Department of Psychiatry

Background: Schizophrenia (SZ) is characterized by altered development of layer 3 pyramidal neurons (L3PNs) in the dorsolateral prefrontal cortex (DLPFC). Subtypes of DLPFC L3PNs, which furnish projections to ipsilateral posterior

parietal cortex (IP) or contralateral DLPFC (CP), differ in maturation trajectory. To determine whether alternative splicing (AS) of mRNAs contributes to development of IP and CP L3PNs we quantified AS in these L3PNs from pre-pubertal and adult rhesus macaques.

Methods: CP and IP L3PNs in the DLPFC were identified by fluorescent retrograde tracers in 9 pre-pubertal and 8 adult macaques. Pools of IP and CP neurons were collected by laser microdissection and underwent RNA-sequencing. AS/pathway analyses were performed with LeafCutter/PANTHER. FDR-corrected p-values < 0.05 and AS > 10% were considered significant.

Results: In IP/CP L3PNs, 231/157 genes demonstrated significant AS between pre-pubertal and adult samples, with 43 AS genes in both subtypes. Genes with developmental AS in IP L3PNs, or, in both IP and CP L3PNs were overrepresented in synaptic neurotransmission and dendritic morphology pathways.

Conclusion: The shared developmental AS differences in IP and CP L3PNs (e.g., GRIN1 and GABRG2) may contribute to functional and structural maturation of both subtypes. However, the more extensive developmental AS differences in IP L3PNs suggests a particular role for AS in their maturation. For instance, developmental differences in dendrite-targeted CDC42, a key regulator of dendritic spine density, were greater only in IP subtypes. Reports that these genes demonstrate altered AS and/or expression in SZ suggests AS may play a role in altered L3PN development in SZ.

F35. Protein 4.1N Plays a Cell-Type Specific Role in Hippocampal Glutamatergic Synapse Regulation

Anna Pushkin, USC

Many glutamatergic synapse proteins contain a 4.1N protein binding domain. However, a role for 4.1N in the regulation of glutamatergic neurotransmission has been controversial. Here, we observe significantly higher expression of protein 4.1N in granule neurons of the dentate gyrus (DG granule neurons) compared with other hippocampal regions. We discover that reducing 4.1N expression in rat DG granule neurons of either sex results in a significant reduction in glutamatergic synapse function that is caused by a decrease in the number of glutamatergic synapses. By contrast, we find reduction of 4.1N expression in hippocampal CA1 pyramidal neurons has no impact on basal glutamatergic neurotransmission. We also find 4.1N's C-Terminal Domain to be nonessential to its role in the regulation of glutamatergic synapses of DG granule neurons. Instead, we show that 4.1N's FERM domain is essential for supporting synaptic AMPA receptor function in these neurons. Altogether, this work demonstrates a novel, cell-type specific role for protein 4.1N in governing glutamatergic synapse function.

F36. Thalamocortical Circuits and Orexin Input Underlying Control of Risk, Reward and Effortful Behavior

Rachel Mikofsky, Weill Cornell Medical College of Cornell University

Background: A longstanding obstacle in understanding and treatment for mood disorders has been mechanisms underlying spontaneous changes in internal states, motivation and risk and reward perception, especially at the level of neural circuits. Undoubtedly, many circuits are involved but converging evidence highlights a potential role for a circuit linking the medial prefrontal cortex (mPFC), paraventricular thalamus (PVT) and orexin inputs from the hypothalamus. Reciprocal circuits between the mPFC and PVT have been implicated in regulating arousal, reward-seeking and avoidance behavior, with the anterior PVT (aPVT) more implicated in motivation and approach and the posterior PVT (pPVT) more implicated in avoidance. Furthermore, PVT activity is modulated by orexin inputs from the hypothalamus, which is associated with motivation, arousal, and response to stress. Methods: Fiber photometry was used to observe neural activity during freely-moving behavior in a task of effortful reward-seeking in conflict with risky contexts. Green and red fluorescent genetically encoded calcium sensors were injected into mPFC, aPVT and pPVT to target reciprocal projections, and a novel fluorescent orexin sensor was used to monitor hypothalamic orexin input to the aPVT and pPVT during behavior. Results: Activity aPVT-mPFC and pPVT-mPFC projections correlated with real-time behavioral decisions towards effortful reward-seeking or risk-avoidance, while activity in mPFC-PVT projections correlated with post-reward feedback. Orexin activity in the PVT correlated with longer timescale behavioral predispositions towards approach or avoidance behavior. Conclusions: These results support the role of PVT < - > mPFC and hypothalamic orexin inputs to PVT in regulating short-term and long-term behavioral decisions surrounding effortful reward-seeking and risk-avoidance.

F37. Balancing Role of Sortilin in Synaptic Plasticity and Mood State

Dongik Park, Centers for proteins in memory (PROMEMO), Aarhus university, Denmark

Background: Sortilin is a sorting receptor engaging in cellular trafficking processes in trans-Golgi network but also in signal transduction at the plasma membrane by teaming up with co-receptors. Recent evidence suggests that sortilin may play a crucial role in synaptic plasticity and psychiatric disorders.
Methods: Multi-dimensional analyses including confocal microscopy, electrophysiology, quantitative proteomics and behavioral phenotyping were performed using Sort1-/- and hSORT1 overexpressing transgenic mice to understand how sortilin could contribute to alterations relevant to mental disorders. Human (epi-)genetic data and clinical patient specimens were further investigated to find the association of sortilin with mental disorders.

Results: Sortilin deficiency resulted in decreases of dendritic complexity and spine density. Human sortilin gene SORT1 had genetic and epigenetic associations with bipolar disorder and major depressive disorder, respectively. Quantitative proteomics analysis identified systemic alterations in synaptic plasticity-related molecular pathways by sortilin deficiency. Altered sortilin levels led to dysregulated synaptic plasticity and behavioral phenotypes relevant to emotional and cognitive features of psychiatric disorders. Antidepressant and mood stabilizer normalized dysregulated sortilin levels in the brain. In addition, primary hippocampal neurons with altered sortilin levels showed significantly impaired temporal BDNF dynamics. Surprisingly, soluble sortilin was able to restore impaired dendritic neurite branch numbers and synaptic plasticity of sortilin deficient mice. Furthermore, serum sortilin levels in patients were found to be a promising diagnostic biomarker for multiple mental disorders.

Conclusion: Our data suggest that sortilin plays a crucial role in synaptic activity and behavioral regulation linked to psychiatric disorders.

F38. Escitalopram Induced Pancreatitis

Joseph Dube, Henry Ford Jackson Hospital

Background: Escitalopram is an FDA approved selective serotonin reuptake inhibitor (SSRI) for treatment of major depressive disorder and generalized anxiety disorder. Escitalopram's mechanism of action includes binding to the sodium-dependent serotonin transporter protein (SERT) located on the presynaptic neuron. SERT works by serotonin re-uptake from the synaptic cleft by the presynaptic neuron. When SERT is inactivated by escitalopram, the amount of serotonin in the synaptic cleft is increased. Drug-induced pancreatitis represents up to 5% of all acute pancreatitis cases. We present a rare case of escitalopram exposure leading to acute pancreatitis evaluated by our consult-liaison psychiatry service.
Methods: A literature review was conducted using Cochrane, PubMed, Embase, Clinical Key, Medline, and Web of Science. The literature review was done using the following search terms: escitalopram induced pancreatitis, Lexapro induced pancreatitis, escitalopram and pancreatitis, acute pancreatitis and escitalopram, Lexapro and acute pancreatitis, and SSRI use and pancreatitis.

Results: Our detailed literature review demonstrated a significant association between SSRIs and acute pancreatitis; the risk was much higher in the first few weeks following initiation of SSRIs. We found two proposed mechanisms for the association between SSRIs and acute pancreatitis: SSRIs causing cellular apoptosis leading to acute pancreatic injury and SSRIs causing inhibition of insulin secretion leading to pancreatic insult.

Conclusion: Through our literature review and understanding of proposed mechanisms for escitalopram induced pancreatitis, we were able to make informed treatment recommendations leading to resolution of our patient's acute pancreatitis.

F39. Pharmacogenomics in a Dish: Lithium and Valproic Acid Molecular Response QTLs in Human Neural Progenitor Cells

Brandon Le, University of North Carolina at Chapel Hill

Background: Lithium (Li) and valproic acid (VPA) treat bipolar disorder, but clinical responses vary and their mechanisms are largely unknown. Genetic influences on clinical responses are limited by sample-size, polypharmacy, and varied compliance, duration, and dosing across participants. Here, we applied a "pharmacogenomics in a dish" approach to characterize genetic influences on gene regulatory responses to these compounds within primary human neural progenitor cells (hNPCs).
Methods: We profiled chromatin accessibility via ATAC-seq and gene expression via RNA-seq in 78 genotyped hNPC lines after exposure to clinically-relevant concentrations of LiCl, VPA, or vehicle. Genetic effects on chromatin accessibility and gene expression were estimated by mapping quantitative trait loci (caQTLs and eQTLs, respectively).

Results: Chromatin accessibility at thousands of regulatory elements changed in response to Li (> 10,000) or VPA (> 45,000). Transcription factor binding site motifs with roles in neurodevelopment, such as RFX and LHX6, were enriched within chromatin opened by Li or VPA treatment, respectively. We detected 493 (Li) and 7,700 (VPA) differentially expressed genes following treatment. Stimulus-specific caQTLs altered 20,762 (Li) and 4,239 (VPA) chromatin accessibility peaks. Stimulus-specific eQTLs altered expression of 464 (Li) and 447 (VPA) eGenes.

Conclusion: We characterized gene regulatory responses to Lithium and VPA in hNPCs. Context-specific QTL mapping increased discovery of caQTLs by up to 80% and of eQTLs by 50% compared to ca/eQTLs detected at vehicle conditions. Integrating results with pharmacogenomic GWAS and molecular comparisons of responders versus non-responders may prioritize variants and genes that can predict or improve treatment outcomes.

F40. Identification, Characterization, and Optimization of Highly-Selective D2 Dopamine Receptor Antagonists With Potential as Antipsychotics With Reduced Side Effect Profiles

Ashley N. Nilson, National Institute of Neurological Disorders and Stroke, National Institutes of Health

All FDA-approved antipsychotics antagonize the D2 dopamine receptor (D2R), which is their mechanism of action for treating schizophrenia. Unfortunately, all current antipsychotics interact with numerous other receptors leading to off-target side effects such as sedation, weight gain, and diabetes. We identified a novel D2R antagonist, MLS6916, from a high throughput screen that showed exceptional D2R selectivity when counter-screened against 168 receptors using a functional assay. This unprecedented selectivity suggests that MLS6916 might exhibit fewer off-target side effects. Despite being a promising lead, MLS6916 exhibited poor metabolic stability in rat liver microsomes. We explored structure-activity relationships with more than 120 analogs to identify compounds with improved metabolic stability. NCGC1360 was identified as an analog that exhibited both high affinity for the D2R and improved metabolic stability in liver microsomes (human > rat > mouse). We further determined the pharmacokinetic profiles of the most promising analogs in mice. Two of these analogs exhibited t1/2 values of 1-6 hr in both plasma and brain. Importantly, the analogs exhibited > 0.5 brain-plasma ratios with Cmax concentrations > 10 μM indicating excellent brain penetration. One of these analogs, NCGC1360, did not induce catalepsy in mice up to 10 mg/kg suggesting that it may have reduced on-target side effect liability. NCGC1360 was also active in assays that predict antipsychotic efficacy including reduction of amphetamine-stimulated hyperlocomotion or reversal of amphetamine-induced impairment of pre-pulse inhibition of acoustic startle. In summary, we have identified lead antipsychotic candidates with exceptional D2R-selectivity, excellent brain penetrance, and are predicted to have fewer on/off-target side-effects.

F41. Selective Serotonin Reuptake Inhibitors Associated With Increased Mortality Risk in Breast Cancer Patients in Northern Israel

Avital Fischer, Stanford University

Background: Approximately 1:6 women in the USA take antidepressants and a third use selective serotonin reuptake inhibitors (SSRIs) after breast cancer diagnosis. Serotonin receptor (5-HTR2B) expression in the breast and serotonin production has been identified as an indicator of poor breast cancer prognosis. This study investigates the association between SSRI use at different time intervals relative to breast cancer diagnosis on survival.

Methods: A population-based sample of 6959 consecutive, newly diagnosed breast cancer cases in Northern Israel was included. Patients were recruited from January 2000 and followed up through March 2020. Participants completed risk factor questionnaires regarding medical, reproductive and family history, medication use and health habits. Full prescription data were available through the Israeli national Clalit medical database. Multivariate Cox proportional hazard models were used to determine survival according to SSRI use.

Results: Use of SSRIs in the 5 years prior to breast cancer diagnosis was associated with a 66% increase in overall mortality (HRadj 1⁄41.66; CI: 1.05–2.63). SSRI use that initiated after breast cancer diagnosis was associated with an 81% increase in mortality (HRadj =1.81; CI: 1.58–2.06). Use of SSRIs in the 5 years post-diagnosis was associated with a dose–response increase (P < 0.001) in long-term mortality (> 5 years). Heavy SSRI use (_x0002_24 prescription fills) after diagnosis was associated with nearly doubling in mortality (HR =1.99; CI: 1.39–2.83).

Conclusion: SSRI use prior to and after breast cancer diagnosis is associated with increased mortality in breast cancer patients. Additional research is needed to better understand mechanisms mediating this association.

F42. GABA-Daba-Doo: New-Onset Psychosis and Catatonia in First-Time Baclofen Use

Monika Jankowicz, Henry Ford Jackson Hospital

Background: Baclofen is a widely prescribed CNS relaxant for muscle spasms. Baclofen is a renally excreted GABA(B) agonist in pre-/post-synaptic neurons leading to reduction in muscular spasticity. Catatonia and psychosis have been associated with an abnormal balance between GABA(A) and GABA(B) receptors. For improved awareness of the risks of baclofen use in the context of chronic kidney (CKD), a case of new-onset psychosis and catatonia in first-time baclofen use will be presented.

Methods: We searched Pubmed and Science Direct via keywords {(baclofen + toxicity), (baclofen + CKD), (baclofen + psychosis), (baclofen + catatonia)} 29 case reports, 2 animal studies, 5 retrospective studies, and 3 systematic reviews.

Case/Results: A 58 year-old female with CKD stage 3 and no psychiatric history presented to the ED with altered mentation in the setting of first-time baclofen use. Stroke, seizure, and infectious processes were ruled out. Patient demonstrated persecutory delusions involving staff, auditory and visual hallucinations, echolalia, verbigeration, ambitendency, rigidity, perseveration, and gegenhalten.

Conclusion: With a history of CKD stage 3, new-onset psychosis and catatonia that began resolving within 24 hours of baclofen ingestion, it is likely that the patient experienced neurotoxicity due to GABA(A) and GABA(B) imbalance. In one study of 401 patients with CKD, the prevalence of baclofen-induced neurotoxicity was 7.0%. The minimum daily dose required to induce neurotoxic effects was as little as 5-10mg. With widespread use and potential CNS neurotoxic effects, providers would benefit from greater awareness of risks with Baclofen use in the setting of CKD and appropriate renal dosing.

F43. Sex Differences in the Functional Network Correlates of Childhood Psychosis-Like Experiences

Elvisha Dhamala, Feinstein Institute for Medical Research

Background: Sex differences exist in the expression of psychotic disorders. Males exhibit earlier onset and greater negative symptoms, while females display greater affective symptoms and social functioning. However, whether these differences exist in childhood psychosis-like experiences and map onto distinct functional brain networks is unknown. Sex-specific brain-based predictive models can be used to quantify the shared and unique neural correlates of distinct behaviors (including cognition and psychopathology) across the sexes.

Methods: Using resting-state functional MRI and behavioral data (n=5260, ages 9-10, 2571 females, Adolescent Brain Cognitive Development study), we characterize the sex-specific resting-state functional connectivity correlates of childhood psychosis-like experiences. Childhood psychosis-like experiences were measured in terms of the number and overall severity of symptoms (including hallucinations and delusions) using the Prodromal Questionnaire. We used cross-validated sex-specific brain-based predictive models to establish sex-specific functional connectivity correlates of childhood psychosis-like experiences.

Results: Brain-based models accurately predicted the number of symptoms in males and females, as well as the overall severity in males and females. Functional connections associated with number of symptoms and severity were strongly correlated across measures, and moderately correlated across sexes. Functional connections within/between limbic and somatomotor networks were associated with the expression of psychosis-like symptoms in males, whereas connections within/between limbic, temporal parietal, default, and attention networks were associated in females.

Conclusions: The expression of psychosis-like experiences emerges in childhood and can be reliably predicted based on individual functional connectivity. Moreover, these symptoms are associated with distinct functional networks in males and females.

F44. Comparing Associations of Family History and Polygenic Risk for Schizophrenia With Mental Health Symptoms in Diverse Ancestry Youth in the Adolescent Brain Cognitive Development Study

Mahnoor Hyat, University of Washington

Background: Behavioral and cognitive signs precede schizophrenia (SCZ) and SCZ polygenic risk scores (PRS) are associated with mental health symptoms in European ancestry youth. To explore genetically-mediated precursors of SCZ across diverse groups, we examined whether SCZ-PRS predicts emotional and behavioral symptoms in children with European, African, and Admixed American ancestry in the Adolescent Brain Cognitive Development study (ABCD).

Method: Ancestry groups were assigned using a Random Forest classifier applied to merged ABCD and HapMap3 data, yielding 5733 European, 1668 African, and 1264 Admixed American ancestry individuals (47.4% female; mean age=9.92 yrs). SCZ-PRS were calculated using PRScsx, z-scored within ancestry groups, and tested for association with family history of psychosis and Child Behavior Checklist (CBCL) scores. Covariates included sex, age, ancestry principal components, and genetic relatedness matrices.

Results: Across groups, having a first-degree relative with psychosis was associated with elevated SCZ-PRS (p=0.032). No significant links were found between SCZ-PRS and the eight CBCL sub-scales in European or Admixed American children, whereas higher SCZ-PRS was nominally associated with lower Anxious-Depressed scores in African ancestry children (p=0.026). Across groups, PRS didn't relate to CBCL scores.

Conclusion: The absence of associations between SCZ-PRS and CBCL at 9-10 years aligns with a prior study on European ancestry children in ABCD; this study extends it to African and Admixed American ancestry children. These findings may hint at CBCL limitations or potentially weak predictive power of emotional/behavior problems for SCZ in the US. Future analyses will incorporate cognitive, social and motor functioning and longitudinal analysis.

F45. Using Ultra-Rare Variants Across Diverse Ancestries to Power Gene Discovery for Schizophrenia
Julia Sealock, The Broad Institute
Background: The SCHEMA Consortium is dedicated to using rare variant association scans (RVAS) identify specific genes associated with schizophrenia by leveraging variants predicted to disrupt protein function. Recent initiatives have increased the genetic diversity of schizophrenia analyses. We will present results for the updated multi-ancestry schizophrenia RVAS.
Methods: We sequenced the exomes of 50,661 cases and 163,581 controls from samples from 5 continents. Variants were restricted to ultra-rare (minor allele count < = 10) damaging variants. We determined if schizophrenia cases are enrichment of damaging URVs by regressing schizophrenia status on the number of URVs in constrained genes within each annotation class. Additionally, the enrichment analysis was stratified by ancestry. Finally, we conducted a RVAS of damaging URVs.

Results: Schizophrenia cases showed increased burden of damaging URVs, including PTVs (pvalue = 6.83 x 10-6, OR = 1.32) and damaging missense variants (pvalue = 0.026, OR = 1.09), and the associations were consistent across ancestries. Schizophrenia cases were enriched for PTVs (pvalue = 0.02, OR = 4.18) and damaging missense variants (pvalue = 0.36, OR = 1.26) within previously identified SCHEMA genes. The RVAS replicated several genes, including SETD1A, SP4, and XPO7.

Conclusions: Increasing genetic diversity of RVAS will provide a more complete understanding of the genetic architecture of schizophrenia and advance equity in psychiatric genetics. We conducted the largest multi-ancestry RVAS of schizophrenia and replicated several previously identified schizophrenia risk genes. We plan to incorporate an additional 15,000 cases and investigate the effects of ancestry on the gene associations.

F46. Dysregulated mRNA Translation and Schizophrenia-Relevant Behaviours in Mice
Brandon Rodrigue, Carleton University
Background: Dysregulation of protein translation has been implicated in several neuropsychiatric diseases such as schizophrenia (SCZ). Interestingly, an exome study discovered a de novo mutation in the eukaryotic initiation factor 4E binding protein 2 (4E-BP2KI) gene in a patient with SCZ, leading us to examine how perturbations to the mammalian target of rapamycin complex 1 (mTORC1) -4E-BP2 translation pathway can create a SCZ-like phenotype in mice.
Methods: In vitro analysis of the interaction between the mutant recombinant human protein and mTORC1 was performed with the phosphorylation rate analyzed via western blot. To test whether the mutation decreases function in vivo, 4E-BP2 knockout (KO) mice were used with 4E-BP2KI mice for behavioural assays, which include amphetamine-induced locomotion and pre-pulse inhibition of acoustic startle (PPI).

Results: In vitro analysis of the recombinant mutant protein indicated that phosphorylation by mTORC1 was increased compared to WT. In vivo, we found that adult male 4E-BP2KO mice had a higher sensitivity to amphetamine (31855□2590 a.u.c.) compared to WT controls (16018□1684 a.u.c.). Male 4E-BP2KI adult mice (4120□217.9 a.u.c.) were trending higher in this task compared to WT (2957□244.0 a.u.c.). No effects of amphetamine were found in females. Male and female 4E-BP2KO mice demonstrated deficits of startle inhibition (14.19□5.25%) compared to WT (32.41□8.26%) in the PPI task.

Conclusion: These results suggest the 4E-BP2KI mutation causes reduced protein function, leading to a SCZ-like phenotype in male, but not in female mice. Further research examining the dopaminergic system will aid in determining the cellular mechanism underlying this phenotype.

F47. Systematic Investigation of Allelic Regulatory Activity of Schizophrenia-Associated Common Variants

Sool Lee, University of North Carolina at Chapel Hill

Genome-wide association studies (GWASs) have successfully identified 145 genomic regions that contribute to schizophrenia risk, but linkage disequilibrium makes it challenging to discern causal variants. We performed a massively parallel reporter assay (MPRA) on 5,173 fine-mapped schizophrenia GWAS variants in primary human neural progenitors and identified 439 variants with allelic regulatory effects (MPRA-positive variants). Transcription factor binding had modest predictive power, while fine-map posterior probability, enhancer overlap, and evolutionary conservation failed to predict MPRA-positive variants. Furthermore, 64% of MPRA-positive variants did not exhibit expressive quantitative trait loci signature, suggesting that MPRA could identify yet unexplored variants with regulatory potentials. To predict the combinatorial effect of MPRA-positive variants on gene regulation, we propose an accessibility-by-contact model that combines MPRA-measured allelic activity with neuronal chromatin architecture.

F48. Understanding, Diagnosing, and Treating Shared Delusional Disorder

Diana Vo, TTUHSC

Background: Shared delusional disorder, also referred to as shared psychotic disorder, is defined as sharing a specific delusion among two or more people in a close relationship.

Methods: Data and research from various articles that met the inclusion and exclusion criteria were extracted to integrate into one literature review.

Results: It is an uncommon disorder, likely underreported and underdiagnosed. Risk factors for shared delusional disorder identified in this case include the length of the relationship with the primary patient, family member status, history of mental disorder without consistent treatment, stressful life events, age difference, and gender. The risk of transmission between family members is strongly correlated to the degree of perceived familial connection which can differ between individual family members. Shared delusional disorder should be considered in cases where multiple individuals present with similar delusions and have a close relationship. Differential diagnoses include schizophrenia, schizoaffective disorder, mood disorder with psychotic features, and organic or substance-induced conditions, which need to be ruled out. Treatment for shared delusional disorder involves separation from the primary patient, antipsychotics, antidepressants, psychotherapy, and electroconvulsive therapy (ECT).

Conclusion: Although uncommon, shared delusional disorder has major implications for patients and their families. It's important to realize how it can present in addition to clues to look for in order to effectively diagnose and treat these patients.

F49. Multivariate Stratification of Clinical Severity and Genetic Risk in Psychotic Disorders: A Longitudinal, Registry-Based Approach

Evan Giangrande, Massachusetts General Hospital; Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard

Background: Despite successful efforts to identify risk variants, the genetic etiology of psychotic disorders remains poorly understood. Previous studies have often utilized superficial psychosis phenotyping (e.g., self-reported diagnosis), which inadequately captures heterogeneity in disease severity and trajectory. Longitudinal electronic health record and registry data enable deeper and perhaps more clinically relevant phenotyping, but also present analytic challenges including missingness, cohort effects, and selection bias.

Method: We integrated longitudinal clinical data from a population registry, genotypes, whole-exome sequences from the Finnish SUPER study (over 10,000 participants with psychotic disorders). Longitudinal hospitalization and prescription data were drawn from population registries. Participants completed a battery of questionnaires, interviews, and cognitive assessments during data collection (2015-2018). First, we developed a multivariate index of psychotic illness that adjusted for biases including changes in diagnostic criteria, hospitalization, and prescribing practice. We then examined the extent to which severity differences were associated with distinct polygenic risk profiles, rare variant burden, and relevant clinical features.

Results: Our method stratified participants with psychotic disorder based on clinical severity, identifying trajectories of disease course. Phenotypic severity differences were associated with genetic differences at both the common and rare variant levels, and with distinct patterns of psychiatric and somatic comorbidity.

Conclusion: Leveraging deep, longitudinal phenotyping helps carve apart the clinical and genetic heterogeneity in psychotic disorders. Future work will extend this approach to other psychiatric phenotypes and data structures.

F50. Unique Pathways Underly Psychotic-like Experiences in Adolescents of Diverse Ancestries

Dylan Hughes, Semel Institute for Neuroscience and Human Behavior

Background: Psychotic-like experiences (PLEs) occur normatively during adolescence, but may index risk for development of a psychotic disorder in a subset of individuals. Polygenic score (PGS) analyses offer a method through which genetic risk for psychosis can be assessed. However, PGSs in non-White individuals remain largely understudied. This study seeks to investigate how the genetic basis of PLEs in adolescents might differ by ancestral group.

Methods: Data from 8,457 adolescents across 5 timepoints (repeated measures; ages 9-16) from the Adolescent Brain Cognitive Development (ABCD) study were used to assess the relationship between PGS and PLEs as measured by the Prodromal Questionnaire Brief – Child Version (PQBC). Within European (EUR), African (AFR), and Admixed American (AMR) subjects, schizophrenia whole-genome PGS (SCZ WG-PGS) and SCZ PGS partitioned by 18 gene sets (modules) were generated. Each gene module comprises genes that are co-expressed across the lifespan within the brain.

Results: Within EUR participants, SCZ WG-PGS showed significant association with PQBC (ß = 0.235, q = 0.03). Conversely, in AMR participants, there was no main effect of SCZ WG-PGS; however, two modules showed nominally significant associations (ßs = -0.43, 0.44; q > 0.05) which differed from those showing associations in EUR participants. In AFR subjects, there were no significant associations.

Conclusion: Contrary to previous studies on younger ABCD participants, current results provide evidence for an SCZ-related genetic vulnerability to PLEs in EUR adolescents. Furthermore, PGS in AMR individuals suggest that etiology of PLEs in this population may differ from those in a EUR population.

F51. Neurobiological Mechanisms Mediating Cognitive Deficits in a 2-Hit Immune Activation Chronic Stress Model

Rachel Rahn, Weill Cornell Medical College

Background: Genome-wide association studies indicate that immune dysregulation plays a role in many psychiatric disorders including depression, and epidemiological data suggest a largely unexplored link between childhood infections and the later diagnosis of depression and other stress-related psychiatric disorders. Relatively little is known about how early-life immune activation influences stress susceptibility and behavior in adults. Investigating the impact of developmental immune activation on adult cognition could shed light on immune mechanisms associated with stress-related psychiatric disorders.

Methods: Thy1-GCaMP6s mice were used to collect resting-state and task-based widefield calcium imaging data from excitatory pyramidal neurons in the adult mouse cortex. Mice were administered an intraperitoneal injection of lipopolysaccharide (LPS) at postnatal day (P)21 and subjected to a 7-day unpredictable mild stress paradigm in adulthood. LPS+stress mice were subsequently compared to control groups, including stress only mice, to determine if LPS injection during the juvenile period amplified or otherwise affected stress-related cognitive measures, including cognitive flexibility.

Results: Developmental immune activation and unpredictable mild stress in adulthood altered the functional connectome of mice, including decreases in frontoparietal resting state connectivity between left frontal and left parietal seed regions (LPS+stress vs. controls, p=.0050; stress only vs. controls, p=.076). LPS+stress mice also displayed differences from control groups in multiple cognitive behavioral assays, including the reversal domain of cognitive flexibility.

Conclusion: These findings demonstrate that developmental immune activation and adult stress impact cognitive behavior, including cognitive flexibility, in adult mice and alter the functional connectome, including a reduction in resting-state frontoparietal connectivity in excitatory pyramidal neurons.

F52. Thalamic-Hippocampal Interplay in Self-Harm and Aggression

Sora Shin, Virginia Tech

Self-harm and aggression are prevalent among teenagers exposed to early life trauma (ELT). Growing evidence indicates that self-harm and aggression co-occur, which has been termed "dual-harm", yet we know far less about the neurobiological underpinnings of dual-harm and how they adapt in response to ELT. We found that systemic injection of L-type calcium channels (LTCCs) agonist, Bay K 8644, elicits dual-harm in mice in a dose-dependent manner. Moreover, we found that young adult mice exposed to ELT (e.g., infant-mother/littermate separation for 23 hr at postnatal day 3) show increased vulnerability to dual-harm. The thalamic nucleus reuniens (RE) contains vGlut2-positive neurons highly expressing LTCCs. Using in vivo calcium imaging, we have demonstrated that vGlut2 RE neurons in animals exposed to ELT show sensitized activity during self-biting behaviors. We also identified that ventral hippocampus (vHip)-projecting vGlut2 RE neurons send axon collaterals to other brain areas, including mPFC. Using chemogenetic manipulation, we found that the activation of vHip-projecting vGlut2 neurons, but not mPFC-projecting vGlut2 RE, increases the vulnerability to dual-harm. In addition, optogenetic inhibition of the vHip-projecting vGlut2 neurons normalized the exacerbated dual-harm in ELT mice. We propose that LTCC signaling in the downstream target-defined vGlut2 RE circuit is a primary biological substrate that mediates the occurrence of dual-harm. These results transform our understanding of self-harm and aggression, which will provide new insight into the circuit-specific roles of vGlut2 RE neurons in driving the risk of dual-harm in numerous psychiatric diseases.

F53. Circuit Mechanism of Syncam 1-Restricted Resilience to Stress

Robert Williams, University of Virginia

Background: Stressful experience can result in cognitive and behavioral impairments, such as stress and depression, as well as structural and functional alterations in the brain. It is generally thought that brain plasticity promotes resilience to stress, but it is still unclear if this is indeed the case.

Methods: To test this notion directly, we used a mouse model of increased plasticity, Synaptic Cell Adhesion Molecule 1 knock-out mice (SynCAM 1 KO mice). SynCAM 1 KO mice have prolonged visual critical period and enhanced cortical synaptic plasticity. We used a subchronic unpredictable stress paradigm to induce stress responses in wild-type and KO mice, and behavioral, physiological, and electrophysiological measures to determine if KO mice show increased resilience to subchronic stress.

Results: We found that subchronic stress induces a robust physiological stress response in both WT and KO mice, but only WT mice showed behavioral alterations common after stress induction in mouse models.

Conclusions: Our results suggest that increased plasticity promotes behavioral resilience to stress.

F54. Corticotropin Releasing Factor Dynamics in Learned Threats

Jhah Cook, Yale University School of Medicine

Traumatic experiences can lead to long-lasting alterations in stress-related brain regions, including the medial prefrontal cortex (mPFC), locus coeruleus (LC), and paraventricular hypothalamus (PVH). Dysregulation of the neuropeptide corticotropin-releasing factor (CRF) has been implicated in trauma-related disorder, including by genome-wide association studies have implicating CRF receptor 1 (CRFR1) in risk for post traumatic stress disorder. In order to understand the role of CRF in stress-related threat processing, we sought to identify a role for CRF in stress-sensitized moment-to-moment threat processing. To address this gap, we used computational behavior tracking, pharmacology, and neuropeptide sensor techniques in the stress-enhanced fear learning (SEFL) model of PTSD. Our results revealed that administration of a selective CRFR1 antagonist (antalarmin) blocked the stress sensitization of contextual fear learning in the SEFL model. Furthermore, computational behavior tracking (MoSeq) unveiled distinct stress-related behavioral states that were also altered by the CRFR1antagonist. To gain deeper insights into CRF dynamics during stress sensitization, we used fiber photometry of GRAB sensors (GRAB-CRF3.0) to measure CRF release in response to learned and innate fear stimuli. Validation experiments demonstrated CRF release in the mPFC in response to diverse threatening stimuli. Subsequently, we conducted GRAB-CRF3.0 recordings during the SEFL behavioral paradigm. We will also utilize optogenetic perturbation to clarify distinct functions of CRF release in the context of learned threat processing. By delineating neuropeptide dynamics in threat-related behaviors, our findings shed light on the potential of CRFR1 antagonism in attenuating the effects of SEFL following prior exposure to traumatic stressors.

F55. Evolutionary Conservation of Putative Suicidality-Related Risk Genes That Produce Diminished Motivation Corrected by Clozapine, Lithium and Antidepressants

Donard Dwyer, LSU Health Shreveport

Background: Genome wide association studies (GWAS) and candidate gene analyses have identified genetic variants and genes that may increase the risk for suicidal thoughts and behaviors (STBs). Important unresolved issues surround these tentative risk variants such as the characteristics of the associated genes and how they elicit STBs.
Methods: Putative suicidality-related risk genes (PSRGs) were identified by comprehensive literature search and were characterized with respect to evolutionary conservation, participation in gene interaction networks and their associated phenotypes. Evolutionary conservation was established with database searches and BLASTP queries, whereas gene-gene interactions were ascertained with GeneMANIA. We then examined whether mutations in risk-gene counterparts in C. elegans produced a diminished motivation phenotype previously linked to suicide risk factors.

Results: 105 suicide risk-gene candidates were identified and found to be: 1) highly conserved during evolution, 2) enriched for essential genes, 3) involved in significant gene-gene interactions, and 4) associated with psychiatric disorders, metabolic disturbances and asthma/allergy. Evaluation of 17 mutant strains with loss-of-function/deletion mutations in PSRG orthologs revealed that 11 mutants showed significant reduction of motivation that manifested as immobility in a foraging assay. Immobility was corrected in some or all of the mutants with clozapine, lithium and tricyclic antidepressant drugs. In addition, 5-HT2 receptor and muscarinic receptor antagonists restored goal-directed behavior in most or all of the mutants.

Conclusions: These studies increase our confidence in the validity of suicide risk genes and provide initial clues about possible mechanisms that mediate STBs. New understanding and treatments for STBs may emerge from this research.

F56. Neuroimmune Signals, FCMRI Connectivity and Forebrain Cholinergic Neuron Disruption by Alcohol and in Adolescent Binge Drinking Models

Fulton T. Crews, The University of North Carolina at Chapel Hill

Background. Emerging studies suggest fcMRI neuronal networks are disrupted by alcohol and alcohol induced proinflammatory signaling. HMGB1 is a nuclear protein expressed in all brain cells that can activate multiple TLRs altering excitability.
Methods: Magnetic resonance Imaging, standard neurochemistry measures of mRNA (PCR) and protein, rat in vivo, ex-vivo brain slice culture and human post-mortem brain.

Results: Preclinical and human post-mortem brain studies find alcohol use disorder (AUD) and models of rat adolescent intermittent binge-ethanol (AIE) increase expression of Toll-like receptors (TLRs), the TLR agonist HMGB1 and other proinflammatory genes. Acute ethanol increases HMGB1 release and increases fcMRI brain regional connectivity. Acute intoxication and fcMRI responses find adolescents have lower responses than adults. In contrast, AIE reduces adult fcMRI cortical connectivity, reduces ChAT+cholinergic neurons and increases perseveration-behavioral flexibility deficits. Studies in ex vivo forebrain culture find ethanol and causes HMGB1 release, and a loss of ChAT+ neurons, effects that are mimicked by application of HMGB1. Ethanol in vivo and ex vivo induced the epigenetic repressive markers RE-1 silencing transcription factor (REST) and H3K9me2 on cholinergic gene promoters. Treatment with the HMGB1 antagonist glycyrrhizin and other anti-inflammatory drugs as well as inhibitors of REST and the H3K9me2 methyltransferase G9a reverse epigenetic silencing of the cholinergic neuron phenotype. HMGB1-TLR signaling induces REST and G9a cholinergic phenotype silencing consistent with proinflammatory signaling altering transcription, independent of cell death that is reversible.

Conclusions: Ethanol induction of HMGB1-TLR signaling and epigenetic silencing of cholinergic neurons contribute to fcMRI DMN-SN network dysfunction (Funded by NIH-NIAAA).

F57. Need for Speed: Ultra-Rapid Metabolism of CYP2D6 and its Implications for Substance Abuse

Janani Udaya-Shankar, Henry Ford Jackson Hospital

Introduction: Genetic variations play a crucial role in the pharmacokinetics and response to psychiatric medications. Cytochrome P450 2D6 (CYP2D6) is responsible for the metabolism of a wide range of psychotropic medications. Altered CYP2D6 activity due to genetic polymorphisms can significantly impact the efficacy and safety of these medications. We present a case of a patient with ultra-rapid metabolism of CYP2D6 and its implications on psychiatric treatment, to include potential links to substance abuse.

Methods: We searched Pubmed, Scopus, and Web of Science using the keywords: CYP 2D6, ultra-rapid metabolism, pharmacogenetics, substance use. Clinical assessment, pharmacogenetic testing, and history were obtained. Genotyping was performed using PCR.

Case/Results: 45-yo M with a history of major depressive disorder, ADHD, and substance use. The patient's CYP2D6 genotype revealed a deleted and duplicated allele, which resulted in an ultra-rapid metabolizer phenotype. Prior to genotyping, the patient demonstrated poor response to various medications, necessitating dose escalation and frequent medication changes.

Discussion: The ultra-rapid metabolism of CYP2D6 has significant implications for psychiatric treatment. Standard doses of psychotropic medications, particularly those metabolized by CYP2D6, may result in suboptimal therapeutic outcomes. The expedited breakdown of medications could lead to reduced drug concentrations, limiting their efficacy and potentially contributing to treatment resistance. Ultra-rapid metabolizers may be at higher risk for substance abuse because they may experience a quicker onset and shorter duration of the desired effects of certain substances, potentially contributing to a cycle of increased use.

F58. Maternal Immune Activation and Adolescent Cannabis Synergistically Impair Neurotransmission in Dorsal Striatum: Role of Glial and Neuroimmune Mechanisms

Kateryna Murlanova, State University of New York at Buffalo

Background: Both in utero exposure to maternal immune activation (MIA) and cannabis use during adolescence have been associated with an increased risk for the development of psychotic disorders. Both environmental factors activate neuroinflammatory signaling during the sensitive neurodevelopmental periods and cause excitation-inhibition imbalance. We hypothesized that convergence of neuroinflammatory signaling activated by both environmental factors leads to synergistic alterations in neurotransmission and subsequent behavioral abnormalities.

Methods: MIA was induced by a viral mimetic, polyriboinosinic-polyribocytidilic acid [Poly(I:C), 5 mg/kg; IP] to gestating dams (CD1 mice, GD 12.5). Male and female offspring received delta-9-tetrahydrocannabinol (THC; 8 mg/kg; SC) or vehicle during adolescence (PND 30-51) and were evaluated in a series of behavioral tests as adults (PND 72-90). Brain microdialysis was used to assess extracellular levels glutamate, GABA, and dopamine in mouse dorsal striatum. Brain slice electrophysiological recordings were performed to assess gliotransmission to striatum medium spiny neurons. Transcriptomic profiling was conducted using the nCounter Glial Panel (NanoString).

Results: We found that the MIA x THC interaction increased exploratory behaviors in the Hole Board Test (increased head dipping), the Open Field (increased rearing), Elevated Plus Maze (increased open space exploration) and elevated sensitivity to amphetamine (2 mg/kg, IP) in female but not male mice. MIA x THC interaction led to hyperactivity of striatal dopamine neurotransmission and glutamatergic gliotransmission. Transcriptomic profiling of striatal tissue revealed glial-specific signatures of inflammation in double-hit mice.

Conclusion: MIA and adolescent THC synergistically activate inflammatory signaling to produce neurobehavioral alterations in adult mice in a sex-dependent manner.

F59. Investigating Roles of Cortical GABAergic Interneurons in Cocaine Seeking Behavior After Withdrawal

Minju Jeong, University of California San Diego

Drug addiction is characterized by a compulsive and persistent desire for substances regardless of negative consequences. Repeated use of addictive drugs induces long-lasting changes in the function of reward-related neural circuits, including the medial prefrontal cortex (mPFC). The mPFC has critical roles in controlling compulsiveness by estimating causality, predicting future outcomes, and resulting in proper decisions. It has been implicated that abnormal inhibitory GABAergic signals in the mFPC may cause compulsive behaviors including drug craving and relapse. Notably, cortical GABAergic interneurons are comprised of heterogeneous cell types, regulating cortical inputs and outputs differently to orchestrate complex behaviors however, underlying neural circuit mechanisms of the mPFC in drug seeking behavior still remain unknown. Here, we investigated how distinct mPFC interneurons contribute to regulate activity of cortico-striatal and cortico-mesolimbic circuits underlying cocaine seeking behaviors in newly developed head-fixed mice model by employing chronic two-photon and fiber photometry calcium imaging as well as chemogenetic and optogenetic techniques. Our results revealed that distinct interneurons in the mPFC are critically involved in cocaine seeking by regulating different cortical outputs. Our study suggests fundamental insights into cortical inhibitory mechanisms for drug addictive behavior, proposing new therapeutical targets.

F60. Astrocytic Creb Regulates Transcriptomic and Behavioral Responses to Cocaine

Leanne Holt, Icahn School of Medicine At Mount Sinai

Drug addiction represents an enormous healthcare burden. To better understand its biological underpinnings, investigations of the transcriptional response to drugs of abuse have demonstrated lasting changes in gene expression throughout the brain's reward circuitry. Historically focused on neurons, emerging evidence increasingly implicates astrocytes in disorders of the nervous system, including addiction. However, the astrocyte-specific transcriptome and its regulation have not been investigated.

We utilized whole cell sorting and RNA-sequencing to characterize the astrocyte transcriptome in several key brain regions involved in reward-processing, including the nucleus accumbens and prefrontal cortex following cocaine self-administration, withdrawal, and "relapse" in mice. Viral-mediated manipulation of CREB activity selectively in NAc astrocytes was used in combination with a variety of addiction-related behaviors.

We determined that astrocytes exhibit robust regionally- and contextually-specific transcriptional signatures. Subsequent bioinformatic analysis revealed CREB as a highly-ranked predicted upstream regulator, and CUT and RUN-sequencing identified increased binding of CREB in astrocytes following cocaine administration. We found that astrocytic CREB increases the rewarding and reinforcing properties of cocaine. Interestingly, this effect is sex-specific, with no change in preference found in females.

Together, these data demonstrate that the astrocyte transcriptome responds robustly to cocaine administration and indicates, for the first time, that CREB is a cocaine-induced transcriptional regulator in astrocytes that increases the rewarding properties of cocaine. These findings are particularly interesting, as previously published work demonstrates opposite effects with neuronal CREB in NAc: increased neuronal CREB activity results in cocaine aversion. Ongoing studies are investigating the molecular mechanism by which astrocytic CREB regulates addiction-related behaviors.

F61. Single Nuclei Transcriptomics of Human and Monkey Striatum Implicates DNA Damage and Neuroinflammation in Opioid Use Disorder

BaDoi Phan, University of Pittsburgh

The striatum in the brain is involved in various behavioral functions, including reward, and disease processes, such as opioid use disorder (OUD). Further understanding of the role of striatal subregions in reward behaviors and their potential associations with OUD requires molecular identification of specific striatal cell types in human brain. The human striatum contains subregions based on different anatomical, functional, and physiological properties, with the dorsal striatum further divided into caudate and putamen. Both caudate and putamen are involved in altered reward processing, formation of habits, and development of negative affect states associated with OUD. Using single nuclei RNA-sequencing of human postmortem caudate and putamen, we identified canonical neuronal cell types in striatum (e.g. dopamine receptor 1 or 2 expressing neurons, D1 or D2) and less abundant subpopulations, including D1/D2-hybrid neurons and multiple classes of interneurons. By comparing unaffected subjects to subjects with OUD, we found neuronal-specific differences in pathways related to neurodegeneration, interferon response, and DNA damage. DNA damage markers were also elevated in striatal neurons of rhesus macaques following chronic opioid administration. We also identified sex-dependent differences in the expression of stress-induced transcripts among astrocytes and oligodendrocytes from female subjects with OUD. Thus, we describe striatal cell types and leverage these data to gain insights into molecular alterations in human striatum associated with opioid addiction.