BRAIN & BEHAVIOR RESEARCH FOUNDATION

2024 Young Investigators

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

" BBRF Young Investigators represent a new generation of researchers who will pioneer breakthroughs in mental health research. We are excited to be able to support the work of these young scientists, who will apply powerful new technologies and insights to understanding, treating, and curing mental illness."

September 2024

We are pleased to present the 2024 Young Investigator grantees of the Brain & Behavior Research Foundation.

Initiated in 1987, the BBRF Young Investigator Grant program provides support for the most promising young scientists conducting neurobiological and psychiatric research. This program facilitates innovative research through support of early-career basic, translational, and clinical investigators.

We are proud to report that since 1987 BBRF has provided more than $461 million in research grants to more than 5,600 scientists around the world.

This year, the Foundation's Scientific Council, led by Dr. Judy Ford and comprised of 195 world-renowned scientists with expertise in every area of brain research, reviewed more than 700 grant applications and selected the 150 meritorious research projects summarized in the pages that follow.

The 2024 BBRF Young Investigators are focused on a broad range of psychiatric illnesses. While many of their projects have relevance in multiple disorders, this year, as in past years, more than half of all the grants we have awarded are relevant to the study or treatment of depression or schizophrenia. Many of the 2024 projects also have relevance for anxiety disorders, addiction/substance-use disorders, PTSD, as well as suicide prevention. Attention to these areas reflects the prevalence of these conditions in the general population and the urgent need for new and improved treatments.

This year for the first time we specify Young Investigator projects that are pertinent to the early years of life — "Childhood and Adolescence" and "Prenatal Brain Development." In fact, one in four of the newly awarded grants fall into these new categories. The new categories reflect that many psychiatric illnesses begin to manifest symptomatically in the years before adulthood; and that in many cases, biological factors that give rise to these symptoms have their roots early in life, before birth and/or in the childhood and adolescent years.

A number of 2024 Young Investigators seek to better understand the role of the body's immune system in the causation of mental illnesses. Other studies explore how the pathways that connect the brain and the digestive system—the "gut-brain axis"—may be implicated in depression and other mood disorders, as well as other psychiatric disorders.

Another notable trend is the attention being focused on specific symptoms such as anhedonia that are experienced across several distinct psychiatric diagnoses. Anhedonia is the inability to seek pleasure; it also manifests as a loss of interest and motivation in normal activities. People with depression and anxiety often experience anhedonia, but so do people in the depressive phase of bipolar disorder as well as some people with schizophrenia.

As always, our new group of Young Investigators are using the very latest methods and technologies in the pursuit of new insights, and in a few cases, are testing brand new technologies for the first time. One example includes testing a device called "a lab on a contact lens," a telemedicine monitoring tool for home-based, non-invasive analysis of mental health. Several projects use new or recently developed methods of non-invasive brain stimulation to treat depression or other disorders including addiction, anxiety and PTSD. These projects are a sampling of the kind of out-of-the-box research that will offer the best hope for improved treatments, cures, and methods of prevention for our loved ones.

100% of every dollar donated for research is invested in our research grants. Our operating expenses are covered by separate foundation grants.

With your donations we can continue to fund innovative scientists across the field of neuropsychiatry. We thank our generous donors for supporting scientists in brain and behavior research so that more people can live full, happy, and productive lives.

Sincerely,

Jeffrey Borenstein, M.D.
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*Many projects are relevant in more than one category; in the pages that follow, grantee project descriptions appear under each category for which they are relevant.

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"BBRF Young Investigator grants fund groundbreaking research aimed at reducing suffering in people with mental illness. These early-career scientists are pushing the boundaries in basic and clinical research to establish new approaches to early prediction, prevention, and intervention and to develop next-generation therapies that offer hope for those with brain and behavior illnesses."

Judith M. Ford, Ph.D.

SINCE 1987

AWARDED
6,700
GRANTS

FUNDED
$461M+
GRANTS

THE 2024 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.4 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

748
YOUNG INVESTIGATOR APPLICATIONS

150
YOUNG INVESTIGATOR GRANTS AWARDED

$10.4
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (123 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (24 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (26 Grants)
To recognize early signs of mental illness and treat as early as possible

New Technologies (8 Grants)
To advance or create new ways of studying and understanding the brain

About 82 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 16 percent of the 2024 grants fund projects that specifically aim to develop **next-generation therapies.**

About 17 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 5 percent of projects fund the development of **new technologies** that will power both basic research and new developments in the clinic.

Several projects have multiple classifications.

Seventy-four percent of grantees are from the United States (111 grantees). Twenty-six percent of grantees come from 14 other countries (39 grantees): Australia, Austria, Belgium, Brazil, Canada, France, Germany, Ireland, The Netherlands, Singapore, Spain, Sweden, Uganda, United Kingdom.

ADDICTION/SUBSTANCE-USE DISORDERS

Laika Aguinaldo, Ph.D., University of California, San Diego, will use machine learning to better understand the power of brain and behavioral patterns to predict the emergence of substance use, suicidal thoughts and behaviors (STBs), and their co-occurrence. The team will use data from the NIH's ongoing Adolescent Brain Cognitive Development (ABCD) study, which has gathered data from 11,878 children, ages 9-14, across the US. They will examine factors such as brain structure and function, behavior, substance use, and demographic details at different stages of development. The aim is to identify structural and functional brain and neurobehavioral features at early timepoints (at baseline and year 2) associated with changes over time in substance use, STBs, and substance use and STBs together at subsequent time points (year 2 and year 4).

Diagnostic Tools/Early Intervention

Miguel Barretto-García, Ph.D., Washington University, St. Louis, notes that the degree to which time "discounts" value is particularly debilitating in patients suffering from neurological disorders. In addiction, frontopolar dementia, and major depression, patients may be impulsive, make poor financial decisions, and form unhealthy lifestyle habits. Previous work has largely studied the neural circuitry controlling reward processing to account for these behavioral features, but the mechanism that incorporates reward into choice remains poorly understood. This project will investigate the neural mechanisms of the orbitofrontal cortex (OFC) in monkeys during intertemporal choice. Rhesus monkeys will choose between two options that vary on three dimensions: juice type, quantity, and delay in timing of juice delivery. The team will record and analyze neuronal activity in central OFC; analyze behavior using computational models of intertemporal choice; and analyze neuronal data by identifying encoded decision variables.

Basic Research

Erin Campbell, Ph.D., University of Newcastle, Australia, has developed a rodent model to test the hypothesis that the serotonin system mediates alcohol craving. This hypothesis is supported by the lab's finding that lorcaserin, a serotonin 2C receptor agonist, successfully reduces alcohol craving in treatment-seeking humans with alcohol use disorder. Lorcaserin was used clinically as a weight-loss agent, but unexpected off-target effects preclude its continued long-term use. Nonetheless, its well defined mechanism of action presents a rare opportunity for reverse translation—using findings from the clinic to inform research on the serotonin receptor system in craving and relapse. The long-term aim is to comprehensively validate new treatments for alcohol use disorder that can be successfully translated back to the clinic.

Next-Generation Therapies

Basic Research

Yifeng Cheng, Ph.D., Johns Hopkins University, wants to reveal how drug abuse disrupts reward decision processes in neural networks in the brain's basal ganglia. Specifically, this project seeks to elucidate the impact of chronic ethanol (EtOH) exposure on neural encoding and information flow within the basal ganglia circuits, specifically examining the dorsomedial striatum (DMS), globus pallidus externus (GPe), and substantia nigra reticulata (SNr), which are pivotal for cognitive flexibility and decision-making. The team's previous study implies that chronic EtOH exposure alters the balance between the basal ganglia's direct (DMS→SNr) and indirect (DMS→GPe→SNr) pathways. This study will therefore first explore EtOH's impact on neural encoding of decision variables in basal ganglia direct and indirect pathways, then test whether selective manipulation of these circuits' activity rescues EtOH-induced deficits on action selection.

Basic Research

Kauê Costa, Ph.D., University of Alabama at Birmingham, notes deficits in mapping associations between distinct stimuli, actions, and outcomes, despite their relevance for substance-use disorders (SUD). A person may get sick after drinking too much and consequently start avoiding alcohol, but they may then also start avoiding bars, liquor stores, and other places associated with alcohol availability, even though those places by themselves were never paired with the adverse consequences of drinking. Humans and rats with a history of chronic drug use show deficits in tasks that require these types of mental models of the world, even after weeks of abstinence, and the inability to use higher-order associations to guide behavior can predispose to relapse. This project will directly measure how different types of dopamine prediction errors are affected in a rat model of SUD. It will also investigate whether different forms of stimulation of the orbitofrontal cortex, including one known to improve drug-induced behavioral deficits, affect dopamine signaling after experience with cocaine self-administration.

Basic Research

Priscila Dib Goncalves, Ph.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, will build upon her earlier findings to examine the impact of high exposure to adverse childhood experiences (ACEs). She will then focus on the effects of having a family history of alcohol and substance-related problems and on frontal brain development during early adolescence (at ages 11-12) and future cannabis and alcohol use in adolescence (at ages 14-15). She will use data from a large, diverse, and longitudinal study, the NIH's Adolescent Brain and Cognitive Development (ABCD) study. The team will also examine whether caregiver support could be a protective factor.

Basic Research

Yang Li, Ph.D., Washington University School of Medicine, seeks to better understand fentanyl use and brain impact. Dr. Li says that intravenous drug self-administration is widely considered to be the gold standard for preclinical phenotyping of substance use and misuse, yet epigenetic reprogramming and gene dysregulation in fentanyl-responsive neurons across multiple stages of substance use along with their locations are not well understood. This study aims to generate preliminary single-cell multimodal datasets from a mouse model of fentanyl use. The aim is to elucidate the fundamental genetic and epigenetic mechanisms of fentanyl use in cell populations in the nucleus accumbens and to test the hypothesis that substance-use disorder pathology can be traced to gene expression changes across responsive cell types that maintain normal brain cell functions and are lost in drug-taking animals.

Basic Research

Carolina Luft, Ph.D., Pontifical Catholic University of Rio Grande do Sul, Brazil, aims to uncover the effects of a stressful childhood on the composition of the gut microbiome and the immune system. By using machine learning, the team hopes to identify markers in the gut or immune system that can predict how well someone with alcohol use disorder (AUD) might respond to treatment or show resilience. They will collect blood to examine cytokine levels and stool samples to evaluate the composition of the gut microbiome. Additionally, they will transplant fecal microbiota from individuals with early-life adversity and those without this history into young mice with no microbiota of their own. In transplanted rodents, they will evaluate behavioral and immune alterations and alcohol consumption. This may help reveal how the gut microbiome influences the immune system and behavior in people who have faced childhood adversity and struggle with alcohol use.

Basic Research

Diagnostic Tools/Early Intervention

Peter Manza, Ph.D., National Institute on Alcohol Abuse & Alcoholism (NIAAA/NIH), says that supplementation with ketone bodies, an alternative energy source to glucose, has emerged as a promising therapeutic for substance use disorders. Boosting ketones may have the potential to ameliorate reductions in opioid signaling and in brain energetics, which Dr. Manza hypothesizes would blunt withdrawal symptoms and improve opioid use disorder (OUD) treatment retention. The team recently found that a ketogenic diet reduced alcohol withdrawal in alcohol use disorder—yet a ketogenic diet regimen is extremely strict and difficult to maintain. In 40 individuals with moderate-to-severe OUD they now want to test the therapeutic efficacy of a ketone supplement (KS) drink, a non-invasive dietary supplement that increases ketone levels within 30 minutes of ingestion and lasts for about 4 hours. They hypothesize that KS compared to placebo will decrease craving, withdrawal severity, and hyperalgesia. If successful, KS could be an easy-to-administer adjunctive therapeutic for OUD.

Next-Generation Therapies

Freddyson Martinez-Rivera, Ph.D., University of Florida, notes that across species, drug seeking associated with substance use disorders (SUDs) is mediated by neural alterations in brain reward circuitry in which the nucleus accumbens (NAc) is central. Alterations in NAc are broadly implicated in drug-seeking behavior. Extinction-based therapies should promote abstinence and minimize relapse in individuals suffering from SUDs. Despite the known involvement of the NAc in this approach, the cellular dynamics of NAc during extinction are not well-elucidated, hindering the development of potential adjunct pharmaceuticals that could increase the therapeutic efficacy of extinction interventions. One approach to improving the efficacy of extinction in clinical settings is to combine it with other strategies (e.g., exposure to punitive outcomes) that also promote patients refraining from relapse. The proposed project will take this approach, combining extinction with an explicit conflict scenario involving punitive results (analogous to contingency management). This behavioral approach will be tested in an animal model of cocaine dependence in conjunction with state-of-the-art approaches aimed at elucidating specific (potentially druggable) circuits within NAc.

Basic Research

Next-Generation Therapies

Suzanne Nolan, Ph.D., Vanderbilt University, studies the mesolimbic dopamine system, implicated in the etiology of substance use disorder, schizophrenia, and major depression. Dopamine release in the nucleus accumbens (NAc) terminals and input-mediated plasticity upstream of cell bodies within the ventral tegmental area (VTA) have been explored. This project seeks to probe the role of non-canonical forms

of release such as somatodendritic release at the level of cell bodies in the VTA, a part of midbrain dopamine (mDA) release. Specifically, she will study how mDA release relates to time-locked behavioral events and its overall functional significance in the specific context of reward learning. The work will test the hypothesis that mDA release is a distinct axis of mesolimbic dopamine signaling, and therefore represents a novel target for therapeutic control of motivated behaviors.
Basic Research

Brenden Tervo-Clemmens, Ph.D., University of Minnesota, cites past research suggesting developmentally sensitive, striatal-reward and prefrontal-cognitive circuits, along with corresponding adolescent impulsive behavior, are central to adolescent cannabis use and therefore may serve as mechanistic targets for intervention. Integrating recent advances in precision longitudinal neuroimaging and deep phenotyping of "state-level" behavior via smartphones, this project addresses reproducibility issues in brain-behavior studies, seeking to identify person-specific "state-level" mechanisms of cannabis use disorder (CUD) recovery that are essential for future clinical translation. This project hopes to identify markers of fronto-striatal circuits during CUD treatment and compare the relative utility of "state-level" measures to traditional lab-based "trait-level" measures.
Basic Research

Yvan Vachez, Ph.D., INSERM, France, cites recent research suggesting that the subthalamic nucleus (STN) may play a role in impulse control disorders, including compulsive behavior seen in addiction. The ventromedial part of the STN (vmSTN) seems crucial for stopping inappropriate actions, yet it is less active in people with impulse control issues. Dr. Vachez's findings indicate that alcohol consumption increases inhibitory signals to the vmSTN, and that an inhibitory structure called the ventral pallidum (VP) projects onto the vmSTN. Interestingly, the VP is known to encode the value of rewards, but this encoding gets skewed after drinking alcohol. To see if individuals with compulsive alcohol use will show heightened activity in VP neurons projecting to the vmSTN, leading to increased inhibition of the vmSTN and promoting compulsive drinking, the team will monitor and manipulate activity in this brain pathway in rats exhibiting compulsive alcohol use, studying how this pathway adapts in alcohol-seeking behavior. After chemical modulation of this pathway during alcohol self-administration experiments, the team will examine how alcohol exposure alters the genetic makeup of VP neurons projecting to the vmSTN. This will help identify potential targets for neuromodulation therapies.
Basic Research

Terril Verplaetse, Ph.D., Yale University, notes that childhood trauma is one example of early-life stress that confers increased vulnerability to developing alcohol problems in adulthood, in both men and women. Childhood trauma has long lasting effects on the stress response, thereby contributing to changes at the neural systems level and dysregulation of the hypothalamic pituitary adrenal (HPA) axis. Studies of childhood trauma and alcohol use disorder (AUD) in humans have examined peripheral cortisol levels, the primary stress hormone, and results are inconsistent. Because of the discrepancy in peripheral cortisol findings, it is important to examine local production of cortisol in the brain, which is the aim of this project, using the novel radiotracer [18F] FMOZAT together with state-of-the-art PET imaging, to measure levels of 11ß-HSD1, a cortisol-regenerating enzyme, in the living human brain.
Basic Research

Heather Webber, Ph.D., University of Texas Health Science Center at Houston, notes that unlike opioid and other substance use disorders, there are no FDA-approved medications for treatment of stimulant use disorder (StimUD). Behavioral treatments exist, but a large portion of patients will relapse after achieving initial abstinence. This is thought to reflect neuroadaptation of the brain after chronic use of drugs or alcohol. One promising target is the orexin system, involved in regulating arousal and sleep, stress, and reward functioning. Critically, these functions are also major contributors to relapse. Sleep disturbance during early withdrawal can lead to stress and craving, which in turn is associated with treatment drop-out and relapse. Regulating sleep during the early stage of abstinence could increase treatment completion and reduce relapse rates. This study will assess the effects of suvorexant, an orexin receptor antagonist, during early withdrawal from stimulant use in treatment-seeking patients entering residential treatment for StimUD. The team will try to expand these findings by identifying neurobiological markers that can objectively asses brain-related changes associated with suvorexant treatment.
Next-Generation Therapies

Natalie Zlebnik, Ph.D., University of California, Riverside, will explore the potential of endocannabinoids (eCBs) in mitigating cocaine addiction relapse through novel insights into the cortico-accumbal circuitry's role in drug-seeking behavior. Cocaine induces significant molecular and physiological changes in the nucleus accumbens (NAc), a central component of the reward system. Disruption in NAc glutamatergic signaling and eCB homeostasis, particularly 2-arachidonylglycerol (2-AG), has been implicated in the vulnerability to cocaine relapse. This project aims to dissect the mechanism by which eCB signaling in the NAc, particularly through CB1R-dependent 2-AG signaling, can counter glutamatergic inputs from the medial prefrontal cortex (mPFC) that drive cocaine relapse. The project consists of two main aims: examining

the role of accumbal eCBs in regulating cocaine relapse, and investigating the modulation of cortico-accumbal control by eCBs. The findings could help pave the way for developing new eCB-based pharmacotherapies for cocaine use disorder.
Basic Research

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Ryan Doan, Ph.D., Harvard University/Boston Children's Hospital, is interested in DNA variations affecting genes involved in pathways related to methyltransferase enzymes, which play a vital role in regulating gene activity. Previous studies have shown that changes in DNA methylation, a chemical modification that affects gene expression, are associated with ADHD risk. Additionally, prior studies have identified common variations in genes that directly impact methylation levels. This study aims to understand how rare genetic variations in methyltransferase genes contribute to the variability in ADHD symptoms within and between families. The team will use induced pluripotent stem cells (iPSCs) and mice to analyze the effects of these variations on gene expression and methylation. They will then directly compare these signatures against those within members of affected families. By studying family members with varying levels of ADHD severity, they hope to identify molecular signatures associated with the different levels of symptoms.
Basic Research

Cassondra Eng, Ph.D., Stanford University, notes that while research on virtual reality (VR) interventions for children and adults with ADHD show promising outcomes regarding executive function (EF), few studies focus on adolescents. This age group is often overlooked and faces barriers such as low treatment engagement, challenges transitioning from parent-focused to patient-engaged treatment, and lack of parental monitoring. A potential solution is to provide adolescents with access to an immersive interactive intervention perceived as engaging, incorporating evidence-based factors known to improve EF: exercise and cognitively enriching play. The purpose of this study is to investigate the effectiveness of novel active VR interventions to promote EF in adolescents with ADHD and elucidate the neural mechanisms underlying behavioral changes. 120 adolescents ages 14-17 with ADHD will be recruited from the community and Stanford School of Medicine's Psychiatry Outpatient Clinics.
Next-Generation Therapies

Zhongzheng Fu, Ph.D., University of Texas Southwestern Medical Center at Dallas, is interested in action monitoring and control, cognitive processes that monitor distractions and errors and redirect focus to stimuli, actions, and thoughts that are relevant to the current goal. This monitoring-control feedback loop is fundamental to flexible goal-directed behaviors, enabling rapid adaptations in an ever-changing environment. In OCD, ADHD, and schizophrenia, dysfunctions in action monitoring and control lead to impairments in goal-directed behaviors, loss of cognitive flexibility, and poor quality of life. Dr. Fu hypothesizes that neuronal circuitry intrinsic to the basal ganglia computes error signals, which directly influence subsequent actions, independently of activity in the frontal cortex; and that the intensity of error signals in the basal ganglia predicts the size of error-related negativity (ERN) as well as subsequent post-error slowing, a popular behavioral marker for error monitoring. By interrogating the neuronal mechanisms of action monitoring and control in the human basal ganglia, this project could reveal a possible future target for neuromodulation therapy.
Basic Research

Masashi Hasegawa, Ph.D., Rutgers University, is interested in impulsive behaviors caused by deficiency in action inhibition. Impulsivity is a factor in ADHD, among other psychiatric disorders. While behavioral therapies can mitigate impulsive behaviors, there are still unmet needs for therapeutics targeting deficiency in action inhibition, Dr. Hasegawa states. This goal might be achieved by manipulating the activities of specific neurons involved in action inhibition, yet neural mechanisms of action inhibition are not well characterized. The focus of this research is a hyperdirect pathway encompassing the cerebral cortex and subthalamic nucleus (STN) in basal ganglia which seems to be involved in action inhibition. A recent study in animal models suggests that prefrontal cortex (PFC) neurons in this anatomical pathway may play a critical role in action inhibition. To empirically discover if causal relationships between specific neural activities and behaviors can be empirically examined, this project will involve, among other things, profiling the gene expression pattern of the PFC neurons controlling action inhibition. Such PFC neurons in the hyperdirect pathway may be a potential target for the treatment of impulsive behaviors.
Basic Research

Jaekyoon Kim, Ph.D., University of Iowa, wants to better understand cellular and molecular mechanisms of repetitive behaviors, a defining symptom in ADHD, autism spectrum disorder (ASD), schizophrenia, and OCD. One challenge in investigating repetitive behavior in mice is the lack of valid behavioral assays. This project uses rotarod training to provide a quantitative and continuous measure of the acquisition of repetitive behavior via forced motor activity. The rotarod is a behavioral task based on a rotating rod, like a treadmill, that the animal must stay on for as long as possible. The experi-

ments proposed seek to identify molecular mechanisms, cell-type-specific contributions, and circuit-specific patterns of neuronal activity during the acquisition of repetitive behavior in mice that model 16p11.2 deletion syndrome. The hope is to characterize the role of striatal circuits as key mediators of repetitive behaviors and identify potential therapeutic targets for their amelioration.

Basic Research

Hannah Lapp, Ph.D., Dell Medical School, University of Texas at Austin, notes that hyper- or hypo-sensitivity to sensory stimulation and atypical social behavior are often present in individuals with neurodevelopmental disorders such as schizophrenia, ADHD, and autism spectrum disorder. Altered sensory processing during sensitive periods for social development may contribute to adult social deficits. This project uses a genetic mouse model for psychiatric risk that exhibits social impairments and atypical sensory sensitivities pervasive in early life caregiver-offspring interactions. By monitoring oxytocin neurons while pups receive different types of maternal tactile stimulation, the team will measure the precise time-course of oxytocin activation during the earliest social interactions. It is hoped this and related experiments will provide a foundation for understanding the relationship between maternal tactile signals, oxytocin, and the development of social behavior and form a basis for experiments to manipulate discrete neural populations altered in this model with the goal of preventing social impairments.

Basic Research

Martin Munz, Ph.D., University of Alberta, Canada, has developed a new technique called parauterine imaging that allows for in vivo subcellular resolution microscopy, in vivo pharmacology, and in vivo targeted single cell patch clamp recordings from cortical cells in a developing mouse embryo. This method opens new ways to study embryonic cortical circuit formation and will allow the team to explore how cortical development is impacted by DNA mutations associated with autism spectrum disorder, schizophrenia and ADHD. Here the focus is on how changes in the expression of three high-confidence autism risk genes (Pten, Chd8 and Grin2b) that are also associated with schizophrenia and ADHD impact neuronal circuit development. They will observe if changes in the expression of these genes leads to changes in circuit development and physiology in mice.

Basic Research

New Technologies

Heather Snell, Ph.D., Yale University School of Medicine, notes that ADHD has been reported in 50% -70% of individuals with autism spectrum disorder (ASD), while impaired motor coordination or motor performance has also been reported in 88%. The cerebellum, responsible for motor coordination, is also involved in non-motor tasks that are impaired in ASD and ADHD, such as social interaction and attention. Studies have shown that modulation of cerebellar Purkinje cell (PC) pacemaking activity (these cells are the main output neuron of the cerebellar cortex) results in impairment in non-motor tasks. But the molecular mechanisms underlying this cerebellar involvement remain poorly understood. The team will investigate mechanisms underlying motor and non-motor impairment in the context of ASD-ADHD by utilizing two mouse models generated to express a potentially causally linked CACNA1A mutation either throughout the brain, or in specific cerebellar Purkinje cells.

Basic Research

New Technologies

ANXIETY DISORDERS

Elisa Baek, Ph.D., University of Southern California, will leverage recent developments in computational neuroscience to take a fine-grained and naturalistic approach to uncover neural mechanisms underlying altered emotion representation in social anxiety. She will test whether individuals with social anxiety exhibit heterogenous mental representations of emotions (i.e., that are uniquely dissimilar from those without social anxiety), which could impede their ability to infer others' emotions and respond appropriately. She will build upon recent findings suggesting that similarities in mental-state representation of emotions and neural responses to naturalistic stimuli underlie social connection—testing these in the context of social anxiety. The hope is to deepen and extend understanding of the biased socioemotional processing that characterizes social anxiety, with implications for theories of emotion and translational implications with diagnostic or prognostic value for social anxiety.

Basic Research

Liam Barry-Carroll, Ph.D., University of Bordeaux, France, aims to explore the impact of early-life stress (ELS) on the emergence of PTSD, using a model of ELS in rodents. Preliminary data indicates significant alterations in cells called microglia, immune cells unique to the brain. A subset of genes related to extracellular vesicles (EV), tiny bubble-like structures in cells that store and transport materials, are upregulated in mice subjected to ELS. This study, building on this result, aims to elucidate the role of microglia-derived EVs in ELS-induced neurological disturbances. The team seeks to delineate the impact of microglia-derived EVs on the etiology of ELS. This research could have significant implications for understanding the pathophysiology of PTSD and other stress-related disorders and suggest potential prevention and treatment targets.

Basic Research

Johnathan Borland, Ph.D., University of Minnesota, notes that rewarding social interactions, such as asserting oneself, defending one's home territory, or dominant-subordinate relationships, can have beneficial effects on mental and physical health. He proposes they can be mobilized to treat psychiatric disorders. This project investigates the neurobiological underpinnings of dominant interactions and asks whether they manifest differently in males and females. Preliminary data suggests that after repeat "dominance" experiences, females, but not males, display greater calcium signaling in the nucleus accumbens. This study will investigate if dominant interactions differentially impact the reward system in males and females, and if the underlying neurobiology in the mesolimbic dopamine reward circuit is different in males and females.

Basic Research

Daniela Calvigioni, Ph.D., Karolinska Institute, Sweden, studies the pathophysiology of brain circuits that may be implicated in anxiety disorders. She has identified long-range projecting pyramidal neurons sensitive to hormones in the insular cortex that express the receptor for estrogen (Esr1) in female and male mice. The insular cortex, sometimes called the "emotional cortex," is a brain region altered in anxiety patients, with the unique capability to control states of the body (e.g., heartbeat), fear, and emotions in humans. The role of hormone-sensitive neurons in cortical regions and their contribution to sexually dimorphic behaviors has not been explored. By manipulating circuitry in adolescent mice placed under stress, the project will, for instance, enable Dr. Calvigioni to compare responses to stimuli with positive and negative valence of different magnitude, features often altered in psychiatric disorders including anxiety.

Basic Research

Simon Chang, Ph.D., University of Regensburg, Germany, notes that the dopamine (DA) system and midbrain structures such as the ventral tegmental area (VTA) play a pivotal role in the hedonic deficits seen in major depression, affecting motivation and the ability to seek or experience pleasure. The network regulating dopamine biology in the VTA is not fully understood. Research has suggested an area called the interstitial nucleus of the posterior limb of anterior commissure, lateral (IPACL) may contribute to emotion, addiction, and metabolism. Dr. Chang has observed a potential closed-loop circuit between IPACL and the VTA. This project will use rodents to investigate the interplay between the inhibitory neurotransmitter GABA and dopamine in closed loop circuits between IPACL and VTA following exposure to chronic social defeat stress and development of anhedonia. Do changes in the activity of this circuit directly affect anhedonia? The team will study molecular changes occurring after circuit manipulations with hopes of dissecting a mechanism associated with stress-induced anhedonia.

Basic Research

Kevin Clancy, Ph.D., Harvard University/McLean Hospital, seeks to develop proof of principle for the use of an ambulatory, cost-effective non-invasive brain stimulation technique called transcranial alternating current stimulation (tACS) to target trauma-related intrusive memories (TR-Ims) in trauma-exposed adults. He will utilize a form of tACS tuned to a pattern of inhibitory neural activity within the sensory cortex known as alpha oscillations. Prior experiments demonstrated deficits in sensory cortical alpha oscillations in PTSD patients, which were associated with sensory sensitivity, neural network dysfunction, and trauma memory reactivation. Leveraging the ability of alpha-tACS to target this deficient inhibitory activity, or "sensory cortical disinhibition," the team will test if alpha-tACS can reduce the sensory-perceptual vividness and intensity of TR-IMs reactivated by personalized trauma narrative scripts. fMRI will be used to further examine how alpha-tACS can regulate the interactions of neural networks implicated in TR-IMs, offering additional mechanistic insights into this pervasive and difficult-to-treat symptom.

New Technologies

Next-Generation Therapies

Austin Coley, Ph.D., University of California, Los Angeles, is interested in a "lack of granularity" in diagnostic practices. For example, a patient who is sleeping and eating too much may be prescribed the same medicine as one who is sleeping and eating too little. Could this be a factor in efficacy of antidepressants? Dr. Coly will try to discover the answer in the context of anhedonia symptoms. The lab has developed an acute severe stress model (learned helplessness) in rodents to induce anhedonia. Measurements of social behavior as well as consummatory pleasure are used to assess hedonic values. Various methods are used to then manipulate activity within neural pathways. This allows the team to identify and longitudinally track neurons encoding both reward and aversive stimuli within the medial prefrontal cortex, while selectively activating input-specific neurons via optogenetic photostimulation during anhedonic conditions.

Basic Research

Jacob Crouse, Ph.D., University of Sydney, Australia, will leverage 3 large, genetically informative, longitudinal, youth-focused cohorts to explore the existence of a sleep-circadian causal pathway to youth-onset mood disorders. One part of the work uses the Adolescent Brain Cognitive Development (ABCD) Study to examine parent-rated measures of sleep and mental health on >10,000 children ages 9–10 over 2 years of follow-up. A powerful technique called joint modelling will be used to examine whether patterns of sleep (and dynamic change in sleep)—in combination with baseline variables including sex and genetic liability to sleep-circadian traits (e.g., chronotype, sleep duration, circadian amplitude)—can

predict the onset of mental disorders over the follow-up. Another part of the study uses the Brisbane Longitudinal Twin Study to examine whether patterns of sleep (and change over time)—alongside sex and genetic indices of sleep-circadian traits—are associated with onset of depression, hypo/mania, or psychosis in early adulthood. A third part will examine whether patterns of objective sleep-circadian function (and change over time)—combined with genetic indices of sleep-circadian traits—predict transition from a subthreshold to a full-threshold mental disorder over the follow-up.

Diagnostic Tools/Early Intervention

Basic Research

Camila de Avila Dal'Bo, Ph.D., Arizona State University, notes anxiety symptoms in Alzheimer's disease (AD) is present in 40% of patients, and may be a prelude to AD onset. Brain regions implicated in anxiety include the amygdala (AMY), the hippocampus (HIPP), and the prefrontal cortex (PFC). These areas receive moderate to strong connections from the pontine nucleus incertus (NI), and preclinical studies indicate these pathways can influence the level of anxiety-like behaviors in rodents. The neurochemical anatomy of the NI has not been mapped in humans. This project seeks to detect and quantify mRNA levels of Relaxin Family Peptide Receptor 3 (RXFP3) in the human AMY, HIPP, and PFC. The neuropeptide relaxin-3 (RLN3) is primarily expressed in neurons within the NI and is a marker for the NI. mRNA levels will be correlated with anxiety scores from clinical records of patients to assess the impact of aging and Alzheimer's. The hypothesis is that: (i) RXFP3 mRNA levels will be decreased in the AMY, HIPP, and PFC of Alzheimer's subjects compared to controls; and (ii) there will be a negative correlation between RXFP3 levels and anxiety scores.

Basic Research

Alessandro De Nadai, Ph.D., Harvard University/McLean Hospital, will evaluate how pubertal expression of anxiety after ages 9-10 relates to the onset of anxiety two years later, by ages 11-12. The team will assess parent and child reports of pubertal onset, as well as the influence of individual hormones (dehydroepiandrosterone, testosterone, estradiol; Aim 1). They will also explore how gender moderates these effects (Aim 2). Anxiety will be measured through clinical diagnosis as well as parent-report on a continuous scale. The methodology used in this project could help identify causal factors and yield preliminary data that can be used to address these questions across a broader age range.

Basic Research

Mario Fernandez, Ph.D., NeuroCenter Magendie U1215 (INSERM), France, aims to investigate the role of different dorsomedial prefrontal cortex (dmPFC) neuronal populations in the emergence of general and specific neuronal representations. One goal is to elucidate how pyramidal glutamatergic (Pyr) neurons, somatostatin-positive (SST+) interneurons and parvalbumin-positive (PV+) interneurons interact in the dmPFC to allow animals to detect and discriminate danger. Efforts will be made to elucidate the causal involvement of these neuronal populations on the acquisition and expression of defensive memories. Dr. Fernandez will combine a new behavioral paradigm, which exposes mice to safe trials and to multiple threatening situations, with calcium imaging in freely moving mice and with the use of optogenetics to manipulate the activity of distinct neuronal populations. The goal is to better understand neuronal mechanisms that allow animals to detect and discriminate danger, processes essential for the correct expression physiological adaptive defensive behaviors.

Basic Research

Zachary Harvanek, M.D., Ph.D., Yale University/Yale University School of Medicine, will address a gap in our understanding of the response to stress at the molecular level by investigating the role of DNA methylation in acute stress responses among trauma-exposed individuals. The team will add epigenetic measures to data from an existing cohort of 138 individuals with a varied range of past traumatic experiences who underwent laboratory sessions including stress-cue and neutral cue conditions followed by measures of anxiety and HPA-axis signaling and up to 2 years of follow up for psychiatric symptomatology. Using these added epigenetic measures, the team will examine the association between baseline DNA methylation of HPA axis-related genes, specifically FKBP5 and NR3C1, and post-stress anxiety levels, HPA-axis signaling, and longitudinal depression and anxiety. Mediation analyses will test whether DNA methylation links trauma history to these outcomes.

Basic Research

Maryam Hasantash, Ph.D., Columbia University, notes that cognitive flexibility may promote stress resilience by enabling the flexible adjustment of cognitive or behavioral strategies to efficiently cope with stressful experiences. This work proceeds from the notion that if we can understand the neural circuits underlying cognitive flexibility, we may be able to identify new targets for advanced therapeutics to treat the debilitating cognitive impairments in multiple psychiatric disorders. Dr. Hasantash has identified projections from the ventral CA1 (vCA1) region of the hippocampus to the medial orbitofrontal cortex (mOFC) as a novel neural circuit component crucial for reversal learning, an important form of cognitive flexibility This study will test a novel role for vCA1-mOFC projections in regulating individual differences in stress vulnerability. Results have the potential to reveal new neural circuit-based targets for novel drugs or for advanced cognitive-behavioral therapies aimed at improving cognitive flexibility as a means to reduce stress-induced psychiatric disorders.

Basic Research

Ann Iturra Mena, Ph.D., Columbia University, says a critical challenge in exposure therapy for such illnesses as anxiety disorders, PTSD, and OCD is the objective measurement of approach behaviors—approach toward feared stimuli—during exposures. Measuring in-session approach behaviors using validated behavioral codes is time-consuming, requires extensive training, and cannot be conducted in real-time. In this study, the team will generate an AI-based tool to automate the assessment of approach behaviors as indicators of therapeutic progress in exposure therapy. They propose to analyze secondary data from 130 audio recordings obtained from prior exposure therapy studies in pediatric OCD and anxiety disorders (participants aged 7-18). The project has three aims: 1) to identify linguistic indicators (e.g., words, phrases) of approach behaviors using speech-to-text and natural language processing tools; 2) to uncover voice indicators (e.g., tone, pitch, tempo) through voice analytics; and 3) to predict treatment response with a machine learning model based on these audio features. The model will be trained on 80% of the data and tested on the remaining 20%.

Basic Research

Diagnostic Tools/Early Intervention

Charline Kambrun, Ph.D., Harvard University/ Massachusetts General Hospital, will use conditional mouse genetics, anatomical analyses, multiple electrophysiology preparations, and behavioral studies to determine the mechanisms through which peripheral somatosensory neuron dysfunction impacts corticospinal neuron function and may ultimately lead to the development of anxiety-like behaviors in a mouse model of autism spectrum disorder. The team will test whether peripheral somatosensory neuron dysfunction disrupts the anatomy and functional properties of corticospinal neurons, and if these alterations ultimately disrupt gating of tactile information in the spinal cord to contribute to anxiety-like behaviors in mice. Together, these studies will provide a mechanistic understanding for how developmental changes to somatosensory inputs can lead to chronic tactile over-reactivity and anxiety-like behaviors in mice.

Basic Research

Arielle Keller, Ph.D., University of Pennsylvania, will test whether differences in brain network development at the critical transition from childhood to adolescence predispose some (but not all) individuals to executive dysfunction and a greater risk for symptoms of depression and anxiety. This project will leverage big data from a large-scale study of >10,000 youths called the Adolescent Brain Cognitive Development (ABCD) Study. It will apply cutting-edge computational methods to characterize each individual's unique transition from childhood to adolescence. This will facilitate investigating patterns of brain network development during the transition from childhood to adolescence in order to better understand the emergence of executive dysfunction and risk for depression and anxiety. Understanding the person-specific patterns of brain development that may lead some individuals but not others to develop executive dysfunction have the potential to facilitate the development of more targeted treatments and preventions of depression and anxiety in youth.

Diagnostic Tools/Early Intervention

Esther Klingler, Ph.D., VIB-KU Leuven Center for Brain & Disease Research, Belgium, notes emotional dysregulation is observed in many neuropsychiatric disorders, including anxiety disorders, and can be promoted by early life stress (ELS). Connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC) has an important role in anxiety. However, the development of BLA-PFC connectivity, and the interplay between intrinsic genetic programs and extrinsic environmental stressors are poorly understood. This project aims to explore the function of genes and environment in the development of BLA-PFC connectivity at molecular, cellular, and behavioral levels. The hypothesis is that specific genes control the development of BLA-PFC connectivity postnatally, and that ELS impacts the expression of these genes, thereby altering BLA-PFC connectivity. The team will (1) identify dynamic molecular programs at play during the development of BLA-PFC connectivity, by combining axon tracing and single-cell RNA sequencing; (2) investigate the role of select genes and their potential to rescue ELS-associated defects, by manipulating their expression.

Basic Research

Laura Luyten, Ph.D., Leuven University, Belgium, notes evidence suggesting that patients with anxiety are generally less tolerant of uncertainty than healthy controls. Much of this evidence has been obtained with one questionnaire, which has limitations as to how it translates to actual behavior. In 120 patients with anxiety, she will gauge uncertainty tolerance not only with this questionnaire, but also with behavioral tasks that will probe individuals' responses to ambiguous threats. Specifically, she will look at how they learn to fear, but also at fear generalization, extinction and avoidance. Together, these three processes represent how fear spreads to related stimuli, how people learn that something ceases to be dangerous, and how they actively try to prevent contact with the anxiety-evoking situation. In a subset of 24 patients suffering from OCD, behavioral assessment will be coupled with neuroimaging to characterize the functional connectivity of the bed nucleus of the stria terminalis (BST) and its relation to uncertainty tolerance measured with the standard questionnaire and with the novel task.

Basic Research

Kahlilia Morris-Blanco, Ph.D., University of Pennsylvania, has focused on understanding how epigenetic enzymes known as TETs contribute to emotional challenges after a stroke.

The team seeks to understand how TETs either help the brain become more resilient or make it more vulnerable to anxiety and depression after a stroke. To answer this, they will manipulate levels of TET enzymes in mice. Recent advancements in technology enable determination of the impact of epigenetic molecular switches more precisely in different cells of the brain. The team seeks to determine which genes are expressed in areas of the brain implicated in anxiety and depression. They also will observe mood behaviors in the mice to understand if changes in TET enzymes affect emotional states like anxiety and depression. Insights gained could lead to innovative therapies that improve mental health and enhance recovery for people who experience a stroke.
Basic Research

Laura Quinones Camacho, Ph.D., Dell Medical School, University of Texas at Austin, will extend her ongoing study with 3–7-year-olds to explore how parent-child neural synchrony may contribute to the intergenerational transmission of anxiety. The first aim is to examine the link between parent-child neural synchrony and child anxiety symptoms in high- vs low-anxious dyads. The second aim is to examine associations between PFC functional connectivity and anxiety symptoms in young children in high- vs low-anxious dyads. The third aim is to examine parent-child neural synchrony as a predictor of children's PFC functional connectivity in these dyads. Resting-state functional MRI data collected during fear-inducing events will inform the analysis. This research could advance our understanding of the biological mechanisms through which caregivers may influence their children's risk for anxiety. Given the importance of early interventions, findings could provide evidence of possible neurobiological mechanisms of risk that can be used to detect those likely to develop anxiety disorders and to create preventative interventions that can be implemented early in life.
Basic Research

Divyangana Rakesh, Ph.D., Institute of Psychiatry/King's College London, UK, notes that low parental socioeconomic status (SES) is associated with substantially higher risk for psychopathology in adolescents, through the impact of stress on the brain and body. The mechanistic role of pubertal and brain development in the association between low SES and risk for psychopathology remains unknown. Many adolescents from low SES backgrounds are resilient and do not develop psychopathology. Identifying factors that confer such resilience is one goal of this project. The team will capitalize on recently available large-scale population-based longitudinal data (N>11,500) and examine various biological domains, including self-report and hormone-based measures of puberty, and functional MRI, to probe how low SES influences biological development; identify mechanisms linking low SES with depression and anxiety symptoms; and identify modifiable home (e.g., parent acceptance), school (e.g., availability of extra-curricular activities), and neighborhood (e.g., community cohesion) factors that may buffer the influence of low SES on biological development and depression and anxiety.
Basic Research

Natale Sciolino, Ph.D., University of Connecticut, proposes that understanding the neural mechanisms underlying anxiety, and how a high-fat diet modulates these mechanisms, is essential for gaining insights into the link between anxiety and obesity. Emerging evidence suggests that obesity may alter norepinephrine (NE) signaling in the brain, but its impact on negative affective behaviors is unclear. The team has found that activation of NE-containing neurons in the locus coeruleus (LC) induces anxiety-like behaviors in rodents. Downstream targets involved in this process remain poorly understood. Optogenetic stimulation of an NE projection from the LC to the lateral hypothalamic area (LHA) increased anxiety-like behavior in recent experiments. These findings support the hypothesis that heightened NE signaling in the LC-LHA pathway underlies the increase in negative affective behaviors associated with obesity. This project, which will elucidate the function of NE circuits in regulating emotion, could contribute to development of new treatments for obesity-induced anxiety.
Basic Research

Ourania Semelidou, Ph.D., INSERM, France, says that even though a dislike for social touch has been reported by socially anxious individuals, neural responses to touch and the attentional processes necessary to filter this information when it becomes irrelevant have not been adequately studied. This study aims to characterize social and non-social tactile perception and attentional control in response to touch in social anxiety disorder (SAD), at the behavioral and neuronal levels. To this end, the team has developed a novel perceptual decision-making task that will be combined with 2-photon calcium imaging to evaluate neuronal activity with single-cell resolution in a mouse model of social anxiety. Results may provide insight into social and non-social tactile perception and attentional control in SAD focusing in particular on neural mechanisms in the dorsal anterior cingulate cortex.
Basic Research

Joseph Stujenske, M.D., Ph.D., University of Pittsburgh, will leverage an animal model to study whether timing brain stimulation to specific phases of respiration yields different changes in fear memory. Findings from this study have promise for optimizing the delivery of non-invasive brain stimulation to ameliorate various psychiatric symptoms, especially anxiety disorders. Repetitive stimulation (rTMS) of the dorsomedial prefrontal cortex (dmPFC) has been shown to alleviate anxiety disorder symptoms when paired

with exposure to feared situations. However, animal studies have shown mixed results of dmPFC stimulation, suggesting a fear-promoting role for this region. This project aims to reconcile this discordance in a mouse model and develop a brain stimulation method for specifically decreasing fear and anxiety. The hypothesis is that subsets of dmPFC outputs will be differently timed relative to respirations, and therefore inspiration or expiration-timed dmPFC stimulation will have different effects on fear extinction.

Basic Research

Next-Generation Therapies

Jiandong Sun, Ph.D., University of California, Los Angeles, is interested in the ventral subiculum (SUBv) within the hippocampus, instrumental in the brain's stress management and emotional regulation. Although it is established that the SUBv connects with various brain regions involved in stress and emotion regulation, such as the prefrontal cortex and amygdala, the mechanisms through which it shifts from handling acute stress to fostering long-term anxiety disorders are poorly understood. This research aims to shed light on the SUBv's role in stress response, particularly its transition from initial stress reactions to adaptations in chronic stress scenarios. In a mouse model, the team aims to identify and characterize the SUBv cell types activated under both acute and chronic stress conditions. Advanced methodologies will allow delineation of these cells' connections and features, elucidating the SUBv's contribution to stress responses. The effects of selectively activating or inhibiting these targeted cells on anxiety-like behaviors in mice will also be observed.

Basic Research

Hwei Ee Tan, Ph.D., Nanyang Technological University, Singapore, says that the community of microorganisms living in our gut plays a role in the development of depression. While emerging evidence reveals that imbalances in gut bacterial composition are causally linked to depression, less is known about the biological interactions between stress and those resident microorganisms. Presuming that the gut-brain axis is bidirectional, the team hypothesizes that mental stress induces gut microbial imbalances via descending brain-gut pathways. Building on their expertise in the mammalian gut-brain axis, they will test this central hypothesis to provide proof of concept for further inquiry into the "top-down" brain-to-gut dialogue: characterizing gut microbiota changes under stress; and defining neural substrates of stress that influence the microbiome and metabolome. This could provide a framework to uncover how certain foods or supplements such as probiotics may reverse the gut bacterial imbalances linked to stress and depression.

Basic Research

Najah Walton, Ph.D., Tufts University, is exploring the potential of novel neurosteroidogenic biomarkers as predictors of stress-induced psychiatric disorders. Recent advancements in therapeutic strategies, particularly neurosteroid analogs of allopregnanolone, have demonstrated rapid and sustained anxiolytic and antidepressant effects in psychiatric disorders. It is important to determine which individuals will respond to allopregnanolone-based treatments. Dr. Walton's team has demonstrated the impact of chronic stress on neurosteroid synthesis and subsequent network dysfunction in the amygdala. This study will deploy a novel neurosteroidogenic biomarker screening tool to detect neurosteroid markers from various tissue samples obtained from individuals with major depression, PTSD, and generalized anxiety disorder. The hope is to synergistically illuminate molecular dynamics while offering a comprehensive view of neurosteroid production from gene expression to protein synthesis. The team expects to observe reductions in neurosteroid levels in a subset of individuals with a psychiatric diagnosis compared to controls.

Basic Research

Lauren White, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, believes that characterizing neurocognitive risk parameters in children is critical to the study of developmental psychopathology and paves the way for novel treatment and interventions. Heightened threat sensitivity—the recognition, interpretation, and response to real or potential threat cues in the environment—is a strong neurocognitive predictor of anxiety risk. Yet little is known about how heightened threat sensitivity develops and is maintained across time. This is a novel intergenerational study of the Philadelphia Neurodevelopmental Cohort (PNC), a racially diverse cohort of ~10,000 participants assessed at ages 8–21 between 2009-2012, with many participants becoming parents in the last 5 years. In 120 mother-child dyads (children aged 4-7 years), Dr. White will use a multimethod assessment framework with psychiatric (clinical interview, self-report), behavioral (computer tasks), and neural (electroencephalogram: EEG) measures to examine the pathways underlying longitudinal and intergenerational influences on threat sensitivity and anxiety.

Diagnostic Tools/Early Intervention

Ye Wu, Ph.D., University of California, Los Angeles, is interested in prosocial behaviors such as comforting, helping, and resource sharing, to improve others' conditions. These capacities are crucial for enhancing social connections and are evolutionarily conserved from humans to rodents. Deficits in the abilities to perceive others' emotional states and/or to form and maintain positive social relationships are prominent symptoms in a range of neuropsychiatric conditions, including depression, social anxiety disorder, psychopathy, and autism. Dr. Wu seeks to integrate approaches that span behavioral, circuit, and computational levels to further elucidate the neural circuitry underlying prosocial comforting

behavior and investigate its potential disturbance in a mouse model relevant to depression. Specifically, the aim is to identify brain areas that function downstream of the pathway between the medial amygdala (MeA) and medial preoptic area (MPOA) in encoding and regulating prosocial interaction. The team also seeks to determine whether prosocial interaction is compromised in a mouse model of chronic social stress and whether such changes are linked to altered activation patterns in the MeA-MPOA pathway.

Basic Research

Mingmin Zhang, Ph.D., University of California, Los Angeles, is interested in the crucial role of social touch in providing comfort to individuals under stress or pain, a strategy observed across species, including allogrooming in rodents, as well as patting and hugging in humans. Social touch has been proven to reduce anxiety in both humans and rodents. However, the mechanism underlying the social touch-induced anxiolytic effect remains largely unknown. This project will investigate the activity of oxytocin neurons and the release of oxytocin in animals receiving allogrooming and determine the role of oxytocin neurons and oxytocin in the anxiolytic effect induced by social touch. Dr. Zhang believes this study will lead to a more incisive understanding of the neural mechanism underlying the social touch-induced anxiolytic effect and deficits in anxiety among other mental illnesses.

Basic Research

Qiancheng Zhao, Ph.D., Yale University, notes that diabetes is often associated with mental health challenges such as anxiety and depression. The pancreas, a vital organ for maintaining metabolic homeostasis, is tightly controlled by the nervous system. Serving as a crucial link between the body and the brain, the vagus nerve plays pivotal roles in regulating insulin release, glucose homeostasis, and mental well-being. This underscores the potential of targeting vagal pathways to address both diabetes and related mood disorders. This project aims to investigate the vagal pathways underlying communication between the pancreas and the brain and its implications for diabetes and mental health. The proposed study is expected to provide insights into pancreas-brain crosstalk and may inform innovative neural modulatory approaches to precisely regulate metabolism and address associated mental health issues.

Basic Research

Yangzhi Zhu, Ph.D., Terasaki Institute for Biomedical Innovation, seeks to develop a new lab-on-a-contact lens (LoCL) telemedicine monitoring tool for home-based, non-invasive, multiplexed analysis of mental health. The central hypothesis is that a judiciously designed wireless LoCL platform integrated with multiplexed biosensors, as a home-based digital biomedical device, provides real-time noninvasive monitoring of physiological biomarkers (serotonin and cortisol), effectively tracking mental health status and significantly promoting early diagnosis/intervention/management of mental disorders. The team will develop a wireless LoCL platform that simultaneously monitors serotonin and cortisol dynamics from tears. They will ask: What is the feasibility of detecting serotonin and cortisol changes through LoCL? What is the efficiency of wireless data transmission? What is the stability of the LoCL in tear analysis? What is the biosafety of the LoCL? They hope then to conduct in-clinic examinations of the LoCL in human pilot studies, adding LoCL to an ongoing rTMS clinical trial for depression.

Diagnostic Tools/Early Intervention

New Technologies

AUTISM SPECTRUM DISORDERS (ASD)

Gabriela Bodea, Ph.D., University of Queensland, Australia, notes that both genes and environment play a role in causing illnesses including schizophrenia and autism spectrum disorder, but the interaction between them is unclear. New research suggests mobile DNA elements, fragments of DNA that can move around in the genome, colloquially referred to as "jumping genes," are dysregulated in schizophrenia patients. This is important because environmental factors are known to trigger mobile DNA activation that can result in altering gene expression and potentially affecting brain development. This project utilizes the latest techniques to study mobile DNA in brain tissue and explore functional consequences in a schizophrenia animal model.

Basic Research

Caitlin Clements, Ph.D., University of Notre Dame, notes differences in reward processing are associated with numerous neurodevelopmental conditions, including autism and ADHD. Many attempts to understand reward processing characterize differences in clinical populations in adolescence and adulthood, well after disorder onset. This project will mobilize commonly used reward processing tasks in preschool-age children, with the hope of better understanding the vast heterogeneity in response to early intervention among children with autism spectrum disorder (ASD). The project will investigate task validity and performance in 30 ASD and 30 sex-matched non-ASD children ages 3 to 5. Results could support a future longitudinal study leveraging the two novel tasks to be tested as crucial parts of a complete battery of reward processing tasks to understand how the constituent components of reward processing (effort, anticipation, response) develop typically, and diverge in autism during early childhood.

Diagnostic Tools/Early Intervention

Marta Cosin-Tomas, Ph.D., Barcelona Institute for Global Health, Spain, seeks to develop placental biomarkers to enable targeting at-risk neonates and close neuropsychological monitoring starting earlier in life. The research is relevant to neurodevelopmental disorders including schizophrenia and autism spectrum disorder. The project focuses on placental epigenetics, which may be useful as a proxy for placental function and the molecular bridge linking genetic disease-risk variants, placental adaptive responses to environmental insults, and placental dysfunction with long-term phenotypic outcomes. Recent findings suggest patterns of placental DNA methylation (DNAm) are associated with changes in brain development and neuropsychiatric outcomes, for instance by reprogramming the hypothalamic-pituitary-adrenal axis. This project will study placental DNAm signatures associated with early neurodevelopmental outcomes and may identify candidate biomarkers to detect neonates at risk of developing neurodevelopmental complications. The team will use recently generated data on placental DNAm profiles and neurodevelopmental evaluations at various ages (neuropsychological assessments at 6, 8, 18, 28, and 48 months of age) from 480 participants in the Barcelona Life Study Cohort.
Basic Research

Veronika Dudarev, Ph.D., University of British Columbia, Canada, observes that limited research has focused on connecting attention and memory in autism, and has not considered how social anxiety may relate to distinct patterns within and across these processes. Also, that while research on cognitive processes in social anxiety has mainly focused on a sensitivity to emotional cues (e.g. negative v. neutral), studies in autism have often focused on social cues and have not controlled for the emotionality of stimuli. This project seeks to identify distinct "profiles" of cognitive processing within individuals with autism spectrum disorder (ASD) and their relationship to social anxiety, to address the challenges of heterogeneity for future neurobiological inquiries and intervention research. To investigate distinguishable cognitive profiles, the team will examine different cognitive functions (attention and memory) under various experimental conditions (social, nonsocial, negative, neutral) in a large sample (n=360) of young adults with and without ASD as well as varying levels of social anxiety. Data will be analyzed using cluster analysis, a machine learning technique.
Basic Research

Julien Ferent, Ph.D., INSERM, France, notes that during embryonic development, morphogens are secreted and form gradients that direct cell fate in a concentration-dependent manner. Morphogens are signaling molecules that act over long distances to induce responses in cells based on the morphogen concentration of the cells they interact with. As the embryonic nervous system develops, cells undergo distinct stages of differentiation, from progenitors to post-mitotic migrating and maturing neurons. At each step of their development, cells change their behavior in response to extracellular cues such as morphogens. These signals may contribute to the transitions between proliferation, migration, and axon/dendrite growth. This project will investigate how progenitor cells modulate their responses to morphogens during differentiation to induce behaviors strictly required for the formation of the correct neural architecture. Alteration of this circuitry during neurodevelopment may directly affect the organization of neural network structure and thus be linked to the onset of a variety of severe psychiatric disorders, such as schizophrenia, autism spectrum disorders, intellectual disability, or epilepsy. The research will be conducted in animals and humans.
Basic Research

Yi Gu, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS/NIH), is interested in 22q11.2 deletion syndrome (22q11.2DS), a genetic syndrome caused by a microdeletion on chromosome 22 and the strongest known genetic risk factor for schizophrenia. It also occurs in autism spectrum disorder, ADHD, and anxiety disorders. This project proceeds from Dr. Gu's prior study of excitatory neural activity in the mouse medial entorhinal cortex (MEC), a region with similar function to human area of the same name. He found that successful learning was associated with an increase and a subsequent stabilization of spatial consistency of MEC neural activity. Those experiments will now be extended to explore neural activity of the MEC in a mouse model of 22q11.2DS, focusing on the possible impact upon impaired spatial memory. Among other things, this could shed light on activity of human EC during the establishment and maintenance of spatial memory in 22q11.2DS.
Basic Research

Charline Kambrun, Ph.D., Harvard University/Massachusetts General Hospital, will use conditional mouse genetics, anatomical analyses, multiple electrophysiology preparations, and behavioral studies to determine the mechanisms through which peripheral somatosensory neuron dysfunction impacts corticospinal neuron function and may ultimately lead to the development of anxiety-like behaviors in a mouse model of autism spectrum disorder. The team will test whether peripheral somatosensory neuron dysfunction disrupts the anatomy and functional properties of corticospinal neurons, and if these alterations ultimately disrupt gating of tactile information in the spinal cord to contribute to anxiety-like behaviors in mice. Together, these studies will provide a mechanistic understanding for how developmental changes to somatosensory inputs can lead to chronic tactile over-reactivity and anxiety-like behaviors in mice.
Basic Research

Jaekyoon Kim, Ph.D., University of Iowa, wants to better understand cellular and molecular mechanisms of repetitive behaviors, a defining symptom in ADHD, autism spectrum disorder (ASD), schizophrenia, and OCD. One challenge in investigating repetitive behavior in mice is the lack of valid behavioral assays. This project uses rotarod training to provide a quantitative and continuous measure of the acquisition of repetitive behavior via forced motor activity. The rotarod is a behavioral task based on a rotating rod, like a treadmill, that the animal must stay on for as long as possible. The experiments proposed seek to identify molecular mechanisms, cell-type-specific contributions, and circuit-specific patterns of neuronal activity during the acquisition of repetitive behavior in mice that model 16p11.2 deletion syndrome. The hope is to characterize the role of striatal circuits as key mediators of repetitive behaviors and identify potential therapeutic targets for their amelioration.

Basic Research

Hannah Lapp, Ph.D., Dell Medical School, University of Texas at Austin, notes that hyper- or hypo-sensitivity to sensory stimulation and atypical social behavior are often present in individuals with neurodevelopmental disorders such as schizophrenia, ADHD, and autism spectrum disorder. Altered sensory processing during sensitive periods for social development may contribute to adult social deficits. This project uses a genetic mouse model for psychiatric risk that exhibits social impairments and atypical sensory sensitivities pervasive in early life caregiver-offspring interactions. By monitoring oxytocin neurons while pups receive different types of maternal tactile stimulation, the team will measure the precise time-course of oxytocin activation during the earliest social interactions. It is hoped this and related experiments will provide a foundation for understanding the relationship between maternal tactile signals, oxytocin, and the development of social behavior and form a basis for experiments to manipulate discrete neural populations altered in this model with the goal of preventing social impairments.

Basic Research

Hsiang-Yuan Lin, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, is conducting a clinical trial to explore psilocybin-assisted therapy for treatment-resistant depression (TRD) in adults with autism spectrum disorder (ASD). Dr. Lin says this will provide a unique opportunity to adopt a "dense-sampling" approach to investigate antidepressant actions. Neuroimaging studies that densely sample the individual brain (i.e., repeatedly scanning a given individual in combination with repeated behavioral/psychological/physiological measures)—as contrasted with a cross-sectional group-averaging approach—are well-suited, Dr. Lin says, for investigating relationships between brain dynamics and behavioral/psychological variables (states) that vary over relatively short time scales. In a subset of a larger trial, 10 intellectually able/speech-fluent adults with ASD and TRD (aged 18-65 years) who are enrolled in the main trial will receive 8 additional brain functional magnetic resonance imaging (MRI) scans in addition to two MRI scans required in the main clinical trial (given pre- and post-psilocybin administration).

Basic Research

Next-Generation Therapies

Martin Munz, Ph.D., University of Alberta, Canada, has developed a new technique called parauterine imaging that allows for in vivo subcellular resolution microscopy, in vivo pharmacology, and in vivo targeted single cell patch clamp recordings from cortical cells in a developing mouse embryo. This method opens new ways to study embryonic cortical circuit formation and will allow the team to explore how cortical development is impacted by DNA mutations associated with autism spectrum disorder, schizophrenia and ADHD. Here the focus is on how changes in the expression of three high-confidence autism risk genes (Pten, Chd8 and Grin2b) that are also associated with schizophrenia and ADHD impact neuronal circuit development. They will observe if changes in the expression of these genes leads to changes in circuit development and physiology in mice.

Basic Research

New Technologies

Lingdi Nie, Ph.D., Krembil Research Institute/University Health Network, Canada, studies 15q13.3 microdeletion syndrome, a neurodevelopmental and genetic disorder with a deleted region of chromosome 15 containing 10 genes that occurs in about 1 in 55,00 people. It manifests soon after birth and is strongly associated with autism spectrum disorder, epilepsy, and schizophrenia. While previous studies have focused on mouse models of 15q13.3 microdeletion, there is no understanding of the dysfunctional human brain circuits or signaling networks underlying the microdeletion. Using control and patient 15q13.3 microdeletion stem cell lines (5 families), the team generated an in vitro 3D human brain model (a brain organoid) and fused brain region-specific organoids to make synthetic circuits named assembloids. The specific type of assembloid to be used in this project is a dorsal-ventral forebrain assembloid. They will investigate whether impaired inhibitory neurons in 15q13.3 microdeletion cause neural circuit dysfunction in the assembloids.

Basic Research

Heather Snell, Ph.D., Yale University School of Medicine, notes that ADHD has been reported in 50% -70% of individuals with autism spectrum disorder (ASD), while impaired motor coordination or motor performance has also been reported in 88%. The cerebellum, responsible for motor coor-

dination, is also involved in non-motor tasks that are impaired in ASD and ADHD, such as social interaction and attention. Studies have shown that modulation of cerebellar Purkinje cell (PC) pacemaking activity (these cells are the main output neuron of the cerebellar cortex) results in impairment in non-motor tasks. But the molecular mechanisms underlying this cerebellar involvement remain poorly understood. The team will investigate mechanisms underlying motor and non-motor impairment in the context of ASD-ADHD by utilizing two mouse models generated to express a potentially causally linked CACNA1A mutation either throughout the brain, or in specific cerebellar Purkinje cells.

Basic Research

Ye Wu, Ph.D., University of California, Los Angeles, is interested in prosocial behaviors such as comforting, helping, and resource sharing, to improve others' conditions. These capacities are crucial for enhancing social connections and are evolutionarily conserved from humans to rodents. Deficits in the abilities to perceive others' emotional states and/or to form and maintain positive social relationships are prominent symptoms in a range of neuropsychiatric conditions, including depression, social anxiety disorder, psychopathy, and autism. Dr. Wu seeks to integrate approaches that span behavioral, circuit, and computational levels to further elucidate the neural circuitry underlying prosocial comforting behavior and investigate its potential disturbance in a mouse model relevant to depression. Specifically, the aim is to identify brain areas that function downstream of the pathway between the medial amygdala (MeA) and medial preoptic area (MPOA) in encoding and regulating prosocial interaction. The team also seeks to determine whether prosocial interaction is compromised in a mouse model of chronic social stress and whether such changes are linked to altered activation patterns in the MeA-MPOA pathway.

Basic Research

Xiyu Zhu, Ph.D., Gladstone Institutes/University of California, San Francisco, notes that cognitive inflexibility is a transdiagnostic dysfunction observed in various psychopathologies, including schizophrenia and autism spectrum disorder. The team's recent study uncovered a novel callosal projection from parvalbumin (PV) neurons in the prefrontal cortex (PFC) that can bidirectionally regulate cognitive flexibility behaviors. Building on these findings and other genes identified by the Schizophrenia Exome Sequencing Meta-analysis Consortium (SCHEMA), they now aim to determine if PFC callosal PV (cc-PV) circuitry represents a common pathway through which genetic risks contribute to schizophrenia- or ASD-related cognitive deficits. This study promises novel insights into the etiology of these disorders and holds significant translational potential for improving diagnosis and developing biomarker-guided treatment.

Basic Research

BIOLOGY OF THE BRAIN

ILLNESS-LINKED COPY NUMBER VARIATIONS

Paola Giusti-Rodriguez, Ph.D., University of Florida, is interested in recurrent copy number variants (CNVs) which have been identified through genome-wide association studies for multiple psychiatric disorders including schizophrenia, autism spectrum disorder, ADHD, major depression, intellectual developmental disorder, and epilepsy. This project seeks to ascertain the impact on 3D-genome organization in mouse models of human psychiatric CNVs at a single-cell level, to develop better mechanistic understanding of psychiatric CNVs, and provide insight into disease etiology. The team will achieve this through the generation of single-cell chromatin conformation capture data of the cortex from five mouse models of human psychiatric CNVs: 1q21.1(del), 3q29(del), 15q13.3(del), 16p11.2(dup), and 22q11.2(del) and wild-type (WT) mice.

Basic Research

GLIA IN NEURAL DEVELOPMENT

Husniye Kantarci, Ph.D., Dell Medical School, University of Texas at Austin, is interested in dysregulation of neuronal excitability which is implicated in the pathologies of numerous diseases including chronic pain, epilepsy, and neuropsychiatric disorders such as bipolar disorder, anxiety, and depression. The team has uncovered an essential role for glia in the development of neurons into excitable cells. Schwann cells, peripheral glia that ensheath sensory axons, secrete prostaglandin E2 (PGE2) to induce excitability in sensory neurons by upregulating the expression of voltage-gated sodium channels (Navs) that provide neurons with action potential firing abilities. The aims of this study are: 1) determining whether CNS glia (astrocytes and oligodendrocytes) secrete PGE2 to promote excitability in CNS neurons and 2) determining the downstream mechanism of PGE2-induced excitability. The goal is to identify new therapeutic targets in glial mechanisms of brain diseases and determine how glia contribute to the development of a healthy nervous system.

Basic Research

NEURAL BASIS OF SELF-MONITORING

Tadeusz Kononowicz, Ph.D., Paris-Saclay University, France, asks: How is action evaluated and corrected in time? This question, which pertains to brain function in several disorders, brings together two themes: timing and metacognition. Metacognition, defined as self-monitoring, is the ability of a cognitive system to monitor its own computation. Although self-monitoring of external uncertainties has been well studied (e.g., coin flips), the mechanisms for monitoring internal uncertainties, such as the one in estimating the amount of time taken to read this paragraph, are not understood. The team will investigate neural mechanisms involved in temporal pro-

cessing and error monitoring in animal and human models, hoping to shed new light on how temporal information is encoded, processed, and self-evaluated in the brain. Within this framework, the project aims to investigate the hierarchical representation of timing errors within the anterior cingulate cortex (ACC) in rats and humans. Simultaneously, it seeks to explore the hierarchical processing of action timing and timing errors in humans using stimulation methods.

Basic Research

INDIVIDUAL VARIATION IN BRAIN DEVELOPMENT

Julia Moser, Ph.D., University of Minnesota, will characterize individual trajectories of functional network organization within the first year of life, with focus on subcortical-to-cortical connectivity patterns, particularly those involved in the reward system. The goal is to account for individual variations in functional network organization and its trajectory by studying person-specific network topography and topology. The team will enroll 10 families with infants between 1-3 months for one precision imaging scanning visit and one follow up visit after 3-6 months. They will define cortical and subcortical individual functional networks in each participant, their topology (strength of connections within and between networks) and topography (size and shape of networks) and their individual trajectory from first to second visit. This project will leverage technological advances in 7T imaging for precision functional mapping in infants, to shed light on the origins of psychiatric disorders.

Basic Research

ACCELERATED BIOLOGICAL AGING

Julian Mutz, Ph.D., King's College London, UK, notes those with mental disorders are more prone to age-related diseases such as heart disease and diabetes and have a shorter lifespan, on average. Previous studies have established that mental disorders like depression, bipolar disorder and anxiety disorders are associated with markers of accelerated biological aging such as telomere attrition, weak grip strength and increased physical frailty, but it is not known to what extent accelerated aging contributes to the poor physical health outcomes and premature mortality. This project aims 1) to develop a more holistic biological aging clock by integrating metabolomics, proteomics and clinical biomarker data and deploying cutting-edge analytical methods in genetic epidemiology and machine learning; (2) to investigate the impact of accelerated biological aging on the development of age-related diseases and premature death in individuals with mental disorders; (3) to identify factors that might mitigate or exacerbate this process.

Basic Research

ESTROGEN RECEPTORS IN BRAIN DEVELOPMENT

Nevena Radonjic, M.D., Ph.D., Research Foundation for the State University of New York, Upstate Medical University, notes that alterations in estrogen levels during neurodevelopment can have lasting impact on the density of cortical interneurons, the impairment of which has been implicated in disorders such as schizophrenia and ASD. Understanding of estrogen-mediated mechanisms of neurodevelopment is hampered by limited data from human fetal studies. This project asks: Where and when are estrogen receptors expressed on interneuron progenitors in the developing human cerebral cortex? It is hoped this study will provide critical insights into the precise location, cell types, and developmental phases at which estrogen receptors and related genes are expressed in interneuron progenitors in the fetal cerebral cortex. Findings will help elucidate the role of estrogen signaling pathway expression in the fetal brain and enable work to understand the susceptibility of specific brain regions to structural abnormalities related to alteration in levels of estrogen.

Basic Research

CEREBELLAR ALTERATIONS DURING ADOLESCENCE

Adrienne Romer, Ph.D., Virginia Polytechnic Institute and State University, is intrigued by transdiagnostic research that has identified a general psychopathology factor, called the "p-factor," that might account for comorbidity and severity across mental disorder categories. Identifying neural predictors of the p-factor would substantiate its importance in characterizing the shared origins of mental disorders and help us begin to understand the mechanisms through which the p-factor may contribute to risk, she says. Her work focuses on alterations within the cerebellum and a cerebello-thalamo-cerebro-cortical circuit (CTCC), involved in higher-order cognitive processing, in individuals with high p-factor scores. Cerebellar abnormalities have been identified in depression, bipolar disorder, schizophrenia, ADHD, and PTSD. She will explore the possibility that the cerebellum may be particularly important for transdiagnostic psychopathology during youth development as the cerebellar cortex undergoes extensive neurodevelopmental changes during adolescence and young adulthood. This study seeks to provide longitudinal perspective to examine cerebellar alterations as prospective predictors of future transdiagnostic psychopathology. Eighty adolescents aged 14-19 with low to elevated transdiagnostic symptoms but no current or past mental disorder diagnoses will participate in baseline clinical and MRI sessions and a 6-month follow-up clinical session.

Basic Research

LATROPHILINS AND SYNAPSE FORMATION

Hamidreza Shaye, Ph.D., Stanford University, notes that many cell adhesion molecules (CAMs) have been identified which mediate synapse formation, but for most, their interaction network is not well studied. Among them, latrophilins have been identified as key players in the synapse formation process, mediating multiple transcellular interactions with other CAMs. Despite various attempts to study the interactome of latrophilins, knowledge is limited. This project will study the latrophilin-neurexin complex and investigate the physiological phenotype of this complex and its implications in neuropsychiatric diseases. This will include efforts to develop a comprehensive map of the latrophilin interactome and their interaction network. The ultimate goal is to develop a tool that can be used to identify latrophilin binding partners at the synaptic cleft and generate knowledge of the latrophilin protein-protein interaction network.

Basic Research

MICROGLIA IN CIRCUIT DEVELOPMENT

Valerie Tornini, Ph.D., University of California, Los Angeles, notes that microglia, the immune cells of the brain, are required for correct circuit development, yet the mechanisms involving microglia that ensure proper circuit development in early developmental time periods are poorly defined. Also unclear is how microglia are affected in genetic models of neurodevelopmental disorders (NDDs) such as schizophrenia and autism. This project seeks to define the roles of microglia in establishing baseline brain circuitry and behavior in genetic models of NDDs. To investigate how microglia are affected in genetic mutants, and how targeting microglia may affect organismal behaviors, the team will use a zebrafish model in which they will perform behavioral profiling, cell type-specific in vivo manipulations, and robust functional and molecular readouts during early circuit formation.

Basic Research

OPIOID RECEPTORS AND VALENCE PROCESSING

Hector Yarur, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that opioid transmission and dysregulated prefrontal cortex (PFC) activity have been implicated in the inhibitory-control deficits associated with addiction and binge-type eating disorders. While endogenous opioids and their receptors are highly expressed in the PFC, it is not known whether endogenous opioid transmission within the PFC modulates inhibitory control. This project investigates the hypothesis that PFC enkephalin neurons modulate the association of valence with rewarding and aversive stimuli through the release of endogenous enkephalin peptides. The goal is to elucidate the role of endogenous opioid systems in regulating Pavlovian conditioning behavior and gain insights into the microcircuit mechanisms by which opioids modulate PFC circuitry and motivate behavior by targeting specific interneuron subpopulations.

Basic Research

BIPOLAR DISORDER

JinYoung Choi, Ph.D., Harvard University/Massachusetts General Hospital, notes that ketamine and a ketogenic diet influence key neurobiological factors implicated in bipolar disorder, including brain-derived neurotrophic factor, glutamate, and oxidative stress. The hypothesis to be tested is that combining ketamine and the ketogenic diet could synergistically improve bipolar disorder symptoms in both short- and long-term scenarios. The proposed treatment strategy aims to leverage the rapid symptoms-reversal potential of ketamine and the sustained benefits of the ketogenic diet to achieve comprehensive symptom relief. The team will utilize GluN2A knockout mice, which have decreased GluN2A expression like that observed in patients with bipolar disorder. One aim is to delineate changes in energy metabolism and mood following ketamine infusions in the animal model. Another is to assess the combined therapy's effects on bipolar disorder-like symptoms and energy metabolism.

Next-Generation Therapies

Basic Research

Adam Fijtman, M.D., Ph.D., National Institute of Mental Health (NIMH/NIH), will assess how ketamine impacts cognition and magnetoencephalography (MEG) changes in individuals with bipolar disorder (BD). MEG is a non-invasive technique for recording brain function. A group of participants with BD will receive five ketamine infusions over 3 weeks. Cognition will be assessed one day before and one day after the first infusion, as well as one and seven days after the last infusion. The team will use MEG to investigate how ketamine impacts brain circuits associated with cognitive functioning. During MEG sessions, participants will perform two memory tasks. Results will be used to measure gamma power, a proxy measure of neuronal excitation and synaptic potentiation, thought to be associated with ketamine's pro-cognitive effects. The hypothesis is that ketamine will improve different domains of cognition and increase gamma power and that these changes will be more prominent after repeated ketamine infusions.

Next-Generation Therapies

Masashi Hasegawa, Ph.D., Rutgers University, is interested in impulsive behaviors caused by deficiency in action inhibition. Impulsivity is a factor in ADHD, among other psychiatric disorders. While behavioral therapies can mitigate impulsive behaviors, there are still unmet needs for therapeutics targeting deficiency in action inhibition, Dr. Hasegawa states. This goal might be achieved by manipulating the

activities of specific neurons involved in action inhibition, yet neural mechanisms of action inhibition are not well characterized. The focus of this research is a hyperdirect pathway encompassing the cerebral cortex and subthalamic nucleus (STN) in basal ganglia which seems to be involved in action inhibition. A recent study in animal models suggests that prefrontal cortex (PFC) neurons in this anatomical pathway may play a critical role in action inhibition. To empirically discover if causal relationships between specific neural activities and behaviors can be empirically examined, this project will involve, among other things, profiling the gene expression pattern of the PFC neurons controlling action inhibition. Such PFC neurons in the hyperdirect pathway may be a potential target for the treatment of impulsive behaviors.
Basic Research

Maria Koromina, Ph.D., Icahn School of Medicine at Mount Sinai, has fine-mapped 64 genome locations deemed significant for bipolar disorder. Significant "loci" gleaned from a genome-wide association study based on a cohort of European ancestry has been used to identify so-called putative causal variants, i.e., DNA variations with possible causal implications for BD. These loci have been linked to relevant protein-coding genes using data from brain tissues and cell types. A recent a multi-ancestry BD genome-wide association study (GWAS) has identified 298 significant loci. Dr. Koromina aims to extend her established fine-mapping pipeline using these data and related novel resources to prioritize high-confidence variants and genes from this multi-ancestry BD GWAS. She will also explore the translational impact of these results by developing functional polygenic risk predictors and identifying potential opportunities for drug repurposing for BD.
Basic Research

Leila Nabulsi, Ph.D., University of Southern California, notes investigations into how medication-related alterations exacerbate or mitigate structural and functional brain abnormalities in bipolar disorder (BD) have been undertaken in smaller cohorts, making it hard to tell whether they generalize to the broader population. Notably, BD patients are seldom treated with a single medication, and the resulting polypharmacy further complicates efforts to identify brain biomarkers that can help predict treatment response, disease progression, or improved patient outcomes. The team's study with the ENIGMA Consortium will tackle this issue through large-scale analyses, offering the potential to unveil reliable indicators of bipolar disorder and factors that affect it. They will leverage large-scale neuroimaging (MRI) samples (total N=3,700; ages 18-64 years) to examine white matter brain alterations in BD in a fine-grained manner. The hope is to characterize the relationship between various neural profiles, treatment goals, and individual symptoms, to identify biologically grounded targets for novel treatments.
Basic Research

Beier Yao, Ph.D., McLean Hospital, is interested in interoception—the processing, interpretation, and regulation of bodily signals by the brain. There is growing evidence that internal signals from the body can influence a wide range of brain functions, including basic perception, reasoning, emotion, motivation, and sense of self. Disrupted interoception may underlie mood instability in bipolar disorder as well as specific psychotic symptoms related to altered sense of self (e.g., delusion of being controlled by external forces). The team will collect electroencephalogram (EEG), electrocardiogram (ECG), skin conductance, pupil diameter, and self-report data while participants view emotionally evocative images. Relationships between interoception and clinical symptoms (including mood and psychotic symptoms) will also be explored. Potential findings of dysfunctional interoception in bipolar disorder hold the promise to increase our understanding in the role of bodily signals in illness mechanism and inform the development of novel bodily signals-targeted interventions.
Basic Research

BORDERLINE PERSONALITY DISORDER

Miguel Barretto-García, Ph.D., Washington University, St. Louis, notes that the degree to which time "discounts" value is particularly debilitating in patients suffering from neurological disorders. In addiction, frontopolar dementia, and major depression, patients may be impulsive, make poor financial decisions, and form unhealthy lifestyle habits. Previous work has largely studied the neural circuitry controlling reward processing to account for these behavioral features, but the mechanism that incorporates reward into choice remains poorly understood. This project will investigate the neural mechanisms of the orbitofrontal cortex (OFC) in monkeys during intertemporal choice. Rhesus monkeys will choose between two options that vary on three dimensions: juice type, quantity, and delay in timing of juice delivery. The team will record and analyze neuronal activity in central OFC; analyze behavior using computational models of intertemporal choice; and analyze neuronal data by identifying encoded decision variables.
Basic Research

Andreea Diaconescu, Ph.D., Centre for Addiction and Mental Health/University of Toronto, Canada, focuses on borderline personality disorder (BPD), and specifically suicide

risk associated with it. She contends that at the behavioral level, learning from aversive outcomes differs between individuals and can lead to the emergence of suicidal thoughts and behaviors. Increased stress reactivity is a key factor. She proposes that stress sensitivity is represented in interacting brain networks. Specifically, the team hypothesizes that the noradrenergic system and prefrontal projection sites represent stress reactivity. This project will empirically validate competing network mechanisms of stress reactivity in BPD patients with suicidal thoughts and behaviors using fMRI and computational behavioral and brain modeling. The study group will consist of 60 BPD patients, who will perform a cognitive task during fMRI. Subject-specific computational modeling of task behavior and fMRI brain dynamics will test the mechanistic hypotheses of network-related contributions to suicidal ideation and suicidal behavior.

Basic Research

Masashi Hasegawa, Ph.D., Rutgers University, is interested in impulsive behaviors caused by deficiency in action inhibition. Impulsivity is a factor in ADHD, among other psychiatric disorders. While behavioral therapies can mitigate impulsive behaviors, there are still unmet needs for therapeutics targeting deficiency in action inhibition, Dr. Hasegawa states. This goal might be achieved by manipulating the activities of specific neurons involved in action inhibition, yet neural mechanisms of action inhibition are not well characterized. The focus of this research is a hyperdirect pathway encompassing the cerebral cortex and subthalamic nucleus (STN) in basal ganglia which seems to be involved in action inhibition. A recent study in animal models suggests that prefrontal cortex (PFC) neurons in this anatomical pathway may play a critical role in action inhibition. To empirically discover if causal relationships between specific neural activities and behaviors can be empirically examined, this project will involve, among other things, profiling the gene expression pattern of the PFC neurons controlling action inhibition. Such PFC neurons in the hyperdirect pathway may be a potential target for the treatment of impulsive behaviors.

Basic Research

Natassia Robinson, Ph.D., Karolinska Institute, Sweden, aims to identify clinical and psychosocial risk factors for early detection of borderline personality disorder (BPD), vital for guiding timely treatment interventions. She seeks to elucidate the clinical and psycho-social factors at contact with child and adolescent mental health services (CAMHS) that are predictive of subsequent diagnosis of BPD, including BPD with self-injurious behaviors and suicide. Given the early onset of the disorder and the overlap between BPD symptoms and reasons for psychiatric services referral, she hypothesizes that by examining psychosocial and clinical factors in youths, early indicators can be identified that are predictive of BPD and its more severe trajectories. The team will utilize data from several Swedish national registers which span the entire Swedish population (N>10 million). The approach will determine which clinical factors in youths experiencing mental health difficulties can be used to predict adult diagnosis of BPD, and which factors in the pre-onset period can indicate a severe disorder trajectory over a 19-year follow-up.

Diagnostic Tools/Early Intervention

CHILDHOOD & ADOLESENCE

Laika Aguinaldo, Ph.D., University of California, San Diego, will use machine learning to better understand the power of brain and behavioral patterns to predict the emergence of substance use, suicidal thoughts and behaviors (STBs), and their co-occurrence. The team will use data from the NIH's ongoing Adolescent Brain Cognitive Development (ABCD) study, which has gathered data from 11,878 children, ages 9-14, across the US. They will examine factors such as brain structure and function, behavior, substance use, and demographic details at different stages of development. The aim is to identify structural and functional brain and neurobehavioral features at early timepoints (at baseline and year 2) associated with changes over time in substance use, STBs, and substance use and STBs together at subsequent time points (year 2 and year 4).

Diagnostic Tools/Early Intervention

Liam Barry-Carroll, Ph.D., University of Bordeaux, France, aims to explore the impact of early-life stress (ELS) on the emergence of PTSD, using a model of ELS in rodents. Preliminary data indicates significant alterations in cells called microglia, immune cells unique to the brain. A subset of genes related to extracellular vesicles (EV), tiny bubble-like structures in cells that store and transport materials, are upregulated in mice subjected to ELS. This study, building on this result, aims to elucidate the role of microglia-derived EVs in ELS-induced neurological disturbances. The team seeks to delineate the impact of microglia-derived EVs on the etiology of ELS. This research could have significant implications for understanding the pathophysiology of PTSD and other stress-related disorders and suggest potential prevention and treatment targets.

Basic Research

Caitlin Clements, Ph.D., University of Notre Dame, notes differences in reward processing are associated with numerous neurodevelopmental conditions, including autism and ADHD. Many attempts to understand reward processing characterize differences in clinical populations in adoles-

cence and adulthood, well after disorder onset. This project will mobilize commonly used reward processing tasks in preschool-age children, with the hope of better understanding the vast heterogeneity in response to early intervention among children with autism spectrum disorder (ASD). The project will investigate task validity and performance in 30 ASD and 30 sex-matched non-ASD children ages 3 to 5. Results could support a future longitudinal study leveraging the two novel tasks to be tested as crucial parts of a complete battery of reward processing tasks to understand how the constituent components of reward processing (effort, anticipation, response) develop typically, and diverge in autism during early childhood.

Diagnostic Tools/Early Intervention

Jacob Crouse, Ph.D., University of Sydney, Australia, will leverage 3 large, genetically informative, longitudinal, youth-focused cohorts to explore the existence of a sleep-circadian causal pathway to youth-onset mood disorders. One part of the work uses the Adolescent Brain Cognitive Development (ABCD) Study to examine parent-rated measures of sleep and mental health on >10,000 children ages 9–10 over 2 years of follow-up. A powerful technique called joint modelling will be used to examine whether patterns of sleep (and dynamic change in sleep)—in combination with baseline variables including sex and genetic liability to sleep-circadian traits (e.g., chronotype, sleep duration, circadian amplitude)—can predict the onset of mental disorders over the follow-up. Another part of the study uses the Brisbane Longitudinal Twin Study to examine whether patterns of sleep (and change over time)—alongside sex and genetic indices of sleep-circadian traits—are associated with onset of depression, hypo/mania, or psychosis in early adulthood. A third part will examine whether patterns of objective sleep-circadian function (and change over time)—combined with genetic indices of sleep-circadian traits—predict transition from a subthreshold to a full-threshold mental disorder over the follow-up.

Diagnostic Tools/Early Intervention

Basic Research

Christina Cruz, M.D., University of North Carolina at Chapel Hill, seeks ways of supporting teachers who can deliver child mental health care in schools. The key to making this feasible, she maintains, is coaching by school staff. Through a randomized controlled trial, she will study if this care model is feasible, acceptable, and can be delivered in adherence to a care protocol, answering whether school staff will deliver this care model. She will also study whether children's psychiatric symptoms, where present, improve after receiving this care versus children not in care. The study site is the public schools of Manila, Philippines, where a school district has approached Dr. Cruz to develop such a model of care to be used in 73 elementary schools. The administrators have agreed to implement this model in stepwise fashion, with research at each step.

Diagnostic Tools/Early Intervention

Alessandro De Nadai, Ph.D., Harvard University/McLean Hospital, will evaluate how pubertal expression of anxiety after ages 9-10 relates to the onset of anxiety two years later, by ages 11-12. The team will assess parent and child reports of pubertal onset, as well as the influence of individual hormones (dehydroepiandrosterone, testosterone, estradiol; Aim 1). They will also explore how gender moderates these effects (Aim 2). Anxiety will be measured through clinical diagnosis as well as parent-report on a continuous scale. The methodology used in this project could help identify causal factors and yield preliminary data that can be used to address these questions across a broader age range.

Basic Research

Elvisha Dhamala, Ph.D., Feinstein Institute for Medical Research/Northwell Health, is interested in psychotic-like experiences (PLEs)—prodromal symptoms that resemble aspects of psychosis but do not meet the full diagnostic criteria for a psychotic disorder. They may represent a critical transdiagnostic biomarker of psychiatric illness in youth. This research will use a large sample of youth (n=6319) from the Adolescent Brain Cognitive Development Study, with the aim of quantifying functional networks that underlie PLEs in a sex-specific manner and to evaluate whether such sex-specific markers predict the onset of specific psychiatric illnesses during adolescence using brain-based predictive modeling. This work may establish the sex-specific functional brain markers of PLEs in children and the diagnostic specificity of those markers in adolescents. Once identified, these biomarkers could be used to predict the onset of psychiatric illnesses in youth with a single baseline neuroimaging scan, while considering the individual's sex.

Diagnostic Tools/Early Intervention

Priscila Dib Goncalves, Ph.D., Research Foundation for Mental Hygiene, Inc./Nathan Kline Institute, will build upon her earlier findings to examine the impact of high exposure to adverse childhood experiences (ACEs). She will then focus on the effects of having a family history of alcohol and substance-related problems and on frontal brain development during early adolescence (at ages 11-12) and future cannabis and alcohol use in adolescence (at ages 14-15). She will use data from a large, diverse, and longitudinal study, the NIH's Adolescent Brain and Cognitive Development (ABCD) study. The team will also examine whether caregiver support could be a protective factor.

Basic Research

Cassondra Eng, Ph.D., Stanford University, notes that while research on virtual reality (VR) interventions for children and adults with ADHD show promising outcomes regarding executive function (EF), few studies focus on adolescents. This age group is often overlooked and faces barriers such as low treatment engagement, challenges transitioning from parent-focused to patient-engaged treatment, and lack of parental monitoring. A potential solution is to provide adolescents with access to an immersive interactive intervention perceived as engaging, incorporating evidence-based factors known to improve EF: exercise and cognitively enriching play. The purpose of this study is to investigate the effectiveness of novel active VR interventions to promote EF in adolescents with ADHD and elucidate the neural mechanisms underlying behavioral changes. 120 adolescents ages 14-17 with ADHD will be recruited from the community and Stanford School of Medicine's Psychiatry Outpatient Clinics.

Next-Generation Therapies

Ann Iturra Mena, Ph.D., Columbia University, says a critical challenge in exposure therapy for such illnesses as anxiety disorders, PTSD, and OCD is the objective measurement of approach behaviors—approach toward feared stimuli—during exposures. Measuring in-session approach behaviors using validated behavioral codes is time-consuming, requires extensive training, and cannot be conducted in real-time. In this study, the team will generate an AI-based tool to automate the assessment of approach behaviors as indicators of therapeutic progress in exposure therapy. They propose to analyze secondary data from 130 audio recordings obtained from prior exposure therapy studies in pediatric OCD and anxiety disorders (participants aged 7-18). The project has three aims: 1) to identify linguistic indicators (e.g., words, phrases) of approach behaviors using speech-to-text and natural language processing tools; 2) to uncover voice indicators (e.g., tone, pitch, tempo) through voice analytics; and 3) to predict treatment response with a machine learning model based on these audio features. The model will be trained on 80% of the data and tested on the remaining 20%.

Basic Research

Diagnostic Tools/Early Intervention

Liat Itzhaky, Ph.D., Columbia University, is interested in the safety planning intervention (SPI), a brief, protocol-driven suicide prevention tool that assists the individual at suicide risk in recognizing and knowing their warning signs for an emerging suicidal crisis. It also helps the person identify personalized coping strategies, based on the elements of distraction and interpersonal support, to employ to stop the escalation of the crisis and prevent suicidal behaviors. The effectiveness of using the SPI's coping strategies has never been evaluated in adolescents, and mediators of its effect on mitigating suicide risk are unknown. This project seeks to evaluate the effectiveness of using the SPI's coping strategies to reduce suicidal ideation severity, frequency, and duration among depressed adolescents and to examine the mediating effect of stress reduction. The hypothesis is that the use of distraction strategies and interpersonal support, established through the use of the SPI, will reduce the experience of stress and, thus, decrease suicide risk. A randomized control trial will be conducted with 88 depressed adolescents.

Diagnostic Tools/Early Intervention

Kiera James, Ph.D., University of Pittsburgh, will test a theory pertinent to suicide prevention. A brain-based measure of internal attention to social threat information, she hypothesizes, may help identify disrupted processing of competing and potentially positive socio-affective cues that promote social connectedness, which in turn may lead to increases in suicidal thoughts and behaviors (STBs). The more teen girls remember and think about cues of social threat, she proposes, the more they will look for similar cues in their future social interactions, which may prevent them from processing other cues (e.g., a smile) that foster a sense of connectedness. The team will use a machine learning approach to multivariate pattern classification of participants' brain waves (EEG) in response to cues of social threat (i.e., angry faces) during the delay period of a novel working memory task. This approach will be used to assess enhanced representation of social threat information in working memory, signaling sustained internal attention to such information. 50 female youths aged 12-17 will be recruited who are at high risk for STBs based on a recent history of STB or self-harm. Data will support recruitment for a new study visit during which participants will complete the EEG working memory task.

Diagnostic Tools/Early Intervention

Arielle Keller, Ph.D., University of Pennsylvania, will test whether differences in brain network development at the critical transition from childhood to adolescence predispose some (but not all) individuals to executive dysfunction and a greater risk for symptoms of depression and anxiety. This project will leverage big data from a large-scale study of >10,000 youths called the Adolescent Brain Cognitive Development (ABCD) Study. It will apply cutting-edge computational methods to characterize each individual's unique transition from childhood to adolescence. This will facilitate investigating patterns of brain network development during the transition from childhood to adolescence in order to better understand the emergence of executive dysfunction and risk for depression and anxiety. Understanding the person-specific patterns of brain development that may lead some individuals but not others to develop executive dysfunction have the potential to

facilitate the development of more targeted treatments and preventions of depression and anxiety in youth.
Diagnostic Tools/Early Intervention

Esther Klingler, Ph.D., VIB-KU Leuven Center for Brain & Disease Research, Belgium, notes emotional dysregulation is observed in many neuropsychiatric disorders, including anxiety disorders, and can be promoted by early life stress (ELS). Connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC) has an important role in anxiety. However, the development of BLA-PFC connectivity, and the interplay between intrinsic genetic programs and extrinsic environmental stressors are poorly understood. This project aims to explore the function of genes and environment in the development of BLA-PFC connectivity at molecular, cellular, and behavioral levels. The hypothesis is that specific genes control the development of BLA-PFC connectivity postnatally, and that ELS impacts the expression of these genes, thereby altering BLA-PFC connectivity. The team will (1) identify dynamic molecular programs at play during the development of BLA-PFC connectivity, by combining axon tracing and single-cell RNA sequencing; (2) investigate the role of select genes and their potential to rescue ELS-associated defects, by manipulating their expression.
Basic Research

Hannah Lapp, Ph.D., Dell Medical School, University of Texas at Austin, notes that hyper- or hypo-sensitivity to sensory stimulation and atypical social behavior are often present in individuals with neurodevelopmental disorders such as schizophrenia, ADHD, and autism spectrum disorder. Altered sensory processing during sensitive periods for social development may contribute to adult social deficits. This project uses a genetic mouse model for psychiatric risk that exhibits social impairments and atypical sensory sensitivities pervasive in early life caregiver-offspring interactions. By monitoring oxytocin neurons while pups receive different types of maternal tactile stimulation, the team will measure the precise time-course of oxytocin activation during the earliest social interactions. It is hoped this and related experiments will provide a foundation for understanding the relationship between maternal tactile signals, oxytocin, and the development of social behavior and form a basis for experiments to manipulate discrete neural populations altered in this model with the goal of preventing social impairments.
Basic Research

Carolina Luft, Ph.D., Pontifical Catholic University of Rio Grande do Sul, Brazil, aims to uncover the effects of a stressful childhood on the composition of the gut microbiome and the immune system. By using machine learning, the team hopes to identify markers in the gut or immune system that can predict how well someone with alcohol use disorder (AUD) might respond to treatment or show resilience. They will collect blood to examine cytokine levels and stool samples to evaluate the composition of the gut microbiome. Additionally, they will transplant fecal microbiota from individuals with early-life adversity and those without this history into young mice with no microbiota of their own. In transplanted rodents, they will evaluate behavioral and immune alterations and alcohol consumption. This may help reveal how the gut microbiome influences the immune system and behavior in people who have faced childhood adversity and struggle with alcohol use.
Basic Research

Julia Moser, Ph.D., University of Minnesota, will characterize individual trajectories of functional network organization within the first year of life, with focus on subcortical-to-cortical connectivity patterns, particularly those involved in the reward system. The goal is to account for individual variations in functional network organization and its trajectory by studying person-specific network topography and topology. The team will enroll 10 families with infants between 1-3 months for one precision imaging scanning visit and one follow up visit after 3-6 months. They will define cortical and subcortical individual functional networks in each participant, their topology (strength of connections within and between networks) and topography (size and shape of networks) and their individual trajectory from first to second visit. This project will leverage technological advances in 7T imaging for precision functional mapping in infants, to shed light on the origins of psychiatric disorders.
Basic Research

Laura Quinones Camacho, Ph.D., Dell Medical School, University of Texas at Austin, will extend her ongoing study with 3–7-year-olds to explore how parent-child neural synchrony may contribute to the intergenerational transmission of anxiety. The first aim is to examine the link between parent-child neural synchrony and child anxiety symptoms in high- vs low-anxious dyads. The second aim is to examine associations between PFC functional connectivity and anxiety symptoms in young children in high- vs low-anxious dyads. The third aim is to examine parent-child neural synchrony as a predictor of children's PFC functional connectivity in these dyads. Resting-state functional MRI data collected during fear-inducing events will inform the analysis. This research could advance our understanding of the biological mechanisms through which caregivers may influence their children's risk for anxiety. Given the importance of early interventions, findings could provide evidence of possible neurobiological mechanisms of risk that can be used to detect those likely to develop anxiety disorders and to create preventative interventions that can be implemented early in life.
Basic Research

Divyangana Rakesh, Ph.D., Institute of Psychiatry/King's College London, UK, notes that low parental socioeconomic status (SES) is associated with substantially higher risk for psychopathology in adolescents, through the impact of stress on the brain and body. The mechanistic role of pubertal and brain development in the association between low SES and risk for psychopathology remains unknown. Many adolescents from low SES backgrounds are resilient and do not develop psychopathology. Identifying factors that confer such resilience is one goal of this project. The team will capitalize on recently available large-scale population-based longitudinal data (N>11,500) and examine various biological domains, including self-report and hormone-based measures of puberty, and functional MRI, to probe how low SES influences biological development; identify mechanisms linking low SES with depression and anxiety symptoms; and identify modifiable home (e.g., parent acceptance), school (e.g., availability of extra-curricular activities), and neighborhood (e.g., community cohesion) factors that may buffer the influence of low SES on biological development and depression and anxiety.
Basic Research

Natassia Robinson, Ph.D., Karolinska Institute, Sweden, aims to identify clinical and psychosocial risk factors for early detection of borderline personality disorder (BPD), vital for guiding timely treatment interventions. She seeks to elucidate the clinical and psycho-social factors at contact with child and adolescent mental health services (CAMHS) that are predictive of subsequent diagnosis of BPD, including BPD with self-injurious behaviors and suicide. Given the early onset of the disorder and the overlap between BPD symptoms and reasons for psychiatric services referral, she hypothesizes that by examining psychosocial and clinical factors in youths, early indicators can be identified that are predictive of BPD and its more severe trajectories. The team will utilize data from several Swedish national registers which span the entire Swedish population (N>10 million). The approach will determine which clinical factors in youths experiencing mental health difficulties can be used to predict adult diagnosis of BPD, and which factors in the pre-onset period can indicate a severe disorder trajectory over a 19-year follow-up.
Diagnostic Tools/Early Intervention

Adrienne Romer, Ph.D., Virginia Polytechnic Institute and State University, is intrigued by transdiagnostic research that has identified a general psychopathology factor, called the "p-factor," that might account for comorbidity and severity across mental disorder categories. Identifying neural predictors of the p-factor would substantiate its importance in characterizing the shared origins of mental disorders and help us begin to understand the mechanisms through which the p-factor may contribute to risk, she says. Her work focuses on alterations within the cerebellum and a cerebello-thalamo-cerebro-cortical circuit (CTCC), involved in higher-order cognitive processing, in individuals with high p-factor scores. Cerebellar abnormalities have been identified in depression, bipolar disorder, schizophrenia, ADHD, and PTSD. She will explore the possibility that the cerebellum may be particularly important for transdiagnostic psychopathology during youth development as the cerebellar cortex undergoes extensive neurodevelopmental changes during adolescence and young adulthood. This study seeks to provide longitudinal perspective to examine cerebellar alterations as prospective predictors of future transdiagnostic psychopathology. Eighty adolescents aged 14-19 with low to elevated transdiagnostic symptoms but no current or past mental disorder diagnoses will participate in baseline clinical and MRI sessions and a 6-month follow-up clinical session.
Basic Research

Brenden Tervo-Clemmens, Ph.D., University of Minnesota, cites past research suggesting developmentally sensitive, striatal-reward and prefrontal- cognitive circuits, along with corresponding adolescent impulsive behavior, are central to adolescent cannabis use and therefore may serve as mechanistic targets for intervention. Integrating recent advances in precision longitudinal neuroimaging and deep phenotyping of "state-level" behavior via smartphones, this project addresses reproducibility issues in brain-behavior studies, seeking to identify person-specific "state-level" mechanisms of cannabis use disorder (CUD) recovery that are essential for future clinical translation. This project hopes to identify markers of fronto-striatal circuits during CUD treatment and compare the relative utility of "state-level" measures to traditional lab-based "trait-level" measures.
Basic Research

Michelle Thai, Ph.D., McLean Hospital, notes adolescent females with depression tend to ruminate, or think over and over about negative things, and have difficulty savoring positive events. Rumination is associated with worse depression outcomes and often persists despite treatment. Although savoring can protect against depression and increase positive mood, the brain circuitry implicated in savoring has largely been unexplored in depression. This study will investigate how brain activity differs during savoring and rumination in female adolescents with and without depression. 35 female adolescents with depression and an equal number without any psychiatric diagnoses will complete an MRI scan during which they will be presented with statements designed to elicit rumination, savoring, or a neutral control condition. The team expects to see greater activation in brain regions involved in negative affect and greater functional connectivity among brain regions involved in negative affect during rumination, and less activation in brain regions involved in

positive affect and lower functional connectivity in brain regions involved in positive affect during savoring.
Basic Research

Halide Turkozer, M.D., Harvard University/McLean Hospital, proposes we don't know enough about the biological diversity and distinct risk groups among youth at familial high risk for psychosis and psychotic disorders such as schizophrenia. This makes it hard to predict who might develop psychosis and to formulate effective ways to prevent it. The goal in this project is to identify subgroups among familial high-risk children (ages 9-10) based on neurocognitive functioning in the baseline Adolescent Brain Cognitive Development (ABCD) Study dataset. The team will investigate these subgroups' likelihood of developing psychotic-like symptoms and psychosis-related brain patterns in the 2- and 4-year follow-up data. They predict familial high-risk children who show neurocognitive impairments at baseline are at a higher risk for developing psychotic-like symptoms and psychosis-related brain patterns later in adolescence. Results could advance psychosis research by identifying a specific target group for preventative interventions during childhood.
Basic Research
Diagnostic Tools/Early Intervention

Terril Verplaetse, Ph.D., Yale University, notes that childhood trauma is one example of early-life stress that confers increased vulnerability to developing alcohol problems in adulthood, in both men and women. Childhood trauma has long lasting effects on the stress response, thereby contributing to changes at the neural systems level and dysregulation of the hypothalamic pituitary adrenal (HPA) axis. Studies of childhood trauma and alcohol use disorder (AUD) in humans have examined peripheral cortisol levels, the primary stress hormone, and results are inconsistent. Because of the discrepancy in peripheral cortisol findings, it is important to examine local production of cortisol in the brain, which is the aim of this project, using the novel radiotracer [18F] FMOZAT together with state-of-the-art PET imaging, to measure levels of 11ß-HSD1, a cortisol-regenerating enzyme, in the living human brain.
Basic Research

Lauren White, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, believes that characterizing neurocognitive risk parameters in children is critical to the study of developmental psychopathology and paves the way for novel treatment and interventions. Heightened threat sensitivity—the recognition, interpretation, and response to real or potential threat cues in the environment—is a strong neurocognitive predictor of anxiety risk. Yet little is known about how heightened threat sensitivity develops and is maintained across time. This is a novel intergenerational study of the Philadelphia Neurodevelopmental Cohort (PNC), a racially diverse cohort of ~10,000 participants assessed at ages 8–21 between 2009-2012, with many participants becoming parents in the last 5 years. In 120 mother-child dyads (children aged 4-7 years), Dr. White will use a multimethod assessment framework with psychiatric (clinical interview, self-report), behavioral (computer tasks), and neural (electroencephalogram: EEG) measures to examine the pathways underlying longitudinal and intergenerational influences on threat sensitivity and anxiety.
Diagnostic Tools/Early Intervention

Jiahe Zhang, Ph.D., Northeastern University, focuses on rumination, or the tendency to engage in repetitive thinking or dwelling on negative feelings, which contributes to major depressive disorder (MDD) onset, maintenance, and recurrence. Previous research suggests mindfulness-based real-time fMRI neurofeedback (mbNF) engages brain circuits involved in rumination and attentional problems in MDD and schizophrenia. The team will conduct a proof-of-concept study that uses closed-loop neuromodulation methodology to test the feasibility of a novel, personalized depression treatment approach for youth. They will compute individual-specific rumination markers (RMs) using in-scanner experience sampling and subsequently train participants to volitionally down-regulate RM activity via mbNF. This pilot study will recruit 15 university students with a current diagnosis of MDD and follow them longitudinally over 6 months of the school year. Each participant will attend six in-person lab sessions.
Next-Generation Therapies

DEPRESSION

Amanda Arulpragasam, Ph.D., Brown University/Ocean State Research Institute, Inc., aims to evaluate the feasibility of applying low intensity transcranial-focused ultrasound (FUS), a form of non-invasive brain stimulation, to target the dorsal anterior cingulate cortex (dACC). The aim is to observe its impact on anhedonia, the lack of motivation or inability to experience pleasure that is an important symptom of depression. The team will use fMRI task-based localization coupled with individualized targeting to examine the effects of dACC-targeted FUS on task behavior and brain perfusion in 20 patients with depression. This pilot project will provide data bearing on the feasibility of using this relatively new brain stimulation technique to modulate a brain region thought to be implicated in anhedonia.
Next-Generation Therapies

Vanessa Babineau, Ph.D., Columbia University, is interested in prenatal programming, the process by which aspects

of a pregnant person's life shape fetal development. Fetal exposure to maternal depression in pregnancy is associated with altered infant brain development, specifically amygdala network connectivity; implicated in stress processing; and associated with anxiety and depression in children and adults. The team will test whether maternal prenatal PTSD leads to altered newborn brain connectivity and whether this is associated with infant emotion regulation problems. For this research, 7,500 mother-infant pairs were recruited during pregnancy and followed postnatally. Maternal PTSD and depression were assessed in pregnancy and postpartum; newborns underwent fMRI brain scans; infant emotion regulation was assessed. Findings will inform prevention and intervention for pregnant individuals and their babies by treating PTSD in pregnancy even in the absence of depression, at a critical period for both parent and child with a two-generation impact.

Basic Research

Diagnostic Tools/Early Intervention

Miguel Barretto-García, Ph.D., Washington University, St. Louis, notes that the degree to which time "discounts" value is particularly debilitating in patients suffering from neurological disorders. In addiction, frontopolar dementia, and major depression, patients may be impulsive, make poor financial decisions, and form unhealthy lifestyle habits. Previous work has largely studied the neural circuitry controlling reward processing to account for these behavioral features, but the mechanism that incorporates reward into choice remains poorly understood. This project will investigate the neural mechanisms of the orbitofrontal cortex (OFC) in monkeys during intertemporal choice. Rhesus monkeys will choose between two options that vary on three dimensions: juice type, quantity, and delay in timing of juice delivery. The team will record and analyze neuronal activity in central OFC; analyze behavior using computational models of intertemporal choice; and analyze neuronal data by identifying encoded decision variables.

Basic Research

Mandakh Bekhbat, Ph.D., Emory University, seeks to identify novel immuno-metabolic mechanisms and biomarkers associated with deficits in reward pathways underlying symptoms of anhedonia in patients with depression. Anhedonia, a deficit in pleasure and motivation, is a core symptom of major depressive disorder thought to involve alterations in dopamine and reward circuitry. Recent evidence suggests that inflammation and metabolic disturbances may interact to contribute to anhedonia. This project tests the hypothesis that impaired glucose tolerance is associated with reward circuit deficits and lower motivation, and that these changes will map onto increased monocyte glycolysis. The aim is to reveal metabolic mechanisms in both the brain and peripheral immune cells that may underlie symptoms of anhedonia, while establishing a set of functional biomarkers to inform future strategies to reverse the effects of inflammation-related glucose dysfunction on the brain and behavior.

Basic Research

Diagnostic Tools/Early Intervention

Mirjam Bloemendaal, Ph.D., Johann Wolfgang Goethe University, Germany, hypothesizes that bacteria in the gut play a role in antidepressant treatment resistance. The gut microbiome is the collection of trillions of bacteria living in the gut and has many functions in the body that are important for our health. Along the "gut-brain-axis," gut microbiota interact with the central nervous system. Some bacteria can't grow in the presence of antidepressant medication in the gut, leading to a change in the equilibrium of the gut microbiome. This change may contribute to treatment resistance. This project will compare the gut microbiota in feces of depressed patients who do and do not respond well to antidepressant treatment; their function in the gut will be characterized, for instance with respect to serotonin production. Results could help inform interventions such as probiotics, intended to protect gut microbiota from any negative effects of antidepressants and thereby improve treatment response.

Basic Research

Johnathan Borland, Ph.D., University of Minnesota, notes that rewarding social interactions, such as asserting oneself, defending one's home territory, or dominant-subordinate relationships, can have beneficial effects on mental and physical health. He proposes they can be mobilized to treat psychiatric disorders. This project investigates the neurobiological underpinnings of dominant interactions and asks whether they manifest differently in males and females. Preliminary data suggests that after repeat "dominance" experiences, females, but not males, display greater calcium signaling in the nucleus accumbens. This study will investigate if dominant interactions differentially impact the reward system in males and females, and if the underlying neurobiology in the mesolimbic dopamine reward circuit is different in males and females.

Basic Research

Alexei Bygrave, Ph.D., Tufts University, is studying a gene that encodes a protein called tumor necrosis factor receptor associated factor 3 (Traf3), variations of which have been linked to elevated risk for major depressive disorder (MDD) and suicidal thoughts and behaviors. Traf3 has scarcely been studied in the brain, though it is known to be an important signaling adaptor molecule in immune cells. This project tests the hypothesis that Traf3 regulates the properties of glutamatergic synapses received by parvalbumin interneurons, thus perhaps meaning that the protein can confer psy-

chiatric risk. The team will first test if Traf3 regulates the stability of glutamatergic synapses in inhibitory interneurons, then evaluate if mice with Traf3 genetically "knocked out" in parvalbumin inhibitory interneurons exhibit behavioral characteristics relevant to mood disorders such as MDD.
Basic Research

Simon Chang, Ph.D., University of Regensburg, Germany, notes that the dopamine (DA) system and midbrain structures such as the ventral tegmental area (VTA) play a pivotal role in the hedonic deficits seen in major depression, affecting motivation and the ability to seek or experience pleasure. The network regulating dopamine biology in the VTA is not fully understood. Research has suggested an area called the interstitial nucleus of the posterior limb of anterior commissure, lateral (IPACL) may contribute to emotion, addiction, and metabolism. Dr. Chang has observed a potential closed-loop circuit between IPACL and the VTA. This project will use rodents to investigate the interplay between the inhibitory neurotransmitter GABA and dopamine in closed loop circuits between IPACL and VTA following exposure to chronic social defeat stress and development of anhedonia. Do changes in the activity of this circuit directly affect anhedonia? The team will study molecular changes occurring after circuit manipulations with hopes of dissecting a mechanism associated with stress-induced anhedonia.
Basic Research

Roselyne Chauvin, Ph.D., University of Washington, seeks to characterize sleep-wake mechanisms leading to alterations of functional brain networks, in the hope of obtaining insights that can inform development of new treatments to correct these network changes—possibly linked to the symptom of anhedonia—in people with major depressive disorder (MDD). This project specifically aims to identify circuits in the nucleus accumbens (NAcc) underlying anhedonia and sleepiness. This could enable the team to track circuit alterations more accurately in MDD patients. The concept stems from the lab's pilot studies demonstrating that tracking sleepiness during functional magnetic resonance imaging (fMRI) facilitates tracking and localizing NAcc circuitry affected by sleepiness, which in turn partly overlaps with circuits affected by anhedonia.
Basic Research

Austin Coley, Ph.D., University of California, Los Angeles, is interested in a "lack of granularity" in diagnostic practices. For example, a patient who is sleeping and eating too much may be prescribed the same medicine as one who is sleeping and eating too little. Could this be a factor in efficacy of antidepressants? Dr. Coly will try to discover the answer in the context of anhedonia symptoms. The lab has developed an acute severe stress model (learned helplessness) in rodents to induce anhedonia. Measurements of social behavior as well as consummatory pleasure are used to assess hedonic values. Various methods are used to then manipulate activity within neural pathways. This allows the team to identify and longitudinally track neurons encoding both reward and aversive stimuli within the medial prefrontal cortex, while selectively activating input-specific neurons via optogenetic photostimulation during anhedonic conditions.
Basic Research

Katharine Dunlop, Ph.D., Unity Health Toronto, Canada, says the brain ages differently for each person, and how it does may reveal more about health risks than chronological age alone. The team will use advanced brain imaging to study brain aging in major depressive disorder (MDD). They will examine data from over 3,000 depressed and healthy individuals, collected from numerous trials across five countries through the COORDINATE-MDD consortium. Using algorithms to predict brain age, they hope to identify specific brain regions associated with accelerated aging. This may allow them to identify specific brain aging-related changes associated with different symptoms of depression and cognitive impairments. They will also explore whether combining different depression symptoms and brain aging patterns can help classify MDD into distinct subtypes. This could indicate whether certain subtypes of MDD show more pronounced brain aging than others and open the question of how they may respond differently to treatments.
Diagnostic Tools/Early Intervention

Franco Giarrocco, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that in major depression and OCD, alterations have been observed in the brain's ability to either acquire or properly use the appropriate motivational values of stimuli and actions. The cortico-basal ganglia circuitry is likely the most important motif of the brain mediating these functions. Dr. Giarrocco hypothesizes that the brain encodes multiple representations of stimulus and action values across different motor systems, and that the learning process relies on the dynamic interaction among value representations across the cortico-basal ganglia network. To test this, the team will perform simultaneous, large-scale neuronal recordings across motivational and motor areas within cortico-striatal-pallidal circuits in non-human primates performing a task in which they learn the value of visual stimuli. Challenging current theories, the team aims to lay groundwork for novel hypotheses on how dysfunctions within this circuitry contribute to MDD and OCD.
Basic Research

Zachary Harvanek, M.D., Ph.D., Yale University/Yale University School of Medicine, will address a gap in our understanding of the response to stress at the molecular level by investigating the role of DNA methylation in acute stress responses among trauma-exposed individuals. The team will

add epigenetic measures to data from an existing cohort of 138 individuals with a varied range of past traumatic experiences who underwent laboratory sessions including stress-cue and neutral cue conditions followed by measures of anxiety and HPA-axis signaling and up to 2 years of follow up for psychiatric symptomatology. Using these added epigenetic measures, the team will examine the association between baseline DNA methylation of HPA axis-related genes, specifically FKBP5 and NR3C1, and post-stress anxiety levels, HPA-axis signaling, and longitudinal depression and anxiety. Mediation analyses will test whether DNA methylation links trauma history to these outcomes.

Basic Research

Maryam Hasantash, Ph.D., Columbia University, notes that cognitive flexibility may promote stress resilience by enabling the flexible adjustment of cognitive or behavioral strategies to efficiently cope with stressful experiences. This work proceeds from the notion that if we can understand the neural circuits underlying cognitive flexibility, we may be able to identify new targets for advanced therapeutics to treat the debilitating cognitive impairments in multiple psychiatric disorders. Dr. Hasantash has identified projections from the ventral CA1 (vCA1) region of the hippocampus to the medial orbitofrontal cortex (mOFC) as a novel neural circuit component crucial for reversal learning, an important form of cognitive flexibility This study will test a novel role for vCA1-mOFC projections in regulating individual differences in stress vulnerability. Results have the potential to reveal new neural circuit-based targets for novel drugs or for advanced cognitive-behavioral therapies aimed at improving cognitive flexibility as a means to reduce stress-induced psychiatric disorders.

Basic Research

Zoe Hawks, Ph.D., McLean Hospital, reasons that depressed mood will increase when individuals feel lonely and/or isolated, and hypothesizes that cognition will buffer this association, such that depressed mood is less impacted by loneliness and isolation in moments when individuals are highly attentive and quickly responsive. However, what is true in general is likely not true of all individuals. In addition to identifying social and cognitive risk factors that predict depression, this project will use data-driven approaches to characterize dynamic patterns of social and cognitive information processing that predict depression within specific subgroups of people. This innovative approach could advance mechanistically informed subtyping in depression and holds promise to identify personalized targets for behavioral intervention.

Diagnostic Tools/Early Intervention

Sarah Herzog, Ph.D., Columbia University, proceeds from evidence in peripheral blood, cerebrospinal fluid (CSF), postmortem brain tissue, and neuroimaging studies demonstrating a role for altered excitatory glutamate (Glu) and inhibitory GABA neurotransmission in the pathogenesis of suicidal behavior in depressed individuals. While the precise mechanism linking Glu/GABA to suicide risk is unclear, a potential link in this relationship may implicate physical pain processing. This project will use functional magnetic resonance spectroscopy in 50 currently depressed subjects with and without a recent history of suicidal behavior to establish: 1) whether suicidal behavior in depression is associated with altered Glu/GABA concentrations in the anterior cingulate cortex (ACC); 2) whether pain-responsive dynamic brain Glu/GABA activity in the ACC differs as a function of history of suicidal behavior; and 3) the relationship of pain-responsive dynamic brain Glu/GABA activity in the ACC to subjective pain ratings and pain tolerance.

Basic Research

Orna Issler, Ph.D., New York University, has performed an initial exploration of the contribution of long non-coding RNAs (lncRNAs) to depression, and discovered robust regulation of lncRNAs in post-mortem brain tissue of cases compared to a control. But little is known about the cell type-specific role of lncRNAs in depression, particularly in astrocytes, a prevalent glial cell in the brain. While there is evidence for dramatic structural and functional changes in astrocytes in depression and chronic stress, no comprehensive studies have focused on the roles of lncRNAs in astrocytes in depression. Dr. Issler will focus on EMX2OS, an astrocyte-enriched lncRNA which is downregulated in the medial frontal cortex (mPFC) in postmortem brain samples of depressed men. In living mice, the team will try to demonstrate the role of EMX2OS, hypothesizing that stress will compromise multiple features of astrocyte morphology and that EMX2OS will attenuate these negative effects.

Basic Research

Liat Itzhaky, Ph.D., Columbia University, is interested in the safety planning intervention (SPI), a brief, protocol-driven suicide prevention tool that assists the individual at suicide risk in recognizing and knowing their warning signs for an emerging suicidal crisis. It also helps the person identify personalized coping strategies, based on the elements of distraction and interpersonal support, to employ to stop the escalation of the crisis and prevent suicidal behaviors. The effectiveness of using the SPI's coping strategies has never been evaluated in adolescents, and mediators of its effect on mitigating suicide risk are unknown. This project seeks to evaluate the effectiveness of using the SPI's coping strategies to reduce suicidal ideation severity, frequency, and duration among depressed adolescents and to examine the mediating effect of stress reduction. The hypothesis is that the use of distraction strategies and interpersonal support, established

through the use of the SPI, will reduce the experience of stress and, thus, decrease suicide risk. A randomized control trial will be conducted with 88 depressed adolescents.
Diagnostic Tools/Early Intervention

Arielle Keller, Ph.D., University of Pennsylvania, will test whether differences in brain network development at the critical transition from childhood to adolescence predispose some (but not all) individuals to executive dysfunction and a greater risk for symptoms of depression and anxiety. This project will leverage big data from a large-scale study of >10,000 youths called the Adolescent Brain Cognitive Development (ABCD) Study. It will apply cutting-edge computational methods to characterize each individual's unique transition from childhood to adolescence. This will facilitate investigating patterns of brain network development during the transition from childhood to adolescence in order to better understand the emergence of executive dysfunction and risk for depression and anxiety. Understanding the person-specific patterns of brain development that may lead some individuals but not others to develop executive dysfunction have the potential to facilitate the development of more targeted treatments and preventions of depression and anxiety in youth.
Diagnostic Tools/Early Intervention

Bora Kim, M.D., Stanford University, seeks to trace the neural network effects of intermittent theta burst stimulation, a rapid-acting non-invasive brain stimulation therapy that has been very effective in treating major depression. A targeted and accelerated version of iTBS (aiTBS) in which treatments are given over 5 days is the basis of Stanford Neuromodulation Therapy (SNT), approved in 2023 by the FDA for commercialization. It might be considered a rapid anti-suicide modality; however, evidence of its mechanism regarding its stimulation effect on reducing suicidality is still understudied. This study aims to bridge this gap by investigating the neural network effects of aiTBS on improvement in suicide-related symptoms. Through a comprehensive whole-brain approach analysis of functional connectivity patterns, the team seeks to examine suicide-specific neural networks that benefit from aiTBS. They will utilize an existing dataset from a randomized controlled study applying SNT to treatment-resistant depression.
Next-Generation Therapies

Esther Klingler, Ph.D., VIB-KU Leuven Center for Brain & Disease Research, Belgium, notes emotional dysregulation is observed in many neuropsychiatric disorders, including anxiety disorders, and can be promoted by early life stress (ELS). Connectivity between the basolateral amygdala (BLA) and prefrontal cortex (PFC) has an important role in anxiety. However, the development of BLA-PFC connectivity, and the interplay between intrinsic genetic programs and extrinsic environmental stressors are poorly understood. This project aims to explore the function of genes and environment in the development of BLA-PFC connectivity at molecular, cellular, and behavioral levels. The hypothesis is that specific genes control the development of BLA-PFC connectivity postnatally, and that ELS impacts the expression of these genes, thereby altering BLA-PFC connectivity. The team will (1) identify dynamic molecular programs at play during the development of BLA-PFC connectivity, by combining axon tracing and single-cell RNA sequencing; (2) investigate the role of select genes and their potential to rescue ELS-associated defects, by manipulating their expression.
Basic Research

Sangjun Lee, Ph.D., University of Minnesota, proceeds from a hypothesis suggesting cognitive impairment in major depression arises from an abnormality in brain connectivity between the frontal and parietal cortical regions. During cognition, cortical traveling waves emerge as a neural oscillation pattern in the frontoparietal cortex. Traveling waves consist of spatially coherent oscillations characterized by a gradual phase shift of brain oscillations across the cortex. According to Dr. Lee, it would be fruitful to establish a causal link between a phase shift of traveling waves in the frontoparietal network and impaired cognition. This project seeks to test the feasibility of manipulating traveling waves through noninvasive brain stimulation, which could represent a promising technique for alleviating cognitive impairment. In a double-blinded, placebo-controlled, randomized trial, Dr. Lee hopes to apply traveling wave stimulation to participants to manipulate traveling waves in the frontoparietal cortex while they perform two cognitive-related tasks (attention and memory tasks).
Next-Generation Therapies

Hsiang-Yuan Lin, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, is conducting a clinical trial to explore psilocybin-assisted therapy for treatment-resistant depression (TRD) in adults with autism spectrum disorder (ASD). Dr. Lin says this will provide a unique opportunity to adopt a "dense-sampling" approach to investigate antidepressant actions. Neuroimaging studies that densely sample the individual brain (i.e., repeatedly scanning a given individual in combination with repeated behavioral/psychological/physiological measures)—as contrasted with a cross-sectional group-averaging approach—are well-suited, Dr. Lin says, for investigating relationships between brain dynamics and behavioral/psychological variables (states) that vary over relatively short time scales. In a subset of a larger trial, 10 intellectually able/speech-fluent adults with ASD and TRD (aged 18-65 years) who are enrolled in the

main trial will receive 8 additional brain functional magnetic resonance imaging (MRI) scans in addition to two MRI scans required in the main clinical trial (given pre- and post-psilocybin administration).

Basic Research

Next-Generation Therapies

Clara McCarthy, Ph.D., Vanderbilt University, notes that human studies using PET neuroimaging suggest a relationship between ketamine's administration in major depression and the availability of metabotropic glutamate receptors type 5 (mGluR5) that correlates with the antidepressant response to ketamine. She proposes to study the role of mGluR5 signaling on the molecular pathways that trigger ketamine-induced synaptic potentiation and behavioral effects. Preliminary results suggest that synaptic activation of mGluR5 signaling drives calcium-signaling events spatially segregated from those triggered by NMDA receptor activity. This concomitant mGluR5 activity may be critical for ketamine-induced synaptic potentiation in hippocampal slices. These findings suggest that mGluR5 signaling is one of the key targets for ketamine that links ketamine with synaptic potentiation and, ultimately, to rapid antidepressant action. Elucidating this aspect of ketamine action could provide a new perspective on design of effective rapidly acting antidepressants to alleviate depression.

Basic Research

Next-Generation Therapies

Kahlilia Morris-Blanco, Ph.D., University of Pennsylvania, has focused on understanding how epigenetic enzymes known as TETs contribute to emotional challenges after a stroke. The team seeks to understand how TETs either help the brain become more resilient or make it more vulnerable to anxiety and depression after a stroke. To answer this, they will manipulate levels of TET enzymes in mice. Recent advancements in technology enable determination of the impact of epigenetic molecular switches more precisely in different cells of the brain. The team seeks to determine which genes are expressed in areas of the brain implicated in anxiety and depression. They also will observe mood behaviors in the mice to understand if changes in TET enzymes affect emotional states like anxiety and depression. Insights gained could lead to innovative therapies that improve mental health and enhance recovery for people who experience a stroke.

Basic Research

Suzanne Nolan, Ph.D., Vanderbilt University, studies the mesolimbic dopamine system, implicated in the etiology of substance use disorder, schizophrenia, and major depression. Dopamine release in the nucleus accumbens (NAc) terminals and input-mediated plasticity upstream of cell bodies within the ventral tegmental area (VTA) have been explored. This project seeks to probe the role of non-canonical forms of release such as somatodendritic release at the level of cell bodies in the VTA, a part of midbrain dopamine (mDA) release. Specifically, she will study how mDA release relates to time-locked behavioral events and its overall functional significance in the specific context of reward learning. The work will test the hypothesis that mDA release is a distinct axis of mesolimbic dopamine signaling, and therefore represents a novel target for therapeutic control of motivated behaviors.

Basic Research

Marco Pagliusi Jr, Ph.D., University of São Paulo, Brazil, notes chronic pain is not usually recognized as a typical symptom of depression, yet epidemiological studies show a strong association between the two. He proceeds from his recent finding uncovering a novel function of the rostral ventromedial medulla (RVM), a key structure for the descending pain modulatory system, in stress-related behavioral impairments. Aiming to uncover new pathways in the RVM's contribution to chronic stress-induced behavioral impairments, he will investigate the contribution of RVM-targeting structures, including the periaqueductal gray (PAG) and anterior cingulate cortex (ACC), to behavioral impairments induced by chronic stress. He hopes thereby to bridge a gap in our understanding of the neurobiological mechanisms underlying the comorbidity between depression and chronic pain.

Basic Research

Mohammed Mostafizur Rahman, Ph.D., Harvard University, seeks greater understanding of the molecular mechanisms governing the neuronal circuits orchestrating parenting behavior. This project aims to merge deep brain calcium imaging with spatial transcriptomics to delve into the molecular properties of functionally segregated clusters of neurons within the medial preoptic area (MPOA) of the hypothalamus. These distinct functional clusters encode the timing of various parenting behaviors in rodents, such as pup retrieval, grooming, and interaction during adult-pup sessions. Importantly, they exhibit unique gene expression patterns enabling differential interactions with hormones. The hope is to uncover molecular alterations within MPOA neuronal clusters, shedding light on the mechanisms underlying physiological modulation leading to behavioral aberrations in stressed mice. Ultimately, the team endeavors to pave the way for innovative interventions tailored to alleviate the burdens of postpartum depression on both maternal caregivers and their offspring.

Basic Research

Divyangana Rakesh, Ph.D., Institute of Psychiatry/King's College London, UK, notes that low parental socioeconomic status (SES) is associated with substantially higher risk for psychopathology in adolescents, through the impact of stress

on the brain and body. The mechanistic role of pubertal and brain development in the association between low SES and risk for psychopathology remains unknown. Many adolescents from low SES backgrounds are resilient and do not develop psychopathology. Identifying factors that confer such resilience is one goal of this project. The team will capitalize on recently available large-scale population-based longitudinal data (N>11,500) and examine various biological domains, including self-report and hormone-based measures of puberty, and functional MRI, to probe how low SES influences biological development; identify mechanisms linking low SES with depression and anxiety symptoms; and identify modifiable home (e.g., parent acceptance), school (e.g., availability of extra-curricular activities), and neighborhood (e.g., community cohesion) factors that may buffer the influence of low SES on biological development and depression and anxiety.
Basic Research

Soroosh Sanatkhani, Ph.D., Columbia University, is using low-intensity focused ultrasound (LIFU) to modulate the anterior cingulate cortex (ACC), a brain region involved in emotional regulation and cognitive control and dysregulated in depression. Using mice that are exposed to chronic stress to mimic major depression, the team will use a combination of advanced imaging methods to investigate how LIFU changes blood flow, brain cell activity, and network dynamics of the ACC. They hypothesize that the ACC responds differently to LIFU depending on the parameters of the ultrasound waves, such as their frequency, intensity, and duration. They hypothesize that these changes are mediated by different pathways and mechanisms. This knowledge will help them develop a treatment paradigm to restore normal function disrupted in major depressive disorder.
Next-Generation Therapies

Karel Scheepstra, M.D., Ph.D., Amsterdam University Medical Centers, The Netherlands, will investigate reduced numbers of synapses in people with treatment-resistant depression, using PET scans featuring a new ligand that binds to synapses. Patients being treated with ECT will undergo two scans: one scan before ECT and one after completing the treatment. The aim is to show that ECT restores synapses in the brain. This is the first study using this new brain scan and will hopefully shed new light on the working mechanisms of ECT.
Basic Research
Next-Generation Therapies
New Technologies

Tien Hong Stanley Seah, Ph.D., University of Pittsburgh, says sexual- and gender-minority young adults (SGMYA) are disproportionately impacted by depression. Neurobiological processes underlying these disparities and associated protective factors are understudied. Peer rejection experiences, a potent risk factor for depression and particularly salient for SGMYA, may provide a unique social context for understanding depression inequities. Altered neural activation and functional connectivity during social rejection in the social pain network encompassing the dorsal anterior cingulate cortex (dACC) and anterior insula (aINS) may exacerbate risk for depression. This project leverages an ongoing longitudinal study of high-risk SGMYA (N=100) that will provide 1) fMRI data on neural and emotional responses to real-world peer rejection, and 2) 6-month ecological momentary assessment of emotion differentiation. The aim is to test how reactivity to social rejection interacts with negative emotion differentiation to predict depressive symptoms.
Basic Research

Urszula Skupio, Ph.D., Research Foundation for Mental Hygiene, Inc./NKI, notes that social buffering, the phenomenon by which the presence of others can reduce the negative consequences of stressful experiences, has been observed in both humans and rodents, yet the precise mechanisms by which social interactions can offset the impact of stress on the development of depressive symptoms such as anhedonia remain elusive. In the face of the loneliness crisis, understanding neural circuitry behind social buffering could pave the way for innovative treatment. This project will monitor real-time activity of dopamine and GABA neurons in the ventral tegmental area (important in reward processing) during restraint stress, social interaction, and a subsequent reward-based task. The team will selectively manipulate these neuronal populations in behaving animals, elucidating their causal relationship in mediating the effects of social interaction on stress and reward-seeking behaviors. They will also modulate dopamine and/or GABA neurons in the ventral tegmental area in behaving mice hoping to bolster resilience.
Basic Research

Rachel June Smith, Ph.D., University of Alabama at Birmingham, will map connectivity networks in epilepsy patients with depression using electrical stimulation. Over 30% of patients with drug-resistant epilepsy also suffer from depression. Neural networks that are common in epilepsy often overlap with those associated with depression, but the causal relationships indicative of which brain regions impose the pathological activity on other brain regions have not been revealed. The team will use single-pulse electrical stimulation (SPES) to map depression-effective connectivity networks in epilepsy patients and infer potential deep-brain stimulation strategies optimized for treatment-resistant depression. The hypothesis is that pathologically strong connections from the limbic structures (i.e., the hippocampus and amygdala) will produce large cortico-cortical evoked potentials and increased high frequency power in cortico-cortical spectral

responses in depression-relevant brain structures.

Next-Generation Therapies

Basic Research

Benjamin Spurny-Dworak, Ph.D., Medical University of Vienna, Austria, will perform direct evaluation of serotonin deficit in major depressive disorder (MDD) using tryptophan deuterium magnetic resonance spectroscopy. While PET is capable of quantifying serotonin receptors, transporters, or enzymes involved in its metabolism, measures of direct neurotransmitter content have been unsuccessful. Hydrogen magnetic resonance spectroscopy (1H-MRS), an MR-based method, offers the possibility for the non-invasive in vivo quantification of the main neurotransmitter GABA and glutamate levels among other metabolites in the human brain. To extend the use of 2H-MRS and finally receive direct insights into serotonin metabolism of the brain in MDD patients, the team aims to compare serotonin metabolism for the first time in humans between MDD patients and a control cohort using D-tryptophan 2H-MRS. Among other things, this work might provide evidence for or refute the monoamine hypothesis in depression and investigate potentially altered serotonin metabolism in psychiatric conditions. In subsequent clinical studies, the team will assess treatment effects on serotonin metabolism after different pharmacological or biological psychiatric interventions.

Basic Research

New Technologies

Brian Sweis, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, will perform research rooted in principles of neuroeconomics, an emerging field of decision science that quantifies how the brain constrains complex choices, how circuits encode reward value, and how this is influenced by one's affective state. He has developed a set of neuroeconomic decision-making tasks validated for use in mice, rats, monkeys, and humans, offering novel approaches to study decision-making in a manner that is biologically tractable and readily translatable across species. These efforts shed light on how individuals weigh the consequences of prior choices when making future decisions. The team will record, in animals, the activity of large populations of single neurons from key structures in the brain's reward system implicated in stress and decision-making information processing. They hypothesize neurons linked to previously stressful episodes will causally drive the influence of regret on future behavior. This project could enhance our understanding of how depression can distort the lens through which individuals perceive their past actions.

Basic Research

Hwei Ee Tan, Ph.D., Nanyang Technological University, Singapore, says that the community of microorganisms living in our gut plays a role in the development of depression. While emerging evidence reveals that imbalances in gut bacterial composition are causally linked to depression, less is known about the biological interactions between stress and those resident microorganisms. Presuming that the gut-brain axis is bidirectional, the team hypothesizes that mental stress induces gut microbial imbalances via descending brain-gut pathways. Building on their expertise in the mammalian gut-brain axis, they will test this central hypothesis to provide proof of concept for further inquiry into the "top-down" brain-to-gut dialogue: characterizing gut microbiota changes under stress; and defining neural substrates of stress that influence the microbiome and metabolome. This could provide a framework to uncover how certain foods or supplements such as probiotics may reverse the gut bacterial imbalances linked to stress and depression.

Basic Research

Michelle Thai, Ph.D., McLean Hospital, notes adolescent females with depression tend to ruminate, or think over and over about negative things, and have difficulty savoring positive events. Rumination is associated with worse depression outcomes and often persists despite treatment. Although savoring can protect against depression and increase positive mood, the brain circuitry implicated in savoring has largely been unexplored in depression. This study will investigate how brain activity differs during savoring and rumination in female adolescents with and without depression. 35 female adolescents with depression and an equal number without any psychiatric diagnoses will complete an MRI scan during which they will be presented with statements designed to elicit rumination, savoring, or a neutral control condition. The team expects to see greater activation in brain regions involved in negative affect and greater functional connectivity among brain regions involved in negative affect during rumination, and less activation in brain regions involved in positive affect and lower functional connectivity in brain regions involved in positive affect during savoring.

Basic Research

Nicholas Trapp, M.D., University of Iowa, notes difficulties faced by clinicians in trying to distinguish a major depressive episode from other causes of depressive symptoms and trying to assess treatment response. This project will study EEG biomarkers of depression symptom severity in 3 samples: 1) patients with major depressive disorder; 2) patients undergoing a noninvasive form of brain stimulation (TMS) for treatment of a major depressive episode; and 3) patients with intracranial electrodes and scalp EEG combined. Biomarkers could be an invaluable clinical tool for the personalized assessment of depression symptoms and response to treatment. In the future this could be combined with targeted brain stimulation procedures, both invasive and noninvasive, to provide an immediate "read-out" of symptoms that could

guide adjustments and optimization of stimulation parameters with direct or indirect clinician supervision.
Diagnostic Tools/Early Intervention

Najah Walton, Ph.D., Tufts University, is exploring the potential of novel neurosteroidogenic biomarkers as predictors of stress-induced psychiatric disorders. Recent advancements in therapeutic strategies, particularly neurosteroid analogs of allopregnanolone, have demonstrated rapid and sustained anxiolytic and antidepressant effects in psychiatric disorders. It is important to determine which individuals will respond to allopregnanolone-based treatments. Dr. Walton's team has demonstrated the impact of chronic stress on neurosteroid synthesis and subsequent network dysfunction in the amygdala. This study will deploy a novel neurosteroidogenic biomarker screening tool to detect neurosteroid markers from various tissue samples obtained from individuals with major depression, PTSD, and generalized anxiety disorder. The hope is to synergistically illuminate molecular dynamics while offering a comprehensive view of neurosteroid production from gene expression to protein synthesis. The team expects to observe reductions in neurosteroid levels in a subset of individuals with a psychiatric diagnosis compared to controls.
Basic Research

Bo Wang, Ph.D., Harvard University/Massachusetts General Hospital, aims to develop and validate phenotyping and prediction models for accurate detection of postpartum depression (PPD) and early identification of individuals at high risk of PPD. Recent advancement in large language models (LLMs) offers an opportunity to develop precise phenotypes without substantial annotated data or billing codes in the electronic health records (EHRs). The team will develop an LLM-based model to identify PPD cases in Mass General Brigham (MGB), a large healthcare system consisting of approximately 7 million patients from 8 hospitals. They also will develop and validate sequential machine learning models such as neural ordinary differential equation (neural ODE)-based models, for risk estimation of a new mother developing PPD within one year postpartum. Finally, they will examine whether prediction performance improves by incorporating social determinants of health and genetic data in their model.
Diagnostic Tools/Early Intervention

Junsung Woo, Ph.D., Baylor College of Medicine, wants to know more about how astrocytes contribute to circuit dysfunction associated with depression. The team has reported that astrocyte transcription factor NFIA plays an essential role in the physiological activities of astrocytes, neuronal circuit activity, and brain function in the adult hippocampus. This has led to the hypothesis that astrocytic NFIA contributes to depression and associated suicide by regulating amygdala circuit function. To determine whether astrocytic NFIA affects amygdala circuit function and associated depressive behaviors, the team uses NFIA gain-of-function (GOF) and loss-of-function (LOF) mouse models. In this project, they will dissect amygdala-specific NFIA transcriptional networks and confirm this in human samples. They seek to determine the role of astrocytic NFIA in amygdala circuit activity and function using NFIA GOF and LOF mice models. Further, they hope to decipher how astrocytic NFIA regulates amygdala circuits through the GABA-MAOB pathway. (MAOB is a monoamine metabolizing enzyme.) They seek to identify the target gene of NFIA using RNA sequencing and manipulate the target gene with pharmacological and genetic tools.
Basic Research

Ye Wu, Ph.D., University of California, Los Angeles, is interested in prosocial behaviors such as comforting, helping, and resource sharing, to improve others' conditions. These capacities are crucial for enhancing social connections and are evolutionarily conserved from humans to rodents. Deficits in the abilities to perceive others' emotional states and/or to form and maintain positive social relationships are prominent symptoms in a range of neuropsychiatric conditions, including depression, social anxiety disorder, psychopathy, and autism. Dr. Wu seeks to integrate approaches that span behavioral, circuit, and computational levels to further elucidate the neural circuitry underlying prosocial comforting behavior and investigate its potential disturbance in a mouse model relevant to depression. Specifically, the aim is to identify brain areas that function downstream of the pathway between the medial amygdala (MeA) and medial preoptic area (MPOA) in encoding and regulating prosocial interaction. The team also seeks to determine whether prosocial interaction is compromised in a mouse model of chronic social stress and whether such changes are linked to altered activation patterns in the MeA-MPOA pathway.
Basic Research

Jiahe Zhang, Ph.D., Northeastern University, focuses on rumination, or the tendency to engage in repetitive thinking or dwelling on negative feelings, which contributes to major depressive disorder (MDD) onset, maintenance, and recurrence. Previous research suggests mindfulness-based real-time fMRI neurofeedback (mbNF) engages brain circuits involved in rumination and attentional problems in MDD and schizophrenia. The team will conduct a proof-of-concept study that uses closed-loop neuromodulation methodology to test the feasibility of a novel, personalized depression treatment approach for youth. They will compute individual-specific rumination markers (RMs) using in-scanner experience sampling and subsequently train participants to volitionally down-regulate RM activity via mbNF. This

pilot study will recruit 15 university students with a current diagnosis of MDD and follow them longitudinally over 6 months of the school year. Each participant will attend six in-person lab sessions.

Next-Generation Therapies

Tingxin Zhang, Ph.D., University of Texas Southwestern Medical Center at Dallas, proceeds from research showing a reduction in myelin volume in various brain regions in major depressive disorder (MDD) patients, suggesting the involvement of myelination in the etiology of MDD and other depression-related disorders. Within the mammalian central nervous system, oligodendrocytes mediate myelination. Recent research indicates that myelin not only provides insulation for axons, but also offers critical trophic support for them. Dr. Zhang will create a mouse model to genetically map myelin patterns at single-axon resolution. By utilizing these mice, the team will determine myelin pattern changes in various neuron cell types at the single-axon level across multiple brain areas, such as the lateral prefrontal cortex, medial prefrontal cortex, and nucleus accumbens, in multiple MDD mouse models. They will then employ in vivo proximity labeling to explore the oligodendrocyte-axon interactome network in MDD mouse models to elucidate the molecular mechanisms underlying myelin dysfunctions in MDD patients. They will also test whether genetic manipulations can prevent or reverse depression-like behaviors in MDD mouse models.

Basic Research

Qiancheng Zhao, Ph.D., Yale University, notes that diabetes is often associated with mental health challenges such as anxiety and depression. The pancreas, a vital organ for maintaining metabolic homeostasis, is tightly controlled by the nervous system. Serving as a crucial link between the body and the brain, the vagus nerve plays pivotal roles in regulating insulin release, glucose homeostasis, and mental well-being. This underscores the potential of targeting vagal pathways to address both diabetes and related mood disorders. This project aims to investigate the vagal pathways underlying communication between the pancreas and the brain and its implications for diabetes and mental health. The proposed study is expected to provide insights into pancreas-brain crosstalk and may inform innovative neural modulatory approaches to precisely regulate metabolism and address associated mental health issues.

Basic Research

Yangzhi Zhu, Ph.D., Terasaki Institute for Biomedical Innovation, seeks to develop a new lab-on-a-contact lens (LoCL) telemedicine monitoring tool for home-based, non-invasive, multiplexed analysis of mental health. The central hypothesis is that a judiciously designed wireless LoCL platform integrated with multiplexed biosensors, as a home-based digital biomedical device, provides real-time noninvasive monitoring of physiological biomarkers (serotonin and cortisol), effectively tracking mental health status and significantly promoting early diagnosis/intervention/management of mental disorders. The team will develop a wireless LoCL platform that simultaneously monitors serotonin and cortisol dynamics from tears. They will ask: What is the feasibility of detecting serotonin and cortisol changes through LoCL? What is the efficiency of wireless data transmission? What is the stability of the LoCL in tear analysis? What is the biosafety of the LoCL? They hope then to conduct in-clinic examinations of the LoCL in human pilot studies, adding LoCL to an ongoing rTMS clinical trial for depression.

Diagnostic Tools/Early Intervention

New Technologies

EATING DISORDERS

Miguel Barretto-García, Ph.D., Washington University, St. Louis, notes that the degree to which time "discounts" value is particularly debilitating in patients suffering from neurological disorders. In addiction, frontopolar dementia, and major depression, patients may be impulsive, make poor financial decisions, and form unhealthy lifestyle habits. Previous work has largely studied the neural circuitry controlling reward processing to account for these behavioral features, but the mechanism that incorporates reward into choice remains poorly understood. This project will investigate the neural mechanisms of the orbitofrontal cortex (OFC) in monkeys during intertemporal choice. Rhesus monkeys will choose between two options that vary on three dimensions: juice type, quantity, and delay in timing of juice delivery. The team will record and analyze neuronal activity in central OFC; analyze behavior using computational models of intertemporal choice; and analyze neuronal data by identifying encoded decision variables.

Basic Research

Maxime Chevee, Ph.D., Vanderbilt University, proposes in the context of eating disorders that the psychological effects induced by imbalances in feeding result from changes in the fundamental mechanisms of learning. At the center of learning and internal state-dependent modulation of behavior is dopamine release and regulation in the striatum. Her data indicate that food restriction specifically enhances the dopamine response to movement in the dorsomedial striatum (DMS), while dopamine release evoked by salient external stimuli remains constant. The central question of this project is: what is the mechanism by which food restriction alters dopamine release in response to specific stimuli but not others, and how do these effects impact learning? Results could identify the cell type-specific effects of changes in

energy balance on the dopaminergic system and reveal which molecular pathways hold promise as therapeutic targets.
Basic Research

Alexandre Fisette, Ph.D., Université du Québec à Trois-Rivières Canada, will focus on the intriguing interplay between hypothalamic perineuronal nets (PNNs) and Agouti-related protein-expressing (Agrp) neurons, addressing their potential role in eating disorders, encompassing both obesity and anorexia nervosa. Agrp neurons, pivotal in energy balance regulation, exhibit a dual nature implicated in hyperphagia and anorexia. The research explores how disruptions in PNNs, specialized extracellular matrix structures surrounding neurons, contribute to alterations in Agrp neuron activity, subsequently affecting feeding behavior and metabolic outcomes. The hypothesis is that the degradation of PNNs, observed in metabolic imbalances, may restore undesirable plasticity, contributing to the defense of unhealthy body weight. The project aims to elucidate this by characterizing the metabolic regulation of hypothalamic PNNs, exploring physiological consequences of PNN modulation, and understanding the subsequent molecular changes in Agrp neurons.
Basic Research

Masashi Hasegawa, Ph.D., Rutgers University, is interested in impulsive behaviors caused by deficiency in action inhibition. Impulsivity is a factor in ADHD, among other psychiatric disorders. While behavioral therapies can mitigate impulsive behaviors, there are still unmet needs for therapeutics targeting deficiency in action inhibition, Dr. Hasegawa states. This goal might be achieved by manipulating the activities of specific neurons involved in action inhibition, yet neural mechanisms of action inhibition are not well characterized. The focus of this research is a hyperdirect pathway encompassing the cerebral cortex and subthalamic nucleus (STN) in basal ganglia which seems to be involved in action inhibition. A recent study in animal models suggests that prefrontal cortex (PFC) neurons in this anatomical pathway may play a critical role in action inhibition. To empirically discover if causal relationships between specific neural activities and behaviors can be empirically examined, this project will involve, among other things, profiling the gene expression pattern of the PFC neurons controlling action inhibition. Such PFC neurons in the hyperdirect pathway may be a potential target for the treatment of impulsive behaviors.
Basic Research

Hector Yarur, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that opioid transmission and dysregulated prefrontal cortex (PFC) activity have been implicated in the inhibitory-control deficits associated with addiction and binge-type eating disorders. While endogenous opioids and their receptors are highly expressed in the PFC, it is not known whether endogenous opioid transmission within the PFC modulates inhibitory control. This project investigates the hypothesis that PFC enkephalin neurons modulate the association of valence with rewarding and aversive stimuli through the release of endogenous enkephalin peptides. The goal is to elucidate the role of endogenous opioid systems in regulating Pavlovian conditioning behavior and gain insights into the microcircuit mechanisms by which opioids modulate PFC circuitry and motivate behavior by targeting specific interneuron subpopulations.
Basic Research

OBSESSIVE-COMPUSIVE DISORDER (OCD)

Zhongzheng Fu, Ph.D., University of Texas Southwestern Medical Center at Dallas, is interested in action monitoring and control, cognitive processes that monitor distractions and errors and redirect focus to stimuli, actions, and thoughts that are relevant to the current goal. This monitoring-control feedback loop is fundamental to flexible goal-directed behaviors, enabling rapid adaptations in an ever-changing environment. In OCD, ADHD, and schizophrenia, dysfunctions in action monitoring and control lead to impairments in goal-directed behaviors, loss of cognitive flexibility, and poor quality of life. Dr. Fu hypothesizes that neuronal circuitry intrinsic to the basal ganglia computes error signals, which directly influence subsequent actions, independently of activity in the frontal cortex; and that the intensity of error signals in the basal ganglia predicts the size of error-related negativity (ERN) as well as subsequent post-error slowing, a popular behavioral marker for error monitoring. By interrogating the neuronal mechanisms of action monitoring and control in the human basal ganglia, this project could reveal a possible future target for neuromodulation therapy.
Basic Research

Franco Giarrocco, Ph.D., National Institute of Mental Health (NIMH/NIH), notes that in major depression and OCD, alterations have been observed in the brain's ability to either acquire or properly use the appropriate motivational values of stimuli and actions. The cortico-basal ganglia circuitry is likely the most important motif of the brain mediating these functions. Dr. Giarrocco hypothesizes that the brain encodes multiple representations of stimulus and action values across different motor systems, and that the learning process relies on the dynamic interaction among value representations across the cortico-basal ganglia network. To test this, the team will perform simultaneous, large-scale neuronal recordings across motivational and motor areas within cortico-striatal-pallidal circuits in non-human primates performing a task in which they learn the value of

visual stimuli. Challenging current theories, the team aims to lay groundwork for novel hypotheses on how dysfunctions within this circuitry contribute to MDD and OCD.
Basic Research

Ann Iturra Mena, Ph.D., Columbia University, says a critical challenge in exposure therapy for such illnesses as anxiety disorders, PTSD, and OCD is the objective measurement of approach behaviors—approach toward feared stimuli—during exposures. Measuring in-session approach behaviors using validated behavioral codes is time-consuming, requires extensive training, and cannot be conducted in real-time. In this study, the team will generate an AI-based tool to automate the assessment of approach behaviors as indicators of therapeutic progress in exposure therapy. They propose to analyze secondary data from 130 audio recordings obtained from prior exposure therapy studies in pediatric OCD and anxiety disorders (participants aged 7-18). The project has three aims: 1) to identify linguistic indicators (e.g., words, phrases) of approach behaviors using speech-to-text and natural language processing tools; 2) to uncover voice indicators (e.g., tone, pitch, tempo) through voice analytics; and 3) to predict treatment response with a machine learning model based on these audio features. The model will be trained on 80% of the data and tested on the remaining 20%.
Basic Research
Diagnostic Tools/Early Intervention

Jaekyoon Kim, Ph.D., University of Iowa, wants to better understand cellular and molecular mechanisms of repetitive behaviors, a defining symptom in ADHD, autism spectrum disorder (ASD), schizophrenia, and OCD. One challenge in investigating repetitive behavior in mice is the lack of valid behavioral assays. This project uses rotarod training to provide a quantitative and continuous measure of the acquisition of repetitive behavior via forced motor activity. The rotarod is a behavioral task based on a rotating rod, like a treadmill, that the animal must stay on for as long as possible. The experiments proposed seek to identify molecular mechanisms, cell-type-specific contributions, and circuit-specific patterns of neuronal activity during the acquisition of repetitive behavior in mice that model 16p11.2 deletion syndrome. The hope is to characterize the role of striatal circuits as key mediators of repetitive behaviors and identify potential therapeutic targets for their amelioration.
Basic Research

Liming Qiu, M.D., University of Pennsylvania, will leverage the unique multi-modal dataset available from a clinical trial already in progress to investigate neural networks involved in OCD. The hypothesis is that network connectivity strength to prefrontal cortex and cingulate regions may be important in modulating OCD symptoms and predictive of deep-brain stimulation (DBS) outcomes. Important regions of the PFC and ACC will first be identified; various connectivity measures from selected DBS targets to these regions of interest will be then calculated using structural and functional magnetic resonance imaging. These connectivity indices will be aggregated and input into a supervised machine learning algorithm to identify a potential predictive model. Group analysis across subjects will finally be performed to identify common pathways to build a simplified model of an OCD network. This could advance our understanding of OCD circuits and inform DBS site selection for future treatment of treatment-resistant OCD.
Basic Research
Next-Generation Therapies

OTHER DISORDERS

ALZHEIMER'S

Camila de Avila Dal'Bo, Ph.D., Arizona State University, notes anxiety symptoms in Alzheimer's disease (AD) is present in 40% of patients, and may be a prelude to AD onset. Brain regions implicated in anxiety include the amygdala (AMY), the hippocampus (HIPP), and the prefrontal cortex (PFC). These areas receive moderate to strong connections from the pontine nucleus incertus (NI), and preclinical studies indicate these pathways can influence the level of anxiety-like behaviors in rodents. The neurochemical anatomy of the NI has not been mapped in humans. This project seeks to detect and quantify mRNA levels of Relaxin Family Peptide Receptor 3 (RXFP3) in the human AMY, HIPP, and PFC. The neuropeptide relaxin-3 (RLN3) is primarily expressed in neurons within the NI and is a marker for the NI. mRNA levels will be correlated with anxiety scores from clinical records of patients to assess the impact of aging and Alzheimer's. The hypothesis is that: (i) RXFP3 mRNA levels will be decreased in the AMY, HIPP, and PFC of Alzheimer's subjects compared to controls; and (ii) there will be a negative correlation between RXFP3 levels and anxiety scores.
Basic Research

EPILEPSY

Lingdi Nie, Ph.D., Krembil Research Institute/University Health Network, Canada, studies 15q13.3 microdeletion syndrome, a neurodevelopmental and genetic disorder with a deleted region of chromosome 15 containing 10 genes that occurs in about 1 in 55,00 people. It manifests soon after birth and is strongly associated with autism spectrum disorder, epilepsy, and schizophrenia. While previous studies have focused on mouse models of 15q13.3 microdeletion, there is no understanding of the dysfunctional human brain circuits or signaling networks underlying the microdeletion. Using control and patient 15q13.3 microdeletion stem cell lines (5 families), the team generated an in vitro 3D human brain model (a brain organoid) and fused brain region-specific organoids to make synthetic circuits named assembloids. The specific type of assembloid to be used in this project is

a dorsal-ventral forebrain assembloid. They will investigate whether impaired inhibitory neurons in 15q13.3 microdeletion cause neural circuit dysfunction in the assembloids.
Basic Research

EPILEPSY

Rachel June Smith, Ph.D., University of Alabama at Birmingham, will map connectivity networks in epilepsy patients with depression using electrical stimulation. Over 30% of patients with drug-resistant epilepsy also suffer from depression. Neural networks that are common in epilepsy often overlap with those associated with depression, but the causal relationships indicative of which brain regions impose the pathological activity on other brain regions have not been revealed. The team will use single-pulse electrical stimulation (SPES) to map depression-effective connectivity networks in epilepsy patients and infer potential deep-brain stimulation strategies optimized for treatment-resistant depression. The hypothesis is that pathologically strong connections from the limbic structures (i.e., the hippocampus and amygdala) will produce large cortico-cortical evoked potentials and increased high frequency power in cortico-cortical spectral responses in depression-relevant brain structures.
Next-Generation Therapies
Basic Research

PARKINSON'S DISEASE

Nikolai Gil Reyes, M.D., University of Toronto/University Health Network, Canada, studies 22q11.2 microdeletion syndrome, which conveys a 1 in 4 risk of developing schizophrenia—the strongest known risk factor for the illness. Individuals with the 22q11.2 microdeletion are also prone to motor side effects such as parkinsonism. In the general population, risk for Parkinson's Disease (PD) and parkinsonism arises from cumulative effects of multiple common and rare genetic variants. Individuals with the 22q11.2 microdeletion thus represent a high-risk human model, providing the opportunity to determine whether genetic risk factors for PD/parkinsonism expression also contribute to the risk for parkinsonism related to antipsychotic medications. The objective of this study is to answer this question, using a nested case-control design to study the world's largest cohort of adults with 22q11.2DS. The work could provide novel data on genetic factors affecting risk for parkinsonism associated with antipsychotics. Findings from this study can be combined with other risk factors to guide risk stratification for parkinsonism.
Basic Research

STROKE

Kahlilia Morris-Blanco, Ph.D., University of Pennsylvania, has focused on understanding how epigenetic enzymes known as TETs contribute to emotional challenges after a stroke. The team seeks to understand how TETs either help the brain become more resilient or make it more vulnerable to anxiety and depression after a stroke. To answer this, they will manipulate levels of TET enzymes in mice. Recent advancements in technology enable determination of the impact of epigenetic molecular switches more precisely in different cells of the brain. The team seeks to determine which genes are expressed in areas of the brain implicated in anxiety and depression. They also will observe mood behaviors in the mice to understand if changes in TET enzymes affect emotional states like anxiety and depression. Insights gained could lead to innovative therapies that improve mental health and enhance recovery for people who experience a stroke.
Basic Research

TRAUMATIC BRAIN INJURY

Dongtak Lee, Ph.D., Harvard University/Brigham and Women's Hospital, Inc., aims to develop a novel intranasal gene therapy approach for efficient and targeted delivery of RNA therapeutics to attenuate neuroinflammation associated with mild traumatic brain injury (mTBI). By leveraging a unique nasal formulation (NF) and engineered lipid nanoparticles (LNPs), the team will encapsulate siRNAs against NLRP3—a promising target for mTBI—within LNPs. The NF, exhibiting extended residence time in the nasal cavity, enables controlled release of therapeutic agents and transient permeabilization of tight nasal epithelial junctions, facilitating brain delivery.
Next-Generation Therapies
New Technologies

POST-TRAUMATIC STRESS DISORDER (PTSD)

Vanessa Babineau, Ph.D., Columbia University, is interested in prenatal programming, the process by which aspects of a pregnant person's life shape fetal development. Fetal exposure to maternal depression in pregnancy is associated with altered infant brain development, specifically amygdala network connectivity; implicated in stress processing; and associated with anxiety and depression in children and adults. The team will test whether maternal prenatal PTSD leads to altered newborn brain connectivity and whether this is associated with infant emotion regulation problems. For this research, 7,500 mother-infant pairs were recruited during pregnancy and followed postnatally. Maternal PTSD and depression were assessed in pregnancy and postpartum; newborns underwent fMRI brain scans; infant emotion regulation was assessed. Findings will inform prevention and intervention for pregnant individuals and their babies by treating PTSD in pregnancy even in the absence of depres-

sion, at a critical period for both parent and child with a two-generation impact.

Basic Research

Diagnostic Tools/Early Intervention

Liam Barry-Carroll, Ph.D., University of Bordeaux, France, aims to explore the impact of early-life stress (ELS) on the emergence of PTSD, using a model of ELS in rodents. Preliminary data indicates significant alterations in cells called microglia, immune cells unique to the brain. A subset of genes related to extracellular vesicles (EV), tiny bubble-like structures in cells that store and transport materials, are upregulated in mice subjected to ELS. This study, building on this result, aims to elucidate the role of microglia-derived EVs in ELS-induced neurological disturbances. The team seeks to delineate the impact of microglia-derived EVs on the etiology of ELS. This research could have significant implications for understanding the pathophysiology of PTSD and other stress-related disorders and suggest potential prevention and treatment targets.

Basic Research

Johnathan Borland, Ph.D., University of Minnesota, notes that rewarding social interactions, such as asserting oneself, defending one's home territory, or dominant-subordinate relationships, can have beneficial effects on mental and physical health. He proposes they can be mobilized to treat psychiatric disorders. This project investigates the neurobiological underpinnings of dominant interactions and asks whether they manifest differently in males and females. Preliminary data suggests that after repeat "dominance" experiences, females, but not males, display greater calcium signaling in the nucleus accumbens. This study will investigate if dominant interactions differentially impact the reward system in males and females, and if the underlying neurobiology in the mesolimbic dopamine reward circuit is different in males and females.

Basic Research

Fenglin Cao, Ph.D., Western Washington University, notes the lateral nucleus of the amygdala (LA) is of particular interest in PTSD studies due to its pivotal role in fear memory formation and consolidation upon trauma exposure. Although previous studies have highlighted the importance of LA neurons in encoding fear memories and the necessity of synaptic plasticity for associating conditional and unconditional stimuli during fear memory formation, the specific neural circuits and mechanisms facilitating synaptic plasticity in the LA are not fully understood. By investigating the neural inputs to the LA and their impact on synaptic plasticity, this study aims to uncover circuitry mechanisms in PTSD, enhancing our understanding of the neuroplasticity associated with fear conditioning behaviors. The specific focus is circuitry connecting the LA with the parvicellular part of ventral posteromedial nucleus in the thalamus, which is involved in fear-associated learning and memory.

Basic Research

Kevin Clancy, Ph.D., Harvard University/McLean Hospital, seeks to develop proof of principle for the use of an ambulatory, cost-effective non-invasive brain stimulation technique called transcranial alternating current stimulation (tACS) to target trauma-related intrusive memories (TR-Ims) in trauma-exposed adults. He will utilize a form of tACS tuned to a pattern of inhibitory neural activity within the sensory cortex known as alpha oscillations. Prior experiments demonstrated deficits in sensory cortical alpha oscillations in PTSD patients, which were associated with sensory sensitivity, neural network dysfunction, and trauma memory reactivation. Leveraging the ability of alpha-tACS to target this deficient inhibitory activity, or "sensory cortical disinhibition," the team will test if alpha-tACS can reduce the sensory-perceptual vividness and intensity of TR-IMs reactivated by personalized trauma narrative scripts. fMRI will be used to further examine how alpha-tACS can regulate the interactions of neural networks implicated in TR-IMs, offering additional mechanistic insights into this pervasive and difficult-to-treat symptom.

New Technologies

Next-Generation Therapies

Xin Deng, Ph.D., McLean Hospital, suggests that while brain regions implicated in PTSD pathology, including amygdala, medial prefrontal cortex (mPFC) and hippocampus, are well-characterized, a more detailed and specific understanding of the neural circuits mediating fear suppression might be needed for more effective PTSD treatments. The proposed experiments focus on amygdala neurons expressing neuropeptide corticotropin-releasing factor (CRF) which are involved in fear-on circuits and known to play essential roles in fear and anxiety-related behavioral responses. Dr. Deng will explore the contributions of synaptic plasticity mechanisms in projections from the mPFC to CRF-positive neurons in the basolateral amygdala (BLA) to fear memory and fear extinction. The proposed studies may advance our mechanistic understanding of how plasticity changes in specific neural circuits contribute to the suppression of fear memory, possibly suggesting novel therapeutic approaches for PTSD treatments through modulation of the signal flow in fear memory/extinction-mediating neural circuits.

Basic Research

Mario Fernandez, Ph.D., NeuroCenter Magendie U1215 (INSERM), France, aims to investigate the role of different dorsomedial prefrontal cortex (dmPFC) neuronal populations

in the emergence of general and specific neuronal representations. One goal is to elucidate how pyramidal glutamatergic (Pyr) neurons, somatostatin-positive (SST+) interneurons and parvalbumin-positive (PV+) interneurons interact in the dmPFC to allow animals to detect and discriminate danger. Efforts will be made to elucidate the causal involvement of these neuronal populations on the acquisition and expression of defensive memories. Dr. Fernandez will combine a new behavioral paradigm, which exposes mice to safe trials and to multiple threatening situations, with calcium imaging in freely moving mice and with the use of optogenetics to manipulate the activity of distinct neuronal populations. The goal is to better understand neuronal mechanisms that allow animals to detect and discriminate danger, processes essential for the correct expression physiological adaptive defensive behaviors.

Basic Research

Thomas Hainmueller, M.D., Ph.D., New York University, will perform high-density recordings of hundreds of single neurons simultaneously throughout the temporal lobe in a mouse model of PTSD and characterize trauma-related memory reactivation and abnormal processing of trauma-related stimuli. Preliminary data in healthy animals show profound differences in the propagation of "startling" vs. "non-startling" stimuli through the temporal lobe, indicating different modes of processing. This project will investigate altered hippocampal processing of trauma-related triggers and abnormal reactivation of trauma-associated cell assemblies with chronically implanted high-density recording electrodes in mice and correlate their occurrence with the severity of PTSD-like symptoms. The team will disrupt aberrant propagation of trauma-related neuronal activity sequences through optogenetic manipulation of inhibitory interneuron circuits to probe the effectiveness of such interventions for symptom control and reversal.

Basic Research

Next-Generation Therapies

Zachary Harvanek, M.D., Ph.D., Yale University/Yale University School of Medicine, will address a gap in our understanding of the response to stress at the molecular level by investigating the role of DNA methylation in acute stress responses among trauma-exposed individuals. The team will add epigenetic measures to data from an existing cohort of 138 individuals with a varied range of past traumatic experiences who underwent laboratory sessions including stress-cue and neutral cue conditions followed by measures of anxiety and HPA-axis signaling and up to 2 years of follow up for psychiatric symptomatology. Using these added epigenetic measures, the team will examine the association between baseline DNA methylation of HPA axis-related genes, specifically FKBP5 and NR3C1, and post-stress anxiety levels, HPA-axis signaling, and longitudinal depression and anxiety. Mediation analyses will test whether DNA methylation links trauma history to these outcomes.

Basic Research

Maryam Hasantash, Ph.D., Columbia University, notes that cognitive flexibility may promote stress resilience by enabling the flexible adjustment of cognitive or behavioral strategies to efficiently cope with stressful experiences. This work proceeds from the notion that if we can understand the neural circuits underlying cognitive flexibility, we may be able to identify new targets for advanced therapeutics to treat the debilitating cognitive impairments in multiple psychiatric disorders. Dr. Hasantash has identified projections from the ventral CA1 (vCA1) region of the hippocampus to the medial orbitofrontal cortex (mOFC) as a novel neural circuit component crucial for reversal learning, an important form of cognitive flexibility This study will test a novel role for vCA1-mOFC projections in regulating individual differences in stress vulnerability. Results have the potential to reveal new neural circuit-based targets for novel drugs or for advanced cognitive-behavioral therapies aimed at improving cognitive flexibility as a means to reduce stress-induced psychiatric disorders.

Basic Research

Ann Iturra Mena, Ph.D., Columbia University, says a critical challenge in exposure therapy for such illnesses as anxiety disorders, PTSD, and OCD is the objective measurement of approach behaviors—approach toward feared stimuli—during exposures. Measuring in-session approach behaviors using validated behavioral codes is time-consuming, requires extensive training, and cannot be conducted in real-time. In this study, the team will generate an AI-based tool to automate the assessment of approach behaviors as indicators of therapeutic progress in exposure therapy. They propose to analyze secondary data from 130 audio recordings obtained from prior exposure therapy studies in pediatric OCD and anxiety disorders (participants aged 7-18). The project has three aims: 1) to identify linguistic indicators (e.g., words, phrases) of approach behaviors using speech-to-text and natural language processing tools; 2) to uncover voice indicators (e.g., tone, pitch, tempo) through voice analytics; and 3) to predict treatment response with a machine learning model based on these audio features. The model will be trained on 80% of the data and tested on the remaining 20%.

Basic Research

Diagnostic Tools/Early Intervention

Munir Kutlu, Ph.D., Rowan University, proceeds from a theory that elevated levels of acetylcholine (ACh), a neurotransmitter key for cognitive processes such as memory and attention, as well as overreactive nicotinic ACh receptors, are associated with worsened PTSD symptoms in humans. To understand the role

of ACh in the extinction of fear memories, the team will use advanced neural imaging techniques to measure ACh levels in the anterior insula, a brain region key to introspective feedback, during both fear learning and fear extinction in mice. They expect insular ACh levels will increase during the learning of fear and decrease during the process of extinction. Using the gene-editing tool CRISPR to eliminate a specific sub-group of nicotinic ACh receptors in the anterior insula, they will test whether the insular ß2-containing nAChRs control fear extinction. They hypothesize that the elimination of ß2-containing nAChRs will result in more efficient fear extinction.

Basic Research

Joseph Stujenske, M.D., Ph.D., University of Pittsburgh, will leverage an animal model to study whether timing brain stimulation to specific phases of respiration yields different changes in fear memory. Findings from this study have promise for optimizing the delivery of non-invasive brain stimulation to ameliorate various psychiatric symptoms, especially anxiety disorders. Repetitive stimulation (rTMS) of the dorsomedial prefrontal cortex (dmPFC) has been shown to alleviate anxiety disorder symptoms when paired with exposure to feared situations. However, animal studies have shown mixed results of dmPFC stimulation, suggesting a fear-promoting role for this region. This project aims to reconcile this discordance in a mouse model and develop a brain stimulation method for specifically decreasing fear and anxiety. The hypothesis is that subsets of dmPFC outputs will be differently timed relative to respirations, and therefore inspiration or expiration-timed dmPFC stimulation will have different effects on fear extinction.

Basic Research

Next-Generation Therapies

Najah Walton, Ph.D., Tufts University, is exploring the potential of novel neurosteroidogenic biomarkers as predictors of stress-induced psychiatric disorders. Recent advancements in therapeutic strategies, particularly neurosteroid analogs of allopregnanolone, have demonstrated rapid and sustained anxiolytic and antidepressant effects in psychiatric disorders. It is important to determine which individuals will respond to allopregnanolone-based treatments. Dr. Walton's team has demonstrated the impact of chronic stress on neurosteroid synthesis and subsequent network dysfunction in the amygdala. This study will deploy a novel neurosteroidogenic biomarker screening tool to detect neurosteroid markers from various tissue samples obtained from individuals with major depression, PTSD, and generalized anxiety disorder. The hope is to synergistically illuminate molecular dynamics while offering a comprehensive view of neurosteroid production from gene expression to protein synthesis. The team expects to observe reductions in neurosteroid levels in a subset of individuals with a psychiatric diagnosis compared to controls.

Basic Research

Lauren White, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, believes that characterizing neurocognitive risk parameters in children is critical to the study of developmental psychopathology and paves the way for novel treatment and interventions. Heightened threat sensitivity—the recognition, interpretation, and response to real or potential threat cues in the environment—is a strong neurocognitive predictor of anxiety risk. Yet little is known about how heightened threat sensitivity develops and is maintained across time. This is a novel intergenerational study of the Philadelphia Neurodevelopmental Cohort (PNC), a racially diverse cohort of ~10,000 participants assessed at ages 8–21 between 2009-2012, with many participants becoming parents in the last 5 years. In 120 mother-child dyads (children aged 4-7 years), Dr. White will use a multimethod assessment framework with psychiatric (clinical interview, self-report), behavioral (computer tasks), and neural (electroencephalogram: EEG) measures to examine the pathways underlying longitudinal and intergenerational influences on threat sensitivity and anxiety.

Diagnostic Tools/Early Intervention

PRENATAL BRAIN DEVELOPMENT

Vanessa Babineau, Ph.D., Columbia University, is interested in prenatal programming, the process by which aspects of a pregnant person's life shape fetal development. Fetal exposure to maternal depression in pregnancy is associated with altered infant brain development, specifically amygdala network connectivity; implicated in stress processing; and associated with anxiety and depression in children and adults. The team will test whether maternal prenatal PTSD leads to altered newborn brain connectivity and whether this is associated with infant emotion regulation problems. For this research, 7,500 mother-infant pairs were recruited during pregnancy and followed postnatally. Maternal PTSD and depression were assessed in pregnancy and postpartum; newborns underwent fMRI brain scans; infant emotion regulation was assessed. Findings will inform prevention and intervention for pregnant individuals and their babies by treating PTSD in pregnancy even in the absence of depression, at a critical period for both parent and child with a two-generation impact.

Basic Research

Diagnostic Tools/Early Intervention

Marta Cosin-Tomas, Ph.D., Barcelona Institute for Global Health, Spain, seeks to develop placental biomarkers to enable targeting at-risk neonates and close neuropsychological mon-

itoring starting earlier in life. The research is relevant to neurodevelopmental disorders including schizophrenia and autism spectrum disorder. The project focuses on placental epigenetics, which may be useful as a proxy for placental function and the molecular bridge linking genetic disease-risk variants, placental adaptive responses to environmental insults, and placental dysfunction with long-term phenotypic outcomes. Recent findings suggest patterns of placental DNA methylation (DNAm) are associated with changes in brain development and neuropsychiatric outcomes, for instance by reprogramming the hypothalamic-pituitary-adrenal axis. This project will study placental DNAm signatures associated with early neurodevelopmental outcomes and may identify candidate biomarkers to detect neonates at risk of developing neurodevelopmental complications. The team will use recently generated data on placental DNAm profiles and neurodevelopmental evaluations at various ages (neuropsychological assessments at 6, 8, 18, 28, and 48 months of age) from 480 participants in the Barcelona Life Study Cohort.
Basic Research

Julien Ferent, Ph.D., INSERM, France, notes that during embryonic development, morphogens are secreted and form gradients that direct cell fate in a concentration-dependent manner. Morphogens are signaling molecules that act over long distances to induce responses in cells based on the morphogen concentration of the cells they interact with. As the embryonic nervous system develops, cells undergo distinct stages of differentiation, from progenitors to post-mitotic migrating and maturing neurons. At each step of their development, cells change their behavior in response to extracellular cues such as morphogens. These signals may contribute to the transitions between proliferation, migration, and axon/dendrite growth. This project will investigate how progenitor cells modulate their responses to morphogens during differentiation to induce behaviors strictly required for the formation of the correct neural architecture. Alteration of this circuitry during neurodevelopment may directly affect the organization of neural network structure and thus be linked to the onset of a variety of severe psychiatric disorders, such as schizophrenia, autism spectrum disorders, intellectual disability, or epilepsy. The research will be conducted in animals and humans.
Basic Research

Husniye Kantarci, Ph.D., Dell Medical School, University of Texas at Austin, is interested in dysregulation of neuronal excitability which is implicated in the pathologies of numerous diseases including chronic pain, epilepsy, and neuropsychiatric disorders such as bipolar disorder, anxiety, and depression. The team has uncovered an essential role for glia in the development of neurons into excitable cells. Schwann cells, peripheral glia that ensheath sensory axons, secrete prostaglandin E2 (PGE2) to induce excitability in sensory neurons by upregulating the expression of voltage-gated sodium channels (Navs) that provide neurons with action potential firing abilities. The aims of this study are: 1) determining whether CNS glia (astrocytes and oligodendrocytes) secrete PGE2 to promote excitability in CNS neurons and 2) determining the downstream mechanism of PGE2-induced excitability. The goal is to identify new therapeutic targets in glial mechanisms of brain diseases and determine how glia contribute to the development of a healthy nervous system.
Basic Research

Martin Munz, Ph.D., University of Alberta, Canada, has developed a new technique called parauterine imaging that allows for in vivo subcellular resolution microscopy, in vivo pharmacology, and in vivo targeted single cell patch clamp recordings from cortical cells in a developing mouse embryo. This method opens new ways to study embryonic cortical circuit formation and will allow the team to explore how cortical development is impacted by DNA mutations associated with autism spectrum disorder, schizophrenia and ADHD. Here the focus is on how changes in the expression of three high-confidence autism risk genes (Pten, Chd8 and Grin2b) that are also associated with schizophrenia and ADHD impact neuronal circuit development. They will observe if changes in the expression of these genes leads to changes in circuit development and physiology in mice.
Basic Research
New Technologies

Nevena Radonjic, M.D., Ph.D., Research Foundation for the State University of New York, Upstate Medical University, notes that alterations in estrogen levels during neurodevelopment can have lasting impact on the density of cortical interneurons, the impairment of which has been implicated in disorders such as schizophrenia and ASD. Understanding of estrogen-mediated mechanisms of neurodevelopment is hampered by limited data from human fetal studies. This project asks: Where and when are estrogen receptors expressed on interneuron progenitors in the developing human cerebral cortex? It is hoped this study will provide critical insights into the precise location, cell types, and developmental phases at which estrogen receptors and related genes are expressed in interneuron progenitors in the fetal cerebral cortex. Findings will help elucidate the role of estrogen signaling pathway expression in the fetal brain and enable work to understand the susceptibility of specific brain regions to structural abnormalities related to alteration in levels of estrogen.
Basic Research

Ai Tian, Ph.D., University of Calgary/The Hospital for Sick Children, Canada, notes that administration of early-life immune challenges in animal models has resulted in

postnatal behavior changes. This suggests a potential causal role for inflammation in schizophrenia. Microglia, the main immune cells of the central nervous system, are pivotal players in inflammation. Further study of association between schizophrenia, microglia, and inflammation requires an in vitro platform that resembles the human brain. Dr. Tian has developed a 3D co-culture platform by building assembloids containing neurons, astrocytes, and microglia derived from isogenic human pluripotent stem cells. In this project, the platform will be challenged with proinflammatory cytokines that mimic maternal immune activation and/or genetic variants associated with patients, to investigate the impact of inflammatory dysregulation on neuroimmune mechanisms of schizophrenia.

Basic Research

Valerie Tornini, Ph.D., University of California, Los Angeles, notes that microglia, the immune cells of the brain, are required for correct circuit development, yet the mechanisms involving microglia that ensure proper circuit development in early developmental time periods are poorly defined. Also unclear is how microglia are affected in genetic models of neurodevelopmental disorders (NDDs) such as schizophrenia and autism. This project seeks to define the roles of microglia in establishing baseline brain circuitry and behavior in genetic models of NDDs. To investigate how microglia are affected in genetic mutants, and how targeting microglia may affect organismal behaviors, the team will use a zebrafish model in which they will perform behavioral profiling, cell type-specific in vivo manipulations, and robust functional and molecular readouts during early circuit formation.

Basic Research

Yingying Zhang, Ph.D., Harvard University/Boston Children's Hospital, has established a human C4A transgenic mouse model. Genetic studies have identified that higher copy number of complement component C4A, a key component of innate immunity, is a major risk factor for schizophrenia. Mice overexpressing C4A exhibit excessive complement-mediated microglia engulfment of neuronal synapses and develop neuropsychiatric phenotypes resembling negative symptoms in schizophrenia. The team's preliminary data identify increased monocyte infiltration into the choroid plexus (ChP), accompanied by hydrocephalus and dramatically enlarged cerebral ventricles (ventriculomegaly), in HuC4A-overexpressing mice prior to the onset of behavioral anomalies. This project aims to elucidate the mechanism of how complement overactivation can cause ChP inflammation and ventriculomegaly, and investigate a causal relationship between ChP inflammation and schizophrenia-like neuropsychiatric manifestations.

Basic Research

PSYCHOSIS

Jacob Crouse, Ph.D., University of Sydney, Australia, will leverage 3 large, genetically informative, longitudinal, youth-focused cohorts to explore the existence of a sleep-circadian causal pathway to youth-onset mood disorders. One part of the work uses the Adolescent Brain Cognitive Development (ABCD) Study to examine parent-rated measures of sleep and mental health on >10,000 children ages 9–10 over 2 years of follow-up. A powerful technique called joint modelling will be used to examine whether patterns of sleep (and dynamic change in sleep)—in combination with baseline variables including sex and genetic liability to sleep-circadian traits (e.g., chronotype, sleep duration, circadian amplitude)—can predict the onset of mental disorders over the follow-up. Another part of the study uses the Brisbane Longitudinal Twin Study to examine whether patterns of sleep (and change over time)—alongside sex and genetic indices of sleep-circadian traits—are associated with onset of depression, hypo/mania, or psychosis in early adulthood. A third part will examine whether patterns of objective sleep-circadian function (and change over time)—combined with genetic indices of sleep-circadian traits—predict transition from a subthreshold to a full-threshold mental disorder over the follow-up.

Diagnostic Tools/Early Intervention

Basic Research

Elvisha Dhamala, Ph.D., Feinstein Institute for Medical Research/Northwell Health, is interested in psychotic-like experiences (PLEs)—prodromal symptoms that resemble aspects of psychosis but do not meet the full diagnostic criteria for a psychotic disorder. They may represent a critical transdiagnostic biomarker of psychiatric illness in youth. This research will use a large sample of youth (n=6319) from the Adolescent Brain Cognitive Development Study, with the aim of quantifying functional networks that underlie PLEs in a sex-specific manner and to evaluate whether such sex-specific markers predict the onset of specific psychiatric illnesses during adolescence using brain-based predictive modeling. This work may establish the sex-specific functional brain markers of PLEs in children and the diagnostic specificity of those markers in adolescents. Once identified, these biomarkers could be used to predict the onset of psychiatric illnesses in youth with a single baseline neuroimaging scan, while considering the individual's sex.

Diagnostic Tools/Early Intervention

Tom Franken, M.D., Ph.D., Washington University School of Medicine, has revealed how a systematically organized neural microarchitecture signals how borders in visual scenes are grouped into foreground objects. How these neural signals contribute to perception is not understood. This question has pertinence to psychotic disorders such as schizophrenia, in which

this aspect of perception is impaired. Macaque monkeys will be trained to report their perception of objects in ambiguous visual scenes. By illuminating light-sensitive ion channels (opsins) in an area called V4, Dr. Franken will deliver light to activate and inactivate the key clusters of neural tissue. Analysis of how this affects performance in the task and of neural activity in the cluster could yield insight into the causal role of these neural circuits in perception. Because these perceptual computations are specifically disrupted in psychotic disorders, a mechanistic understanding could ultimately support development of novel therapies and diagnostic tools.

Basic Research

Leanna Hernandez, Ph.D., University of California, Los Angeles, notes the largest genetic association with schizophrenia lies in a genomic region harboring many genes important for immune functioning. A large portion of this genetic signal has been localized to the complement component 4A (C4A) gene, which acts in the brain to tag synapses for elimination. These findings have led to the hypothesis that overactivation of C4A in the brain may cause excessive synaptic pruning, ultimately conferring risk for schizophrenia, in line with previous evidence of accelerated cortical thinning. This project will: 1) assess the impact of genetically predicted C4A gene expression on longitudinal change in gray matter cortical thickness and surface area over 2 years; 2) assess the relationship between predicted C4A gene expression and change in clinical measures of psychosis over time; and 3) evaluate whether including predicted C4A gene expression into existing risk calculators improves our ability to predict conversion to psychosis.

Basic Research

Diagnostic Tools/Early Intervention

Katie Lavigne, Ph.D., McGill University, Canada, is interested in predictive coding dysfunction, which may be a driver of positive symptoms (e.g., delusions) in schizophrenia and other psychotic disorders. The predictive coding framework explains how the brain updates its expectations based on new experience. Recent advances in ultra-high field magnetic resonance imaging (UHF MRI, e.g., at 7 Tesla), now make it possible to distinguish between brain activity occurring at separate layers of the cortex (e.g., superficial, middle, and deep layers). Animal models of predictive coding and postmortem studies indicate that feedforward signals (from lower- to higher-order regions) originate in superficial layers and terminate in middle layers, whereas feedback signals (from higher- to lower-order regions) originate in deep cortical layers and terminate in deep and superficial layers. This layer-specificity provides an exciting opportunity to investigate the role of feedforward and feedback mechanisms on delusions in schizophrenia. The aim of this work is to examine layer-specificity of predictive coding in schizophrenia and how it contributes to delusions. This study will include 30 patients with schizophrenia or related psychotic disorders and 30 matched healthy controls.

Basic Research

Emmanuel Mwesiga, M.D., Ph.D., Makerere University, Uganda, has found that meat and legumes appear to protect against cognitive impairment, while cassava worsens cognitive impairment, in Ugandan first-episode schizophrenia (FES) patients. These novel findings have been cautiously received. Assigning a specific food as an exposure may have led to a misclassification bias, given that different food groups contain various dietary intake biomarkers (DIBs) that may or may not be related to cognitive impairment. Further, it is essential to account for the influence of biological (genetics, immunology, sex, gut microbiota), clinical (diagnosis, drugs and physical exercise,) and environmental (welfare, cultural beliefs, food portions, cooking styles and eating patterns) factors on generation of DIBs. This project reflects the need to improve dietary exposure assessment, via nutrimetabolomics, an intersection of metabolomics and nutrition research, to objectively examine dietary exposure. It will 1) examine the dietary intake biomarkers generated from nine food groups in FES patients and healthy controls; 2) examine the effect of biological, clinical, and environmental factors on the dietary intake markers generated in Ugandan first-episode schizophrenia patients and healthy controls. Twenty first-episode schizophrenia patients and matched controls will be enrolled for this one-year observational study.

Basic Research

Danielle Pratt, Ph.D., Northwestern University, is interested in the role of mental imagery in the context of hallucinations and other perceptual abnormalities experienced in psychosis and schizophrenia. For people with psychosis, she notes, it is theorized that too much weight is given to prior mental models, causing a failure in model updating upon mismatches, and leading individuals to perceive prior predictions as sensations in the absence of stimuli. Others, investigating the mechanisms of mental imagery in non-psychiatric populations, find that when imagined signals are vivid enough, they can become subjectively indistinguishable from reality. This study will examine the role of mental imagery in perceptual abnormality formation using samples of people at clinical high-risk for psychosis (CHR) who experience perceptual abnormalities (N = 40), CHR individuals who do not experience perceptual abnormalities (N = 40), and healthy controls (N = 40). Among the aims is to examine whether the mechanisms of mental imagery can be incorporated into a predictive coding model to create a more complete understanding of how perceptual abnormalities occur.

Basic Research

Nikolai Gil Reyes, M.D., University of Toronto/University Health Network, Canada, studies 22q11.2 microdeletion syndrome, which conveys a 1 in 4 risk of developing schizophrenia—the strongest known risk factor for the illness. Individuals with the 22q11.2 microdeletion are also prone to motor side effects such as parkinsonism. In the general population, risk for Parkinson's Disease (PD) and parkinsonism arises from cumulative effects of multiple common and rare genetic variants. Individuals with the 22q11.2 microdeletion thus represent a high-risk human model, providing the opportunity to determine whether genetic risk factors for PD/parkinsonism expression also contribute to the risk for parkinsonism related to antipsychotic medications. The objective of this study is to answer this question, using a nested case-control design to study the world's largest cohort of adults with 22q11.2DS. The work could provide novel data on genetic factors affecting risk for parkinsonism associated with antipsychotics. Findings from this study can be combined with other risk factors to guide risk stratification for parkinsonism.

Basic Research

Rik Schalbroeck, Ph.D., Amsterdam University Medical Centers, The Netherlands, proposes that by measuring dopamine function, it might be possible to predict which individuals develop a psychotic disorder, with heightened dopamine activity indicating greater risk. However, dopamine in the brain is currently measured with expensive and invasive imaging techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), which cannot be easily implemented in clinical settings for predictive purposes. In recent years, a neuromelanin-sensitive magnetic resonance imaging sequence (NM-MRI) has been developed, which can visualize neuromelanin deposits in the substantia nigra (SN). The accumulation of neuromelanin in this brain region is related to striatal dopamine activity. This project will investigate the sensitivity of NM-MRI to dopaminergic alterations preceding the onset of psychotic disorders by studying high-risk individuals.

Basic Research

Diagnostic Tools/Early Intervention

Satoshi Terada, Ph.D., Columbia University, suggests that neural oscillations, rhythmic electrical patterns observed in electroencephalography (EEG), represent potentially reliable biomarkers for diseases such as schizophrenia. Dr. Terada says most studies on neural oscillation biomarkers have targeted limited oscillation patterns that rely on arbitrary and conventional frequency ranges, attempting to evaluate symptoms alone. Successful applications have yet to be achieved. To tackle this challenge, he proposes a novel framework for analytical models of neural oscillations—novel computational models of neural oscillations to predict multi-level dysfunctions in neuropsychiatric diseases. He will use an integrated system of ultrafast 3-dimensional acousto-optical deflector microscopy with a novel real-time motion correction platform and transparent graphene electrodes, and will conduct 2-photon voltage imaging from soma and dendrites of single pyramidal cells in WT and Df(16)+/- mice. The goal is a comprehensive diagnostic framework of disease related neural abnormalities across synaptic, cellular, and circuit levels.

Basic Research

New Technologies

Ralitsa Todorova, Ph.D., Collège de France, France, notes that hippocampal dysfunction in schizophrenia is characterized by hippocampal atrophy as well as hippocampal hyperactivity. The former may be related to some of the negative symptoms of schizophrenia, including impaired episodic memory, while the latter has been linked to some of the positive symptoms, most notably hallucinations. Yet the neural mechanism linking hippocampal hyperactivity to hallucinations remains unclear. Recent advances in neural recording technology and decoding techniques now make it possible to reliably decode sensory activity from neuronal activity. This project aims to leverage these innovations to directly detect hallucinatory activity in visual areas in a mouse model of schizophrenia in a sensory conditioning paradigm designed to induce hallucinations.

Basic Research

Halide Turkozer, M.D., Harvard University/McLean Hospital, proposes we don't know enough about the biological diversity and distinct risk groups among youth at familial high risk for psychosis and psychotic disorders such as schizophrenia. This makes it hard to predict who might develop psychosis and to formulate effective ways to prevent it. The goal in this project is to identify subgroups among familial high-risk children (ages 9-10) based on neurocognitive functioning in the baseline Adolescent Brain Cognitive Development (ABCD) Study dataset. The team will investigate these subgroups' likelihood of developing psychotic-like symptoms and psychosis-related brain patterns in the 2- and 4-year follow-up data. They predict familial high-risk children who show neurocognitive impairments at baseline are at a higher risk for developing psychotic-like symptoms and psychosis-related brain patterns later in adolescence. Results could advance psychosis research by identifying a specific target group for preventative interventions during childhood.

Basic Research

Diagnostic Tools/Early Intervention

Veith Weilnhammer, M.D., Ph.D., University of California, Berkeley, asks: How do hallucinations acquire their content? The team will investigate hallucinatory experiences in humans as well as in artificial neural networks that are trained to recognize objects. The responses of artificial neural networks closely resemble the activity of neurons that play a part in human object

recognition. Yet, just like humans, artificial neural networks can be prone to "hallucinate" objects that are not present in their input. This project aims to elucidate whether artificial hallucinations can improve our understanding of human hallucinations. It will entail systematic investigation of the phenomenon of visual hallucinations in artificial neural networks and human participants. By studying convergences between biological and artificial neural networks, the work could generate a fine-grained computational model that simulates hallucinatory experiences in machines. By linking human behavior and neuroimaging to artificial neural networks, it has the potential to translate into future clinical innovations for the diagnosis and treatment of psychotic disorders such as schizophrenia.

Basic Research

Nicholas Wright, Ph.D., University of North Carolina at Chapel Hill, is interested in receptors for glutamate, the main excitatory neurotransmitter; dysregulation of these receptors is strongly associated with schizophrenia. He notes targeting of metabotropic glutamate receptors (mGluRs) has high therapeutic potential, in view of studies showing that group II mGluR (mGluR2/3) agonists ameliorate psychosis induced by blockers of NMDA receptors. Promising drug leads have failed in clinical trials, possibly because distinct mGluR subtypes form heterodimeric assemblies in the brain. Additionally, it remains to be seen what other effectors and signaling partners mGluRs physically interact with at chemical synapses. To interrogate these fundamental questions, this project seeks to investigate the structural architecture and functional properties of native mGluR assemblies isolated from brain tissue.

Basic Research

Beier Yao, Ph.D., McLean Hospital, is interested in interoception—the processing, interpretation, and regulation of bodily signals by the brain. There is growing evidence that internal signals from the body can influence a wide range of brain functions, including basic perception, reasoning, emotion, motivation, and sense of self. Disrupted interoception may underlie mood instability in bipolar disorder as well as specific psychotic symptoms related to altered sense of self (e.g., delusion of being controlled by external forces). The team will collect electroencephalogram (EEG), electrocardiogram (ECG), skin conductance, pupil diameter, and self-report data while participants view emotionally evocative images. Relationships between interoception and clinical symptoms (including mood and psychotic symptoms) will also be explored. Potential findings of dysfunctional interoception in bipolar disorder hold the promise to increase our understanding in the role of bodily signals in illness mechanism and inform the development of novel bodily signals-targeted interventions.

Basic Research

SCHIZOPHRENIA

Samantha Abram, Ph.D., University of California, San Francisco/San Francisco VA Medical Center, is interested in avolition, or difficulty in initiating and sustaining goal-oriented behavior. It is a strong predictor of poor functional outcomes in schizophrenia and largely resistant to available treatments. Dr. Abram seeks to uncover the underlying mechanisms of avolition using a combination of neurostimulation, specifically theta-burst stimulation (TBS), and neuroimaging tools such as electroencephalography (EEG) and magnetic resonance imaging (MRI). The aim is to evaluate whether stimulation of the episodic memory network with TBS improves memory performance and EEG-derived markers of corresponding network function in a large sample of people with schizophrenia.

Next-Generation Therapies

Gabriela Bodea, Ph.D., University of Queensland, Australia, notes that both genes and environment play a role in causing illnesses including schizophrenia and autism spectrum disorder, but the interaction between them is unclear. New research suggests mobile DNA elements, fragments of DNA that can move around in the genome, colloquially referred to as "jumping genes," are dysregulated in schizophrenia patients. This is important because environmental factors are known to trigger mobile DNA activation that can result in altering gene expression and potentially affecting brain development. This project utilizes the latest techniques to study mobile DNA in brain tissue and explore functional consequences in a schizophrenia animal model.

Basic Research

Marta Cosin-Tomas, Ph.D., Barcelona Institute for Global Health, Spain, seeks to develop placental biomarkers to enable targeting at-risk neonates and close neuropsychological monitoring starting earlier in life. The research is relevant to neurodevelopmental disorders including schizophrenia and autism spectrum disorder. The project focuses on placental epigenetics, which may be useful as a proxy for placental function and the molecular bridge linking genetic disease-risk variants, placental adaptive responses to environmental insults, and placental dysfunction with long-term phenotypic outcomes. Recent findings suggest patterns of placental DNA methylation (DNAm) are associated with changes in brain development and neuropsychiatric outcomes, for instance by reprogramming the hypothalamic-pituitary-adrenal axis. This project will study placental DNAm signatures associated with early neurodevelopmental outcomes and may identify candidate biomarkers to detect neonates at risk of developing neurodevelopmental complications. The team will use recently generated data on placental DNAm profiles and

neurodevelopmental evaluations at various ages (neuropsychological assessments at 6, 8, 18, 28, and 48 months of age) from 480 participants in the Barcelona Life Study Cohort.

Basic Research

Henry Cowan, Ph.D., Michigan State University, says individuals with schizophrenia spectrum disorders (SSD) experience a disrupted sense of self, manifesting in part through an altered sense of agency (SoA)—the feeling that "I caused an event to occur." Disturbed SoA contributes to psychotic experiences including delusions and hallucinations. SoA emerges from integration of "bottom-up" and "top-down" mechanisms. "Bottom-up" mechanisms shrink the perceived time between an action and its consequence while "top-down" mechanisms attribute ambiguous stimuli to one's own actions. Both mechanisms are known to be altered in SSD. The project seeks, in a cohort of individuals (50 SSD, 40 healthy controls), to establish scalable markers of disturbed SoA with validated links to neurocognitive mechanisms, symptoms, functioning, and lived experience. Such markers could contribute to better understanding of disturbed SoA through large-scale studies, psychometric analyses, clinical trials, and fine-grained assessment and screening in clinical practice.

Basic Research

Diagnostic Tools/Early Intervention

Jacob Crouse, Ph.D., University of Sydney, Australia, will leverage 3 large, genetically informative, longitudinal, youth-focused cohorts to explore the existence of a sleep-circadian causal pathway to youth-onset mood disorders. One part of the work uses the Adolescent Brain Cognitive Development (ABCD) Study to examine parent-rated measures of sleep and mental health on >10,000 children ages 9–10 over 2 years of follow-up. A powerful technique called joint modelling will be used to examine whether patterns of sleep (and dynamic change in sleep)—in combination with baseline variables including sex and genetic liability to sleep-circadian traits (e.g., chronotype, sleep duration, circadian amplitude)—can predict the onset of mental disorders over the follow-up. Another part of the study uses the Brisbane Longitudinal Twin Study to examine whether patterns of sleep (and change over time)—alongside sex and genetic indices of sleep-circadian traits—are associated with onset of depression, hypo/mania, or psychosis in early adulthood. A third part will examine whether patterns of objective sleep-circadian function (and change over time)—combined with genetic indices of sleep-circadian traits—predict transition from a subthreshold to a full-threshold mental disorder over the follow-up.

Diagnostic Tools/Early Intervention

Basic Research

Elvisha Dhamala, Ph.D., Feinstein Institute for Medical Research/Northwell Health, is interested in psychotic-like experiences (PLEs)—prodromal symptoms that resemble aspects of psychosis but do not meet the full diagnostic criteria for a psychotic disorder. They may represent a critical transdiagnostic biomarker of psychiatric illness in youth. This research will use a large sample of youth (n=6319) from the Adolescent Brain Cognitive Development Study, with the aim of quantifying functional networks that underlie PLEs in a sex-specific manner and to evaluate whether such sex-specific markers predict the onset of specific psychiatric illnesses during adolescence using brain-based predictive modeling. This work may establish the sex-specific functional brain markers of PLEs in children and the diagnostic specificity of those markers in adolescents. Once identified, these biomarkers could be used to predict the onset of psychiatric illnesses in youth with a single baseline neuroimaging scan, while considering the individual's sex.

Diagnostic Tools/Early Intervention

Michael-John Dolan, Ph.D., Trinity College, Dublin, Ireland, has observed that a notable portion of schizophrenia risk genes (both common and rare) are expressed in microglia, the immune cells of the brain. Although some evidence points to a role of the immune system in schizophrenia, how genetic risk impacts microglia function is unknown. Dr. Dolan aims to dissect the impact of common and rare genetic risk on the function of human microglia, leveraging a novel induced-pluripotent stem cell (iPSC) toolbox for modelling this cell type that he previously developed. One part of the work seeks to decode the total impact of common but low-risk variants on human microglial function; a second seeks to understand how rare but high-risk genetic variants could impact microglial biology.

Basic Research

Iris Donga Vilares, Ph.D., University of Minnesota, suggests that hallucinations and delusions, core symptoms of schizophrenia, could be caused by an over-reliance on prior beliefs relative to current/incoming sensory information. If this proves true, it could offer a simple computational explanation about the genesis of hallucinations and delusions, and potentially be used as a biomarker for schizophrenia. She will use a combination of behavioral data, computational modeling, and brain imaging to test three possible explanations for findings to date, which have been inconsistent. She will assess the feasibility of using the relative reliance on prior information as a biomarker for hallucinations and delusions. Results could provide novel neurocomputational insights into the genesis of positive symptoms in schizophrenia, such as hallucinations and delusions, and lay the foundation for the potential use of the relative reliance on prior vs. current

information as a biomarker for hallucinations and delusions in schizophrenia.

Basic Research

Diagnostic Tools/Early Intervention

Julien Ferent, Ph.D., INSERM, France, notes that during embryonic development, morphogens are secreted and form gradients that direct cell fate in a concentration-dependent manner. Morphogens are signaling molecules that act over long distances to induce responses in cells based on the morphogen concentration of the cells they interact with. As the embryonic nervous system develops, cells undergo distinct stages of differentiation, from progenitors to post-mitotic migrating and maturing neurons. At each step of their development, cells change their behavior in response to extracellular cues such as morphogens. These signals may contribute to the transitions between proliferation, migration, and axon/dendrite growth. This project will investigate how progenitor cells modulate their responses to morphogens during differentiation to induce behaviors strictly required for the formation of the correct neural architecture. Alteration of this circuitry during neurodevelopment may directly affect the organization of neural network structure and thus be linked to the onset of a variety of severe psychiatric disorders, such as schizophrenia, autism spectrum disorders, intellectual disability, or epilepsy. The research will be conducted in animals and humans.

Basic Research

Tom Franken, M.D., Ph.D., Washington University School of Medicine, has revealed how a systematically organized neural microarchitecture signals how borders in visual scenes are grouped into foreground objects. How these neural signals contribute to perception is not understood. This question has pertinence to psychotic disorders such as schizophrenia, in which this aspect of perception is impaired. Macaque monkeys will be trained to report their perception of objects in ambiguous visual scenes. By illuminating light-sensitive ion channels (opsins) in an area called V4, Dr. Franken will deliver light to activate and inactivate the key clusters of neural tissue. Analysis of how this affects performance in the task and of neural activity in the cluster could yield insight into the causal role of these neural circuits in perception. Because these perceptual computations are specifically disrupted in psychotic disorders, a mechanistic understanding could ultimately support development of novel therapies and diagnostic tools.

Basic Research

Zhongzheng Fu, Ph.D., University of Texas Southwestern Medical Center at Dallas, is interested in action monitoring and control, cognitive processes that monitor distractions and errors and redirect focus to stimuli, actions, and thoughts that are relevant to the current goal. This monitoring-control feedback loop is fundamental to flexible goal-directed behaviors, enabling rapid adaptations in an ever-changing environment. In OCD, ADHD, and schizophrenia, dysfunctions in action monitoring and control lead to impairments in goal-directed behaviors, loss of cognitive flexibility, and poor quality of life. Dr. Fu hypothesizes that neuronal circuitry intrinsic to the basal ganglia computes error signals, which directly influence subsequent actions, independently of activity in the frontal cortex; and that the intensity of error signals in the basal ganglia predicts the size of error-related negativity (ERN) as well as subsequent post-error slowing, a popular behavioral marker for error monitoring. By interrogating the neuronal mechanisms of action monitoring and control in the human basal ganglia, this project could reveal a possible future target for neuromodulation therapy.

Basic Research

Yi Gu, Ph.D., National Institute of Neurological Disorders and Stroke (NINDS/NIH), is interested in 22q11.2 deletion syndrome (22q11.2DS), a genetic syndrome caused by a microdeletion on chromosome 22 and the strongest known genetic risk factor for schizophrenia. It also occurs in autism spectrum disorder, ADHD, and anxiety disorders. This project proceeds from Dr. Gu's prior study of excitatory neural activity in the mouse medial entorhinal cortex (MEC), a region with similar function to human area of the same name. He found that successful learning was associated with an increase and a subsequent stabilization of spatial consistency of MEC neural activity. Those experiments will now be extended to explore neural activity of the MEC in a mouse model of 22q11.2DS, focusing on the possible impact upon impaired spatial memory. Among other things, this could shed light on activity of human EC during the establishment and maintenance of spatial memory in 22q11.2DS.

Basic Research

Leanna Hernandez, Ph.D., University of California, Los Angeles, notes the largest genetic association with schizophrenia lies in a genomic region harboring many genes important for immune functioning. A large portion of this genetic signal has been localized to the complement component 4A (C4A) gene, which acts in the brain to tag synapses for elimination. These findings have led to the hypothesis that overactivation of C4A in the brain may cause excessive synaptic pruning, ultimately conferring risk for schizophrenia, in line with previous evidence of accelerated cortical thinning. This project will: 1) assess the impact of genetically predicted C4A gene expression on longitudinal change in gray matter cortical thickness and surface area over 2 years; 2) assess the relationship between predicted C4A gene expression and change in clinical measures of psychosis over time; and 3) evaluate whether including predicted C4A gene expression

into existing risk calculators improves our ability to predict conversion to psychosis.

Basic Research

Diagnostic Tools/Early Intervention

Kevin Kelley, M.D., Ph.D., Stanford University, has developed an experimental platform which uses cortical organoids transplanted into rodents. This platform offers a powerful approach to modeling human neurodevelopment, including complex neuronal structure and activity-dependent processes. Transplanted cortical organoids relative to organoids grown in the laboratory display advanced maturation and this has enabled the discovery of cellular defects from patient-derived stem cells. This project will apply the transplanted organoid system to understanding schizophrenia pathogenesis with the goal of establishing a tractable and relevant human neuron model of schizophrenia. The cross-disciplinary experiments proposed may help to uncover schizophrenia risk gene pathogenesis in human neurons. It is hoped this work will lay the foundation for therapeutically targeting cellular phenotypes associated with schizophrenia risk-gene mutations, which could help catalyze a new era in treatments.

Basic Research

Jaekyoon Kim, Ph.D., University of Iowa, wants to better understand cellular and molecular mechanisms of repetitive behaviors, a defining symptom in ADHD, autism spectrum disorder (ASD), schizophrenia, and OCD. One challenge in investigating repetitive behavior in mice is the lack of valid behavioral assays. This project uses rotarod training to provide a quantitative and continuous measure of the acquisition of repetitive behavior via forced motor activity. The rotarod is a behavioral task based on a rotating rod, like a treadmill, that the animal must stay on for as long as possible. The experiments proposed seek to identify molecular mechanisms, cell-type-specific contributions, and circuit-specific patterns of neuronal activity during the acquisition of repetitive behavior in mice that model 16p11.2 deletion syndrome. The hope is to characterize the role of striatal circuits as key mediators of repetitive behaviors and identify potential therapeutic targets for their amelioration.

Basic Research

Hannah Lapp, Ph.D., Dell Medical School, University of Texas at Austin, notes that hyper- or hypo-sensitivity to sensory stimulation and atypical social behavior are often present in individuals with neurodevelopmental disorders such as schizophrenia, ADHD, and autism spectrum disorder. Altered sensory processing during sensitive periods for social development may contribute to adult social deficits. This project uses a genetic mouse model for psychiatric risk that exhibits social impairments and atypical sensory sensitivities pervasive in early life caregiver-offspring interactions. By monitoring oxytocin neurons while pups receive different types of maternal tactile stimulation, the team will measure the precise time-course of oxytocin activation during the earliest social interactions. It is hoped this and related experiments will provide a foundation for understanding the relationship between maternal tactile signals, oxytocin, and the development of social behavior and form a basis for experiments to manipulate discrete neural populations altered in this model with the goal of preventing social impairments.

Basic Research

Katie Lavigne, Ph.D., McGill University, Canada, is interested in predictive coding dysfunction, which may be a driver of positive symptoms (e.g., delusions) in schizophrenia and other psychotic disorders. The predictive coding framework explains how the brain updates its expectations based on new experience. Recent advances in ultra-high field magnetic resonance imaging (UHF MRI, e.g., at 7 Tesla), now make it possible to distinguish between brain activity occurring at separate layers of the cortex (e.g., superficial, middle, and deep layers). Animal models of predictive coding and postmortem studies indicate that feedforward signals (from lower- to higher-order regions) originate in superficial layers and terminate in middle layers, whereas feedback signals (from higher- to lower-order regions) originate in deep cortical layers and terminate in deep and superficial layers. This layer-specificity provides an exciting opportunity to investigate the role of feedforward and feedback mechanisms on delusions in schizophrenia. The aim of this work is to examine layer-specificity of predictive coding in schizophrenia and how it contributes to delusions. This study will include 30 patients with schizophrenia or related psychotic disorders and 30 matched healthy controls.

Basic Research

Martin Munz, Ph.D., University of Alberta, Canada, has developed a new technique called parauterine imaging that allows for in vivo subcellular resolution microscopy, in vivo pharmacology, and in vivo targeted single cell patch clamp recordings from cortical cells in a developing mouse embryo. This method opens new ways to study embryonic cortical circuit formation and will allow the team to explore how cortical development is impacted by DNA mutations associated with autism spectrum disorder, schizophrenia and ADHD. Here the focus is on how changes in the expression of three high-confidence autism risk genes (Pten, Chd8 and Grin2b) that are also associated with schizophrenia and ADHD impact neuronal circuit development. They will observe if changes in the expression of these genes leads to changes in circuit development and physiology in mice.

Basic Research

New Technologies

Emmanuel Mwesiga, M.D., Ph.D., Makerere University, Uganda, has found that meat and legumes appear to protect against cognitive impairment, while cassava worsens cognitive impairment, in Ugandan first-episode schizophrenia (FES) patients. These novel findings have been cautiously received. Assigning a specific food as an exposure may have led to a misclassification bias, given that different food groups contain various dietary intake biomarkers (DIBs) that may or may not be related to cognitive impairment. Further, it is essential to account for the influence of biological (genetics, immunology, sex, gut microbiota), clinical (diagnosis, drugs and physical exercise,) and environmental (welfare, cultural beliefs, food portions, cooking styles and eating patterns) factors on generation of DIBs. This project reflects the need to improve dietary exposure assessment, via nutrimetabolomics, an intersection of metabolomics and nutrition research, to objectively examine dietary exposure. It will 1) examine the dietary intake biomarkers generated from nine food groups in FES patients and healthy controls; 2) examine the effect of biological, clinical, and environmental factors on the dietary intake markers generated in Ugandan first-episode schizophrenia patients and healthy controls. Twenty first-episode schizophrenia patients and matched controls will be enrolled for this one-year observational study.

Basic Research

Lingdi Nie, Ph.D., Krembil Research Institute/University Health Network, Canada, studies 15q13.3 microdeletion syndrome, a neurodevelopmental and genetic disorder with a deleted region of chromosome 15 containing 10 genes that occurs in about 1 in 55,00 people. It manifests soon after birth and is strongly associated with autism spectrum disorder, epilepsy, and schizophrenia. While previous studies have focused on mouse models of 15q13.3 microdeletion, there is no understanding of the dysfunctional human brain circuits or signaling networks underlying the microdeletion. Using control and patient 15q13.3 microdeletion stem cell lines (5 families), the team generated an in vitro 3D human brain model (a brain organoid) and fused brain region-specific organoids to make synthetic circuits named assembloids. The specific type of assembloid to be used in this project is a dorsal-ventral forebrain assembloid. They will investigate whether impaired inhibitory neurons in 15q13.3 microdeletion cause neural circuit dysfunction in the assembloids.

Basic Research

Suzanne Nolan, Ph.D., Vanderbilt University, studies the mesolimbic dopamine system, implicated in the etiology of substance use disorder, schizophrenia, and major depression. Dopamine release in the nucleus accumbens (NAc) terminals and input-mediated plasticity upstream of cell bodies within the ventral tegmental area (VTA) have been explored. This project seeks to probe the role of non-canonical forms of release such as somatodendritic release at the level of cell bodies in the VTA, a part of midbrain dopamine (mDA) release. Specifically, she will study how mDA release relates to time-locked behavioral events and its overall functional significance in the specific context of reward learning. The work will test the hypothesis that mDA release is a distinct axis of mesolimbic dopamine signaling, and therefore represents a novel target for therapeutic control of motivated behaviors.

Basic Research

Christopher Parkhurst, M.D., Ph.D., Weill Cornell Medical College, has in past work found that in mice, dysbiosis, or a change in the composition of the gut microbiome, results in impaired fear-extinction seen in schizophrenia patients and in mouse models of schizophrenia, as well as altered neuronal function within the medial prefrontal cortex (mPFC). These neuronal and behavioral abnormalities are the result, he has since shown, of a group of microbiota-derived chemical messengers that alter the interaction of microglia, the immune cells of the brain, and neurons. The goals of this project are to understand (1) how these messengers are sensed by microglia, and (2) how they are disrupted in patients with schizophrenia, with the ultimate goal of developing novel therapies targeted at modulation of the gut microbiota.

Basic Research

Danielle Pratt, Ph.D., Northwestern University, is interested in the role of mental imagery in the context of hallucinations and other perceptual abnormalities experienced in psychosis and schizophrenia. For people with psychosis, she notes, it is theorized that too much weight is given to prior mental models, causing a failure in model updating upon mismatches, and leading individuals to perceive prior predictions as sensations in the absence of stimuli. Others, investigating the mechanisms of mental imagery in non-psychiatric populations, find that when imagined signals are vivid enough, they can become subjectively indistinguishable from reality. This study will examine the role of mental imagery in perceptual abnormality formation using samples of people at clinical high-risk for psychosis (CHR) who experience perceptual abnormalities (N = 40), CHR individuals who do not experience perceptual abnormalities (N = 40), and healthy controls (N = 40). Among the aims is to examine whether the mechanisms of mental imagery can be incorporated into a predictive coding model to create a more complete understanding of how perceptual abnormalities occur.

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Basic Research

Diagnostic Tools/Early Intervention

Rajyashree Sen, Ph.D., Columbia University, hopes to determine how the dorsomedial prefrontal cortex (dmPFC) encodes individual identities and processes social memory, and how such neural encoding may be impaired in schizophrenia. The exact processes by which the dmPFC encodes and preserves individual identity representations remain elusive, and such representations have not yet been studied in mouse models of schizophrenia. Dr. Sen has developed a quantitative social paradigm which allows a freely behaving test mouse to interact with multiple stimulus animals, as he records the activity of excitatory neurons at single-cell resolution in the dmPFC. This project involves determining how the dmPFC's identity and social memory representations are affected in a schizophrenia mouse model, aiming to uncover the mechanisms by which the dmPFC influences social cognition deficits in schizophrenia.

Basic Research

Satoshi Terada, Ph.D., Columbia University, suggests that neural oscillations, rhythmic electrical patterns observed in electroencephalography (EEG), represent potentially reliable biomarkers for diseases such as schizophrenia. Dr. Terada says most studies on neural oscillation biomarkers have targeted limited oscillation patterns that rely on arbitrary and conventional frequency ranges, attempting to evaluate symptoms alone. Successful applications have yet to be achieved. To tackle this challenge, he proposes a novel framework for analytical models of neural oscillations—novel computational models of neural oscillations to predict multi-level dysfunctions in neuropsychiatric diseases. He will use an integrated system of ultrafast 3-dimensional acousto-optical deflector microscopy with a novel real-time motion correction platform and transparent graphene electrodes, and will conduct 2-photon voltage imaging from soma and dendrites of single pyramidal cells in WT and Df(16)+/- mice. The goal is a comprehensive diagnostic framework of disease related neural abnormalities across synaptic, cellular, and circuit levels.

Basic Research

New Technologies

Ai Tian, Ph.D., University of Calgary/The Hospital for Sick Children, Canada, notes that administration of early-life immune challenges in animal models has resulted in postnatal behavior changes. This suggests a potential causal role for inflammation in schizophrenia. Microglia, the main immune cells of the central nervous system, are pivotal players in inflammation. Further study of association between schizophrenia, microglia, and inflammation requires an in vitro platform that resembles the human brain. Dr. Tian has developed a 3D co-culture platform by building assembloids containing neurons, astrocytes, and microglia derived from isogenic human pluripotent stem cells. In this project, the platform will be challenged with proinflammatory cytokines that mimic maternal immune activation and/or genetic variants associated with patients, to investigate the impact of inflammatory dysregulation on neuroimmune mechanisms of schizophrenia.

Basic Research

Ralitsa Todorova, Ph.D., Collège de France, France, notes that hippocampal dysfunction in schizophrenia is characterized by hippocampal atrophy as well as hippocampal hyperactivity. The former may be related to some of the negative symptoms of schizophrenia, including impaired episodic memory, while the latter has been linked to some of the positive symptoms, most notably hallucinations. Yet the neural mechanism linking hippocampal hyperactivity to hallucinations remains unclear. Recent advances in neural recording technology and decoding techniques now make it possible to reliably decode sensory activity from neuronal activity. This project aims to leverage these innovations to directly detect

hallucinatory activity in visual areas in a mouse model of schizophrenia in a sensory conditioning paradigm designed to induce hallucinations.

Basic Research

Halide Turkozer, M.D., Harvard University/McLean Hospital, proposes we don't know enough about the biological diversity and distinct risk groups among youth at familial high risk for psychosis and psychotic disorders such as schizophrenia. This makes it hard to predict who might develop psychosis and to formulate effective ways to prevent it. The goal in this project is to identify subgroups among familial high-risk children (ages 9-10) based on neurocognitive functioning in the baseline Adolescent Brain Cognitive Development (ABCD) Study dataset. The team will investigate these subgroups' likelihood of developing psychotic-like symptoms and psychosis-related brain patterns in the 2- and 4-year follow-up data. They predict familial high-risk children who show neurocognitive impairments at baseline are at a higher risk for developing psychotic-like symptoms and psychosis-related brain patterns later in adolescence. Results could advance psychosis research by identifying a specific target group for preventative interventions during childhood.

Basic Research

Diagnostic Tools/Early Intervention

Alban Voppel, Ph.D., McGill University, Canada, will use neuroimaging, natural language processing (NLP), and neuromodulation to investigate and address alogia (speech difficulties) in schizophrenia. Among other things this project will use advanced NLP techniques to quantify negative speech features from recorded interviews, related to prosody, speech density, and fluency. Using large datasets from the Psychosis Consortium and the completed TOPSY study, comprising 370+ individuals, the team will analyze speech samples collected during standardized tasks and correlate these NLP-derived variables with assessments of alogia. This will enable them to map language variables to clinically rated symptom severity. They will also investigate neural circuitry underlying alogia by mapping frontotemporal connectivity using resting-state functional magnetic resonance imaging (fMRI). By examining the relationship between measured speech characteristics and brain connectivity patterns in the TOPSY set of participants they seek to understand the neural basis of expressive speech deficits in schizophrenia.

Basic Research

Ryan Walsh, Ph.D., Memorial Sloan-Kettering Cancer Center, proceeds from studies of patient data implicating PVALB+ cortical interneurons in cellular processes implicated in schizophrenia. PVALB+ cells are a subtype of inhibitory neuron that regulates local network activity in the cortex. Studying the specific function of these neurons in schizophrenia is difficult, as they cannot be safely isolated from patients and prior attempts to produce them in the lab have not demonstrated cells possessing necessary levels of maturity and functionality. To address this issue, the team has developed a human pluripotent stem cell (hPSC)-derived cerebral organoid that supports the derivation and maturation of bonifide PVALB+ cortical interneurons. They will use a cortical assembloid system to define schizophrenia-associated defects in cortical interneurons, both early developmental defects in immature interneurons and late cortical network-level defects in cortical assembloids containing mature PVALB+ interneurons. The platform may have utility in screening future novel treatments.

Basic Research

Veith Weilnhammer, M.D., Ph.D., University of California, Berkeley, asks: How do hallucinations acquire their content? The team will investigate hallucinatory experiences in humans as well as in artificial neural networks that are trained to recognize objects. The responses of artificial neural networks closely resemble the activity of neurons that play a part in human object recognition. Yet, just like humans, artificial neural networks can be prone to "hallucinate" objects that are not present in their input. This project aims to elucidate whether artificial hallucinations can improve our understanding of human hallucinations. It will entail systematic investigation of the phenomenon of visual hallucinations in artificial neural networks and human participants. By studying convergences between biological and artificial neural networks, the work could generate a fine-grained computational model that simulates hallucinatory experiences in machines. By linking human behavior and neuroimaging to artificial neural networks, it has the potential to translate into future clinical innovations for the diagnosis and treatment of psychotic disorders such as schizophrenia.

Basic Research

Frederike Winkel, Ph.D., University of London/Maudsley Hospital/King's College London, UK, seeks to understand the developmental trajectory of schizophrenia pathology and identify novel treatment strategies that will alleviate a wider spectrum of schizophrenia symptoms. Previous work from the lab has shown that reducing excitatory synapses received by parvalbumin (PV)-expressing interneurons through specific deletion of tyrosine kinase receptor ErbB4 causes a schizophrenia-like phenotype through increased cortical excitability, impaired gamma oscillations, and disrupted cognitive function. Unpublished results show abnormally increased locomotor activity and elevated dopamine levels in the dorsal striatum of these mice. In this project, the aims are to explore how interneuron dysfunction in the forebrain causes hyper-

dopaminergia in the striatum, and, subsequently, whether normalizing interneuron function can prevent and/or interrupt the progression of schizophrenia pathology in mice.
Basic Research

Nicholas Wright, Ph.D., University of North Carolina at Chapel Hill, is interested in receptors for glutamate, the main excitatory neurotransmitter; dysregulation of these receptors is strongly associated with schizophrenia. He notes targeting of metabotropic glutamate receptors (mGluRs) has high therapeutic potential, in view of studies showing that group II mGluR (mGluR2/3) agonists ameliorate psychosis induced by blockers of NMDA receptors. Promising drug leads have failed in clinical trials, possibly because distinct mGluR subtypes form heterodimeric assemblies in the brain. Additionally, it remains to be seen what other effectors and signaling partners mGluRs physically interact with at chemical synapses. To interrogate these fundamental questions, this project seeks to investigate the structural architecture and functional properties of native mGluR assemblies isolated from brain tissue.
Basic Research

Yingying Zhang, Ph.D., Harvard University/Boston Children's Hospital, has established a human C4A transgenic mouse model. Genetic studies have identified that higher copy number of complement component C4A, a key component of innate immunity, is a major risk factor for schizophrenia. Mice overexpressing C4A exhibit excessive complement-mediated microglia engulfment of neuronal synapses and develop neuropsychiatric phenotypes resembling negative symptoms in schizophrenia. The team's preliminary data identify increased monocyte infiltration into the choroid plexus (ChP), accompanied by hydrocephalus and dramatically enlarged cerebral ventricles (ventriculomegaly), in HuC4A-overexpressing mice prior to the onset of behavioral anomalies. This project aims to elucidate the mechanism of how complement overactivation can cause ChP inflammation and ventriculomegaly, and investigate a causal relationship between ChP inflammation and schizophrenia-like neuropsychiatric manifestations.
Basic Research

Xiaoqing Zhou, Ph.D., Harvard University/Massachusetts General Hospital, seeks to bridge the gap in our comprehension of schizophrenia by pinpointing specific brain circuits and malfunctions. This project focuses on the thalamus, which acts as a communication hub, passing information to various cortical areas, critical for cognition and sensory processing. Understanding how thalamic connections with the cortex might contribute to schizophrenia is at the forefront of current research. The project employs a mouse with a genetic mutation linked to schizophrenia in humans that displays behaviors and brain patterns that mirror those in the disorder. The use of sophisticated imaging, specifically high-field 14T functional magnetic resonance imaging (fMRI), will offer a window into the brain's workings, illuminating the interplay between the thalamus and the anterior cingulate cortex—a region implicated in the emotional and cognitive symptoms of schizophrenia.
Basic Research

Xiyu Zhu, Ph.D., Gladstone Institutes/University of California, San Francisco, notes that cognitive inflexibility is a transdiagnostic dysfunction observed in various psychopathologies, including schizophrenia and autism spectrum disorder. The team's recent study uncovered a novel callosal projection from parvalbumin (PV) neurons in the prefrontal cortex (PFC) that can bidirectionally regulate cognitive flexibility behaviors. Building on these findings and other genes identified by the Schizophrenia Exome Sequencing Meta-analysis Consortium (SCHEMA), they now aim to determine if PFC callosal PV (cc-PV) circuitry represents a common pathway through which genetic risks contribute to schizophrenia- or ASD-related cognitive deficits. This study promises novel insights into the etiology of these disorders and holds significant translational potential for improving diagnosis and developing biomarker-guided treatment.
Basic Research

SUICIDE PREVENTION

Laika Aguinaldo, Ph.D., University of California, San Diego, will use machine learning to better understand the power of brain and behavioral patterns to predict the emergence of substance use, suicidal thoughts and behaviors (STBs), and their co-occurrence. The team will use data from the NIH's ongoing Adolescent Brain Cognitive Development (ABCD) study, which has gathered data from 11,878 children, ages 9-14, across the US. They will examine factors such as brain structure and function, behavior, substance use, and demographic details at different stages of development. The aim is to identify structural and functional brain and neurobehavioral features at early timepoints (at baseline and year 2) associated with changes over time in substance use, STBs, and substance use and STBs together at subsequent time points (year 2 and year 4).
Diagnostic Tools/Early Intervention

Brian Albanese, Ph.D., Texas A&M University, notes longstanding theories of suicidal thoughts and behaviors (STBs) positing they are driven in part by the desire to escape or avoid intense emotional distress. Individual differences in sensitivity to aversive avoidance, he proposes, may place some at heightened vulnerability. He will use event-related potentials (ERPs) to index appetitive and aversive avoidance reward activity and

employ ecological momentary assessment (EMA)—moment-to-moment assessment tools—with the hope of predicting short-term, dynamic changes in suicide risk. One aim is to explain real-time, ecologically valid changes in suicide risk during an intensive follow-up period. The study will recruit adult participants (N = 60) with major depressive disorder: 30 with clinically significant suicidal thoughts and 30 never-suicidal depressed controls.

Diagnostic Tools/Early Intervention

Hongsheng Gui, Ph.D., Henry Ford Health System, seeks to better understand the phenotypic and genetic relationships between social isolation and suicidality in population-based and community-based samples. One part of the research will consist of cross-phenotype genetic epidemiology analyses to address in parallel different aspects of putative connections from social isolation to suicidality. Another part will leverage a collaboration with local aging service agencies and primary care medical centers to collect targeted survey responses (every 6 months) from the community-based samples (n=200). These will be used to investigate the temporal relationship between social isolation and changes in suicidality. This project will be an early attempt to use all these unique and generalizable genomic and phenomics data sources together to answer important questions on the causal pathway from social isolation to increased suicide risk in different ancestry groups.

Diagnostic Tools/Early Intervention

Sarah Herzog, Ph.D., Columbia University, proceeds from evidence in peripheral blood, cerebrospinal fluid (CSF), post-mortem brain tissue, and neuroimaging studies demonstrating a role for altered excitatory glutamate (Glu) and inhibitory GABA neurotransmission in the pathogenesis of suicidal behavior in depressed individuals. While the precise mechanism linking Glu/GABA to suicide risk is unclear, a potential link in this relationship may implicate physical pain processing. This project will use functional magnetic resonance spectroscopy in 50 currently depressed subjects with and without a recent history of suicidal behavior to establish: 1) whether suicidal behavior in depression is associated with altered Glu/GABA concentrations in the anterior cingulate cortex (ACC); 2) whether pain-responsive dynamic brain Glu/GABA activity in the ACC differs as a function of history of suicidal behavior; and 3) the relationship of pain-responsive dynamic brain Glu/GABA activity in the ACC to subjective pain ratings and pain tolerance.

Basic Research

Liat Itzhaky, Ph.D., Columbia University, is interested in the safety planning intervention (SPI), a brief, protocol-driven suicide prevention tool that assists the individual at suicide risk in recognizing and knowing their warning signs for an emerging suicidal crisis. It also helps the person identify personalized coping strategies, based on the elements of distraction and interpersonal support, to employ to stop the escalation of the crisis and prevent suicidal behaviors. The effectiveness of using the SPI's coping strategies has never been evaluated in adolescents, and mediators of its effect on mitigating suicide risk are unknown. This project seeks to evaluate the effectiveness of using the SPI's coping strategies to reduce suicidal ideation severity, frequency, and duration among depressed adolescents and to examine the mediating effect of stress reduction. The hypothesis is that the use of distraction strategies and interpersonal support, established through the use of the SPI, will reduce the experience of stress and, thus, decrease suicide risk. A randomized control trial will be conducted with 88 depressed adolescents.

Diagnostic Tools/Early Intervention

Kiera James, Ph.D., University of Pittsburgh, will test a theory pertinent to suicide prevention. A brain-based measure of internal attention to social threat information, she hypothesizes, may help identify disrupted processing of competing and potentially positive socio-affective cues that promote social connectedness, which in turn may lead to increases in suicidal thoughts and behaviors (STBs). The more teen girls remember and think about cues of social threat, she proposes, the more they will look for similar cues in their future social interactions, which may prevent them from processing other cues (e.g., a smile) that foster a sense of connectedness. The team will use a machine learning approach to multivariate pattern classification of participants' brain waves (EEG) in response to cues of social threat (i.e., angry faces) during the delay period of a novel working memory task. This approach will be used to assess enhanced representation of social threat information in working memory, signaling sustained internal attention to such information. 50 female youths aged 12-17 will be recruited who are at high risk for STBs based on a recent history of STB or self-harm. Data will support recruitment for a new study visit during which participants will complete the EEG working memory task.

Diagnostic Tools/Early Intervention

Bora Kim, M.D., Stanford University, seeks to trace the neural network effects of intermittent theta burst stimulation, a rapid-acting non-invasive brain stimulation therapy that has been very effective in treating major depression. A targeted and accelerated version of iTBS (aiTBS) in which treatments are given over 5 days is the basis of Stanford Neuromodulation Therapy (SNT), approved in 2023 by the FDA for commercialization. It might be considered a rapid anti-suicide modality; however, evidence of its mechanism regarding its stimulation effect on reducing suicidality is still understudied. This study aims to bridge this gap by investigating the neural network effects of aiTBS on improvement in

suicide-related symptoms. Through a comprehensive whole-brain approach analysis of functional connectivity patterns, the team seeks to examine suicide-specific neural networks that benefit from aiTBS. They will utilize an existing dataset from a randomized controlled study applying SNT to treatment-resistant depression.

Next-Generation Therapies

Junsung Woo, Ph.D., Baylor College of Medicine, wants to know more about how astrocytes contribute to circuit dysfunction associated with depression. The team has reported that astrocyte transcription factor NFIA plays an essential role in the physiological activities of astrocytes, neuronal circuit activity, and brain function in the adult hippocampus. This has led to the hypothesis that astrocytic NFIA contributes to depression and associated suicide by regulating amygdala circuit function. To determine whether astrocytic NFIA affects amygdala circuit function and associated depressive behaviors, the team uses NFIA gain-of-function (GOF) and loss-of-function (LOF) mouse models. In this project, they will dissect amygdala-specific NFIA transcriptional networks and confirm this in human samples. They seek to determine the role of astrocytic NFIA in amygdala circuit activity and function using NFIA GOF and LOF mice models. Further, they hope to decipher how astrocytic NFIA regulates amygdala circuits through the GABA-MAOB pathway. (MAOB is a monoamine metabolizing enzyme.) They seek to identify the target gene of NFIA using RNA sequencing and manipulate the target gene with pharmacological and genetic tools.

Basic Research

Institutions of the 2024 Young Investigators, at the time of grant award

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Arizona State University

Barcelona Institute for Global Health, Spain

Baylor College of Medicine

Brown University/Ocean State Research Institute, Inc.

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Dell Medical School, University of Texas at Austin (3)

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