BRAIN & BEHAVIOR RESEARCH FOUNDATION

2023 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."

October 2023

We are pleased to present the 2023 Young Investigator grantees of the Brain & Behavior 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 awarded more than $450 million to fund 6,500 grants to more than 5,400 leading scientists around the world.

This year, the Foundation's Scientific Council, led by Dr. Herbert Pardes and comprised of 180 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 2023 Young Investigators are focused on a broad range of psychiatric illnesses. More than half of all projects are relevant to the study or treatment of depression and schizophrenia. Addiction/substance-use disorders, anxiety, and PTSD are also at the focus of many of the 2023 projects, reflecting their prevalence in the population and the critical need for new and improved treatments.

Our new grantees are at the cutting edge of progress in brain and psychiatric research. Ten of the 2023 grantees will be using a technology for their studies that was developed and first used by several past grantees. Called iPSC (inducted pluripotent stem cell) technology, it harnesses the power of stem cells, the "mother cells" from which all the body's cells develop. iPSC technology enables researchers to sample skin cells from individuals with serious illnesses and reprogram them in the lab to redevelop as neurons and other brain cells. This year's grantees will use this method to study the origins of pathology in schizophrenia, autism, OCD, ADHD, and PTSD—in a way that was not possible just a few years ago.

Non-invasive brain stimulation is another technology that past BBRF grantees have pioneered, and is being used by a number of young scientists. One 2023 grantee will investigate the potential effectiveness of low-intensity focused ultrasound (LIFU) to treat anxiety and depression; another grantee will explore its possible use in treating aspects of schizophrenia. A third grantee will study the application of transcranial focused ultrasound (tFUS) in such illnesses as PTSD, anxiety, and OCD.

Reflecting the explosion of interest in psychedelics, seven projects explore the mechanisms through which psychedelic drugs such as psilocybin appear to bring relief to at least some people with depression and PTSD. Other researchers are focused on the gut microbiome—the collection of microorganisms that populate our gut. Four 2023 grantees will investigate aspects of what is sometimes called the "gut-brain axis." Eight research projects attempt to uncover why the sexes are affected in divergent ways in certain neuropsychiatric disorders.

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.
President & CEO

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*These statistics reflect the fact that many projects are relevant in more than one category; in the pages that follow, grantee project descriptions appear under each relevant category

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" BBRF Young Investigator grants have led to groundbreaking research that has improved the lives of people living with mental illness. These early-career scientists are making significant strides in basic research, early intervention and diagnostic tools, new technologies, and next-generation therapies that will offer the best hope for change and advances in treatments for brain and behavior illnesses."

Herbert Pardes, M.D.
President of the BBRF Scientific Council
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SINCE 1987

AWARDED

6,500

GRANTS

FUNDED

$450M+

GRANTS

THE 2023 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.2 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

713

YOUNG
INVESTIGATOR
APPLICATIONS

150

YOUNG
INVESTIGATOR
GRANTS
AWARDED

$10.2

MILLION AWARDED
IN YOUNG
INVESTIGATOR
GRANTS

RESEARCH CATEGORIES

Basic Research (114 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (43 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (13 Grants)
To recognize early signs of mental illness and treat as early as possible

New Technologies (7 Grants)
To advance or create new ways of studying and understanding the brain

About 76 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 29 percent of the 2023 grants fund projects that specifically aim to develop **next-generation therapies.**

About 9 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-six percent of grantees are from the United States (114 grantees). Twenty-four percent of grantees come from 16 other countries (36 grantees): Australia, Austria, Brazil, Canada, Denmark, France, Germany, Ghana, India, Italy, Norway Portugal, The Netherlands, Spain, Sweden, United Kingdom.

THE 2023 BBRF YOUNG INVESTIGATOR GRANTEES

ADDICTION / SUBSTANCE-USE DISORDERS

Lillian J. Brady, Ph.D., Vanderbilt University, notes the stark disparity between the prevalence and prognosis of substance use disorder (SUD) in females, and the paucity of data describing the unique neural circuitry underlying sexual dimorphisms in SUD. This research seeks to define how sexual dimorphism in dopamine system regulation and function underlie differences in reward learning. To better understand how estradiol exerts effects through nicotinic acetylcholine receptors (nAChRs) and how that relates to SUD, the team will test the hypothesis that extracellular calcium levels contribute to estradiol potentiation of dopamine release through nAChR activation. They will investigate sex differences and estradiol regulation of extracellular calcium effects on endogenous and exogenous nAChR activation. They also will test the hypothesis that estradiol potentiation of dopamine release alters sex-specific behavioral responses to sensory reinforcement through α4-nAChRs.
Basic Research

Sarah J. Brislin, Ph.D., Rutgers University, is interested in comorbidity in addictive disorders like substance use disorders (SUD) and gambling disorder. 24% of individuals with alcohol use disorder (AUD) also meet criteria for nicotine dependence, and individuals with gambling disorder are up to 6 times more likely to have a comorbid substance use disorder. This study will provide pilot data for a long-term research program aimed at identifying and discriminating between neural factors that contribute to risk across addictive disorders and those that selectively contribute to the expression of specific clinical presentations (i.e., risk specific to alcohol use disorder). The team will examine how 1) genetic liability for SUD and related behaviors and 2) key environmental factors such as trauma exposure and neighborhood enrichment moderate associations between neural signatures of inhibitory control, reward responsivity, and emotion processing. The study will collect neuroimaging (structural, functional) data from 70 adults enrolled in treatment at the Rutgers University Behavioral Health Center who endorse concerns related to substance use or gambling.
Basic Research

Julia M. Cox, Ph.D., Northwestern University, has developed a decision-making task for mice based on natural foraging behavior. This enables analysis of how mice use expected benefits and costs when deciding whether to pursue drug or non-drug rewards. The team will compare performance in this task before and after mice are exposed to opioids to identify how opioid dependence changes how choice is affected by costs and benefits associated with drug and non-drug rewards. They will monitor neural activity in the striatum before and after exposure to opioids, to see changes in how these neurons represent information about drug and non-drug rewards following opioid exposure. They also will inhibit these neurons before and after opioid exposure to understand how they causally contribute to reward-seeking behavior and to identify how their control is changed by opioid dependence.
Basic Research

Prashant C. Donthamsetti, Ph.D., Vanderbilt University, believes the next frontier in understanding the relationship between dopamine circuits, reward, and addiction will be to uncover the activation dynamics and behavioral roles of specific subpopulations of dopamine receptors in the brain. The team is developing a toolkit that will allow them to detect and manipulate dopamine receptor function in behaving animals with receptor subtype, cellular, subcellular, and spatiotemporal specificity. They will use a novel biosensor to measure the activation profile of dopamine receptors in behaving mice, as well as the acute and long-term effects of cocaine on this pattern of activity. Next, they will use targeted photo-pharmacology to better understand the behavioral roles of specific dopamine receptors, as well as the effect of cocaine on their function. This may provide insight into how drugs of abuse alter the dopamine system at the molecular level and could guide the development of new therapeutics for treating addiction.
Basic Research

Gabor Egervari, M.D., Ph.D., Washington University, St. Louis, notes that epigenetic mechanisms such as histone acetylation have emerged as key players in the development of alcohol use disorder (AUD). Aetylation of histones, which facilitates DNA accessibility and gene expression, increases in the brain following alcohol exposure. The dynamic and reversible nature of histone acetylation makes this process a promising therapeutic target. Dr. Egervari's prior work showed that the main breakdown product of alcohol metabolism, acetate, is a direct substrate for histone acetylation in the brain, which in turn drives the expression of genes related to learning and memory. This novel and surprising epigenetic effect of alcohol metabolites is mediated by the nuclear metabolic enzyme ACSS2 (Acetyl-CoA Synthetase

2). This study seeks to establish the ACSS2-dependent epigenetic effect of alcohol metabolites as a critical pathway underlying voluntary alcohol consumption and to identify novel molecular mechanisms that drive drinking.

IDCII *Basic Research*

Yasmin Escobedo Lozoya, Ph.D., Harvard Medical School/Harvard University, seeks to build on her recent discovery of a specialized subtype of brain serotonin-producing neuron (r2Hoxa2-Pet1) that controls the strength or durability of cocaine-reward memory and cocaine-seeking behavior. This neuron group has the potential to communicate with and regulate downstream neural circuits in the brain through the deployment of serotonin and glutamate. Dual transmitter release raises the possibility of signaling across different time scales and valence, with serotonin acting more slowly, exerting excitatory or inhibitory influence depending on the nature of the receptor expressed by the downstream neurons, and glutamate acting quickly, with excitatory influence. In addition to possible dual signaling ability, these r2Hoxa2-Pet1 neurons display a unique axon specialization that ensheaths the targeted neuron cell body with numerous connections (boutons) that form a pericellular basket. The hypothesis is that this configuration confers privileged control over the targeted neuron, suggesting the ability of r2Hoxa2-Pet1 neurons to override other neural inputs and thus significantly influence the firing of downstream neurons and, ultimately, circuit activity that may control the strength of rewarding, drug-related memories.

IDCII *Basic Research*

Giulia R. Fois, Ph.D., Interdisciplinary Institute for Neuroscience–CNRS / University of Bordeaux, France, notes that acetylcholine (ACh) release in the medial prefrontal cortex (mPFC) is essential to numerous cognitive functions; and that disruptions of cortical ACh transmission has been implicated in several disorders, including ADHD, Alzheimer's disease, schizophrenia, and addictive behavior. In rodents, the team will establish the causal role of the cholinergic SI/DB→vmPFC and B→dmPFC projections in attention using ACh pathway optogenetic activation and inhibition. They will characterize how these two ACh projections can alter vmPFC and dmPFC neuronal processes to control attention. This can contribute to better understanding of mPFC neuronal processes underlying attention. In helping advance the neurobiology of attention the research may aid in the development of more effective cognitive enhancer drugs in disorders in which attention is dysfunctional.

IDCII *Basic Research*

Megan E. Fox, Ph.D., Pennsylvania State University, has found that chronic stress and fentanyl abstinence create similar types of damage to neurons in the nucleus accumbens (NAc). She showed that a specific type of NAc neuron (D1-neuron) loses dendrites and that this "dendritic atrophy" drives the behavioral response to stress or opioid abstinence. No studies have directly tested the link between NAc D1-neuron structural changes after stress and the risk for increased intravenous (IV) fentanyl self-administration and stress-induced relapse. This project, using rodents, will test the hypothesis that the dendritic atrophy of D1-neurons after chronic stress increases the vulnerability to self-administer high levels of IV fentanyl; and that the fentanyl experience weakens D1-neurons even further, increasing susceptibility to stress-induced relapse. Some molecules changed by chronic stress may also be changed by fentanyl self-administration; blocking their effects on D1-neurons might reduce stress-induced relapse to opioid-seeking.

IDCII *Basic Research*

Constanza Garcia Keller, Ph.D., Medical College of Wisconsin, notes that a life-threatening event increases the incidence of PTSD, which carries a 30%-50% comorbidity with substance use disorders (SUDs). Such comorbidity results in greater drug use and poorer treatment outcomes. Cannabis is among the most widely used drugs, particularly in veterans and in those suffering from PTSD. Few studies have evaluated the interaction between cannabis use and stress. This project builds on the team's prior finding that key neuroadaptations produced by acute stress and addictive drugs in the cortico-accumbens glutamatergic circuit may be shared, raising the possibility that the shared substrates not only contribute to each disorder individually but may also facilitate comorbid PTSD and SUDs. Understanding biological mechanisms can inform rational drug design to treat comorbid PTSD and SUDs.

IDCII *Basic Research*

Ming-Fen Ho, Ph.D., Mayo Clinic College of Medicine, Minnesota, studies acamprosate, one of the few drugs approved to treat alcohol use disorder (AUD). Only about half of patients achieve optimal outcomes. This project seeks to understand mechanisms underlying variation in acamprosate efficacy and their interaction with the biology associated with alcohol relapse, especially steroid hormones associated with acamprosate treatment response. The team aims to identify baseline steroid hormones associated with treatment response. They hypothesize baseline steroid hormones including testosterone, estradiol, progesterone, cortisol/corticosterone, and aldosterone will differ between patients who maintained sobriety and those who relapse, and that those differences will provide insight into mechanisms involved in variation in drug response phenotypes.

IDCII *Basic Research*

IDCII *Next-Generation Therapies*

Elizabeth N. Holly, Ph.D., Rutgers University, notes adolescent social isolation has been linked to increased vulnerability to psychiatric disorders in adulthood, including major depression, anxiety disorders, and substance use disorders. She proposes that as the dopamine system is undergoing critical maturation during adolescence, adolescent social isolation disrupts dopaminergic development and subsequent function, leading to persistent perturbations in goal-directed behaviors. To test this, she will conduct experiments in rodents to determine how adolescent social isolation changes dopamine dynamics during goal-directed behavior in adulthood, and perform optogenetic manipulations to determine the causality of these changes in dopamine signaling. Elucidating the neural mechanisms driving these effects may open the door for transdiagnostic therapeutic interventions.

Basic Research

Barbara Juarez, Ph.D., University of Maryland, Baltimore, seeks to elucidate the neural substrates involved in short- and long-term opioid withdrawal, with a view to identification of therapeutic targets to mitigate these symptoms. Focus will be on the parabrachial nucleus (PBN). Calcitonin gene-related peptide (CGRP) neurons of the PBN play a critical role in the early sensory processing of aversive spinal and visceral inputs. These neurons the project this information to brain regions involved in aversion. Dr. Juarez hypothesizes that PBN-CGRP neurons are involved in both the short-term and long-term negative symptoms associated with opioid withdrawal.

Basic Research

Robert Kagabo, Ph.D., University of Utah, notes an important excluded group in smoking cessation studies are those with psychiatric illness and substance-use disorders. Dr. Kagabo believes there is an urgent need to understand how smoking cessation interventions work among individuals with these conditions, especially opioid use disorders. He will interview nurses and psychiatric technicians followed by four focus groups of 5–6 psychiatric inpatients who smoke and have opioid use disorders to better understand the smoking behavior and preferred smoking cessation methods, if any, in this population. The team will then conduct a trial in which participants will be randomized in two conditions, either a one-time brief advice or 4 sessions of brief advice. Participants will also receive nicotine replacement therapies (NRT) in form of patches and gum. The trial will be followed by data analysis to understand what methods did better and to explore the association between quitting smoking and psychiatric hospital readmission.

Next-Generation Therapies

Hao Li, M.D., Ph.D., Northwestern University, has demonstrated that the neuropeptide neurotensin (NT), released from the paraventricular nucleus of the thalamus (PVT), can selectively promote reward or punishment learning, depending on the amount released into the amygdala. This suggests NT plays a crucial role in switching between positive and negative valence processing and may be involved in reward-seeking in the face of punishment. PVT neurons receive input from the medial prefrontal cortex (mPFC), and data indicate that inactivating mPFC-PVT inputs suppresses PVT NT neural responses to both reward and punishment-predictive cues, strongly suggesting a role for mPFC inputs in modulating PVT NT release. The central hypothesis of this project is that PVT NT release plays an essential neuromodulatory role in regulating punishment resistance and is gated by the mPFC. The goal is a comprehensive understanding of neuropeptidergic mechanisms in motivated behaviors.

Basic Research

Debora Masini, Ph.D., Stockholm University, Sweden, notes pathological aggression can arise in psychiatric disorders such as bipolar disorder, substance abuse, ADHD, and conduct disorders. Though it is common, clinicians lack treatment options. Pharmacotherapy often involves sedation and physical restraint for the acute stage whereas chronic cases are treated with a combination of mood regulators such as SSRIs, lithium, beta-blockers, and antipsychotics. Sedation carries risk and complicates diagnosis, whereas chronic aggression can be drug-resistant and treatment further limited by side effects. This project seeks a novel treatment strategy, specifically tailored to control aggression across different disease modalities. Dr. Masini will focus on a primary node in the neuronal circuitry that coordinates aggression. Located in the hypothalamus, the PMv works as an "aggression igniter." She aims to describe the plastic changes that occur with experience, particularly when the behavioral motif of aggression first emerges. By comparing neuronal activity in rodents that develop an aggressive phenotype with those that don't, she aims to elucidate how some individuals restrain aggression while others are drawn toward it.

Basic Research
Next-Generation Therapies

Brittany D. Needham, Ph.D., Indiana University, recently characterized a causative link between a small molecule produced by gut microbiota and anxiety-like phenotypes in mice. This molecule, a bacterial metabolite called 4-ethylphenyl sulfate (4EPS), circulates in the host and enters the brain. In mice, 4EPS causes key changes in neurological profiles, including increased brain activity in regions associated with fear and anxiety, aberrant myelination patterns, and exacerbated anxiety-like behavior. In a subsequent clinical trial, the team found that drug treatment that lowered 4EPS exposure led to ameliorated anxiety and irritability scores in teenagers with ASD and comorbid anxiety. This work has established a

direct link between a gut-derived signal and anxiety-related phenotypes in the context of ASD. This project aims to quantify longitudinal urinary levels of 4EPS and six additional related gut-derived metabolites in 200 psychiatric patients diagnosed with a range of conditions including addiction, depression, mood, and anxiety disorders.

◫◫◫ *Next-Generation Therapies*

Ashley C. Parr, Ph.D., University of Pittsburgh, studies mesocorticolimbic dopamine (DA) circuit dysfunction, which is central to several psychiatric disorders that emerge during adolescence, including substance use disorders, mood disorders, and schizophrenia. This circuit continues to undergo specialization during adolescence to support the transition to adult levels of decision-making. Dr. Parr is interested in molecular and epigenetic mechanisms mediating normative and impaired mesocorticolimbic DA innervation during adolescence, including microRNA regulators of gene expression—in particular, microRNA-218, which regulates DCC axonal guidance cue signaling to determine the extent of dopamine connectivity to frontal and striatal systems, disruptions of which lead to aberrant mesocorticolimbic circuit organization and deficits in decision-making processes. microRNA-218 can be measured in human saliva, providing a potential readout of its expression in the brain. The team will obtain novel saliva indices of microRNA-218, aiming to develop a model of mesocorticolimbic DA maturation.

◫◫◫ *Basic Research*

William E. Pelham III, Ph.D., University of California, San Diego, who studies addiction, will leverage data from a study of 11,880 adolescents assessed repeatedly between ages 9–10 and 19–20 years old. The focus is on three family processes: how frequently and intensely parents argue and fight in the home (conflict); how warm, nurturing, and accepting parents are toward their teen (warmth); and how well parents monitor their teen's whereabouts and activities (monitoring). The team will apply data-driven discovery techniques to identify distinct brain profiles of teens, then evaluate how the impact of conflict, warmth, and monitoring on high-risk drinking and drug abuse differs for teens with each brain profile and whether these differences can be used to more accurately identify teens unlikely to benefit from family-process-focused therapies.

◫◫◫ *Basic Research*
◫◫◫ *Diagnostic Tools/Early Intervention*

David Saunders, M.D., Ph.D., Columbia University, explores mindfulness-based interventions (MBI) for the prevention of substance-use disorders (SUD). The project builds on his randomized controlled trial of a novel MBI for SUD prevention, called "MINDS-UP", and will investigate feasibility, neural mechanisms (functional and structural MRI) and efficacy. The sample consists of 60 adolescents ages 10-14 at high risk for SUD, drawn from a cohort of Puerto Rican youth enrolled in the Boricua Youth Study, an epidemiological study on the development of psychiatric disorders (n=2,491). Participants are randomized to receive either MINDS-UP or a standardized substance-use prevention program. Drawing upon collection of pre- and post-intervention levels of stress biomarkers and subjective reports of stress in the trial, this study seeks to investigate the underlying biologic mechanisms of action underpinning MINDS-UP.

◫◫◫ *Next-Generation Therapies*

Damiano Terenzi, Ph.D., Institut de Neurosciences de la Timone, France, aims to test whether humans suffering from alcohol use disorder (AUD) can modulate their behavior under the influence of a peer's presence; and to assess the neurobiological correlates of such possible modulations. Since addictive behaviors can be considered the result of a lack of inhibitory control leading to compulsive use, the team will exploit a "stop signal task" (SST), a paradigm known to specifically engage brain regions involved in inhibitory control: frontal areas and the subthalamic nucleus (STN). To determine if the social context can influence the control of inhibition and therefore of impulsivity in alcohol addiction, a novel fMRI version of the SST will be performed by 30 individuals with AUD and 30 healthy matched controls under different conditions. The study of proximal social factors and their influence on addiction is a rapidly growing field that holds promise for the development of effective harm-reduction policies.

◫◫◫ *Next-Generation Therapies*

Christopher W. Tschumi, Ph.D., University of Washington, focuses on the mesostriatal pathway, which plays a critical role in reward learning and motivated behavior. Dysfunction in this pathway is associated with disrupted reward processing and is relevant in schizophrenia, autism, and addiction. The Kv3 voltage-gated potassium channel is a protein currently being targeted for pharmacotherapeutics to treat schizophrenia. A drug targeting the Kv3.1 subunit improves mesostriatal network activity and reward processing in schizophrenia patients, but the degree to which Kv3 can be targeted to treat other brain and behavior disorders is not known. This project seeks to understand how better to harness Kv3 activity for the treatment by exploring how it functions physiologically to drive reward processing. Results could provide a framework for studying how Kv3 variants found in human patients disrupt mesostriatal network activity and behavior, a possible basis for new therapeutics.

◫◫◫ *Basic Research*

Andrew M. Wikenheiser, Ph.D., University of California, Los Angeles, is interested in counterfactual thinking—the

ability to think about events that could have happened in the past or that might happen in the future, but that are not presently occurring. This type of thinking is essential for decision-making, including those made in the context of addictive behavior. Previous studies have linked the hippocampus to counterfactual thinking, but it is still unclear how the hippocampus actually enables this type of thinking. To explore this question, the team has developed a rat decision-making task that elicits counterfactual thinking and is well-suited to investigating hippocampal representations. The aim is to determine how the hippocampus contributes to counterfactual thinking about reward. By understanding the neural mechanisms underlying counterfactual thinking, researchers may be able to develop new treatments for disorders characterized by disordered decision-making patterns. *Basic Research*

Andrea S. Young, Ph.D., Johns Hopkins University, will use person- and variable-centered approaches to understanding how racial discrimination, reactions to discrimination, and place, impact substance use and behavioral health service use. The project will utilize data from the most recent longitudinal mental health and substance use survey of the U.S. general population, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), waves 1 and 2. Among the questions explored: Is living in an urban, suburban, or rural area associated with experiencing racial discrimination among Black adults? Are experiences of discrimination and reactions to it associated with substance use and health service use? Does place moderate the association between discrimination/reactions to discrimination and service use? *Basic Research*

Rui Zhang, Ph.D., National Institute on Alcohol Abuse & Alcoholism/NIH, notes that commonly used pharmacological sleep treatments fail to improve sleep or decrease illicit drug use in opioid use disorder (OUD). The team will perform a pilot intervention study for OUD patients to determine effects of bright light therapy (BLT) on circadian rhythm, rest-activity rhythm, and sleep; and to determine effects of BLT on brain function and whether changes in sleep and circadian rhythm mediate the effect. A randomized, placebo-controlled trial will be conducted to assess the effect of a home-based BLT on OUD recovery. Twenty OUD patients will be assigned either to bright white light or to dim-red light placebo for 2 weeks. The hypothesis is that BLT will normalize sleep and circadian outcomes in OUD patients and thereby improve mood and reduce craving. *Next-Generation Therapies*

Qingyu Zhao, Ph.D., Stanford University, will examine 485 adolescents in data from the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), fol-lowing their drinking patterns for 8 years from adolescence through young adulthood. All participants were no-to-low drinkers during high school. The multi-year neuroimaging, behavioral, and neuropsychological measures before age 18 years (capturing brain connectome, personality traits, depression and mood, and cognitive and motor functioning) will be entered into a novel longitudinal multi-modal deep learning model that forecasts the risk of heavy drinking at or after 18 years. To capture the highly variable developmental pathways to heavy drinking onset, the project will study the role of sex and adverse childhood experiences in modifying the pattern of risk factors. Behavioral factors will inform the design of interventional programs by targeting modifiable behaviors, while neural factors will inform the design of novel cognitive behavioral intervention. Findings will shed light on the design of sex-specific preventive programs uniquely tailored to individuals with adverse childhood experiences, as they are associated with higher risk than those without such experiences. *Diagnostic Tools/Early Intervention*

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Davide Aprile, Ph.D., University of Milan, Italy, notes that mutations in a gene called CHD8 are a high-risk factor for the development of autism spectrum disorder symptoms, and a disparate range of behavioral manifestations including OCD, ADHD, and sleep disturbances. To investigate if mutations in this gene could affect brain development and functions of specific cell types, Dr. Aprile will use brain organoids, a 3D in vitro model derived from control and patients' stem cells. He hopes to recapitulate in a dish the brain circuitry disrupted in the cognitive and behavioral manifestations of ASD, OCD and ADHD by fusing in a so-called assembloid three different types of organoids: cortical, thalamic, and cerebellar, and will study how mutations in CHD8 can affect their development and function. *Basic Research*

Gerard J. Broussard, Ph.D., Princeton University, aims to establish the circuit basis of inhibitory control in a cerebellum-dependent task. This is pertinent to the fact that a number of neurodevelopmental disorders, such as ADHD, OCD, schizophrenia, and autism, include an impaired ability to inhibit context-inappropriate behavioral responses. The cerebellum is an important regulator of inhibitory control. Dr. Broussard has developed a cerebellum-dependent motor learning task that requires suppression of response to a moderately intense stimulus to allow a well-timed anticipatory response to an aversive unconditioned stimulus. In this project he aims to track activity in all input pathways to

the cerebellum during task learning and to use viral tracing techniques to establish the parts of the brain where the cerebellum influences activity during the task.
𝕀𝔻𝔻𝕀 *Basic Research*

Giulia R. Fois, Ph.D., Interdisciplinary Institute for Neuroscience–CNRS / University of Bordeaux, France, notes that acetylcholine (ACh) release in the medial prefrontal cortex (mPFC) is essential to numerous cognitive functions; and that disruptions of cortical ACh transmission has been implicated in several disorders, including ADHD, Alzheimer's disease, schizophrenia, and addictive behavior. In rodents, the team will establish the causal role of the cholinergic SI/DB→vmPFC and B→dmPFC projections in attention using ACh pathway optogenetic activation and inhibition. They will characterize how these two ACh projections can alter vmPFC and dmPFC neuronal processes to control attention. This can contribute to better understanding of mPFC neuronal processes underlying attention. This can help advance the neurobiology of attention and may aid in the development of more effective cognitive enhancer drugs in disorders in which attention is dysfunctional.
𝕀𝔻𝔻𝕀 *Basic Research*

J. Wren Kim, Ph.D., University of California, Berkeley, proceeds from emerging evidence suggesting that hyperexcitability of neural circuits underlies many phenotypes of Fragile X Syndrome (FXS), including ADHD, sensory hypersensitivity, seizure, and anxiety. Approximately 80% of children with FXS are also diagnosed with attention deficit disorder (ADD) or ADHD. Dr. Kim maintains that better understanding of hyperexcitability at a neuronal level will bring new insights to many FXS phenotypes, including ADHD. This study involves interrogation of the molecular mechanisms of neuronal hyperexcitability and identification of genetic modifiers of hyperexcitability in FXS using a well-established mouse model of FXS. It is hoped new genetic and molecular perspectives on hyperexcitability will provide mechanistic insights into hyperexcitability-related comorbidities in FXS.
𝕀𝔻𝔻𝕀 *Basic Research*

Nataliia Kozhemiako, Ph.D., Brigham and Women's Hospital/Harvard University, notes that while sex is an important factor with respect to the risk and severity of neurodevelopmental disorders (NDDs), it is unclear whether disrupted sleep manifests similarly in boys and girls. Given that multiple aspects of sleep architecture also show sexually dimorphic normative developmental trajectories, this project seeks to elucidate the effect of sex on sleep neurophysiology across multiple NDDs including ADHD, autism spectrum disorder (ASD), intellectual disabilities, and cerebral palsy. Using data from the National Sleep Research Resource, the team will analyze a large sample of clinical whole-night sleep electroencephalograms (EEG) recorded in children with NDD diagnoses. They will investigate sex differences in sleep structure and timing as well as the prevalence of sleep-related disorders. They will further quantify key facets of sleep neurophysiology by analyzing specific EEG signatures.
𝕀𝔻𝔻𝕀 *Basic Research*

Yang Liu, Ph.D., University of Alberta, Canada, has developed a machine-learning model using large-scale population-level health and surveillance data to identify ADHD among 23,247 kindergarten children, aged 5–6 in 2016, in a 4-year follow-up window. Dr. Liu now will follow this group for 4 more years, and track if they have ADHD between 2020 and 2024. The team has the following goals: 1) to explore the trajectory of ADHD diagnoses for girls and boys separately, 2) to build an ADHD prediction model for girls, 3) to identify predictive risk factors underlying ADHD prediction of girls, and 4) to evaluate whether a model developed in a previous study can predict future ADHD diagnoses beyond the 4-year window used for model training.
𝕀𝔻𝔻𝕀 *Basic Research*
𝕀𝔻𝔻𝕀 *Diagnostic Tools/Early Intervention*

Debora Masini, Ph.D., Stockholm University, Sweden, notes pathological aggression can arise in psychiatric disorders such as bipolar disorder, substance abuse, ADHD, and conduct disorders. Though it is common, clinicians lack treatment options. Pharmacotherapy often involves sedation and physical restraint for the acute stage whereas chronic cases are treated with a combination of mood regulators such as SSRIs, lithium, beta-blockers, and antipsychotics. Sedation carries risk and complicates diagnosis, whereas chronic aggression can be drug-resistant and treatment further limited by side effects. This project seeks a novel treatment strategy, specifically tailored to control aggression across different disease modalities. Dr. Masini will focus on a primary node in the neuronal circuitry that coordinates aggression. Located in the hypothalamus, the PMv works as an "aggression igniter." She aims to describe the plastic changes that occur with experience, particularly when the behavioral motif of aggression first emerges. By comparing neuronal activity in rodents that develop an aggressive phenotype with those that don't, she aims to elucidate how some individuals restrain aggression while others are drawn toward it.
𝕀𝔻𝔻𝕀 *Basic Research*
𝕀𝔻𝔻𝕀 *Next-Generation Therapies*

Marianne Oldehinkel, Ph.D., Donders Institute for Brain, Cognition and Behaviour, The Netherlands, notes that the role of altered dopaminergic signaling in the brain and its link to altered reward processing in ASD and ADHD has not been fully explored because non-invasive brain imaging approaches like MRI are unable to differentiate between

dopaminergic projections and projections from other neurotransmitter systems. Dr. Oldehinkel has shown that dopaminergic projections in the human striatum can be investigated in resting-state functional MRI data using connectopic mapping (CM), an approach for characterizing fine-grained, overlapping modes of functional connectivity in the brain. This project aims to demonstrate that dopaminergic dysfunction is present as a dimensional, cross-diagnostic phenotype in ADHD and ASD. The hypothesis is that the dopaminergic connectivity mode tracks inter-individual differences along a spectrum of altered reward-related behavior across control individuals, individuals with ADHD, and individuals with ASD. The work could reveal a biomarker for diagnosis and (dopaminergic) treatment targeted for individual patients.

IDCI *Next-Generation Therapies*
IDCI *Basic Research*

Alessandro Piccin, Ph.D., Université de Bordeaux, France, proceeds from the idea that a dysfunctional orbitofrontal cortex (OFC) might be central in ADHD pathology. Dr. Piccin has shown that silencing noradrenergic inputs from the locus coeruleus to the ventral and lateral parts of the OFC prevents the update of action-outcome associations following environmental change. This project will examine the possibility that abnormal noradrenergic signaling in the ventral and lateral parts of the OFC underlies flexibility impairments in a rat model of ADHD. The team will attempt to rescue behavioral and brain alterations in the rat model of the disease by using viral technologies and cutting-edge optical approaches to inhibit or excite specific noradrenergic projections while imaging in real-time neural activity in the target regions.

IDCI *Basic Research*

Eszter Szekely, Ph.D., McGill University, Canada, will study the sex-specific effects of prenatal environmental adversity and genetic susceptibility on brain structure and function in childhood ADHD. The team will use a computational approach that enables the streamlined analysis of multiple gene-by-environment interactions (GxE), critical in studying complex phenotypes like ADHD. Data will be derived from three international cohorts (Generation R: N=5,298; GUSTO: N=1,176; and MAVAN: N=590) to study the sex-specific interaction effect of prenatal maternal adversity and offspring polygenic risk for ADHD on ADHD symptomatology; and evaluate whether anomalous fronto-striatal connections, which are key neural correlates of ADHD, can explain this association The ultimate aim is to develop evidence-based sex-specific risk identification and treatment methods for ADHD that take account of sex differences at the genomic, environmental, and neural level.

IDCI *Basic Research*

ANXIETY DISORDERS

Vineet Augustine, Ph.D., University of California, San Diego, notes that changes in cardiovascular physiology like blood pressure, heart rate, and respiration are essential for proper expression of emotional states like anxiety. Yet it is becomingly increasingly clear that these somatic changes may themselves feed back into the brain to influence its activity as wells as behavior. This research leverages the cardiovascular system to understand the role of the body-brain interface in maintaining physiological homeostasis and regulating behavior in anxiety. Specific foci include: 1) What are the genetic, anatomical and functional characteristics of cardiac sensory neurons? 2) How does cardiovascular physiology influence central processing and eventually behavior in anxiety states?

IDCI *Basic Research*

Erica B. Baller, M.D., University of Pennsylvania, is studying mechanisms of anxiety in patients with multiple sclerosis (MS). About half of MS patients are affected. MS is characterized by lesions in white matter; studies of otherwise healthy individuals with anxiety have described associations between white matter variability and anxiety symptoms, specifically in tracts that connect functional hubs of the frontoparietal and default mode networks. Using a technique called lesion network mapping (LNM) in a cohort of 3,737 MS patients, Dr. Baller aims to construct a white matter anxiety network from fascicles that connect the frontoparietal and default mode networks, and examine whether MS lesions preferentially impact fascicles in this network; and to delineate how anxiety in adults with MS is associated with white matter lesion location and burden.

IDCI *Basic Research*

Laurie Bayet, Ph.D., American University, will pilot new ways to measure complex social communication skills in human infants with and without a family history of social anxiety disorder, schizophrenia, or autism. The team will use safe, non-invasive, high-resolution measures of brain activity (fNIRS), looking behavior, and pupil size (eye-tracking). They combine these state-of-the-art tools with machine learning and computational modeling. The object, first, is to measure how infants' brains perceive face movements at 6–8-months; then assess how infants make sense of social communication scenarios at 13–15-months. Finally, the team will examine longitudinal associations between these measures and caregiver reports of infants' social-emotional skills at 18-months. A better understanding of how these skills emerge and contribute to later outcomes may be critical for uncovering how social anxiety disorder, schizophrenia, and autism develop.

IDCI *Basic Research*

Andrea Boscutti, M.D., UTHealth Houston, will use low-intensity focused ultrasound stimulation (LIFU), an emerging technique, targeting the amygdala in individuals with major depression and anxiety. LIFU offers greater precision and the ability to stimulate deep brain structures without damaging adjacent structures. The team will use LIFU to suppress amygdala activity in patients with MDD and moderate to severe anxiety symptoms, and will use MRI, acquired prior to treatment, to simulate the propagation of ultrasound waves into brain tissue, ensuring accurate delivery of the intervention. Subjects will undergo two stimulations sessions. In one, active stimulation will be delivered. In the other, a placebo version of the stimulation will be performed. The hypothesis is that LIFU, by suppressing amygdala activity, can reduce depression and anxiety.

⬛ *Next-Generation Therapies*
⬛ *New Technologies*

Jessica I. Buthmann, Ph.D., Stanford University, is interested in early-life stress (ELS), which is associated with increased risk for the development of psychopathology, in particular, depression and anxiety. The developmental trajectories leading from ELS exposure to vulnerability to or resilience against depression and anxiety are not well understood. The team will use data from a cohort of 220 9- to 13-year-old children, to examine the effects of ELS on psychobiological functioning across adolescence. They will include measures of exposure to ELS (type, onset, duration), caregiving and home environment, neighborhood-level environmental and socio-economic conditions, neural structure and function, and depression and anxiety at four time points across 8 years. The team will use several longitudinal statistical approaches to examine trajectories of depression and anxiety symptoms and will elucidate the roles of ELS, the physical and psychosocial environment, neural structure and function, and their interactions, in predicting the onset of depression and anxiety in adolescence.

⬛ *Diagnostic Tools/Early Intervention*

Cristiana Cruceanu, Ph.D., Karolinska Institute, Sweden, aims to understand how stress hormones and different antidepressants affect brain development during pregnancy, which may affect behavioral and cognitive outcomes in the life of the child; and the risk-benefit balance between chronic exposure to stress hormones during pregnancy and treatment with different drugs. This research will be performed non-invasively, using 3-D models of the human brain derived from stem cells that have been reprogrammed from skin samples of different individuals. This will allow testing of several commonly prescribed drugs to compare the effects of treatment in males and females. This approach could have important clinical implications, as a data-driven risk-benefit score will be devised for clinicians to use when advising their

pregnant or soon-to-be pregnant patients on the best course of antidepressant treatment.

⬛ *Basic Research*

Nicholas Alonzo Frost, M.D., Ph.D., University of Utah, seeks to understand how anxiety-related and social information are differentially encoded within the medial prefrontal cortex (mPFC). In previous work the lab demonstrated that ensemble activity within the mPFC encodes information relevant to social interactions. Preliminary experiments demonstrated that these ensembles are distinct from ensemble activity when the mouse is engaged in anxiety-related behavior. Dr. Frost hypothesizes that social and anxiety-related ensemble activity in the mPFC may be differentially recruited in response to two opposing inputs from the ventral hippocampus (vHPC). He aims to quantify the role of these distinct vHPC projections in the generation of specific ensembles during anxiety-related behaviors and social interaction.

⬛ *Basic Research*

Janos Fuzik, Ph.D., Karolinska Institute, Sweden, studies panic disorder (PD), which has 2.5 times higher occurrence in women than in men. Dr. Fuzik aims to understand the pathophysiology of critical brain circuits in the development of PD. He wants to establish the neuronal identity of highly involved circuits in periaqueductal gray matter (PAG) and investigate how stressful stimuli evoke circuit imbalance in a sex-dimorphic manner leading to maladaptive behaviors in PD. A plethora of neurophysiological mechanisms are influenced by sex hormones, including excitatory-inhibitory balance, neuronal excitability, and inhibitory synaptic transmission. Distinct neuronal subpopulations of the PAG express high levels of estrogen receptor-alpha, and therefore are prone to modulation by estradiol level fluctuations, which may contribute to sex differences in PD. This project seeks to reveal the key neuronal types and their connectivity changes in the ventromedial hypothalamus (VMH)-PAG connectome that underlie panic-like states, and thereby reveal candidate molecular targets for development of new sex-specific treatments.

⬛ *Basic Research*

Marta Garcia-Forn, Ph.D., Icahn School of Medicine at Mount Sinai, aims to investigate the role of the DDX3X gene in the generation and function of glutamatergic neurons, and its contribution to anxiety-like behaviors. Mutations in the X-linked RNA helicase DDX3X cause a neurodevelopmental disorder affecting mainly females and manifesting with intellectual disability, autism spectrum disorder, and often anxiety and self-injurious behaviors. This project will study how alterations in cortical glutamatergic lineages caused by DDX3X mutations lead to behavioral deficits, including anxiety-related behaviors. The project is expected to bring a new understanding of how cortical development shapes

neuronal diversity that contributes to complex behaviors and may shed light on comorbidity between autism and other psychiatric conditions.

DNA *Basic Research*

Erin E. Hisey, Ph.D., McLean Hospital, notes that circuit and molecular deficits that result from early-life trauma (ELT) are not well understood. While animal models of early life neglect are commonly used, models of abuse are nearly absent. She seeks to test such an animal model. Using chronic social defeat stress in juvenile mice (jCSDS), the lab has developed a novel model of ELT that produces profound impacts on behavior and underlying brain activity. One of the areas most strongly activated during re-exposure to juvenile trauma cues is a key component of the hippocampal formation, the lateral entorhinal cortex (LEC). This project will investigate the role of LEC in the retrieval of juvenile trauma memories in the adult brain, aiming to attain in-depth characterization of circuit- and molecular-level changes in the adult brain as a result of juvenile trauma with the object of identifying future targets for modulation in psychiatric disorders resulting from ELT.

DNA *Basic Research*

Elizabeth N. Holly, Ph.D., Rutgers University, notes adolescent social isolation has been linked to increased vulnerability to psychiatric disorders in adulthood, including major depression, anxiety disorders, and substance use disorders. She proposes that as the dopamine system is undergoing critical maturation during adolescence, adolescent social isolation disrupts dopaminergic development and subsequent function, leading to persistent perturbations in goal-directed behaviors. To test this, she will conduct experiments in rodents to determine how adolescent social isolation changes dopamine dynamics during goal-directed behavior in adulthood, and perform optogenetic manipulations to determine the causality of these changes in dopamine signaling. Elucidating the neural mechanisms driving these effects may open the door for transdiagnostic therapeutic interventions.

DNA *Basic Research*

Alexandra S. Klein, Ph.D., University of California, San Francisco, cites accumulating evidence supporting the idea that controlled breathing can have a positive influence on mental and physical well-being. The underlying neuronal circuits mediating this tight coupling between the control and sensation of respiration and anxiety-related behaviors remain unknown. This project aims to determine how breathing influences anxiety-related behaviors and their underlying neuronal dynamics. Dr. Klein will first identify how distinct breathing rhythms are correlated with specific behavior motifs in tests of anxiety-related behaviors in mice. Then, using large-scale electrophysiology, she will determine how

breathing impacts neuronal representations of aversive experiences. Finally, she will ask how direct control of breathing rhythms impacts anxiety-related behavior and neuronal representations of anxiety states. These experiments will provide a mechanistic understanding of the influence of breathing on anxiety-related behaviors and their underlying neuronal dynamics in emotion-related brain regions.

DNA *Basic Research*

Clare A. McCormack, Ph.D., New York University, is curious about how the brain adapts during the perinatal period, noting that remarkably little is known about the maternal brain during pregnancy. A foundational gap, she notes, is that neuroimaging studies of pregnant women have rarely been conducted. She seeks to examine brain change during pregnancy at more than one time point, the underlying neurobiology of change, and associations between brain and mental health in this critical period. This will enhance understanding of individual differences that contribute to risk or resilience (to postpartum depression, among other illnesses) during this life transition. Leveraging and extending an ongoing prenatal study, pregnant women will complete brain MRI scans at two prenatal time points. The team will examine whether different trajectories of change are associated with depression and anxiety symptoms in the postpartum period. The team will also consider key biological variables (pregnancy hormones, stress hormones, inflammation) as potential factors underlying brain changes during this time.

DNA *Basic Research*

Nicky J. Mehtani, M.D., University of California, San Francisco, is interested in the efficacy of psychedelic-assisted therapies in treating demoralization in palliative care populations, such as terminal cancer patients, as well as racemic ketamine, which is increasingly being used to treat mood and anxiety disorders in outpatient settings. Little is known regarding the feasibility, safety, or efficacy of ketamine therapy among medically complex patients. In a double-blind, randomized controlled pilot trial, the team will investigate whether a single administration of oral liquid ketamine (0.5mg/kg or 1.5mg/kg) in combination with four weekly sessions of existential psychotherapy can be used to rapidly treat moderate-to-severe demoralization and reduce opioid analgesia requirements among patients with pancreatic cancer. Participants will be followed for 35 days following ketamine administration.

DNA *Next-Generation Therapies*

Heidi Catherine Meyer, Ph.D., Boston University, studies the development of neural circuitry involved in emotional control. It is her conviction that early intervention during adolescence, when the brain is still highly plastic, may have the greatest impact on reducing the longevity and severity

of mood and anxiety disorders. Citing research suggesting pubertal development triggers a window of opportunity for recalibration of the HPA axis, her team's work considers how the adolescent brain itself may be leveraged to re-route trajectories of brain development. The dynamic functional remodeling of cortico-hippocampal connections in adolescence acts to fine-tune affective neural activity. This project uses functional ensemble tagging techniques in populations of hippocampal neurons to isolate the memory trace associated with a learned safety cue. The team will explore the possibility that engaging ensembles of tagged "safety neurons" intermittently across adolescence may prime the adult brain for enhanced fear regulation.

🧬 *Basic Research*

Brittany D. Needham, Ph.D., Indiana University, recently characterized a causative link between a small molecule produced by gut microbiota and anxiety-like phenotypes in mice. This molecule, a bacterial metabolite called 4-ethylphenyl sulfate (4EPS), circulates in the host and enters the brain. In mice, 4EPS causes key changes in neurological profiles, including increased brain activity in regions associated with fear and anxiety, aberrant myelination patterns, and exacerbated anxiety-like behavior. In a subsequent clinical trial, the team found that drug treatment that lowered 4EPS exposure led to ameliorated anxiety and irritability scores in teenagers with ASD and comorbid anxiety. This work has established a direct link between a gut-derived signal and anxiety-related phenotypes in the context of ASD. This project aims to quantify longitudinal urinary levels of 4EPS and six additional related gut-derived metabolites in 200 psychiatric patients diagnosed with a range of conditions including addiction, depression, mood, and anxiety disorders.

🧬 *Next-Generation Therapies*

Takuya Osakada, Ph.D., New York University, will focus on dissecting the relationship between oxytocin-related neural circuitry and PTSD. Oxytocin receptor (OXTR)-expressing neurons in some brain regions such as the dorsolateral bed nucleus of the stria terminalis are activated by predictable cued fear, suggesting that OXTRs and oxytocin signaling are deeply implicated in PTSD. The team will use mice to dissect circuitry and perform behavioral assays. They have so far identified a hypothalamic oxytocinergic circuit for social avoidance and have established appropriate behavioral paradigms with various stressors such as social defeat.

🧬 *Basic Research*

Bruno Oriol Porras-Garcia, Ph.D., Institut de Bioenginyeria de Catalunya, Spain, seeks to develop preventive interventions for anxiety and depression symptoms in children and adolescents by promoting emotion regulation (ER) through game-based immersive virtual reality (IVE) cognitive training, which allows users to experience immersive, 3-D environments and events. The team will test Enhance VR, an IVR program designed to improve EF and ER skills among subclinical children and adolescents, in a longitudinal, randomized controlled pilot trial involving 80 participants 10 -18 years old, with medium to high risk of developing anxiety and depression disorders. The VR application and a placebo will be given for 30 mins. twice weekly for 5 weeks. The Enhance VR group will engage in six games targeting cognitive flexibility, planning, reappraisal strategies, working memory, divided and sustained attention, and processing speed. Assessments will be made of depressive and anxiety symptoms, ER, executive function (working memory, cognitive flexibility, inhibition, and planning) and attention.

🧬 *Next-Generation Therapies*

Christopher T. Sege, Ph.D., Medical University of South Carolina, will test a cutting-edge neurostimulation technology—transcranial focused ultrasound (tFUS)—as a tool for directly modulating escape/avoidance behaviors that drive impairment in anxiety, PTSD, and OCD. The central amygdala is the key mediator of rapid escape from imminent threat, and is not directly accessible to conventional neuromodulation technologies such as TMS. Dr. Sege will recruit 40 individuals seeking anxiety or related disorder treatment to complete three in-person laboratory visits: a first visit in which brain structure and escape/avoidance-related functional activity are measured with MRI, and two subsequent visits in which an established escape/avoid task is administered before and after receiving tFUS stimulation to the amygdala or placebo stimulation.

🧬 *Next-Generation Therapies*
🧬 *New Technologies*

Tarjinder Singh, Ph.D., Columbia University, is studying rare genetic variation in major depressive (MDD) and generalized anxiety disorders (GAD), inquiry that has been hampered by limited sample sizes and the heterogeneity of these conditions. He will use genetic data generated by national efforts like the UK Biobank and the All Of Us research program to clarify the contributions of common and rare genetic risks in MDD and GAD, generating a high-quality data set containing all common and rare protein-coding, non-coding, and structural variants for patients with MDD and GAD. These data will be used to quantify the contribution of each class of variation—common and rare, coding and non-coding—to disease risk. Detailed electronic health record data will be used to explore how genetic risk relates to the severity and course of these disorders. Analyses should highlight aspects of MDD and GAD that are more genetically heritable.

🧬 *Basic Research*

Sydney Trask, Ph.D., Purdue University, seeks to develop and test therapeutic strategies that mitigate relapse in anxiety and trauma therapy associated with extinction learning. The original fear memory can be targeted to reduce behavioral responding, with the ultimate goal being to reduce maladaptive behavioral responding and leave it less susceptible to relapse. These procedures take advantage of a brief period of time following memory retrieval in which the memory becomes sensitive to disruption: the reconsolidation window. Dr. Trask has developed a behavioral strategy, "UCS deflation," that aims to open the reconsolidation window and present a weaker version of the feared unconditional stimulus. It can blunt behavior in a context-independent manner, suggesting it could be implemented to create behavioral reductions resistant to relapse. This project will extend the team's prior work showing both extinction and UCS deflation result in reduced neural activity in the basolateral amygdala (BLA) and increased neural activity in the infralimbic cortex (IL).
🧬 *Next-Generation Therapies*

Brad Verhulst, Ph.D., Texas A&M University, hopes that by identifying specific adversity-related mechanisms that amplify genetic risk, research can provide a basis to develop biologically-informed evidence-based interventions to support individuals who experience trauma and prevent or reduce the severity of depression and anxiety symptoms. The team will perform a proof-of-concept genome-wide interaction study that demonstrates acute adversity (childhood maltreatment) and chronic adversity (socioeconomic deprivation) amplify individual genetic predispositions to depression and anxiety. These statistical methods will provide tools to identify the amplifying effect of adversity across the genome and for individual genetic variants. They will use a statistical approach to analyze data from two very large genetically informed datasets (N > 650,000). The goal is to understand how adverse life events amplify the genetic mechanisms that increase the risk and severity of depression and anxiety.
🧬 *Basic Research*

Jessica J. Walsh, Ph.D., University of North Carolina at Chapel Hill, studies the neural mechanisms of sociability, which can be impaired in schizophrenia, depression, anxiety, and autism spectrum disorders. She notes that rapid elevation of serotonin activity enhances sociability and promotes appropriate social behavior, and suggests that the speed and degree of serotonin enhancement may be a critical regulator of its therapeutic effects. MDMA causes sharp increase in serotonin levels, but this effect is only temporary, and deficits resume when serotonin levels return to baseline. Dr. Walsh cites preliminary data suggesting a two-dose regimen of the psychedelic compound MDMA can cause lasting increases in sociability in mice with a specific genetic deletion. She seeks to identify the circuit, cellu-

lar, and molecular adaptations underlying this therapeutic phenomenon.
🧬 *Next-Generation Therapies*

Tao Xie, Ph.D., Washington University School of Medicine, suggests that achieving permanent fear reduction in PTSD, anxiety, or other illnesses requires a better understanding of the neural mechanisms mediating fear extinction. Amygdala-prefrontal circuits play a critical role in fear extinction, and rodent experiments suggest the prelimbic area (PL) and the infralimbic area (IL) could facilitate and inhibit fear responding. In humans, it has been hypothesized that the dorsal anterior cingulate cortex (dACC) and the ventromedial prefrontal cortex (vmPFC) constitute the homologues of PL and IL. This project investigates the neural dynamics and causal functions of human amygdala-prefrontal circuits during fear extinction. Clinically-indicated placement of stereoelectro-encephalography (SEEG) electrodes within wide cortical/subcortical networks to record neural signals and deliver electrical stimulation will provide an pportunity to study the dynamics and causal functions of human amygdala-prefrontal circuits at the small (single-neuron units) and large scale (local field potential).
🧬 *Basic Research*

Wen Xin, Ph.D., University of California, San Francisco, notes recent work indicating a crucial role for myelination in the maintenance of fear memory. The neuronal circuit basis for how myelin influences memory is unclear, however. Parvalbumin (PV) interneurons are an inhibitory neuron subtype that critically regulate neural circuits involved in fear memory formation and regulation; they are also one of the most heavily myelinated neuronal populations in the mammalian cortex. Using newly developed genetic tools, Dr. Xin will test the region- and cell type-specific role of parvalbumin neuron myelination in fear memory formation and preservation, as well as circuit activity in the medial prefrontal cortex of mice following contextual fear conditioning. This may shed light on the complex interplay between neural circuits and myelination during memory formation and retrieval.
🧬 *Basic Research*

AUTISM SPECTRUM DISORDER (ASD)

Sarah D. Ackerman, Ph.D., Washington University, St. Louis, suggests changes in the timing of events in the "critical period" in early development are linked to neurodevelopmental disorders including autism, epilepsy, and schizophrenia. Mechanisms that ensure timely critical-period closure remain elusive. Dr. Ackerman proceeds from her past finding in fruit flies that astrocytes (immune cells in the brain) are essen-

tial for closure of a motor critical period. Using that model system, the lab now seeks to alter the function of neurons and astrocytes to extend or restrict neuronal plasticity, and test the behavioral consequences. Given that autism is linked to precocious critical period closure, they will explore whether astrocytes can be leveraged to reopen plasticity in mature circuits; and whether astrocytes are able to shut down plasticity in the adult brain. This could show how astrocytes tune neural plasticity in development to ensure long-term stability of circuit function and behavior.

🧬 *Basic Research*

Davide Aprile, Ph.D., University of Milan, Italy, notes that mutations in a gene called CHD8 are a high-risk factor for the development of autism spectrum disorder symptoms, and a disparate range of behavioral manifestations including OCD, ADHD, and sleep disturbances. To investigate if mutations in this gene could affect brain development and functions of specific cell types, Dr. Aprile will use brain organoids, a 3D in vitro model derived from control and patients' stem cells. He hopes to recapitulate in a dish the brain circuitry disrupted in the cognitive and behavioral manifestations of ASD, OCD and ADHD by fusing in a so-called assembloid three different types of organoids: cortical, thalamic, and cerebellar, and will study how mutations in CHD8 can affect their development and function.

🧬 *Basic Research*

Laurie Bayet, Ph.D., American University, will pilot new ways to measure complex social communication skills in human infants with and without a family history of social anxiety disorder, schizophrenia, or autism. The team will use safe, non-invasive, high-resolution measures of brain activity (fNIRS), looking behavior, and pupil size (eye-tracking). They combine these state-of-the-art tools with machine learning and computational modeling. The object, first, is to measure how infants' brains perceive face movements at 6-8-months; then assess how infants make sense of social communication scenarios at 13-15-months. Finally, the team will examine longitudinal associations between these measures and caregiver reports of infants' social-emotional skills at 18-months. A better understanding of how these skills emerge and contribute to later outcomes may be critical for uncovering how social anxiety disorder, schizophrenia, and autism develop.

🧬 *Basic Research*

Michelle C.D. Bridi, Ph.D., West Virginia University, studies the relation of the ratio between excitatory and inhibitory signaling (E/I ratio) in the brain and pathology in psychiatric illnesses. The E/I oscillation is controlled by multiple mechanisms and is susceptible to dysregulation if any one of these processes is disrupted. Two mechanisms are sleep and endocannabinoid signaling. Preliminary data show decreased

sleep quality and altered timing of endocannabinoid signaling are linked to E/I dysregulation in mouse lines associated with autism spectrum disorder. The team will evaluate how sleep and endocannabinoid signaling are altered, and how they relate to the E/I ratio oscillation, after subchronic PCP administration. In conjunction with their preliminary studies of autism spectrum disorder, the findings in this study could establish whether E/I dysregulation may be a common theme across models of psychiatric conditions.

🧬 *Basic Research*

Gerard J. Broussard, Ph.D., Princeton University, aims to establish the circuit basis of inhibitory control in a cerebellum-dependent task. This is pertinent to the fact that a number of neurodevelopmental disorders, such as ADHD, OCD, schizophrenia, and autism, include an impaired ability to inhibit context-inappropriate behavioral responses. The cerebellum is an important regulator of inhibitory control. Dr. Broussard has developed a cerebellum-dependent motor learning task that requires suppression of response to a moderately intense stimulus to allow a well-timed anticipatory response to an aversive unconditioned stimulus. In this project he aims to track activity in all input pathways to the cerebellum during task learning and to use viral tracing techniques to establish the parts of the brain where the cerebellum influences activity during the task.

🧬 *Basic Research*

Seungwon (Sebastian) Choi, Ph.D., University of Texas Southwestern Medical Center at Dallas, notes that primary sensory neurons that innervate the skin and detect a wide range of somatosensory stimuli are well-characterized, yet little is known about how peripheral signals are integrated, processed, and conveyed to the brain through ascending somatosensory circuits to generate the perception of touch and pain and behavioral responses. This research seeks to determine the pathophysiological role of ascending somatosensory circuitry in sensory dysfunction in ASD and PTSD. The team previously identified two genetically defined ascending circuit modules that cooperate to convey tactile, thermal, and noxious cutaneous signals from the spinal cord to the lateral parabrachial nucleus (PBNL) of the pons to underlie affective aspects (i.e., emotional "feelings") of touch and pain sensation. The PBNL is a "somatosensory gateway" to the higher brain regions because it receives strong, abundant somatosensory inputs from the spinal cord and broadcasts these signals to limbic areas that control social and emotional behaviors. They now will test the idea that the PBNL represents a key node for pathological touch and pain hypersensitivity in ASD and PTSD.

🧬 *Basic Research*

Marta Garcia-Forn, Ph.D., Icahn School of Medicine at Mount Sinai, aims to investigate the role of the DDX3X gene

in the generation and function of glutamatergic neurons, and its contribution to anxiety-like behaviors. Mutations in the X-linked RNA helicase DDX3X cause a neurodevelopmental disorder affecting mainly females and manifesting with intellectual disability, autism spectrum disorder, and often anxiety and self-injurious behaviors. This project will study how alterations in cortical glutamatergic lineages caused by DDX3X mutations lead to behavioral deficits, including anxiety-related behaviors. The project is expected to bring a new understanding of how cortical development shapes neuronal diversity that contributes to complex behaviors and may shed light on comorbidity between autism and other psychiatric conditions.

Basic Research

Taeyoung Hwang, Ph.D., Lieber Institute for Brain Development, Johns Hopkins University, will study the molecular mechanism of LSD1, a histone-modifying enzyme, to gain insight into how LSD1 inhibition works in the pathobiology of schizophrenia. LSD1, an enzyme removing a specific modification of histone or methylation at a lysine residue, has drawn attention as recent studies showed that LSD1 inhibitors can improve behavioral abnormalities in mouse models of schizophrenia and autism. However, the gene regulatory mechanism directed by LSD1 is unclear in neuronal genomes. The team will probe how LSD1 recognizes specific genomic loci in neurons and will investigate RNA's role in LSD1's localization on the genome while exploring an RNA-based target-specific approach to perturb LSD1.

Basic Research
Next-Generation Therapies

Valentina Ignatova, Ph.D., University of Pennsylvania School of Medicine, points out that given the extreme morphological complexity of neurons, which each can host up to 100,000 synapses, the precise spatiotemporal regulation of protein synthesis is crucial for normal neuronal functions; alterations can manifest themself in neuropathological conditions. Dr. Ignatova studies cytoplasmic FMRP interacting protein 1 (CYFIP1), a regulator of protein translation, and which resides within 15q11.2 chromosomal deletion and duplication, genome anomalies associated with schizophrenia and autism spectrum disorder, respectively. She will test the hypothesis that m6A modifications on mRNA modulate CYIFIP1 interactions with mRNA to alter its synaptic localization and translation. She will use genetically modified mouse models and human neural cell types and organoids derived from patient-specific induced pluripotent stem cells (iPSCs).

Basic Research

J. Wren Kim, Ph.D., University of California, Berkeley, proceeds from emerging evidence suggesting that hyperexcitability of neural circuits underlies many phenotypes of Fragile X Syndrome (FXS), including ADHD, sensory hypersensitivity, seizure, and anxiety. Approximately 80% of children with FXS are also diagnosed with attention deficit disorder (ADD) or ADHD. Dr. Kim maintains that better understanding of hyperexcitability at a neuronal level will bring new insights to many FXS phenotypes, including ADHD. This study involves interrogation of the molecular mechanisms of neuronal hyperexcitability and identification of genetic modifiers of hyperexcitability in FXS using a well-established mouse model of FXS. It is hoped new genetic and molecular perspectives on hyperexcitability will provide mechanistic insights into hyperexcitability-related comorbidities in FXS.

Basic Research

Nataliia Kozhemiako, Ph.D., Brigham and Women's Hospital/Harvard University, notes that while sex is an important factor with respect to the risk and severity of neurodevelopmental disorders (NDDs), it is unclear whether disrupted sleep manifests similarly in boys and girls. Given that multiple aspects of sleep architecture also show sexually dimorphic normative developmental trajectories, this project seeks to elucidate the effect of sex on sleep neurophysiology across multiple NDDs including ADHD, autism spectrum disorder (ASD), intellectual disabilities, and cerebral palsy. Using data from the National Sleep Research Resource, the team will analyze a large sample of clinical whole-night sleep electroencephalograms (EEG) recorded in children with NDD diagnoses. They will investigate sex differences in sleep structure and timing as well as the prevalence of sleep-related disorders. They will further quantify key facets of sleep neurophysiology by analyzing specific EEG signatures.

Basic Research

Marianne Oldehinkel, Ph.D., Donders Institute for Brain, Cognition and Behaviour, The Netherlands, notes that the role of altered dopaminergic signaling in the brain and its link to altered reward processing in ASD and ADHD has not been fully explored because non-invasive brain imaging approaches like MRI are unable to differentiate between dopaminergic projections and projections from other neurotransmitter systems. Dr. Oldehinkel has shown that dopaminergic projections in the human striatum can be investigated in resting-state functional MRI data using connectopic mapping (CM), an approach for characterizing fine-grained, overlapping modes of functional connectivity in the brain. This project aims to demonstrate that dopaminergic dysfunction is present as a dimensional, cross-diagnostic phenotype in ADHD and ASD. The hypothesis is that the dopaminergic connectivity mode tracks inter-individual differences along a spectrum of altered reward-related behavior across control individuals, individuals with ADHD, and individuals with ASD. The work could

reveal a biomarker for diagnosis and (dopaminergic) treatment targeted for individual patients.

IDC *Next-Generation Therapies*
IDC *Basic Research*

Christopher W. Tschumi, Ph.D., University of Washington, focuses on the mesostriatal pathway, which plays a critical role in reward learning and motivated behavior. Dysfunction in this pathway is associated with disrupted reward processing and is relevant in schizophrenia, autism, and addiction. The Kv3 voltage-gated potassium channel is a protein currently being targeted for pharmacotherapeutics to treat schizophrenia. A drug targeting the Kv3.1 subunit improves mesostriatal network activity and reward processing in schizophrenia patients, but the degree to which Kv3 can be targeted to treat other brain and behavior disorders is not known. This project seeks to understand how better to harness Kv3 activity for the treatment by exploring how it functions physiologically to drive reward processing. Results could provide a framework for studying how Kv3 variants found in human patients disrupt mesostriatal network activity and behavior, a possible basis for new therapeutics.

IDC *Basic Research*

Jessica J. Walsh, Ph.D., University of North Carolina at Chapel Hill, studies the neural mechanisms of sociability, which can be impaired in schizophrenia, depression, anxiety, and autism spectrum disorders. She notes that rapid elevation of serotonin activity enhances sociability and promotes appropriate social behavior, and suggests that the speed and degree of serotonin enhancement may be a critical regulator of its therapeutic effects. MDMA causes sharp increase in serotonin levels, but this effect is only temporary, and deficits resume when serotonin levels return to baseline. Dr. Walsh cites preliminary data suggesting a two-dose regimen of the psychedelic compound MDMA can cause lasting increases in sociability in mice with a specific genetic deletion. She seeks to identify the circuit, cellular, and molecular adaptations underlying this therapeutic phenomenon.

IDC *Next-Generation Therapies*

Xiaoting Wu, Ph.D., Icahn School of Medicine at Mount Sinai, noting that social memory impairment may be a major cause of deficits in social communication and social emotional processing, seeks to investigate the neural substrates of social memory to understand impairment of social behaviors in ASD and schizophrenia. This project seeks to understand how the hippocampus creates positive and negative social memories and develop strategies to reverse memory loss of positive social interactions in ASD and schizophrenia-associated mouse models. The hypothesis is that different hippocampal circuitries regulate positive and negative social memories. The team will identify hippocampal circuits that selectively control positive and negative social memories. Dissociating the distinct mechanisms regulating positive and negative social memories may allow the targeting of positive social memories in new therapeutics.

IDC *Basic Research*

BIOLOGY OF THE BRAIN

These projects focus on how the brain works

CHILDHOOD COGNITION & MOTIVATION

Youngsun Theresa Cho, M.D., Ph.D., Yale University, proposes that given the co-occurrence of cognitive and motivational symptoms across numerous psychiatric illnesses, as well as the dynamic development of associated brain systems, individual variability in cognition and motivation during childhood may confer risk for developing illness in adolescence. This project seeks to discover whether cognitive and motivational abilities confer risk for developing psychiatric illness, and whether abilities in childhood can predict illness risk in adolescence. To address this, the team proposes to apply data-driven methods to the large, publicly-available Adolescent Brain Cognitive Development (ABCD) dataset in order to: 1) identify how children vary with respect to cognitive and motivational abilities; 2) identify the neural circuits associated with this variability; and 3) test whether variability in cognition and motivation is associated with future risk for psychiatric illness, using data from longitudinal follow-up.

IDC *Diagnostic Tools/Early Intervention*

EARLY-LIFE IMMUNE CHALLENGES

Emilia Favuzzi, Ph.D., Yale University School of Medicine, seeks to identify biological underpinnings of brain and behavior disorders impacted by early-life immune challenges. To achieve this she will use a model of inflammatory bowel disease in early postnatal mice and focus on cortical GABAergic inhibitory neurons. The project will explore if there are inhibitory subtypes that respond to peripheral immune challenges at early postnatal stages. She will study how exposure to those challenges shapes immune-responsive circuits, and investigate how different cell types in the developing brain are molecularly altered in response to colitis. It has been proposed that inflammatory and psychiatric diseases may share a common underlying biology. Revealing the molecular mechanisms by which immune signals shape responses in the developing brain has the potential to identify these sought-after biological mechanisms. This project will test if extreme or prolonged immune responses occurring at early postnatal stages severely alters brain development and causes behavioral symptoms associated with psychiatric disorders. Findings may provide a biological basis for future immunomodulatory therapeutic interventions to prevent or

treat some cases of mental illness in humans.

DNA Basic Research
DNA Next-Generation Therapies

IMPACT OF PSYCHEDELICS

Srividya Ganapathy, Ph.D., University of California, San Diego, will probe the impact of psychedelic substances on synaptic plasticity, using cortical organoid models of human brain function. Little is known about the mechanisms by which an acute treatment leads to long-term structural and functional effects. For instance, the impact of psychedelics on the excitation/inhibition balance and neural homeostasis is unknown. Dr. Ganapathy will develop state-of-the-art genetically encoded tools to assess the impact of serotonergic psychedelic compounds on the synaptic properties of cortical organoids derived from human induced pluripotent stem cells (iPSCs) to study the immediate impact of psychedelic treatment on synaptic plasticity via imaging changes in voltage and GABA in specific neural circuits.

DNA Next-Generation Therapies

IMPULSIVE AGGRESSION

Debora Masini, Ph.D., Stockholm University, Sweden, notes pathological aggression can arise in psychiatric disorders such as bipolar disorder, substance abuse, ADHD, and conduct disorders. Though it is common, clinicians lack treatment options. Pharmacotherapy often involves sedation and physical restraint for the acute stage whereas chronic cases are treated with a combination of mood regulators such as SSRIs, lithium, beta-blockers, and antipsychotics. Sedation carries risk and complicates diagnosis, whereas chronic aggression can be drug-resistant and treatment further limited by side effects. This project seeks a novel treatment strategy, specifically tailored to control aggression across different disease modalities. Dr. Masini will focus on a primary node in the neuronal circuitry that coordinates aggression. Located in the hypothalamus, the PMv works as an "aggression igniter." She aims to describe the plastic changes that occur with experience, particularly when the behavioral motif of aggression first emerges. By comparing neuronal activity in rodents that develop an aggressive phenotype with those that don't, she aims to elucidate how some individuals restrain aggression while others are drawn toward it.

DNA Basic Research
DNA Next-Generation Therapies

IMPACT OF GENETIC VARIANTS

Mariana Moyses-Oliveira, Ph.D., Sleep Institute, Associação Fundo de Incentivo à Pesquisa, Brazil, is interested in the genetics underlying risk for neuropsychiatric illnesses, noting that the relative impact of protein truncating [gene] variants (PTV) compared to missense mutations is poorly understood. Her team will use human induced pluripotent stem cell (hiPSC) lines to introduce patient-specific PTV and missense perturbations in GRIN2A, a gene implicated in multiple disorders. hiPSC-derived neuronal lineages will have their transcriptome and chromatin accessibility profile defined by RNA-seq to infer the molecular consequences of genomic variants. Divergences and commonalities between neuronal pathways disrupted by each variant type will be contrasted to the molecular targets of specific drugs, the aim being to identify the nodes of coalescence in molecular signatures of neuropsychiatric disorders.

DNA Basic Research

EMOTION REGULATION

Erik C. Nook, Ph.D., Princeton University, notes that psychotherapy seems to reduce symptoms of psychopathology by improving emotion regulation skills. This project aims to extend our understanding of emotion regulation by altering elements of language, i.e., the words people use when regulating. Several linguistic processes have been shown to improve emotion regulation, but a recent set of studies surprisingly revealed that naming one's emotions (i.e., identifying that we're feeling "sad") impeded regulation of those emotions. How, when, and why does emotion naming impede emotion regulation? Among the objects of this research are to determine 1) whether naming impedes regulation for naturalistic and therapeutically relevant stimuli (i.e., autobiographical memories); and 2) whether the inhibiting impact of emotion naming on emotion regulation is evident at both neural and self-reported levels of analysis.

DNA Basic Research

EARLY RESPONSES TO ENVIRONMENT

Albert D. Piersson, Ph.D., University of Cape Coast, Ghana, seeks to gain a better understanding of how the brain develops from the uterus to early life. By studying a birth cohort, the team hopes to identify patterns of brain development related to later outcomes, e.g., cognitive abilities, mental health, and social behavior. Ultrasound can provide detailed information about the brain structures; transcranial doppler ultrasound (TCD) can reveal the brain's blood flow pattern; visual tracking to observe eye and head movements and multimodal MRI can provide detailed information about the brain's structure and function. The study will also collect data on various environmental factors that may influence brain development, such as the mother's exposure during pregnancy and the infants' exposure to air and land pollution, nutrition, cultural practices, and social interactions. By analyzing this data alongside the multimodal neuroimaging results, the team expects to gain a more detailed understanding of how the brain responds to different environmental influence.

DNA Basic Research

SLEEP-RELATED CIRCUITY

Mubarak H. Syed, Ph.D., University of New Mexico, is interested in imbalances in the process by which how the brain generates thousands of different neural cell types regulating complex behaviors, which potentially can lead to neurodevelopmental disorders like autism and schizophrenia. Dr. Syed is particularly interested in neurodevelopmental disorders that are comorbid with sleep disorders. This project focuses on the development of neuron types that regulate sleep behavior. The team has identified a unique neural stem cell that generates sleep-promoting neurons. Steroid hormones appear to play a role in regulating the formation of sleep-promoting neurons and sleep behavior. The team hopes to understand the underlying conserved mechanisms of brain development and disease, based on experiments in insect animal models.

Basic Research

FUNCTIONAL CONSEQUENCES OF GENETIC VARIATIONS

Xuran Wang, Ph.D., Icahn School of Medicine at Mount Sinai, notes that understanding the functional consequences of genetic variations implicated in psychiatric illnesses remains a challenge. High-throughput approaches, such as CRISPR perturbations of genes in neural cells, have been used to explore the effects of genetic variations on cellular processes. However, these are complicated by the fact that changes in cell type and developmental stage can obscure the effects of genetic perturbations on gene expression. This project aims to develop a statistical framework to identify convergent and divergent mechanisms of multiple risk genes in neuropsychiatric disorders—specifically, an algorithm that separates the effects of CRISPR perturbations on cell composition and cell type-specific gene expression. The team will then use this algorithm to identify convergent and divergent pathways of risk genes and construct causal networks from the significant gene expression alterations observed in CRISPR perturbations. This framework will be applied to large-scale CRISPR perturbation data of 75 high-confidence autism genes in human-induced neural progenitor cells.

Basic Research

BIPOLAR DISORDER

Chinnakkaruppan Adaikkan, Ph.D., Indian Institute of Science, India, is studying transcranial electrical stimulation (tES), a noninvasive brain stimulation technology in which an electrical field is applied on the scalp surface, either as direct (tDCS) or alternating current (tACS). The efficacy of tES, which has been tested in depression, schizophrenia, and bipolar disorder, likely depends on multiple parameters, including duration and intensity of stimulation and, most importantly, tES paradigms (anodal or cathodal tDCS or specific frequency of tACS). This project seeks better understanding of the cellular, molecular, and neurophysiological mechanisms of tES, specifically, the relationship between tES and neurons in the local circuit in the prefrontal cortex (PFC) and impacts on neuromodulators such as acetylcholine, dopamine, norepinephrine, and serotonin. The hypothesis is that different paradigms of tES applied on the scalp over the PFC engage different neuromodulators and modify their levels in the PFC.

Basic Research
Next-Generation Therapies

Debora Masini, Ph.D., Stockholm University, Sweden, notes pathological aggression can arise in psychiatric disorders such as bipolar disorder, substance abuse, ADHD, and conduct disorders. Though it is common, clinicians lack treatment options. Pharmacotherapy often involves sedation and physical restraint for the acute stage whereas chronic cases are treated with a combination of mood regulators such as SSRIs, lithium, beta-blockers, and antipsychotics. Sedation carries risk and complicates diagnosis, whereas chronic aggression can be drug-resistant and treatment further limited by side effects. This project seeks a novel treatment strategy, specifically tailored to control aggression across different disease modalities. Dr. Masini will focus on a primary node in the neuronal circuitry that coordinates aggression. Located in the hypothalamus, the PMv works as an "aggression igniter." She aims to describe the plastic changes that occur with experience, particularly when the behavioral motif of aggression first emerges. By comparing neuronal activity in rodents that develop an aggressive phenotype with those that don't, she aims to elucidate how some individuals restrain aggression while others are drawn toward it.

Basic Research
Next-Generation Therapies

Ana P. Silva, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, proceeds from data from genetic, functional, and neuroimaging studies suggesting mitochondrial dysfunction may play a key role in bipolar disorder (BD). Alterations in the DNA sequence of two mitochondrial genes, MT-ND1 and MT-ND2, may have a relevant impact on mitochondrial functions, decreasing the energy production of cells, increasing levels of oxidative stress, and impairing neurotransmission. The team will introduce variations in the DNA sequence of both genes and investigate the effects on mitochondrial functions. Effects on neurotransmission in healthy and bipolar disorder patient-derived neurons will also be studied.

Basic Research

Emma K. Stapp, Ph.D., George Washington University, will test the hypothesis that physical activity drives changes in affect in real time in bipolar disorder (BD), with meaningful variation by age, cognition, and dose. The project seeks to identify whether the positive feedback loop between physical activity and affect observed in depression is observed in BD at different stages of the lifespan, and what amount of physical activity is associated with improved or stabilized affect. The team will investigate ididvuals with BD compared to major depression and other or no disorders, asking how age and cognition influence these interrelationships, with the goal of facilitating understanding of mechanisms relevant to dose (frequency, intensity, volume) and timing of physical activity that may be most beneficial in BD. The team will use data from the NIMH Family Study of Affective Spectrum Disorders, a community-based sample enriched for mood disorders, which assessed physical activity and affect in ~500 individuals aged 11–85.

Next-Generation Therapies

BORDERLINE PERSONALITY DISORDER

Erin A. Kaufman, Ph.D., University of Utah, will assess the relations between sleep, interpersonal stressors, affect, impulsive behaviors, and self-harm across time among 50 adolescents with borderline personality disorder (BPD). They will also assess the effects of a brief sleep intervention on adolescent sleep quality and BPD symptoms. The team hypothesizes that a relation between sleep quantity/quality and BPD symptoms will emerge, such that worsening sleep will predict worsening BPD symptoms in daily life, and vice versa. Further, they hypothesize that sleep improvements will be associated with subsequent BPD symptom improvements. They expect that a brief, sleep-focused intervention will have positive effects on adolescent sleep and BPD symptoms as assessed with equipment for measuring brain wave activity and multiple daily surveys about BPD symptoms and sleep.

Next-Generation Therapies

Fabian Streit, Ph.D., Central Institute of Mental Health, Mannheim, Germany, having formed and led the International Borderline Genomics Consortium and identified risk variants and genes associated with borderline personality disorder (BPD) using genome-wide association studies, now will extend this work by studying epigenome-wide epigenetic and transcriptome-wide gene expression profiles associated with BPD directly in the brain. Environmental effects are often transmitted via epigenetic DNA modifications; such alterations will be explored in postmortem brain tissue of 45 BPD patients and 45 matched controls. The team will use the data to identify DNA positions and regions differentially methylated or differ-

entially expressed in BPD patients, indicating the involvement of specific genes in the disorder, and will apply pathway and network analyses to identify which functional groups of genes are associated with BPD. They also aim to identify genes or pathways with convergent evidence from methylation, gene expression, and the most recent BPD-GWAS, currently under way in over 6,000 BPD patients. This project will be the first to examine DNA methylation and gene expression in brain tissue from BPD patients.

Basic Research

DEPRESSION

Chinnakkaruppan Adaikkan, Ph.D., Indian Institute of Science, India, is studying transcranial electrical stimulation (tES), a noninvasive brain stimulation technology in which an electrical field is applied on the scalp surface, either as direct (tDCS) or alternating current (tACS). The efficacy of tES, which has been tested in depression, schizophrenia, and bipolar disorder, likely depends on multiple parameters, including duration and intensity of stimulation and, most importantly, tES paradigms (anodal or cathodal tDCS or specific frequency of tACS). This project seeks better understanding of the cellular, molecular, and neurophysiological mechanisms of tES, specifically, the relationship between tES and neurons in the local circuit in the prefrontal cortex (PFC) and impacts on neuromodulators such as acetylcholine, dopamine, norepinephrine, and serotonin. The hypothesis is that different paradigms of tES applied on the scalp over the PFC engage different neuromodulators and modify their levels in the PFC.

Basic Research
Next-Generation Therapies

Andrea Boscutti, M.D., UTHealth Houston, will use low-intensity focused ultrasound stimulation (LIFU), an emerging technique, targeting the amygdala in individuals with major depression and anxiety. LIFU offers greater precision and the ability to stimulate deep brain structures without damaging adjacent structures. The team will use LIFU to suppress amygdala activity in patients with MDD and moderate to severe anxiety symptoms, and will use MRI, acquired prior to treatment, to simulate the propagation of ultrasound waves into brain tissue, ensuring accurate delivery of the intervention. Subjects will undergo two stimulations sessions. In one, active stimulation will be delivered. In the other, a placebo version of the stimulation will be performed. The hypothesis is that LIFU, by suppressing amygdala activity, can reduce depression and anxiety.

Next-Generation Therapies
New Technologies

Joshua C. Brown, M.D., Ph.D., McLean Hospital, will test whether combining accelerated rTMS brain stimulation with administration of the antibiotic d-cycloserine can increase brain excitability, which is thought to underlie rTMS treatment response in major depression. The team will randomize 30 patients into two groups who will either receive 10 rTMS treatments with d-cycloserine or placebo. If combined treatment leads to greater brain excitability, as measured by neurophysiology (electromyography and electroencephalography), the team will be poised to test a full 50-treatment protocol in a large group of patients to determine whether this mechanism-guided pharmacologic augmentation of accelerated TMS approach can be adopted to help those not responding to existing protocols.

Next-Generation Therapies

Jessica l. Buthmann, Ph.D., Stanford University, is interested in early-life stress (ELS), which is associated with increased risk for the development of psychopathology, in particular, depression and anxiety. The developmental trajectories leading from ELS exposure to vulnerability to or resilience against depression and anxiety are not well understood. The team will use data from a cohort of 220 9- to 13-year-old children, to examine the effects of ELS on psychobiological functioning across adolescence. They will include measures of exposure to ELS (type, onset, duration), caregiving and home environment, neighborhood-level environmental and socio-economic conditions, neural structure and function, and depression and anxiety at four time points across 8 years. The team will use several longitudinal statistical approaches to examine trajectories of depression and anxiety symptoms and will elucidate the roles of ELS, the physical and psychosocial environment, neural structure and function, and their interactions, in predicting the onset of depression and anxiety in adolescence.

Diagnostic Tools/Early Intervention

Jennifer C. Chan, Ph.D., Icahn School of Medicine at Mount Sinai, addresses whether stress interacts with parity (pregnancies carried for at least 20 weeks) to alter postpartum depression risk. Using a model of postpartum maternal stress, she has found that postpartum stress disrupts both parity-related molecular changes in the hippocampus and improvements on cognitive behavioral tasks. Together, these data suggest a framework by which parity does not on its own impart disease susceptibility, but interacts with chronic postpartum stress to disrupt adaptive brain alterations, which may provide a foundation for brain disorder risk in the future. This project seeks to understand the cellular mechanisms by which postpartum stress enacts long-lasting consequences in behavior, using chemogenetic tools to selectively target and silence trilaminar cells in the hippocampus, with the overall goal to rescue the associated behavioral deficits.

Basic Research

Joshua L. Cohen, M.D., Ph.D., University of California, San Francisco, proceeds from intracranial neural recordings in patients with epilepsy showing that signal coherence between amygdala (AMY) and hippocampus (HPC) is correlated with mood. The team will leverage an ongoing clinical trial of DBS for treatment-resistant major depression in which they implant intracranial electrodes within the putative corticolimbic mood network to systematically assess acute behavioral and neural responses to focal electrical stimulation. Preliminary data show, for the first time in patients with MDD, that AMY-HPC coherence correlates with symptoms of depression and anxiety. The hypothesis is that AMY-HPC coherence is a generalizable marker of depressive symptomology, that therapeutic stimulation will be associated with a reduction in coherence, and AMY-HPC coherence is part of a wider corticolimbic mood circuit.

Next-Generation Therapies

Elise C. Cope, Ph.D., University of Virginia, is interested in the neural basis of social behavior deficits in stress-induced depression. Stimulating neural circuits by deep brain stimulation has suggested that activating neural circuits underlying social behavior may alleviate social deficits in depressed patients. The CA2 region of the hippocampus, with an abundance of perineuronal nets (PNNs), extracellular matrix structures that surround some neurons and regulate their plasticity, has emerged as a critical hub for social memory function. The team hypothesizes that stress-induced depression impairs social memory circuits by disrupting CA2 PNNs, and that targeting CA2 PNNs can alleviate social memory dysfunction. To test this, the team will investigate in mice whether stress-induced depression impairs social memory circuits by disrupting CA2 PNNs. They will then explore whether manipulating PNNs or PNN-associated sulfation patterns can rescue CA2 oscillatory activity and social memory deficits caused by stress.

Next-Generation Therapies
Basic Research

Cristiana Cruceanu, Ph.D., Karolinska Institute, Sweden, aims to understand how stress hormones and different antidepressants affect brain development during pregnancy, which may affect behavioral and cognitive outcomes in the life of the child; and the risk-benefit balance between chronic exposure to stress hormones during pregnancy and treatment with different drugs. This research will be performed non-invasively, using 3-D models of the human brain derived from stem cells that have been reprogrammed from skin samples of different individuals. This will allow testing of several commonly prescribed drugs to compare the effects of treatment in males and females. This approach could have important clinical implications, as a data-driven risk-benefit score will be devised for clinicians to use when advising their

pregnant or soon-to-be pregnant patients on the best course of antidepressant treatment.
IDCI *Basic Research*

Jinye Dai, Ph.D., Icahn School of Medicine at Mount Sinai, cites research suggesting a potential role for ionotropic glutamate receptor delta 1 (GluD1) in the synaptic pathology of depression. Postsynaptic GluD1 is widely expressed in the brain, with higher levels in the prefrontal cortex and habenula. GluD1 may be involved in regulating social behavior and emotion. The link between GluD1 as a genetic factor and as a stress regulator in depression is not fully understood. The team's hypothesis is that GluD1 is a common molecule which links genetic and stress factors in depression etiology by controlling glutamatergic synaptic signaling in the circuit of the medial prefrontal cortex (mPFC) and lateral habenula (LHb), brain regions highly implicated in depression. This will be explored in genetically modified mice.
IDCI *Basic Research*

Neir Eshel, M.D., Ph.D., Stanford University, proposes that anhedonia can involve deficits in either of two parameters, reward potency and motivation to exert effort for reward, and that each maps onto a different component of the dopamine reward system. The hypothesis is that dopamine release in ventral regions such as the nucleus accumbens shell determines reward potency, while dopamine release in dorsal regions such as the dorsomedial prefrontal cortex determines reward motivation. To test this Dr. Eshel will measure dopamine release in both regions as mice perform a behavioral economic task, establish how chronic stress affects their behavior and dopamine release, and then attempt to reverse stress-induced anhedonia through region-specific manipulations of dopamine dynamics. These experiments can help resolve longstanding debates in the field of dopamine and reward, and advance a precision psychiatry approach to the treatment of anhedonia.
IDCI *Basic Research*

Tanner C. Francis, Ph.D., University of South Carolina, aims to develop and test animal models to study depression relapse, and to identify the neuronal population that is hypothesized to trigger such relapse. One pathway in the mood and reward-related nucleus accumbens (NAc) region increases stress response and the likelihood of developing depression symptoms when activated. The team hypothesizes that by inhibiting this pathway, the chances of stress-induced depression relapse will be reduced. They plan to use mice to monitor NAc single-cell neuronal subtype activity over time during stress, recovery, and relapse. They will then selectively inhibit or activate this neuronal population to determine the necessity or sufficiency of these cells in depression relapse.
IDCI *Basic Research*

Polymnia Georgiou, Ph.D., University of Wisconsin-Milwaukee, notes that depression is more common in women than men, but the gender gap narrows in older adults due to the decline in gonadal hormones in both sexes. Fluctuations in 17β-estradiol (E2) are associated with an increased risk of depression in women, and E2 administration has antidepressant effects. Similarly, testosterone has antidepressant effects in men, but it can also have serious side effects. The mechanisms underlying testosterone's antidepressant effects are not well understood, but it is possible for these effects to be mediated through its conversion to E2 and its actions on estrogen receptors. The proposed experiments could provide new insights into the neural mechanisms underlying depression, focusing on estrogen receptor signaling.
IDCI *Basic Research*

Livea D. Godoy, Ph.D., Aarhus University, Denmark, notes that despite advances to understand antidepressant mechanisms in affective disorders, the effects of ketamine dose on cognitive function are not well understood. Ketamine can have a rapid and potent antidepressant effect, but in its impact upon cognition it may vary in different patients (healthy subjects, antidepressant responders vs. non-responders). Dr. Godoy will investigate the effects of ketamine on cognitive function in mice by measuring circuit activity that may be involved with antidepressant response. The hypothesis is that when ketamine restores prefrontal cortex from a hypo-functionality state (below-normal functionality) induced by stress in responders, it precipitates sustained antidepressant effects and also restores cognitive function.
IDCI *Next-Generation Therapies*

Simon B. Goldberg, Ph.D., University of Wisconsin, notes growing evidence supporting the existence of a "gut-brain axis." Recent scientific work suggests the gut microbiome may play an important role in the development and maintenance of various mental illnesses including depression. Dr. Goldberg believes there is a vital need for adequately powered studies clarifying associations between gut microbiome composition and depression that move beyond self-reported symptoms and capture associations with other key behavioral and biological markers of depression. The current study adds analysis of biological samples from a healthy control baseline comparison condition (n = 250) recruited alongside an ongoing randomized controlled trial testing a meditation-based smartphone app for individuals with clinically elevated depression symptoms (n = 1,100). A broad-based assessment of the microbiome, among the measures analyzed in this study, will allow characterization of specific microbiota species, strains, and communities that may be linked to depression.
Next-Generation Therapies,
IDCI *Basic Research*

Eric Goldwaser, M.D., Ph.D., Weill Cornell Medical College, notes that the blood-brain barrier (BBB) maintains neuronal microenvironments and cerebral homeostasis. With notable advances in TMS brain stimulation protocols and clinical BBB approaches, the stage is set to investigate TMS and BBB in depression. BBB assessments typically are invasive, expensive, and not easily tolerated; recent advances in neuroimaging have enabled a non-invasive, non-contrast, 10-minute MRI scan that can reliably and reproducibly assess BBB functioning. This study asks 1) how TMS might modulate or improve the BBB in depression; and 2) to what extent is the BBB a factor in symptom improvements or resistance to TMS treatment? The team will study 150 individuals with depression before and after an accelerated, intensive 5-day TMS protocol that they will be receiving in conjunction with an ongoing trial in the lab.

🧬 *Next-Generation Therapies*
🧬 *Basic Research*

Serena B. Gumusoglu, Ph.D., University of Iowa, hypothesizes that a placental factor may impair blood vessels in the brain, thereby driving risk for maternal depression. One molecular substrate for this interaction between placenta and maternal brain may be extracellular vesicles. The nucleic acid contents of placental vesicles are changed by placental diseases such as preeclampsia, altering expression of blood vessel genes in the brain; whether this directly causes maternal brain blood vessel damage and depression has not been tested. This project will test whether placental vesicles are sufficient to change expression of genes in the brain related to blood vessel function, and whether subsequent brain blood vessel dysfunction and depression occur in a mouse model.

🧬 *Basic Research*

Elizabeth N. Holly, Ph.D., Rutgers University, notes adolescent social isolation has been linked to increased vulnerability to psychiatric disorders in adulthood, including major depression, anxiety disorders, and substance use disorders. She proposes that as the dopamine system is undergoing critical maturation during adolescence, adolescent social isolation disrupts dopaminergic development and subsequent function, leading to persistent perturbations in goal-directed behaviors. To test this, she will conduct experiments in rodents to determine how adolescent social isolation changes dopamine dynamics during goal-directed behavior in adulthood, and perform optogenetic manipulations to determine the causality of these changes in dopamine signaling. Elucidating the neural mechanisms driving these effects may open the door for transdiagnostic therapeutic interventions.

🧬 *Basic Research*

Artemis Iatrou, Ph.D., McLean Hospital/Harvard University, notes one mechanism that could explain converging pathologies in both PTSD and MDD (vascular dysfunction and brain inflammation) is a leaky blood-brain barrier (BBB) that would allow peripheral proinflammatory molecules to enter the brain. The team will probe the link between childhood trauma and comorbid PTSD and MDD. They will map cell-type-specific transcriptomic changes in response to stress and trauma exposure within the perivascular microenvironment and profile the hippocampal perivascular space of people with comorbid PTSD and MDD in single-nucleus resolution. Using patient-derived induced pluripotent stem cell technology, they will reconstruct the BBB in vitro and evaluate the stress response, allowing for timely preventative or therapeutic target identification. The project could provide insight into how maladaptive stress responses and trauma affect the borders of the human brain.

🧬 *Basic Research*

Brett Jones, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada, cites imaging studies providing indirect evidence for the role of synaptogenesis in the therapeutic effects of psilocybin, demonstrating increased functional connectivity in the brain after administration, and correlated with a reduction in depressive symptoms. While this supports synaptogenesis as a potential mechanism of antidepressant action, it has yet to be studied directly in humans. To directly measure whether psilocybin exerts its antidepressant effects through synaptogenesis, the team will use positron emission tomography (PET) to quantify changes in synaptic density after psilocybin administration in adults with treatment-resistant depression.

🧬 *Next-Generation Therapies*
🧬 *Basic Research*

Nikolaos Karalis, Ph.D., Institut du Cerveau/Paris Brain Institute, France, notes the interplay between the neuromodulatory system and activity of the limbic circuit remains little understood, while changes in the activity of each in depression and following drug delivery remain unknown. This project will study changes in neuromodulation and activity of the limbic circuit as well as acute and protracted changes in neuronal patterns of activity after the administration of psilocybin and ketamine in naïve mice and the chronic stress model of depression. It is hoped this will provide a novel perspective on the organization and interplay of two core brain systems and aid in understanding their involvement in depression and its treatment.

🧬 *Basic Research*
🧬 *Next-Generation Therapies*

Aiste Lengvenyte, M.D., University of Montpellier, France, aims to determine whether potential peripheral biomarkers implicated in inflammation, oxidation, and plasticity can predict suicidal events during a 2-year follow-up

in 700+ individuals treated for mood disorders. Peripheral markers used involve inflammation/immune response, oxidative stress, and plasticity in blood plasma samples collected from participants. Machine learning will be used to select the best-performing biological analytes and verify their independence of associations. The team will combine the top biomarkers with scores obtained from the initial clinical information to assess whether this double-approach might perform better than biological or clinical variables alone. The expected outcome is a description of plasma markers associated with suicidal thoughts and behaviors, differentiating between past, present, and future outcomes, and between diagnostic groups.

Diagnostic Tools/Early Intervention

Victor M. Luna, Ph.D., Temple University, notes that unlike major depressive disorder (MDD) in younger adults, late-life depression (LLD) often involves cognitive impairments associated with increased relapse and poor or delayed antidepressant responses. To develop more effective treatments requires understanding how synapses in the aged brain control emotion and memory, Dr. Luna says. His team will investigate synapses in the dentate gyrus (DG) of the hippocampus, which is vulnerable to aging. DG dysfunction impairs the ability to discriminate emotional memories—a characteristic symptom of LLD which can manifest as maladaptive fear generalization or overgeneralization. This project investigates the downstream synaptic targets of adult hippocampal neurogenesis (AHN) to rescue fear overgeneralization in aged mice. One focus will be the role of inhibitory metabotropic glutamate receptor 2 (mGluR2) and excitatory AMPA-type glutamate receptors in fear generalization. The work may establish a framework for identifying pharmacologic targets that take advantage of the plasticity afforded by AHN without having to directly stimulate it, opening new avenues for developing new drug treatments for LLD.

Basic Research
Next-Generation Therapies

Chiara Maffei, Ph.D., Massachusetts General Hospital/Harvard University, aims to improve a neuroimaging technique called diffusion MRI (dMRI) tractography, which makes it possible to investigate some of the major structural connections within depression circuits. A set of subcortical pathways connecting limbic and midbrain regions that have been implicated in the pathogenesis of depression in animal studies still remain inaccessible in humans. This project will use an ultra-high resolution dMRI dataset to image small subcortical pathways in vivo with exceptional anatomical accuracy. Automated tractography will be used to transfer anatomical accuracy of major white matter pathways from higher- to lower-quality dMRI. Ultra-high resolution dMRI data will be collected for 10 healthy subjects to manually label the subcortical depression circuit and create its first human atlas, which will be used to train a global tractography algorithm. This new tool will be employed to reconstruct the subcortical pathways in a large cohort of chronic traumatic brain injury (TBI) patients with and without depression and investigate their tissue microstructure. dMRI will also be used to search for pathway-specific imaging biomarkers of neuroinflammation associated with depression.

Diagnostic Tools/Early Intervention
New Technologies

Jordan Marrocco, Ph.D., Touro University, seeks to evaluate whether the actions of psilocybin occur through a pathway he identified in mouse models of chronic stress. This work pointed to genes that regulate the levels of glucocorticoids, such as cortisol, which are hormones released during the response to stress. This project will test whether psilocybin works in a similar manner, which would lead to a better scientific understanding of how psychedelics exert their benefits for some patients in mental health disorders, in addition to potentially providing new insights into the psychopathology of depression and other psychiatric diseases.

Basic Research
Next-Generation Therapies

Clare A. McCormack, Ph.D., New York University, is curious about how the brain adapts during the perinatal period, noting that remarkably little is known about the maternal brain during pregnancy. A foundational gap, she notes, is that neuroimaging studies of pregnant women have rarely been conducted. She seeks to examine brain change during pregnancy at more than one time point, the underlying neurobiology of change, and associations between brain and mental health in this critical period. This will enhance understanding of individual differences that contribute to risk or resilience (to postpartum depression, among other illnesses) during this life transition. Leveraging and extending an ongoing prenatal study, pregnant women will complete brain MRI scans at two prenatal time points. The team will examine whether different trajectories of change are associated with depression and anxiety symptoms in the postpartum period. The team will also consider key biological variables (pregnancy hormones, stress hormones, inflammation) as potential factors underlying brain changes during this time.

Basic Research

Nicky J. Mehtani, M.D., University of California, San Francisco, is interested in the efficacy of psychedelic-assisted therapies in treating demoralization in palliative care populations, such as terminal cancer patients, as well as racemic ketamine, which is increasingly being used to treat mood and anxiety disorders in outpatient settings. Little is known regarding the feasibility, safety, or efficacy of

ketamine therapy among medically complex patients. In a double-blind, randomized controlled pilot trial, the team will investigate whether a single administration of oral liquid ketamine (0.5mg/kg or 1.5mg/kg) in combination with four weekly sessions of existential psychotherapy can be used to rapidly treat moderate-to-severe demoralization and reduce opioid analgesia requirements among patients with pancreatic cancer. Participants will be followed for 35 days following ketamine administration.

Next-Generation Therapies

Luis Mercado, Ph.D., University of Arkansas for Medical Sciences, notes the fetal and neonatal effects of SSRI antidepressant use during pregnancy are not fully characterized. Data is limited to newborn assessments using scalp electroencephalography (EEG) with no available reports of direct measures of human fetal brain activity on SSRI-exposed fetuses. This research uses a biomagnetic sensing system to directly record the fetal brain signals using a technique called fetal magnetoencephalography (fMEG), which is analogous to EEG. The team will study the brain electrophysiological development of SSRI-exposed fetuses compared with non-exposed fetuses using this non-invasive biomagnetic method. Neonatal follow up will be performed with magnetoencephalography recordings. This novel data will provide quantitative fetal parameters that can have impact on clinical care of pregnant women taking SSRIs as well as care of their children.

Basic Research
Next-Generation Therapies

Heidi Catherine Meyer, Ph.D., Boston University, studies the development of neural circuitry involved in emotional control. It is her conviction that early intervention during adolescence, when the brain is still highly plastic, may have the greatest impact on reducing the longevity and severity of mood and anxiety disorders. Citing research suggesting pubertal development triggers a window of opportunity for recalibration of the HPA axis, her team's work considers how the adolescent brain itself may be leveraged to re-route trajectories of brain development. The dynamic functional remodeling of cortico-hippocampal connections in adolescence acts to fine-tune affective neural activity. This project uses functional ensemble tagging techniques in populations of hippocampal neurons to isolate the memory trace associated with a learned safety cue. The team will explore the possibility that engaging ensembles of tagged "safety neurons" intermittently across adolescence may prime the adult brain for enhanced fear regulation.

Basic Research

Brittany D. Needham, Ph.D., Indiana University, recently characterized a causative link between a small molecule produced by gut microbiota and anxiety-like phenotypes in mice.

This molecule, a bacterial metabolite called 4-ethylphenyl sulfate (4EPS), circulates in the host and enters the brain. In mice, 4EPS causes key changes in neurological profiles, including increased brain activity in regions associated with fear and anxiety, aberrant myelination patterns, and exacerbated anxiety-like behavior. In a subsequent clinical trial, the team found that drug treatment that lowered 4EPS exposure led to ameliorated anxiety and irritability scores in teenagers with ASD and comorbid anxiety. This work has established a direct link between a gut-derived signal and anxiety-related phenotypes in the context of ASD. This project aims to quantify longitudinal urinary levels of 4EPS and six additional related gut-derived metabolites in 200 psychiatric patients diagnosed with a range of conditions including addiction, depression, mood, and anxiety disorders.

Next-Generation Therapies

Anders M. Nelson, Ph.D., New York University, studies how spinal cord injury (SCI) contributes to mental illness. It is difficult to study spinal cord circuits in behaving animals. This research seeks to overcome this limitation by leveraging cutting-edge neuroscience methods to map, monitor, and manipulate spinal and brain circuits in normal and disease models. Depression and anxiety following SCI are strongly associated with the emergence of chronic pain, but the neuronal circuit mechanisms linking these phenomena are poorly understood. One hypothesis is that following SCI, hyperactivity in spinal feedback circuits, particularly the spinothalamic (STT) pathway, drives chronic pain and subsequent depression. This project aims to 1) map the circuit organization of STT neurons, and learn how SCI disrupts this connectivity matrix; 2) determine how SCI changes STT activity and leads chronic pain; 3) treat chronic pain and mental health sequelae by rescuing normal STT activity.

Basic Research
Next-Generation Therapies

Lena K.L. Oestreich, Ph.D., Queensland University of Technology, Australia, studies how depression develops in the months following stroke. There are no tests to identify who is most susceptible and no regions of the brain seem to be particularly vulnerable to the effects of stroke in determining who will develop depression. There is evidence that instead of causing damage to relatively small areas of the brain as seen on traditional MRI scans, strokes may initiate injuries throughout the brain by damaging the connections between the brain area directly affected by the stroke and other regions of the brain. This project will visualize these more subtle injuries across the brain. The team will test if these broader patterns of injury are associated with the development of depression in stroke survivors.

Basic Research

Ashley C. Parr, Ph.D., University of Pittsburgh, studies mesocorticolimbic dopamine (DA) circuit dysfunction, which is central to several psychiatric disorders that emerge during adolescence, including substance use disorders, mood disorders, and schizophrenia. This circuit continues to undergo specialization during adolescence to support the transition to adult levels of decision-making. Dr. Parr is interested in molecular and epigenetic mechanisms mediating normative and impaired mesocorticolimbic DA innervation during adolescence, including microRNA regulators of gene expression—in particular, microRNA-218, which regulates DCC axonal guidance cue signaling to determine the extent of dopamine connectivity to frontal and striatal systems, disruptions of which lead to aberrant mesocorticolimbic circuit organization and deficits in decision-making processes. microRNA-218 can be measured in human saliva, providing a potential readout of its expression in the brain. The team will obtain novel saliva indices of microRNA-218, aiming to develop a model of mesocorticolimbic DA maturation.

Basic Research

Bruno Oriol Porras-Garcia, Ph.D., Institut de Bioenginyeria de Catalunya, Spain, seeks to develop preventive interventions for anxiety and depression symptoms in children and adolescents by promoting emotion regulation (ER) through game-based immersive virtual reality (IVE) cognitive training, which allows users to experience immersive, 3-D environments and events. The team will test Enhance VR, an IVR program designed to improve EF and ER skills among subclinical children and adolescents, in a longitudinal, randomized controlled pilot trial involving 80 participants 10–18 years old, with medium to high risk of developing anxiety and depression disorders. The VR application and a placebo will be given for 30 mins. twice weekly for 5 weeks. The Enhance VR group will engage in six games targeting cognitive flexibility, planning, reappraisal strategies, working memory, divided and sustained attention, and processing speed. Assessments will be made of depressive and anxiety symptoms, ER, executive function (working memory, cognitive flexibility, inhibition, and planning) and attention.

Next-Generation Therapies

María Sancho Alonso, Ph.D., Institut d'Investigacions Biomediques de Barcelona, Spain, notes that alterations in the functional integrity of the serotonin (5-HT) system correlate with the severity of depressive symptoms in Parkinson's Disease (PD), as well as evidence of changes in the functional connectivity of different regions in the ventromedial prefrontal cortex (vmPFC) controlling emotional functions, which may become an early biomarker for the stratification of PD patients at risk for depression. This project explores neural circuits and neurobiological substrates involved in the neuropsychiatric symptoms of PD. The hypothesis is that the dynamics of early-stage depressive dysfunction may trigger neurodegenerative events in PD, leading to long-term changes in brain circuitry, neuronal plasticity, and response to treatments.

Basic Research

Tarjinder Singh, Ph.D., Columbia University, is studying rare genetic variation in major depressive (MDD) and generalized anxiety disorders (GAD), inquiry that has been hampered by limited sample sizes and the heterogeneity of these conditions. He will use genetic data generated by national efforts like the UK Biobank and the All Of Us research program to clarify the contributions of common and rare genetic risks in MDD and GAD, generating a high-quality data set containing all common and rare protein-coding, non-coding, and structural variants for patients with MDD and GAD. These data will be used to quantify the contribution of each class of variation—common and rare, coding and non-coding—to disease risk. Detailed electronic health record data will be used to explore how genetic risk relates to the severity and course of these disorders. Analyses should highlight aspects of MDD and GAD that are more genetically heritable.

Basic Research

Nili Solomonov, Ph.D., Weill Cornell Medical College, will investigate individual-level target engagement of the Positive Valence System (PVS) during a novel social reward psychotherapy for late-life depression. Neurobiological evidence suggests PVS disturbances may be a key mechanism in late-life depression. The PVS, which includes mesolimbic structures, plays a central role in anticipating, obtaining, and responding to rewards. The team will test Engage & Connect, a remotely delivered psychotherapy that aims to alter disturbances of the PVS by increasing engagement in rewarding social activities. They will track each patient's patterns of PVS response to psychotherapy over time; specifically, whether 1) Engage & Connect, compared to a control, SRP (Symptom Review and Psychoeducation), in 46 depressed older adults, will lead to a greater increase in resting-state functional connectivity (rsFC) of the PVS; 2) whether in participants treated with Engage & Connect, compared to SRP, change in rsFC of the PVS will predict greater reduction in depression severity.

Next-Generation Therapies

Brad Verhulst, Ph.D., Texas A&M University, hopes that by identifying specific adversity-related mechanisms that amplify genetic risk, research can provide a basis to develop biologically-informed evidence-based interventions to support individuals who experience trauma and prevent or reduce the severity of depression and anxiety symptoms. The team will perform a proof-of-concept genome-wide interaction study

that demonstrates acute adversity (childhood maltreatment) and chronic adversity (socioeconomic deprivation) amplify individual genetic predispositions to depression and anxiety. These statistical methods will provide tools to identify the amplifying effect of adversity across the genome and for individual genetic variants. They will use a statistical approach to analyze data from two very large genetically informed datasets (N > 650,000). The goal is to understand how adverse life events amplify the genetic mechanisms that increase the risk and severity of depression and anxiety.

 Basic Research

Isabella Wagner, Ph.D., University of Vienna, Austria, notes that depressive symptoms earlier in life have been associated with Alzheimer's Disease (AD) development, even when these symptoms have occurred over two decades before AD onset. Depression and AD share common underlying mechanisms that revolve around a dysfunctional stress response, resulting in increased release of stress hormones, along with deficits of memory-related brain regions, inflammation, and cognitive decline. This project proceeds from the observation that gut bacteria appear altered in depression, AD, and APOE4 risk-gene carriers, and APOE4 was shown to drive its effects on inflammation and neurodegeneration explicitly via gut bacteria. This research will investigate whether there is a connection between the gut microbiome of APOE4 carriers and heightened stress reactivity, in 180 healthy, non-depressed APOE4 carriers and non-carriers (90 per group) between 20 and 35 years old.

 Basic Research

Jessica J. Walsh, Ph.D., University of North Carolina at Chapel Hill, studies the neural mechanisms of sociability, which can be impaired in schizophrenia, depression, anxiety, and autism spectrum disorders. She notes that rapid elevation of serotonin activity enhances sociability and promotes appropriate social behavior, and suggests that the speed and degree of serotonin enhancement may be a critical regulator of its therapeutic effects. MDMA causes sharp increase in serotonin levels, but this effect is only temporary, and deficits resume when serotonin levels return to baseline. Dr. Walsh cites preliminary data suggesting a two-dose regimen of the psychedelic compound MDMA can cause lasting increases in sociability in mice with a specific genetic deletion. She seeks to identify the circuit, cellular, and molecular adaptations underlying this therapeutic phenomenon.

 Next-Generation Therapies

Marc J. Weintraub, Ph.D., University of California, Los Angeles, suggests that while psilocybin has the potential to be a therapeutic agent for depression, it is not the drug, but the therapy enhanced by the drug that will make it an effective and sustaining treatment. He seeks data on therapy accompanying psilocybin, typically an unstandardized supportive therapy called psychedelic-assisted therapy (PAT), and the synergistic effect of psilocybin combined with such psychotherapy. This study will (1) examine the feasibility and acceptability of coupling a standardized, evidenced-based treatment (CBT) with psilocybin in the treatment of adults with recurrent or persistent major depressive disorder (MDD); and (2) will preliminarily examine the synergistic effects of psilocybin with CBT. A randomized double-blind trial will include 30 adults with recurrent or persistent MDD who are in a current major depressive episode.

 Next-Generation Therapies

Christian M. Wood, Ph.D., University of Cambridge. U.K., cites human neuroimaging studies implicating area 25 (scACC-25), a brain region within the subcallosal anterior cingulate cortex, in major depression (MDD). It is overactive in certain patient cohorts and can be ameliorated by successful treatment. However, such correlations between scACC-25 activity and changes in MDD do not provide evidence for a causal link, as compensatory changes cannot be ruled out. Recent evidence in marmosets has revealed the impact of acute changes in scACC-25 activity on emotion-related and physiological processes such as enhanced reactivity to threats and blunted responsivity to reward (anhedonia). In this project, progressive changes in behavioral, physiological, and neurobiological factors will be examined at distinct timepoints over 5 weeks to determine how chronic overactivation in scACC-25 can directly cause symptom-like changes relevant to those seen in MDD patients.

 Basic Research

Mani Yavi, M.D., National Institute of Mental Health (NIMH/NIH), notes the need for investigations to better characterize the pharmacologic profiles and mechanisms of action of ketamine and psilocybin to help develop targeted treatments with a more favorable side-effect profile. Dr. Yavi has generated five treatment-resistant depression (TRD)-derived induced pluripotent stem cell (iPSC) lines plus control lines to differentiate neural cultures. To characterize the effects of ketamine and its metabolite, (2R,6R)- hydroxynorketamine (HNK), from that of serotonergic psychedelics (SPs) such as psilocybin, the team has quantified specific protein expression levels, synaptic density, and dendritic spine morphogenesis. To further understanding of the antidepressant effects of these compounds, they will perform comparative analysis of blood-based biomarkers between ketamine and psilocybin in clinical trials. Biomarker profiling derived from clinical studies would complement the team's ongoing in vitro iPSC dataset, and provide opportunities to complement relevant biobehavioral measures derived from clinical outcome measures.

 Next-Generation Therapies

 Basic Research

Christoph D. F. Zrenner, M.D., Centre for Addiction and Mental Health/University of Toronto, Canada, wants to find out whether a short treatment with personalized TMS neuromodulation therapy has stronger effects in patients with depression than non-personalized TMS. The team will test a non-personalized and three different personalized TMS protocols to find out which is most effective. They will enroll patients participating in an ongoing clinical trial, who will receive a 6-week course of TMS therapy. This will be the first trial comparing different personalized TMS protocols in patients, and it will establish which combination of parameters has the highest therapeutic potential.
Next-Generation Therapies

EATING DISORDERS

Silvia G. Galfrè, Ph.D., University of Pisa, Italy, focuses on pediatric acute-onset neuropsychiatric syndrome (PANS), presenting with sudden onset of neuropsychiatric symptoms triggered by infection or environmental factors. The symptoms include obsessions/compulsions and food restriction. The cause and pathogenesis of PANS are still unclear but may involve changes in immune cell populations and gene expression in peripheral blood mononuclear cells (PBMCs). This study aims to identify specific cell sub-populations and genes involved in PANS using single-cell RNA sequencing techniques on PBMCs from 50 subjects, as well as potential targets for treatment using integrated analysis with plasma metabolomic/proteomic data from patients.
Basic Research

Sasha C. Gorrell, Ph.D., University of California, San Francisco, notes the severe and enduring nature of anorexia nervosa is thought to derive from striatal dysregulation and related compulsivity, much the same way that behaviors become entrenched in obsessive-compulsive disorder (OCD). Dr. Gorrell proposes to adapt a treatment that has worked in OCD to patients with anorexia nervosa. This study leverages resting state functional magnetic resonance imaging and repetitive transcranial magnetic stimulation to build upon existing targets in OCD (right orbitofrontal cortex, OFC) in patients with anorexia nervosa. The team will use an accelerated theta burst neuromodulation protocol directed at the right frontopolar OFC (Broadman area 10), a cortical node in a brain network associated with compulsive behaviors.
Next-Generation Therapies

Roberta Haddad-Tóvolli, Ph.D., Institut D'investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Spain, aims to decipher cellular and molecular mechanisms underlying compulsive eating and anxiety-related states in the offspring of rodent mothers undergoing food cravings and will explore prevention strategies. The project seeks to define the transcriptome of reward-related brain areas underlying predisposition to binge eating disorder in the context of maternal programming at a single-cell resolution; and to explore interventions to modulate gestational food cravings and mitigate negative neuropsychiatric disorders in offspring. This could provide data capable of revealing molecular hallmarks underlying eating disorder susceptibility.
Basic Research

Marito Hayashi, Ph.D., Harvard Medical School, notes that the GI tract and brain communicate continuously to regulate food consumption and GI physiology. This communication begins in the lumen of the GI tract where ingested food and toxins are monitored by intestinal sensory epithelial cells termed enteroendocrine cells (EECs). Because EECs can be targeted via orally delivered drugs, they are an excellent entry point to modulate GI dysfunctions associated with neuropsychiatric disorders. A genetic toolkit Dr. Hayashi has previously established provides an entry point to uncover the functionality of each EEC subtype and respective gut-brain pathways. With these tools to precisely modulate the sensory inputs of gut-brain pathways in vivo, the team aims to uncover gut-brain communication mechanisms with a view to development of therapeutic strategies for eating disorders and neuropsychiatric disorders with GI dysfunctions.
Basic Research

Daniela Herrera Moro Chao, Ph.D., University of Minnesota, notes there is limited evidence regarding mechanisms underlying the sexually dimorphic development of metabolic disease. In the brain, the hypothalamus controls energy homeostasis by fine-tuning feeding and energy expenditure to nutrient availability. Disruption of this regulation results in obesity. While hypothalamic neurons are crucial for the control of energy balance, their activity is tightly dependent on adequate delivery of energy substrates provided by astrocytes. Whether nutritional challenges evoke astrocyte-neuron communication adaptations and their contribution to sex-dimorphism in the pathogenesis of obesity remains unknown. The projects seeks to combine expertise in astrocyte biology and neural control of metabolism to expand understanding of astrocyte-neuron communication in the development of obesity in a sex-dependent manner. The role of the endocannabinoid system in the hypothalamus in shaping sex-specific adaptations in astrocyte biology after obesity will be a particular focus.
Basic Research

Kristin N. Javaras, Ph.D., McLean Hospital/Harvard University, will leverage an ongoing neuroimaging study to test hypotheses about the mechanisms by which acute stressors affect food choice. These hypotheses involve a network called the frontoparietal network that influences choices and

is impaired by stress. The project will also investigate how stressors' impact on food choice differs depending on eating disorder symptoms, such as restrictive and binge eating behavior, which can be present in individuals without eating disorders. Understanding these mechanisms in individuals without psychiatric disorders represents a step toward understanding mechanisms underlying key eating disorder behaviors, such as restrictive and binge eating behavior.

Basic Research

Carolina Makowski, Ph.D., University of California, San Diego, will leverage data from tens of thousands of mother/father/child trios within the Norwegian Mother/Father and Child Cohort (MoBa) to investigate the heterogeneity in the presentation and progression of behavioral and mental health traits in childhood that converge upon an eating disorder (ED) in adolescence. Among the specific aims: 1) identify different profiles based on longitudinal neurobehavioral data (temperament, personality, eating concerns, anxiety) collected in youth from timepoints spanning 6 months to 8 years of age that are predictive of an ED in adolescence (ages 14-19); 2) incorporate genetic and parental data to determine the contribution of youth polygenic scores (e.g., anorexia nervosa, body mass index, neuroticism) and familial history (e.g., maternal and paternal presence/history of an ED diagnosis) factors to each ED risk profile compared to youth without an ED. This work may help uncover the interplay of neurobehavioral development, genetic, and familial factors on ED risk and onset.

Diagnostic Tools/Early Intervention

Rose E. Presby, Ph.D., Scintillon Institute, will test the hypothesis that dysregulation of cerebellar control of dopaminergic activity may underlie the induction and maintenance of eating disorders, varying according to sex. The study includes functional brain imaging data of human subjects preforming a food reward task, and comparing cerebellar-striatal connectivity in male and female participants, with BMI as a covariate to identify mediating effects. A preclinical arm will utilize an animal model of binge-like eating behavior (BLE) in gonadectomized and non-gonadectomized mice. The team will monitor changes in activity of cerebellar and dopamine neurons as BLE develops. After identifying neurons activated during BLE, the team also will locate and functionally characterize the cerebellar striatal circuits that mediate BLE behavior across the sexes.

Basic Research

Laura E. Rupprecht, Ph.D., Duke University, seeks to define the role of a specialized intestinal cell and its connection to the vagus nerve in binge eating disorder. The project builds on research establishing how nutrient choice and gut reward are guided by specialized neuropod cells in the intestine. This project seeks to determine the impact of binge eating disorder on the neuropod cell-to-vagus nerve connection; and to evaluate the role of the neuropod cell in binging and gut reward. The team will measure the activity of the vagus nerve and silence and stimulate cells directly from the intestinal lumen. Defining how the gut communicates to the brain to guide ingestive and reward behaviors may contribute to the development of novel therapies.

Basic Research

Ames K. Sutton Hickey, Ph.D., Temple University, has demonstrated that hunger-promoting agouti-related peptide (AgRP) neurons in the arcuate nucleus are dysregulated following food intake in activity-based anorexia (ABA) mice, and that activation of AgRP neurons can mitigate weight loss by promoting food seeking and decreasing hyperactivity. These results suggest a potential therapeutic avenue to avoid the putatively fatal effects of excessive exercise in people with anorexia. It is still unknown how AgRP neurons coordinate these juxtaposing behaviors in response to ABA, and whether separate AgRP circuits are responsible for promoting food intake versus hyperactivity to diminish the body-weight loss in ABA mice. This project will probe the activity and function of AgRP neurons during meals and voluntary wheel running, and artificially activate projection-defined AgRP circuits potentially coordinating these behavioral outcomes during ABA. The long-term goal is to understand the valence asymmetry associated with hunger, food intake, and hyperactivity in anorexia nervosa, to broaden understanding of the neural circuits governing the decision-making processes that coordinate feeding behavior in complex environments.

Basic Research

Margaret L. Westwater, Ph.D., Yale University School of Medicine, will extend her studies of reward valuation in anorexia nervosa (AN). The question she explores is whether movie-watching can improve detection of altered brain connectivity patterns in AN that, in turn, explain variation in longitudinal symptoms. She will recruit women with acute AN (n=45) and matched controls (n=45) to undergo functional MRI scanning, during which they will complete a validated decision-making task and a movie-watching paradigm that each include food and non-food reward conditions. Group differences in the functional connectivity of canonical brain networks and whether these are modulated by paradigm or reward type will be noted. The team hopes to determine the predictive utility of movie-watching vs. task-based fMRI for longitudinal AN symptoms. The goal is to address key outstanding questions surrounding the role of reward value computation in the pathogenesis of AN.

Basic Research

Andrew M. Wikenheiser, Ph.D., University of California, Los Angeles, is interested in counterfactual thinking—the ability to think about events that could have happened in the past or that might happen in the future, but that are not presently occurring. This type of thinking is essential for decision-making, including those made in the context of addictive behavior. Previous studies have linked the hippocampus to counterfactual thinking, but it is still unclear how the hippocampus actually enables this type of thinking. To explore this question, the team has developed a rat decision-making task that elicits counterfactual thinking and is well-suited to investigating hippocampal representations. The aim is to determine how the hippocampus contributes to counterfactual thinking about reward. By understanding the neural mechanisms underlying counterfactual thinking, researchers may be able to develop new treatments for disorders characterized by disordered decision-making patterns.
Basic Research

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Davide Aprile, Ph.D., University of Milan, Italy, notes that mutations in a gene called CHD8 are a high-risk factor for the development of autism spectrum disorder symptoms, and a disparate range of behavioral manifestations including OCD, ADHD, and sleep disturbances. To investigate if mutations in this gene could affect brain development and functions of specific cell types, Dr. Aprile will use brain organoids, a 3D in vitro model derived from control and patients' stem cells. He hopes to recapitulate in a dish the brain circuitry disrupted in the cognitive and behavioral manifestations of ASD, OCD and ADHD by fusing in a so-called assembloid three different types of organoids: cortical, thalamic, and cerebellar, and will study how mutations in CHD8 can affect their development and function.
Basic Research

Gerard J. Broussard, Ph.D., Princeton University, aims to establish the circuit basis of inhibitory control in a cerebellum-dependent task. This is pertinent to the fact that a number of neurodevelopmental disorders, such as ADHD, OCD, schizophrenia, and autism, include an impaired ability to inhibit context-inappropriate behavioral responses. The cerebellum is an important regulator of inhibitory control. Dr. Broussard has developed a cerebellum-dependent motor learning task that requires suppression of response to a moderately intense stimulus to allow a well-timed anticipatory response to an aversive unconditioned stimulus. In this project he aims to track activity in all input pathways to the cerebellum during task learning and to use viral tracing techniques

to establish the parts of the brain where the cerebellum influences activity during the task.
Basic Research

Gonçalo Cotovio, M.D., Ph.D., Fundação Champalimaud, Portugal, aims to use pooled lesion topography and lesion network mapping to study lesional neuropsychiatric syndromes, including OCD. Lesion topography assesses the overlap of different brain lesions while lesion network mapping reveals which brain networks are associated with each lesion location. One can use these methods to establish links between dysfunctional brain regions or circuits and occurrence of OCD. If successful, these strategies can also reveal new neuromodulation treatment targets, including for transcranial magnetic stimulation (TMS). This research will test the therapeutic relevance of lesional OCD-related brain nodes: after identifying the most consistent brain region, possibly the bilateral medial orbitofrontal cortex, they will conduct a randomized clinical TMS trial to treat OCD patients not responding to treatment, comparing currently approved target with the new target.
Next-Generation Therapies

John Falligant, Ph.D., Hugo W. Moser Research Institute at Kennedy Krieger, Inc/Johns Hopkins University, is interested in stereotypic movement disorder (SMD), characterized by motor behavior that is repetitive, seemingly driven, and nonfunctional. SMD is found in a broad range of psychiatric conditions, including OCD and related disorders, schizophrenia, and frontotemporal dementia. This project will combine quantitative and computational modeling approaches to understand the relative contributions of motivational and motoric variables on self-injurious behavior among individuals with SMD. The team will examine the temporal dynamics of self-injurious behaviors to determine how they correspond to known temporal signatures associated with motivational or motoric dysfunction. This is a first step for investigating distinct behavioral phenotypes of SMD that can yield additional insight into neurobehavioral sources of dysfunction and inform clinical practice.
Basic Research

Adam C. Frank, M.D., Ph.D., University of Southern California, suggests that as the use of wearable and mobile devices and AI/machine-learning (ML) analytics is likely to continue to increase in mental healthcare, gaining patient perspective on these technologies now is critically important to ensure shared understanding and adherence. This study uses qualitative methods to uncover and map themes regarding use of wearable biosensors, smartphone apps, and AI/ML in psychiatry. Interviews will be conducted with adults with moderate to severe OCD, recruited for participation

in a longitudinal biobehavioral study of OCD symptoms and treatment responsiveness. Interviews will broadly assess views on technology use in psychiatry and will also be used to determine if individuals with OCD have specific insight or concerns given the nature of OCD symptoms.

🧬 *Diagnostic Tools/Early Intervention*
🧬 *New Technologies*

Silvia G. Galfrè, Ph.D., University of Pisa, Italy, focuses on pediatric acute-onset neuropsychiatric syndrome (PANS), presenting with sudden onset of neuropsychiatric symptoms triggered by infection or environmental factors. The symptoms include obsessions/compulsions and food restriction. The cause and pathogenesis of PANS are still unclear but may involve changes in immune cell populations and gene expression in peripheral blood mononuclear cells (PBMCs). This study aims to identify specific cell sub-populations and genes involved in PANS using single-cell RNA sequencing techniques on PBMCs from 50 subjects, as well as potential targets for treatment using integrated analysis with plasma metabolomic/proteomic data from patients.

🧬 *Basic Research*

Allison E. Girasole, Ph.D., Harvard Medical School, notes the theory that OCD emerges due to recurrent activity in cortical, basal ganglia, and thalamic loops and that experience-dependent plasticity within these circuits reinforces maladaptive patterns of behavior. She will examine recurrent interactions between the cortex and basal ganglia during ongoing action selection, focusing on the mouse anterior lateral motor cortex (ALM) and the striatum, the primary input nucleus of the basal ganglia. The project's aims are to determine 1) how striatal activity influences motor planning in ALM during action selection, and 2) if striatal activity is necessary for proper action updating in ALM during action selection. This could tell us how cortical and striatal circuits dynamically interact to produce ongoing behavior, ultimately providing insight into the circuit mechanisms of OCD.

🧬 *Basic Research*

Christopher T. Sege, Ph.D., Medical University of South Carolina, will test a cutting-edge neurostimulation technology—transcranial focused ultrasound (tFUS)—as a tool for directly modulating escape/avoidance behaviors that drive impairment in anxiety, PTSD, and OCD. The central amygdala is the key mediator of rapid escape from imminent threat, and is not directly accessible to conventional neuromodulation technologies such as TMS. Dr. Sege will recruit 40 individuals seeking anxiety or related disorder treatment to complete three in-person laboratory visits: a first visit in which brain structure and escape/avoidance-related functional activity are measured with MRI, and two subsequent visits in which an established escape/avoid task

is administered before and after receiving tFUS stimulation to the amygdala or placebo stimulation.

🧬 *Next-Generation Therapies*
🧬 *New Technologies*

OTHER DISORDERS

ALZHEIMER'S DISEASE

Giulia R. Fois, Ph.D., Interdisciplinary Institute for Neuroscience–CNRS / University of Bordeaux, France, notes that acetylcholine (ACh) release in the medial pre-frontal cortex (mPFC) is essential to numerous cognitive functions; and that disruptions of cortical ACh transmission has been implicated in several disorders, including ADHD, Alzheimer's disease, schizophrenia, and addictive behavior. In rodents, the team will establish the causal role of the cholinergic SI/DB→vmPFC and B→dmPFC projections in attention using ACh pathway optogenetic activation and inhibition. They will characterize how these two ACh projections can alter vmPFC and dmPFC neuronal processes to control attention. This can contribute to better understanding of mPFC neuronal processes underlying attention. This can help advance the neurobiology of attention and may aid in the development of more effective cognitive enhancer drugs in disorders in which attention is dysfunctional.

🧬 *Basic Research*

Isabella Wagner, Ph.D., University of Vienna, Austria, notes that depressive symptoms earlier in life have been associated with Alzheimer's Disease (AD) development, even when these symptoms have occurred over two decades before AD onset. Depression and AD share common underlying mechanisms that revolve around a dysfunctional stress response, resulting in increased release of stress hormones, along with deficits of memory-related brain regions, inflammation, and cognitive decline. This project proceeds from the observation that gut bacteria appear altered in depression, AD, and APOE4 risk-gene carriers, and APOE4 was shown to drive its effects on inflammation and neurodegeneration explicitly via gut bacteria. This research will investigate whether there is a connection between the gut microbiome of APOE4 carriers and heightened stress reactivity, in 180 healthy, non-depressed APOE4 carriers and non-carriers (90 per group) between 20 and 35 years old.

🧬 *Basic Research*

CATATONIA

Aaron D. Besterman, M.D., University of California, San Diego, studies catatonia, a complex condition that affects children's behavior, movement, and emotions. He aims to compare the effectiveness of traditional medical tests with

a more advanced approach that includes genetic testing and immune system screening in finding underlying causes. The team will compare two groups of children with catatonia. One group will be identified from hospital records and will have undergone standard medical tests to find the cause of their catatonia. The other group will be a new set of patients who will receive both standard medical tests and additional advanced testing, including genome sequencing and screening for antibodies that attack the brain. They expect that combining standard medical tests with genome sequencing and autoantibody screening will be more effective.

ᗞᏣᒐ *Diagnostic Tools/Early Intervention*

EPILEPSY

Sarah D. Ackerman, Ph.D., Washington University, St. Louis, suggests changes in the timing of events in the "critical period" in early development are linked to neurodevelopmental disorders including autism, epilepsy, and schizophrenia. Mechanisms that ensure timely critical-period closure remain elusive. Dr. Ackerman proceeds from her past finding in fruit flies that astrocytes (immune cells in the brain) are essential for closure of a motor critical period. Using that model system, the lab now seeks to alter the function of neurons and astrocytes to extend or restrict neuronal plasticity, and test the behavioral consequences. Given that autism is linked to precocious critical period closure, they will explore whether astrocytes can be leveraged to reopen plasticity in mature circuits; and whether astrocytes are able to shut down plasticity in the adult brain. This could show how astrocytes tune neural plasticity in development to ensure long-term stability of circuit function and behavior.

ᗞᏣᒐ *Basic Research*

Yiyao Zhang, Ph.D., New York University School of Medicine, will investigate the potential of targeting acetylcholine modulation of the muscarinic receptor subtype M2 in inhibitory interneurons in the hippocampus to treat interictal epileptiform discharges (IEDs) in a rodent model of temporal lobe epilepsy (TLE) and alleviate associated depression symptoms. The aim is to shed light on the potential for targeting acetylcholine modulation of M2 receptors as a novel therapeutic approach for treating IEDs and associated depression symptoms in patients with TLE.

ᗞᏣᒐ *Basic Research*
ᗞᏣᒐ *Next-Generation Therapies*

FRAGILE X

J. Wren Kim, Ph.D., University of California, Berkeley, proceeds from emerging evidence suggesting that hyperexcitability of neural circuits underlies many phenotypes of Fragile X Syndrome (FXS), including ADHD, sensory hypersensitivity, seizure, and anxiety. Approximately 80% of children with FXS are also diagnosed with attention deficit disorder (ADD) or ADHD. Dr. Kim maintains that better understanding of hyperexcitability at a neuronal level will bring new insights to many FXS phenotypes, including ADHD. This study involves interrogation of the molecular mechanisms of neuronal hyperexcitability and identification of genetic modifiers of hyperexcitability in FXS using a well-established mouse model of FXS. It is hoped new genetic and molecular perspectives on hyperexcitability will provide mechanistic insights into hyperexcitability-related comorbidities in FXS.

ᗞᏣᒐ *Basic Research*

FRONTOTEMPORAL DEMENTIA

John Falligant, Ph.D., Hugo W. Moser Research Institute at Kennedy Krieger, Inc/Johns Hopkins University, is interested in stereotypic movement disorder (SMD), characterized by motor behavior that is repetitive, seemingly driven, and nonfunctional. SMD is found in a broad range of psychiatric conditions, including OCD and related disorders, schizophrenia, and frontotemporal dementia. This project will combine quantitative and computational modeling approaches to understand the relative contributions of motivational and motoric variables on self-injurious behavior among individuals with SMD. The team will examine the temporal dynamics of self-injurious behaviors to determine how they correspond to known temporal signatures associated with motivational or motoric dysfunction. This is a first step for investigating distinct behavioral phenotypes of SMD that can yield additional insight into neurobehavioral sources of dysfunction and inform clinical practice.

ᗞᏣᒐ *Basic Research*

IMPULSIVE AGGRESSION

Debora Masini, Ph.D., Stockholm University, Sweden, notes pathological aggression can arise in psychiatric disorders such as bipolar disorder, substance abuse, ADHD, and conduct disorders. Though it is common, clinicians lack treatment options. Pharmacotherapy often involves sedation and physical restraint for the acute stage whereas chronic cases are treated with a combination of mood regulators such as SSRIs, lithium, beta-blockers, and antipsychotics. Sedation carries risk and complicates diagnosis, whereas chronic aggression can be drug-resistant and treatment further limited by side effects. This project seeks a novel treatment strategy, specifically tailored to control aggression across different disease modalities. Dr. Masini will focus on a primary node in the neuronal circuitry that coordinates aggression. Located in the hypothalamus, the PMv works as an "aggression igniter." She aims to describe the plastic changes that occur with experience, particularly when the behavioral motif of aggression first emerges. By comparing neuronal activity in rodents that develop an aggressive phenotype with those that don't, she

aims to elucidate how some individuals restrain aggression while others are drawn toward it.

DNA *Basic Research*
DNA *Next-Generation Therapies*

INTELLECTUAL DISABILITY

Marta Garcia-Forn, Ph.D., Icahn School of Medicine at Mount Sinai, aims to investigate the role of the DDX3X gene in the generation and function of glutamatergic neurons, and its contribution to anxiety-like behaviors. Mutations in the X-linked RNA helicase DDX3X cause a neurodevelopmental disorder affecting mainly females and manifesting with intellectual disability, autism spectrum disorder, and often anxiety and self-injurious behaviors. This project will study how alterations in cortical glutamatergic lineages caused by DDX3X mutations lead to behavioral deficits, including anxiety-related behaviors. The project is expected to bring a new understanding of how cortical development shapes neuronal diversity that contributes to complex behaviors and may shed light on comorbidity between autism and other psychiatric conditions.

DNA *Basic Research*

INTELLECTUAL DISABILITY, CEREBRAL PALSY

Nataliia Kozhemiako, Ph.D., Brigham and Women's Hospital/Harvard University, notes that while sex is an important factor with respect to the risk and severity of neurodevelopmental disorders (NDDs), it is unclear whether disrupted sleep manifests similarly in boys and girls. Given that multiple aspects of sleep architecture also show sexually dimorphic normative developmental trajectories, this project seeks to elucidate the effect of sex on sleep neurophysiology across multiple NDDs including ADHD, autism spectrum disorder (ASD), intellectual disabilities, and cerebral palsy. Using data from the National Sleep Research Resource, the team will analyze a large sample of clinical whole-night sleep electroencephalograms (EEG) recorded in children with NDD diagnoses. They will investigate sex differences in sleep structure and timing as well as the prevalence of sleep-related disorders. They will further quantify key facets of sleep neurophysiology by analyzing specific EEG signatures.

DNA *Basic Research*

MULTIPLE SCLEROSIS

Erica B. Baller, M.D., University of Pennsylvania, is studying mechanisms of anxiety in patients with multiple sclerosis (MS). About half of MS patients are affected. MS is characterized by lesions in white matter; studies of otherwise healthy individuals with anxiety have described associations between white matter variability and anxiety symptoms, specifically in tracts that connect functional hubs of the frontoparietal

and default mode networks. Using a technique called lesion network mapping (LNM) in a cohort of 3,737 MS patients, Dr. Baller aims to construct a white matter anxiety network from fascicles that connect the frontoparietal and default mode networks, and examine whether MS lesions

Panic Disorder

Janos Fuzik, Ph.D., Karolinska Institute, Sweden, studies panic disorder (PD), which has 2.5 times higher occurrence in women than in men. Dr. Fuzik aims to understand the pathophysiology of critical brain circuits in the development of PD. He wants to establish the neuronal identity of highly involved circuits in periaqueductal gray matter (PAG) and investigate how stressful stimuli evoke circuit imbalance in a sex-dimorphic manner leading to maladaptive behaviors in PD. A plethora of neurophysiological mechanisms are influenced by sex hormones, including excitatory-inhibitory balance, neuronal excitability, and inhibitory synaptic transmission. Distinct neuronal subpopulations of the PAG express high levels of estrogen receptor-alpha, and therefore are prone to modulation by estradiol level fluctuations, which may contribute to sex differences in PD. This project seeks to reveal the key neuronal types and their connectivity changes in the ventromedial hypothalamus (VMH)-PAG connectome that underlie panic-like states, and thereby reveal candidate molecular targets for development of new sex-specific treatments.

DNA *Basic Research*

PARKINSON'S DISEASE

María Sancho Alonso, Ph.D., Institut d'Investigacions Biomediques de Barcelona, Spain, notes that alterations in the functional integrity of the serotonin (5-HT) system correlate with the severity of depressive symptoms in Parkinson's Disease (PD), as well as evidence of changes in the functional connectivity of different regions in the ventromedial prefrontal cortex (vmPFC) controlling emotional functions, which may become an early biomarker for the stratification of PD patients at risk for depression. This project explores neural circuits and neurobiological substrates involved in the neuropsychiatric symptoms of PD. The hypothesis is that the dynamics of early-stage depressive dysfunction may trigger neurodegenerative events in PD, leading to long-term changes in brain circuitry, neuronal plasticity, and response to treatments.

DNA *Basic Research*

PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME (PANS)

Silvia G. Galfrè, Ph.D., University of Pisa, Italy, focuses on pediatric acute-onset neuropsychiatric syndrome (PANS), presenting with sudden onset of neuropsychiatric symptoms triggered by infection or environmental factors. The symptoms include obsessions/compulsions and food restriction.

The cause and pathogenesis of PANS are still unclear but may involve changes in immune cell populations and gene expression in peripheral blood mononuclear cells (PBMCs). This study aims to identify specific cell sub-populations and genes involved in PANS using single-cell RNA sequencing techniques on PBMCs from 50 subjects, as well as potential targets for treatment using integrated analysis with plasma metabolomic/proteomic data from patients.

🧬 *Basic Research*

PROLONGED GRIEF DISORDER

Saren H. Seeley, Ph.D., Icahn School of Medicine at Mount Sinai, studies prolonged grief disorder (PGD), a severe form of grieving that can result in chronic emotional pain and problems in daily living. It affects about 1 in 10 people who have experienced the death of a close loved one. This project uses computational psychiatry to better understand the learning mechanisms that contribute to PGD. Computational psychiatry uses mathematical models to study disorders. The goal is to understand how brain activity gives rise to behavior and cognition, and how this can be disrupted in mental illness. Dr. Seeley believes understanding the role of learning in grief is important because it connects two processes that could be working differently in PGD: how new information is stored in memory, and how the brain's reward system functions. The project will investigate whether there is a disruption in habit vs. goal-directed learning in people with PGD, compared to bereaved people without PGD ("typically-grieving") as well as people who have not experienced significant bereavement.

🧬 *Basic Research*

SPINAL CORD INJURY

Anders M. Nelson, Ph.D., New York University, studies how spinal cord injury (SCI) contributes to mental illness. It is difficult to study spinal cord circuits in behaving animals. This research seeks to overcome this limitation by leveraging cutting-edge neuroscience methods to map, monitor, and manipulate spinal and brain circuits in normal and disease models. Depression and anxiety following SCI are strongly associated with the emergence of chronic pain, but the neuronal circuit mechanisms linking these phenomena are poorly understood. One hypothesis is that following SCI, hyperactivity in spinal feedback circuits, particularly the spinothalamic (STT) pathway, drives chronic pain and subsequent depression. This project aims to 1) map the circuit organization of STT neurons, and learn how SCI disrupts this connectivity matrix; 2) determine how SCI changes STT activity and leads chronic pain; 3) treat chronic pain and mental health sequelae by rescuing normal STT activity.

🧬 *Basic Research*

🧬 *Next-Generation Therapies*

STROKE

Lena K.L. Oestreich, Ph.D., Queensland University of Technology, Australia, studies how depression develops in the months following stroke. There are no tests to identify who is most susceptible and no regions of the brain seem to be particularly vulnerable to the effects of stroke in determining who will develop depression. There is evidence that instead of causing damage to relatively small areas of the brain as seen on traditional MRI scans, strokes may initiate injuries throughout the brain by damaging the connections between the brain area directly affected by the stroke and other regions of the brain. This project will visualize these more subtle injuries across the brain. The team will test if these broader patterns of injury are associated with the development of depression in stroke survivors.

🧬 *Basic Research*

TRAUMATIC BRAIN INJURY

Chiara Maffei, Ph.D., Massachusetts General Hospital/Harvard University, aims to improve a neuroimaging technique called diffusion MRI (dMRI) tractography, which makes it possible to investigate some of the major structural connections within depression circuits. A set of subcortical pathways connecting limbic and midbrain regions that have been implicated in the pathogenesis of depression in animal studies still remain inaccessible in humans. This project will use an ultra-high resolution dMRI dataset to image small subcortical pathways in vivo with exceptional anatomical accuracy. Automated tractography will be used to transfer anatomical accuracy of major white matter pathways from higher- to lower-quality dMRI. Ultra-high resolution dMRI data will be collected for 10 healthy subjects to manually label the subcortical depression circuit and create its first human atlas, which will be used to train a global tractography algorithm. This new tool will be employed to reconstruct the subcortical pathways in a large cohort of chronic traumatic brain injury (TBI) patients with and without depression and investigate their tissue microstructure. dMRI will also be used to search for pathway-specific imaging biomarkers of neuroinflammation associated with depression.

🧬 *Diagnostic Tools/Early Intervention*

🧬 *New Technologies*

POST-TRAUMATIC STRESS DISORDER (PTSD)

Seungwon (Sebastian) Choi, Ph.D., University of Texas Southwestern Medical Center at Dallas, notes that primary sensory neurons that innervate the skin and detect a wide range of somatosensory stimuli are well-characterized, yet little is known about how peripheral signals are integrated, processed, and conveyed to the brain through ascending somatosensory circuits to generate the perception of touch and pain and behavioral responses. This research seeks to determine the pathophysiological role of ascending somatosensory circuitry in sensory dysfunction in ASD and PTSD. The team previously identified two genetically defined ascending circuit modules that cooperate to convey tactile, thermal, and noxious cutaneous signals from the spinal cord to the lateral parabrachial nucleus (PBNL) of the pons to underlie affective aspects (i.e., emotional "feelings") of touch and pain sensation. The PBNL is a "somatosensory gateway" to the higher brain regions because it receives strong, abundant somatosensory inputs from the spinal cord and broadcasts these signals to limbic areas that control social and emotional behaviors. They now will test the idea that the PBNL represents a key node for pathological touch and pain hypersensitivity in ASD and PTSD.

Basic Research

Constanza Garcia Keller, Ph.D., Medical College of Wisconsin, notes that a life-threatening event increases the incidence of PTSD, which carries a 30%-50% comorbidity with substance use disorders (SUDs). Such comorbidity results in greater drug use and poorer treatment outcomes. Cannabis is among the most widely used drugs, particularly in veterans and in those suffering from PTSD. Few studies have evaluated the interaction between cannabis use and stress. This project builds on the team's prior finding that key neuroadaptations produced by acute stress and addictive drugs in the cortico-accumbens glutamatergic circuit may be shared, raising the possibility that the shared substrates not only contribute to each disorder individually but may also facilitate comorbid PTSD and SUDs. Understanding biological mechanisms can inform rational drug design to treat comorbid PTSD and SUDs.

Basic Research

Matthew James Girgneti, Ph.D., Yale University School of Medicine, will apply the latest molecular techniques to samples from a new repository of brain tissue from individuals with PTSD to create a large and detailed analysis of the molecular consequences of PTSD. A specific aim is to map the regulatory sequences (open chromatin) in discrete cellular populations (neurons and non-neuronal cells) derived from the dorsolateral prefrontal cortex in a cohort of cases with PTSD and controls. The action of individual genes on molecular and cellular PTSD-associated processes and the molecular networks identified will be validated using iPS-cell derived cultures of human neuronal cell systems. This multidimensional approach provides a roadmap to place PTSD genetic risk variants in molecular context to help identify the underlying regulatory and expression mechanisms through which they act.

Basic Research

Erin E. Hisey, Ph.D., McLean Hospital, notes that circuit and molecular deficits that result from early-life trauma (ELT) are not well understood. While animal models of early life neglect are commonly used, models of abuse are nearly absent. She seeks to test such an animal model. Using chronic social defeat stress in juvenile mice (jCSDS), the lab has developed a novel model of ELT that produces profound impacts on behavior and underlying brain activity. One of the areas most strongly activated during re-exposure to juvenile trauma cues is a key component of the hippocampal formation, the lateral entorhinal cortex (LEC). This project will investigate the role of LEC in the retrieval of juvenile trauma memories in the adult brain, aiming to attain in-depth characterization of circuit- and molecular-level changes in the adult brain as a result of juvenile trauma with the object of identifying future targets for modulation in psychiatric disorders resulting from ELT.

Basic Research

Artemis Iatrou, Ph.D., McLean Hospital/Harvard University, notes one mechanism that could explain converging pathologies in both PTSD and MDD (vascular dysfunction and brain inflammation) is a leaky blood-brain barrier (BBB) that would allow peripheral proinflammatory molecules to enter the brain. The team will probe the link between childhood trauma and comorbid PTSD and MDD. They will map cell-type-specific transcriptomic changes in response to stress and trauma exposure within the perivascular microenvironment and profile the hippocampal perivascular space of people with comorbid PTSD and MDD in single-nucleus resolution. Using patient-derived induced pluripotent stem cell technology, they will reconstruct the BBB in vitro and evaluate the stress response, allowing for timely preventative or therapeutic target identification. The project could provide insight into how maladaptive stress responses and trauma affect the borders of the human brain.

Basic Research

Taylor J. Keding, Ph.D., Yale University, hypothesizes that advanced maturation of resting amygdala-PFC functional connectivity will be associated with increased post-traumatic stress symptoms (PTSS) and that trauma exposure

will moderate this relationship, such that trauma-exposed and trauma-naïve youth will show advanced and delayed (or no difference) in maturation with increasing PTSS, respectively. It remains unclear whether mainstay treatments for PTSS in youth, like trauma-focused cognitive-behavioral therapy (TF-CBT), alleviate symptoms by altering the development of emotion neural circuitry. This study will evaluate whether individual- and circuit-specific indices of altered neurodevelopment are predictive of trauma, PTSS, and TF-CBT treatment response. Machine learning models will predict typical amygdala-PFC circuit development using resting-state functional connectivity from the longitudinal Adolescent Brain Cognitive Development (ABCD) Study. Models will be trained to predict chronological age in 6,000 youth (ages 9-15 years). Deviations from model prediction (brain age gap estimates; BrainAGEs) will be used as indices of circuit maturation in a held-out sample of 1,000 youth.

Basic Research
Next-Generation Therapies

Roger Marek, Ph.D., University of Queensland, Australia, notes that even after full extinction, fear can relapse, a major burden in PTSD patients and leading to the experience of flashbacks outside the clinic. To better understand the neural circuits that drive fear relapse and improve current clinical intervention techniques, this project will use a novel neural tagging approach that allows for an investigation of the neural correlates, pharmacological properties, and circuits involved in fear versus relapsed fear after extinction. The study will focus on the prefrontal cortex, which is critically involved in regulating appropriate fear responses. The team previously identified a neural input into the prefrontal cortex to mediate fear relapse; the precise activation pattern remains unclear. The project seeks to precisely identify the prefrontal neural function to control fear and its relapse after extinction.

Basic Research

Heidi Catherine Meyer, Ph.D., Boston University, studies the development of neural circuitry involved in emotional control. It is her conviction that early intervention during adolescence, when the brain is still highly plastic, may have the greatest impact on reducing the longevity and severity of mood and anxiety disorders. Citing research suggesting pubertal development triggers a window of opportunity for recalibration of the HPA axis, her team's work considers how the adolescent brain itself may be leveraged to re-route trajectories of brain development. The dynamic functional remodeling of cortico-hippocampal connections in adolescence acts to fine-tune affective neural activity. This project uses functional ensemble tagging techniques in populations of hippocampal neurons to isolate the memory trace asso-

ciated with a learned safety cue. The team will explore the possibility that engaging ensembles of tagged "safety neurons" intermittently across adolescence may prime the adult brain for enhanced fear regulation.

Basic Research

Takuya Osakada, Ph.D., New York University, will focus on dissecting the relationship between oxytocin-related neural circuitry and PTSD. Oxytocin receptor (OXTR)-expressing neurons in some brain regions such as the dorsolateral bed nucleus of the stria terminalis are activated by predictable cued fear, suggesting that OXTRs and oxytocin signaling are deeply implicated in PTSD. The team will use mice to dissect circuitry and perform behavioral assays. They have so far identified a hypothalamic oxytocinergic circuit for social avoidance and have established appropriate behavioral paradigms with various stressors such as social defeat.

Basic Research

Joongkyu Park, Ph.D., Wayne State University, seeks intervention targets for PTSD. Both presynaptic and postsynaptic regions contain relevant proteins, but those regions extend from microns to a meter away from the cell bodies of neurons, the main hub of protein production. Therefore, says Dr. Park, it is critical to locally control the compartmental demand for newly synthesized proteins under conditions of healthy memory and distress. Accumulating evidence indicates that synaptic compartments contain the key components of protein synthesis (messenger RNAs and ribosomes). This project investigates the roles of dendritic protein synthesis in a PTSD model (fear conditioning of mice). Knowledge of the functional roles of local protein biogenesis in this behavioral model could reveal pathways of learning and memory and accelerate progress toward treatments for disorders, including PTSD, by providing molecular insights into candidates that can be therapeutically targeted.

Basic Research

Rebecca K. Reh, Ph.D., Cohen Veterans Bioscience, seeking biomarkers in PTSD, will combine signals from resting-state EEG and fMRI to identify the shared signals between the two modalities. Model development will be carried out in 477 veterans deployed to Iraq and/or Afghanistan diagnosed with PTSD, subthreshold PTSD, traumatic brain injury (TBI) and/or major depressive disorder, as well as trauma-exposed healthy controls. Along with rsEEG and fMRI recording sessions, participants completed over 25 different clinical and self-report measures. Dr. Reh will investigate the relationship between brain connectivity and transdiagnostic symptom scores. Modality-independent brain connectivity scores will be associated with PTSD symptom scores before and after a 12-week treatment regime in a validation sample. The goal is to identify stable, modality-independent brain connectivity

patterns that can be accurately mapped to symptom presentation and treatment response to better inform individual diagnosis and treatment decisions.

Diagnostic Tools/Early Intervention

Christopher T. Sege, Ph.D., Medical University of South Carolina, will test a cutting-edge neurostimulation technology—transcranial focused ultrasound (tFUS)—as a tool for directly modulating escape/avoidance behaviors that drive impairment in anxiety, PTSD, and OCD. The central amygdala is the key mediator of rapid escape from imminent threat, and is not directly accessible to conventional neuromodulation technologies such as TMS. Dr. Sege will recruit 40 individuals seeking anxiety or related disorder treatment to complete three in-person laboratory visits: a first visit in which brain structure and escape/avoidance-related functional activity are measured with MRI, and two subsequent visits in which an established escape/avoid task is administered before and after receiving tFUS stimulation to the amygdala or placebo stimulation.

Next-Generation Therapies
New Technologies

Sydney Trask, Ph.D., Purdue University, seeks to develop and test therapeutic strategies that mitigate relapse in anxiety and trauma therapy associated with extinction learning. The original fear memory can be targeted to reduce behavioral responding, with the ultimate goal being to reduce maladaptive behavioral responding and leave it less susceptible to relapse. These procedures take advantage of a brief period of time following memory retrieval in which the memory becomes sensitive to disruption: the reconsolidation window. Dr. Trask has developed a behavioral strategy, "UCS deflation," that aims to open the reconsolidation window and present a weaker version of the feared unconditional stimulus. It can blunt behavior in a context-independent manner, suggesting it could be implemented to create behavioral reductions resistant to relapse. This project will extend the team's prior work showing both extinction and UCS deflation result in reduced neural activity in the basolateral amygdala (BLA) and increased neural activity in the infralimbic cortex (IL).

Next-Generation Therapies

Brad Verhulst, Ph.D., Texas A&M University, hopes that by identifying specific adversity-related mechanisms that amplify genetic risk, research can provide a basis to develop biologically-informed evidence-based interventions to support individuals who experience trauma and prevent or reduce the severity of depression and anxiety symptoms. The team will perform a proof-of-concept genome-wide interaction study that demonstrates acute adversity (childhood maltreatment) and chronic adversity (socioeconomic deprivation) amplify individual genetic predispositions to depression and anxiety.

These statistical methods will provide tools to identify the amplifying effect of adversity across the genome and for individual genetic variants. They will use a statistical approach to analyze data from two very large genetically informed datasets (N > 650,000). The goal is to understand how adverse life events amplify the genetic mechanisms that increase the risk and severity of depression and anxiety.

Basic Research

Tao Xie, Ph.D., Washington University School of Medicine, suggests that achieving permanent fear reduction in PTSD, anxiety, or other illnesses requires a better understanding of the neural mechanisms mediating fear extinction. Amygdala-prefrontal circuits play a critical role in fear extinction, and rodent experiments suggest the prelimbic area (PL) and the infralimbic area (IL) could facilitate and inhibit fear responding. In humans, it has been hypothesized that the dorsal anterior cingulate cortex (dACC) and the ventromedial prefrontal cortex (vmPFC) constitute the homologues of PL and IL. This project investigates the neural dynamics and causal functions of human amygdala-prefrontal circuits during fear extinction. Clinically-indicated placement of stereoelectro-encephalography (SEEG) electrodes within wide cortical/subcortical networks to record neural signals and deliver electrical stimulation will provide an pportunity to study the dynamics and causal functions of human amygdala-prefrontal circuits at the small (single-neuron units) and large scale (local field potential).

Basic Research

Wen Xin, Ph.D., University of California, San Francisco, notes recent work indicating a crucial role for myelination in the maintenance of fear memory. The neuronal circuit basis for how myelin influences memory is unclear, however. Parvalbumin (PV) interneurons are an inhibitory neuron subtype that critically regulate neural circuits involved in fear memory formation and regulation; they are also one of the most heavily myelinated neuronal populations in the mammalian cortex. Using newly developed genetic tools, Dr. Xin will test the region- and cell type-specific role of parvalbumin neuron myelination in fear memory formation and preservation, as well as circuit activity in the medial prefrontal cortex of mice following contextual fear conditioning. This may shed light on the complex interplay between neural circuits and myelination during memory formation and retrieval.

Basic Research

PSYCHOSIS

Shokouh Arjmand, Pharm.D., Aarhus University, Denmark, studies the mechanisms of second-generation antipsychotics (SGAs), which are associated with a constellation of metabolic abnormalities such as hyperglycemia, dyslipidemia, weight gain, and cardiovascular problems. The lab will investigate the involvement of mTOR, a master regulator of cell growth and metabolism, in the pathophysiology of SGA-induced metabolic dysfunctions. They will attempt to prevent or alleviate metabolic adverse effects by modulating the activity of leucine sensors—sestrins, essential in maintaining metabolic homeostasis. Sestrins are found in the brain, muscles, and liver, as well as adipose cells. The study aims to illuminate some of the complexities of SGA pharmacology and, in particular, highlights a nuanced interaction between sestrins, leucine content, and mTORC1 in metabolic homeostasis.

Next-Generation Therapies
Basic Research

David Benrimoh, M.D., Stanford University, studies the earliest stages of psychosis. Until now, most studies using computer models have examined patients at one point in time and have not examined how changes in mood and stress impact the generation of psychotic symptoms. He will examine how changing mood and stress levels influence the beliefs that drive hallucinations. This will be tested in a pilot group of patients who have recently developed or who are at high risk of developing psychosis. Patients will be tested several times over 6 months and will provide brain data (EEG and fMRI) which will be correlated to their performance on the task and their symptoms. The team will determine if the test is sensitive to changes in their symptoms and functioning. This could enable a larger study aiming to confirm and extend the relationships between behavior, symptoms, brain data, and computational parameters observed in the pilot study. The ultimate object is to be able to define the stage of illness based on computational testing.

Diagnostic Tools/Early Intervention

Michelle C.D. Bridi, Ph.D., West Virginia University, studies the relation of the ratio between excitatory and inhibitory signaling (E/I ratio) in the brain and pathology in psychiatric illnesses. The E/I oscillation is controlled by multiple mechanisms and is susceptible to dysregulation if any one of these processes is disrupted. Two mechanisms are sleep and endocannabinoid signaling. Preliminary data show decreased sleep quality and altered timing of endocannabinoid signaling are linked to E/I dysregulation in mouse lines associated with autism spectrum disorder. The team will evaluate how sleep and endocannabinoid signaling are altered, and how they relate to the E/I ratio oscillation, after subchronic PCP

administration. In conjunction with their preliminary studies of autism spectrum disorder, the findings in this study could establish whether E/I dysregulation may be a common theme across models of psychiatric conditions.

Basic Research

Harriet R. Feldman, M.D., Ph.D., The Francis Crick Institute, U.K., explores whether psychosis might be an autoimmune disease. Her research aims to identify potential causes of immune dysregulation in psychosis using deep immunophenotyping. She will take matched cerebrospinal fluid (CSF) and blood samples from 20 people experiencing psychosis and 20 people without psychosis. She will study both mRNA and the proteins on the surface of the cell to gain understanding of the lineage and function of each cell. The team will also sequence the unique B-cell and T-cell receptors in each participant, and use bioinformatics to infer their targets. This will allow detection of an active immune process and whether this process is targeting the brain. Based on this, methods might then be developed to probe a causal role of these immune components in psychosis.

Basic Research

Kaushik J. Lakshminarasimhan, Ph.D., Columbia University, observes that antipsychotic treatments indiscriminately target all dopaminergic pathways, while noting clinical studies showing the increase in dopamine is localized to more dorsal regions of the striatum. To develop better treatments, the team argues, there is a need to understand the specific role of dopamine in different striatal regions and the mechanism by which altering its level gives rise to the symptoms. This project entails building a computational model of parallel corticostriatal loops spanning different striatal subregions to perform auditory detection. The hypothesis is that dopamine in different parts of the striatum encodes different types of prediction errors: dopamine in the ventral striatum encodes reward prediction error to aid reward processing, whereas dopamine in the tail of striatum encodes state prediction errors to aid signal detection. Identifying the circuit mechanisms underlying auditory hallucinations may contribute to the development of novel antipsychotic drugs targeting specific receptors in specific dopaminergic pathways to treat positive symptoms of schizophrenia with greater efficacy.

Basic Research
Next-Generation Therapies

Stuart Oldham, Ph.D., Murdoch Childrens Research Institute/University of Melbourne, Australia, will develop a new method to build generative brain network models, mathematical models that allow simulation of the formation of brain networks in typical and atypical development. By integrating large-scale MRI analyses of adolescent populations with detailed cortical maps of genetic, molecular,

and physiological properties, the team hopes to gain insight into the mechanisms driving network connectivity. This will allow isolation of molecular pathways and properties crucial in determining network connections and disruptions. Using this model, the team will investigate how wiring constraints relate to the presence and severity of psychosis symptoms and cognition in a large cohort of adolescents and young adults.

ⅅⅭ *Basic Research*

Maria Belen Pardi, Ph.D., INSERM, France, researches the causes of abnormal perception and delusions in psychosis. It has been suggested an imbalance in the integration between "bottom-up" sensory and "top-down" internal information may give rise to these. Yet, little is known about where and how these computations are implemented in the brain to produce either accurate or aberrant perception. Dr. Pardi theorizes the auditory disturbances frequently experienced in schizophrenia may implicate aberrant top-down processing in the higher-order auditory thalamo-cortical circuit. This study will precisely target and investigate individual identified neurons and synapses during behavior. How top-down signals are encoded in the higher-order auditory system, how they undergo plasticity during learning, and how they affect perception will be probed; then, how these top-down inputs are integrated with bottom-up sensory inputs to affect cortical processing. The team will also explore how top-down mechanisms are affected in pathological conditions related to high schizophrenia risk in a mouse model.

ⅅⅭ *Basic Research*

Adam J. Rossano, M.D., Ph.D., Children's Hospital of Philadelphia Research Institute, will examine embryonic stem cells engineered to carry a genetic deletion recapitulating 22q11.2 deletion syndrome (22qDS). Individuals with this condition have a 25% risk of developing psychosis. Human imaging and postmortem studies suggest disturbed synaptic plasticity and aberrant balance between excitatory and inhibitory neurotransmission in the forebrain of adolescents contributes to schizophrenia. This project will explore how previously established metabolic, biochemical, and mitochondrial disturbances contributing to the penetrance of psychotic features in 22qDS, impact glutamatergic neurotransmission in a model of human natal synapses. The goal is to understand how alterations in mitochondrial biology disrupt glutamatergic neurotransmission in developing brain with an eye to identification of mechanisms that would provide potential novel therapeutic targets.

ⅅⅭ *Basic Research*

SCHIZOPHRENIA

Sarah D. Ackerman, Ph.D., Washington University, St. Louis, suggests changes in the timing of events in the "critical period" in early development are linked to neurodevelopmental disorders including autism, epilepsy, and schizophrenia. Mechanisms that ensure timely critical-period closure remain elusive. Dr. Ackerman proceeds from her past finding in fruit flies that astrocytes (immune cells in the brain) are essential for closure of a motor critical period. Using that model system, the lab now seeks to alter the function of neurons and astrocytes to extend or restrict neuronal plasticity, and test the behavioral consequences. Given that autism is linked to precocious critical period closure, they will explore whether astrocytes can be leveraged to reopen plasticity in mature circuits; and whether astrocytes are able to shut down plasticity in the adult brain. This could show how astrocytes tune neural plasticity in development to ensure long-term stability of circuit function and behavior.

ⅅⅭ *Basic Research*

Chinnakkaruppan Adaikkan, Ph.D., Indian Institute of Science, India, is studying transcranial electrical stimulation (tES), a noninvasive brain stimulation technology in which an electrical field is applied on the scalp surface, either as direct (tDCS) or alternating current (tACS). The efficacy of tES, which has been tested in depression, schizophrenia, and bipolar disorder, likely depends on multiple parameters, including duration and intensity of stimulation and, most importantly, tES paradigms (anodal or cathodal tDCS or specific frequency of tACS). This project seeks better understanding of the cellular, molecular, and neurophysiological mechanisms of tES, specifically, the relationship between tES and neurons in the local circuit in the prefrontal cortex (PFC) and impacts on neuromodulators such as acetylcholine, dopamine, norepinephrine, and serotonin. The hypothesis is that different paradigms of tES applied on the scalp over the PFC engage different neuromodulators and modify their levels in the PFC.

ⅅⅭ *Next-Generation Therapies*
ⅅⅭ *Basic Research*

Shokouh Arjmand, Pharm.D., Aarhus University, Denmark, studies the mechanisms of second-generation antipsychotics (SGAs), which are associated with a constellation of metabolic abnormalities such as hyperglycemia, dyslipidemia, weight gain, and cardiovascular problems. The lab will investigate the involvement of mTOR, a master regulator of cell growth and metabolism, in the pathophysiology of SGA-induced metabolic dysfunctions. They will attempt to prevent or alleviate metabolic adverse effects by modulating the activity of leucine sensors—sestrins, essential in maintaining metabolic homeostasis. Sestrins are found in

the brain, muscles, and liver, as well as adipose cells. The study aims to illuminate some of the complexities of SGA pharmacology and, in particular, highlights a nuanced interaction between sestrins, leucine content, and mTORC1 in metabolic homeostasis.

🧬 *Next-Generation Therapies*
🧬 *Basic Research*

André M. Bastos, Ph.D., Vanderbilt University, wants to know why neural oscillations in the brain are impaired in people with schizophrenia. The underlying circuit that generates oscillations involves the interplay of inhibitory interneurons (which "pace" the timing of the network) with excitatory neurons. In post-mortem analysis of brains of those diagnosed with schizophrenia, there is selective impairment of different classes of inhibitory interneurons. This breakdown in inhibitory signaling may lead to selective impairments in oscillatory activity, thereby reducing cortical communication. In this research Dr. Bastos seeks to characterize the connection between cortical layers, oscillations, and inhibitory cell types. Working with macaque monkeys, the team will combine state-of-the art light-sheet microscopy with laminar electrophysiology to perform their analysis.

🧬 *Basic Research*

Laurie Bayet, Ph.D., American University, will pilot new ways to measure complex social communication skills in human infants with and without a family history of social anxiety disorder, schizophrenia, or autism. The team will use safe, non-invasive, high-resolution measures of brain activity (fNIRS), looking behavior, and pupil size (eye-tracking). They combine these state-of-the-art tools with machine learning and computational modeling. The object, first, is to measure how infants' brains perceive face movements at 6-8-months; then assess how infants make sense of social communication scenarios at 13–15-months. Finally, the team will examine longitudinal associations between these measures and caregiver reports of infants' social-emotional skills at 18-months. A better understanding of how these skills emerge and contribute to later outcomes may be critical for uncovering how social anxiety disorder, schizophrenia, and autism develop.

🧬 *Basic Research*

David Benrimoh, M.D., Stanford University, studies the earliest stages of psychosis. Until now, most studies using computer models have examined patients at one point in time and have not examined how changes in mood and stress impact the generation of psychotic symptoms. He will examine how changing mood and stress levels influence the beliefs that drive hallucinations. This will be tested in a pilot group of patients who have recently developed or who are at high risk of developing psychosis. Patients will be tested several times over 6 months and will provide brain data (EEG

and fMRI) which will be correlated to their performance on the task and their symptoms. The team will determine if the test is sensitive to changes in their symptoms and functioning. This could enable a larger study aiming to confirm and extend the relationships between behavior, symptoms, brain data, and computational parameters observed in the pilot study. The ultimate object is to be able to define the stage of illness based on computational testing.

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Michelle C.D. Bridi, Ph.D., West Virginia University, studies the relation of the ratio between excitatory and inhibitory signaling (E/I ratio) in the brain and pathology in psychiatric illnesses. The E/I oscillation is controlled by multiple mechanisms and is susceptible to dysregulation if any one of these processes is disrupted. Two mechanisms are sleep and endocannabinoid signaling. Preliminary data show decreased sleep quality and altered timing of endocannabinoid signaling are linked to E/I dysregulation in mouse lines associated with autism spectrum disorder. The team will evaluate how sleep and endocannabinoid signaling are altered, and how they relate to the E/I ratio oscillation, after subchronic PCP administration. In conjunction with their preliminary studies of autism spectrum disorder, the findings in this study could establish whether E/I dysregulation may be a common theme across models of psychiatric conditions.

🧬 *Basic Research*

Gerard J. Broussard, Ph.D., Princeton University, aims to establish the circuit basis of inhibitory control in a cerebellum-dependent task. This is pertinent to the fact that a number of neurodevelopmental disorders, such as ADHD, OCD, schizophrenia, and autism, include an impaired ability to inhibit context-inappropriate behavioral responses. The cerebellum is an important regulator of inhibitory control. Dr. Broussard has developed a cerebellum-dependent motor learning task that requires suppression of response to a moderately intense stimulus to allow a well-timed anticipatory response to an aversive unconditioned stimulus. In this project he aims to track activity in all input pathways to the cerebellum during task learning and to use viral tracing techniques to establish the parts of the brain where the cerebellum influences activity during the task.

🧬 *Basic Research*

Christopher M. Davenport, Ph.D., St. Jude Children's Research Hospital, will study the mechanism of auditory hallucinations using a mouse model of 22q11.2 deletion syndrome (22q11DS), a leading genetic risk factor for schizophrenia. The team will test the hypothesis that combined auditory thalamocortical and cerebellar changes generate auditory phenotypes (of hallucinations) in 22q11DS mice. Prepulse inhibition (PPI) of acoustic startle and hallucination-like

perception in mice will enable the team to gauge changes in mouse behavior. Dr. Davenport will employ targeted viral injections to express designer receptors exclusively activated by designer drugs (DREADDs) to increase or decrease thalamocortical and/or DCN activity to either mimic 22q11DS auditory phenotypes in wild-type mice or reverse phenotypes of 22q11DS mice. These experiments may help establish whether thalamocortical dysfunction contributes to auditory phenotypes of schizophrenia.

🧬 *Basic Research*

John Falligant, Ph.D., Hugo W. Moser Research Institute at Kennedy Krieger, Inc/Johns Hopkins University, is interested in stereotypic movement disorder (SMD), characterized by motor behavior that is repetitive, seemingly driven, and nonfunctional. SMD is found in a broad range of psychiatric conditions, including OCD and related disorders, schizophrenia, and frontotemporal dementia. This project will combine quantitative and computational modeling approaches to understand the relative contributions of motivational and motoric variables on self-injurious behavior among individuals with SMD. The team will examine the temporal dynamics of self-injurious behaviors to determine how they correspond to known temporal signatures associated with motivational or motoric dysfunction. This is a first step for investigating distinct behavioral phenotypes of SMD that can yield additional insight into neurobehavioral sources of dysfunction and inform clinical practice.

🧬 *Basic Research*

Harriet R. Feldman, M.D., Ph.D., The Francis Crick Institute, U.K., explores whether psychosis might be an autoimmune disease. Her research aims to identify potential causes of immune dysregulation in psychosis using deep immunophenotyping. She will take matched cerebrospinal fluid (CSF) and blood samples from 20 people experiencing psychosis and 20 people without psychosis. She will study both mRNA and the proteins on the surface of the cell to gain understanding of the lineage and function of each cell. The team will also sequence the unique B-cell and T-cell receptors in each participant, and use bioinformatics to infer their targets. This will allow detection of an active immune process and whether this process is targeting the brain. Based on this, methods might then be developed to probe a causal role of these immune components in psychosis.

🧬 *Basic Research*

Giulia R. Fois, Ph.D., Interdisciplinary Institute for Neuroscience–CNRS / University of Bordeaux, France, notes that acetylcholine (ACh) release in the medial prefrontal cortex (mPFC) is essential to numerous cognitive functions; and that disruptions of cortical ACh transmission has been implicated in several disorders, including ADHD,

Alzheimer's disease, schizophrenia, and addictive behavior. In rodents, the team will establish the causal role of the cholinergic SI/DB→vmPFC and B→dmPFC projections in attention using ACh pathway optogenetic activation and inhibition. They will characterize how these two ACh projections can alter vmPFC and dmPFC neuronal processes to control attention. This can contribute to better understanding of mPFC neuronal processes underlying attention. This can help advance the neurobiology of attention and may aid in the development of more effective cognitive enhancer drugs in disorders in which attention is dysfunctional.

🧬 *Basic Research*

Wei-Kai Huang, Ph.D., Massachusetts General Hospital, proceeds from evidence of neuroimmune processes mediating gene-environment interactions in schizophrenia. Dr. Huang hypothesizes that maternal immune activation impinges on genetic risk for the illness. Animal studies show that the pro-inflammatory cytokine interleukin-17a (IL-17a) plays a central role in maternal immune activation. The team will build on these studies to elucidate mechanistic underpinnings of IL-17a effects in human brain organoids generated with induced pluripotent stem cells that they have created from schizophrenia patients and matched healthy individuals. By comparing effects of IL-17a exposure in healthy and schizophrenia brain organoids, they will delineate how IL-17a exposure affects normal brain development and identify specific differences that result from IL-17a exposure in schizophrenia brain organoids. They will also elucidate sex-related differences in IL-17a effects.

🧬 *Basic Research*

Taeyoung Hwang, Ph.D., Lieber Institute for Brain Development, Johns Hopkins University, will study the molecular mechanism of LSD1, a histone-modifying enzyme, to gain insight into how LSD1 inhibition works in the pathobiology of schizophrenia. LSD1, an enzyme removing a specific modification of histone or methylation at a lysine residue, has drawn attention as recent studies showed that LSD1 inhibitors can improve behavioral abnormalities in mouse models of schizophrenia and autism. However, the gene regulatory mechanism directed by LSD1 is unclear in neuronal genomes. The team will probe how LSD1 recognizes specific genomic loci in neurons and will investigate RNA's role in LSD1's localization on the genome while exploring an RNA-based target-specific approach to perturb LSD1.

🧬 *Basic Research*
🧬 *Next-Generation Therapies*

Valentina Ignatova, Ph.D., University of Pennsylvania School of Medicine, points out that given the extreme morphological complexity of neurons, which each can host up to 100,000 synapses, the precise spatiotemporal regulation

of protein synthesis is crucial for normal neuronal functions; alterations can manifest themself in neuropathological conditions. Dr. Ignatova studies cytoplasmic FMRP interacting protein 1 (CYFIP1), a regulator of protein translation, and which resides within 15q11.2 chromosomal deletion and duplication, genome anomalies associated with schizophrenia and autism spectrum disorder, respectively. She will test the hypothesis that m6A modifications on mRNA modulate CYIFIP1 interactions with mRNA to alter its synaptic localization and translation. She will use genetically modified mouse models and human neural cell types and organoids derived from patient-specific induced pluripotent stem cells (iPSCs).

Basic Research

Srdan M. Joksimovic, Ph.D., Children's Hospital of Philadelphia/University of Pennsylvania, studies 22q11.2 deletion syndrome (22qDS). Patients have learning and memory deficits and suffer from at least one lifelong psychiatric disorder, and many display comorbid psychopathologies. The subiculum (Sub), the principal output of the hippocampal formation, is one of the brain regions particularly affected in psychiatric disorders, including 22qDS; however, little is known about its contribution to memory impairment. In this project, the team will use a mouse model of 22qDS to better understand the 22qDS-induced alterations in subicular excitability and specific dorsal (dSub) and ventral (vSub) circuitry that mediates spatial, contextual, and social memory processing. They hypothesize that the hyperexcitability of bursting neurons in dSub/vSub that specifically project to the medial entorhinal cortex (mEC) disrupts their memory-processing capabilities, thus crucially contributing to cognitive deficits.

Basic Research

Madhuvanthi Kannan, Ph.D., University of Minnesota, seeks to uncover the relevance of two cortical interneuron-types, defined by the expression of somatostatin (SST+) or neuron-derived neurotrophic factor (NDNF+), to some of the visual deficits seen in schizophrenia. Recent data revealed that SST+ neurons and NDNF+ neurons are substantially activated during behavioral-state transitions (e.g., rest-to-arousal). This suggests these subtypes participate in contextual (top-down) information processing and may have a role in perception. The team will test the hypothesis that a cell-intrinsic loss-of-function in lead candidates may impair the normal activation dynamics of these subtypes in behaving animals during perceptual tasks. Findings may suggest cellular and circuit mechanisms that may underlie some of the visual deficits in schizophrenia.

Basic Research

Kaushik J. Lakshminarasimhan, Ph.D., Columbia University, observes that antipsychotic treatments indiscrimi-

nately target all dopaminergic pathways, while noting clinical studies showing the increase in dopamine is localized to more dorsal regions of the striatum. To develop better treatments, the team argues, there is a need to understand the specific role of dopamine in different striatal regions and the mechanism by which altering its level gives rise to the symptoms. This project entails building a computational model of parallel corticostriatal loops spanning different striatal subregions to perform auditory detection. The hypothesis is that dopamine in different parts of the striatum encodes different types of prediction errors: dopamine in the ventral striatum encodes reward prediction error to aid reward processing, whereas dopamine in the tail of striatum encodes state prediction errors to aid signal detection. Identifying the circuit mechanisms underlying auditory hallucinations may contribute to the development of novel antipsychotic drugs targeting specific receptors in specific dopaminergic pathways to treat positive symptoms of schizophrenia with greater efficacy.

Basic Research
Next-Generation Therapies

Eastman M. Lewis, Ph.D., National Institute of Child Health and Human Development (NICHD/NIH), aims to address gaps in our understanding of prefrontal cortex (PFC) function with the goal of identifying new therapeutic approaches for treating cognitive symptoms in schizophrenia and other disorders. Dysfunction of one group of inhibitory interneurons expressing the protein parvalbumin (PV+ interneurons or PVINs) has been consistently implicated in the pathophysiology of schizophrenia but incomplete information about the function of local PFC function limits applicability. A long-standing hypothesis has been that reduced excitatory N-methyl-D-aspartate receptor (NMDAR) function may contribute to the altered PV+ interneuron function observed schizophrenia. This project uses animal models to test the hypothesis that reduced NMDAR-mediated excitation of PV+ interneurons in adult PFC disinhibits local PFC circuits and alters PFC-dependent behavior.

Basic Research

Alana I. Mendelsohn, M.D., Ph.D., Columbia University, is interested in the role of the basal ganglia in sensory processing dysfunction in schizophrenia. The output of the basal ganglia's auditory pathway is the substantia nigra pars lateralis (SNL), involved in auditory discrimination and projecting to the inferior colliculus, a key node in the brain's auditory chain. Determining how the SNL encodes sensorimotor information during auditory discrimination will allow the team to ask whether aberrant circuit activity underlies sensory processing deficits in schizophrenia. Results could add to understanding of both the circuit mechanisms of perceptual discrimination and the neurobiology of schizophrenia. Clarifying the neural circuits involved in sensory processing

dysfunction could contribute to the development of novel, targeted therapeutic strategies.

⬥ *Basic Research*

Sayan Nandi, Ph.D., Howard University, is interested in understanding molecular and cellular mechanisms underlying neuropsychiatric disorders, particularly microglial dysfunction, which has been implicated in schizophrenia. By using a genetic loss-of-function approach in mice, a specific hypothesis will be tested: whether a timely reduction in the level of Iba1, a microglial-specific, proinflammatory protein, during adolescence and young adulthood, will mitigate abnormalities in brain circuitry and behavior in a drug-induced animal model of schizophrenia.

⬥ *Basic Research*

Stuart Oldham, Ph.D., Murdoch Childrens Research Institute/University of Melbourne, Australia, will develop a new method to build generative brain network models, mathematical models that allow simulation of the formation of brain networks in typical and atypical development. By integrating large-scale MRI analyses of adolescent populations with detailed cortical maps of genetic, molecular, and physiological properties, the team hopes to gain insight into the mechanisms driving network connectivity. This will allow isolation of molecular pathways and properties crucial in determining network connections and disruptions. Using this model, the team will investigate how wiring constraints relate to the presence and severity of psychosis symptoms and cognition in a large cohort of adolescents and young adults.

⬥ *Basic Research*

Maria Belen Pardi, Ph.D., INSERM, France, researches the causes of abnormal perception and delusions in psychosis. It has been suggested an imbalance in the integration between "bottom-up" sensory and "top-down" internal information may give rise to these. Yet, little is known about where and how these computations are implemented in the brain to produce either accurate or aberrant perception. Dr. Pardi theorizes the auditory disturbances frequently experienced in schizophrenia may implicate aberrant top-down processing in the higher-order auditory thalamo-cortical circuit. This study will precisely target and investigate individual identified neurons and synapses during behavior. How top-down signals are encoded in the higher-order auditory system, how they undergo plasticity during learning, and how they affect perception will be probed; then, how these top-down inputs are integrated with bottom-up sensory inputs to affect cortical processing. The team will also explore how top-down mechanisms are affected in pathological conditions related to high schizophrenia risk in a mouse model.

⬥ *Basic Research*

Ashley C. Parr, Ph.D., University of Pittsburgh, studies mesocorticolimbic dopamine (DA) circuit dysfunction, which is central to several psychiatric disorders that emerge during adolescence, including substance use disorders, mood disorders, and schizophrenia. This circuit continues to undergo specialization during adolescence to support the transition to adult levels of decision-making. Dr. Parr is interested in molecular and epigenetic mechanisms mediating normative and impaired mesocorticolimbic DA innervation during adolescence, including microRNA regulators of gene expression—in particular, microRNA-218, which regulates DCC axonal guidance cue signaling to determine the extent of dopamine connectivity to frontal and striatal systems, disruptions of which lead to aberrant mesocorticolimbic circuit organization and deficits in decision-making processes. microRNA-218 can be measured in human saliva, providing a potential readout of its expression in the brain. The team will obtain novel saliva indices of microRNA-218, aiming to develop a model of mesocorticolimbic DA maturation.

⬥ *Basic Research*

Toby Pillinger, Ph.D., Institute of Psychiatry/King's College London, U.K., is exploring possible cardiac side effects of clozapine. The team will use MRI to look at how the heart works in people with schizophrenia prescribed non-clozapine antipsychotics compared to people without mental illness; then, at how the heart changes in people with schizophrenia when the antipsychotic is changed to clozapine. To gain a more detailed understanding of how antipsychotics including clozapine might damage the heart, they will grow heart cells in a dish to see how they behave when exposed to antipsychotics, comparing different types and doses of antipsychotics, noting any changes in heart cell function. They are hoping to identify ways that antipsychotics including clozapine damage the heart, which can then be targeted therapeutically.

⬥ *Next-Generation Therapies*

Tyler Prestwood, M.D., Ph.D., Stanford University, will test the hypothesis that in schizophrenia, there is an abnormal immune response targeting the complement system—part of the immune system which clears pathogens from the body. The team will test for immune responses against different parts of the complement system simultaneously. They will use serum from patients with lupus, an autoimmune disease in which patients often develop immune responses against the complement system. Next, serum from patients with schizophrenia will be examined for complement autoantibodies. If patients with schizophrenia are found to exhibit autoimmune responses against the complement system, this work could uncover new targets for diagnostics and treatment.

⬥ *Basic Research*

Wei Qi, M.D., NYU Langone Health, studies the role of the hippocampus in schizophrenia and examines a novel, circuit-based approach to treatment. Hippocampal hyperactivity and abnormal excitation-inhibition balance are believed to be major mechanisms contributing to symptoms. Dr. Qi has found abnormal left anterior hippocampal connectivity on fMRI brain imaging in patients associated with severity of psychosis symptoms, making it a potential intervention target. Pulsed low-intensity focused ultrasound (PLIFUS) can precisely target deep brain structures and has can alter excitatory/inhibitory balance. This project is a placebo-controlled pilot trial of PLIFUS in 12 schizophrenia patients with moderate psychotic symptoms. The hope is that PLIFUS targeting the anterior hippocampus will reduce the psychosis severity, normalize hippocampal functional connectivity, and be well tolerated.

🧬 *Next-Generation Therapies*
🧬 *New Technologies*

Giulia Quattrocolo, Ph.D., Norwegian University of Science and Technology, Norway, notes that among the cellular deficits observed in postmortem studies of schizophrenia patients there are alterations in dendritic morphology, decrease in dendritic spine number, increase of BDNF, and decrease in reelin. The team has observed these changes, along with deficits in learning and memory, when it has ablated Cajal-Retzius cells from the postnatal hippocampus. During prenatal development they are the main source of reelin, a protein critical for the organization of cortical circuits. In the hippocampus these cells survive into adulthood. This project explores the possible contribution of Cajal-Retzius cells to schizophrenia, studying gene alterations in hippocampal cells caused by ablation of the cells. The team will observe any social behavior changes in mice with CR cells ablated.

🧬 *Basic Research*

Adam J. Rossano, M.D., Ph.D., Children's Hospital of Philadelphia Research Institute, will examine embryonic stem cells engineered to carry a genetic deletion recapitulating 22q11.2 deletion syndrome (22qDS). Individuals with this condition have a 25% risk of developing psychosis. Human imaging and postmortem studies suggest disturbed synaptic plasticity and aberrant balance between excitatory and inhibitory neurotransmission in the forebrain of adolescents contributes to schizophrenia. This project will explore how previously established metabolic, biochemical, and mitochondrial disturbances contributing to the penetrance of psychotic features in 22qDS, impact glutamatergic neurotransmission in a model of human natal synapses. The goal is to understand how alterations in mitochondrial biology disrupt glutamatergic neurotransmission in developing brain with an eye to identification of mechanisms that would provide potential novel therapeutic targets.

🧬 *Basic Research*

Kirsten E. Schoonover, Ph.D., University of Pittsburgh, will investigate the effect of cortical zinc levels and transport on the morphology of excitatory synapses crucial for working memory. Investigation and understanding of zinc homeostasis, and its effect on neural transmission, furthers knowledge of schizophrenia pathology and contributes to the elucidation of shared symptomology among other psychiatric illnesses. Zinc is intricately and crucially involved in synaptic transmission and neuronal homeostasis; abnormalities of the zinc system can result in schizophrenia-like pathology, a potential path to cognitive deficits that is understudied. This project focuses on establishing a direct relationship between levels of zinc transporters and synaptic zinc with measures of synaptic strength and activity in human postmortem dorsolateral prefrontal cortex tissue of 20 matched pairs of subjects with schizophrenia and unaffected comparisons.

🧬 *Basic Research*

Mototaka Suzuki, Ph.D., University of Amsterdam, The Netherlands, notes that abnormal activity of the medial prefrontal cortex (mPFC)—in particular, its decoupling from the mediodorsal thalamic nucleus (MD)—has been linked with schizophrenia. This project, using mouse models of the disease, seeks to identify the cellular mechanism that accounts for the mPFC-MD decoupling. The hypothesis is that metabotropic glutamate receptors in the mPFC determine the coupling between mPFC and MD. The team will use a novel micro-optical probe to directly measure the subcellular coupling of pyramidal cell compartments in an unprecedented way, making it possible to examine the causal relationship between subcellular coupling in a specific cell-type and the activity of a large-scale thalamocortical network. The data will enable evaluation of a possible causal link between a specific type of protein (metabotropic glutamate receptors) in a specific cell-type (L5p) and a large-scale thalamocortical network (mPFC-MD network) that is associated with schizophrenia.

🧬 *Basic Research*
🧬 *New Technologies*

Geoffrey Terral, Ph.D., Albert Einstein College of Medicine, notes that cognitive symptoms and brain changes associated with schizophrenia might be due to disruption of inhibitory neurons. Brain tissue of schizophrenia patients has been shown to have a selective loss of inhibitory neurons. This is associated with altered brain activity and impairments in memory, sleep, perception, and decision-making. But little is known about how different types of inhibitory neurons contribute to behavioral and cognitive dysfunctions in schizophrenia. The goal of this research is to determine the pathophysiological implication of a specific inhibitory neuron class, Somatostatin neuronal Nitric Oxide Synthase cells (SST/nNOS), in schizophrenia-like symptoms. These

cells project over long distances and therefore can control brain activity across different brain regions, suggesting they could regulate neocortical synchrony. The team will examine brain network activity and neural function in vivo while manipulating SST/nNOS cells.

Basic Research

Christopher W. Tschumi, Ph.D., University of Washington, focuses on the mesostriatal pathway, which plays a critical role in reward learning and motivated behavior. Dysfunction in this pathway is associated with disrupted reward processing and is relevant in schizophrenia, autism, and addiction. The Kv3 voltage-gated potassium channel is a protein currently being targeted for pharmacotherapeutics to treat schizophrenia. A drug targeting the Kv3.1 subunit improves mesostriatal network activity and reward processing in schizophrenia patients, but the degree to which Kv3 can be targeted to treat other brain and behavior disorders is not known. This project seeks to understand how better to harness Kv3 activity for the treatment by exploring how it functions physiologically to drive reward processing. Results could provide a framework for studying how Kv3 variants found in human patients disrupt mesostriatal network activity and behavior, a possible basis for new therapeutics.

Basic Research

Jessica J. Walsh, Ph.D., University of North Carolina at Chapel Hill, studies the neural mechanisms of sociability, which can be impaired in schizophrenia, depression, anxiety, and autism spectrum disorders. She notes that rapid elevation of serotonin activity enhances sociability and promotes appropriate social behavior, and suggests that the speed and degree of serotonin enhancement may be a critical regulator of its therapeutic effects. MDMA causes sharp increase in serotonin levels, but this effect is only temporary, and deficits resume when serotonin levels return to baseline. Dr. Walsh cites preliminary data suggesting a two-dose regimen of the psychedelic compound MDMA can cause lasting increases in sociability in mice with a specific genetic deletion. She seeks to identify the circuit, cellular, and molecular adaptations underlying this therapeutic phenomenon.

Next-Generation Therapies

Xiaoting Wu, Ph.D., Icahn School of Medicine at Mount Sinai, noting that social memory impairment may be a major cause of deficits in social communication and social emotional processing, seeks to investigate the neural substrates of social memory to understand impairment of social behaviors in ASD and schizophrenia. This project seeks to understand how the hippocampus creates positive and negative social memories and develop strategies to reverse memory loss of positive social interactions in ASD and schizophrenia-associated mouse models. The hypothesis is that different hip-

pocampal circuitries regulate positive and negative social memories. The team will identify hippocampal circuits that selectively control positive and negative social memories. Dissociating the distinct mechanisms regulating positive and negative social memories may allow the targeting of positive social memories in new therapeutics.

Basic Research

SUICIDE PREVENTION

Steven Lamontagne, Ph.D., National Institute of Mental Health (NIMH/NIH), researches the neural underpinnings of suicide, as well as perturbations that influence these systems (i.e., stress). In a recent pilot study of high-risk patients, his team showed that ketamine had promising effects on normalizing gamma oscillatory patterns within the insular cortex, a region implicated in the transition from suicide ideation to attempt. Although previous studies have established the anti-suicidal ideation properties of ketamine, its ability to modulate the effects of stress on suicide-relevant networks remains unknown. The proposed study uses magnetoencephalography (MEG) to investigate the effects of stress on gamma oscillatory patterns, as well as their modulation by ketamine treatment, in individuals with chronic suicide risk.

Diagnostic Tools/Early Intervention

Aiste Lengvenyte, M.D., University of Montpellier, France, aims to determine whether potential peripheral biomarkers implicated in inflammation, oxidation, and plasticity can predict suicidal events during a 2-year follow-up in 700+ individuals treated for mood disorders. Peripheral markers used involve inflammation/immune response, oxidative stress, and plasticity in blood plasma samples collected from participants. Machine learning will be used to select the best-performing biological analytes and verify their independence of associations. The team will combine the top biomarkers with scores obtained from the initial clinical information to assess whether this double-approach might perform better than biological or clinical variables alone. The expected outcome is a description of plasma markers associated with suicidal thoughts and behaviors, differentiating between past, present, and future outcomes, and between diagnostic groups.

Diagnostic Tools/Early Intervention

BBRF Grants are Making a Difference

Research supported by BBRF grants is playing a vital role on some of the most important fronts in the fight against mental illness

The First Rapid-Acting Antidepressants

In 2019, the FDA approved esketamine, the first-ever rapid-acting antidepressant for patients with treatment-resistant depression, and brexanolone, which can lift postpartum depression within 48 hours. 90 BBRF grants over 20 years helped build the foundation for these long-sought advances.

Non-Invasive Brain Stimulation to Treat Depression, OCD, PTSD

BBRF grants seeded research which led to FDA approval in 2008 of rTMS (repetitive transcranial magnetic stimulation) for treatment-resistant major depression. BBRF grantees are now testing more powerful and faster-acting brain-stimulation technologies with a wide range of potential applications.

Computer-Guided Cognitive Remediation for Enhanced Recovery in Schizophrenia

Recovery may be possible for more people with schizophrenia and other disorders in which cognitive function is impaired, including bipolar disorder and depression. Recently, BBRF-funded scientists have clinically validated computer-guided methods of enhancing verbal and auditory learning capacity, processing speed, working memory, and recall ability in chronic schizophrenia patients.

Lowering the Child's Mental Illness Risk via Maternal Choline Supplements

BBRF grantees have pioneered choline supplementation in the diet of pregnant women to reduce the risk of mental illness in children. Today, the American Medical Association recommends including choline in prenatal vitamin supplements.

Harnessing Stem Cell Technology to Study Autism, Schizophrenia

BBRF grantees have pioneered the use of stem-cell technologies to create functioning brain "organoids"— living test-beds that can be used to assess new drug candidates and well as reveal how genetic variations cause pathologies in the fetal brain as it develops. This research is especially pertinent in autism, schizophrenia and other disorders with developmental roots.

Computer-Guided Early Diagnosis of Mental Illness

BBRF-funded investigators are training machines that, in turn, train themselves—ultimately, to a level of precision not possible in humans— to recognize potentially diagnostic patterns of clinical data or biological markers in schizophrenia, first-episode psychosis, major depression, and bipolar disorder.

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Centre for Addiction and Mental Health, University of Toronto, Canada (3)

Children's Hospital of Philadelphia

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