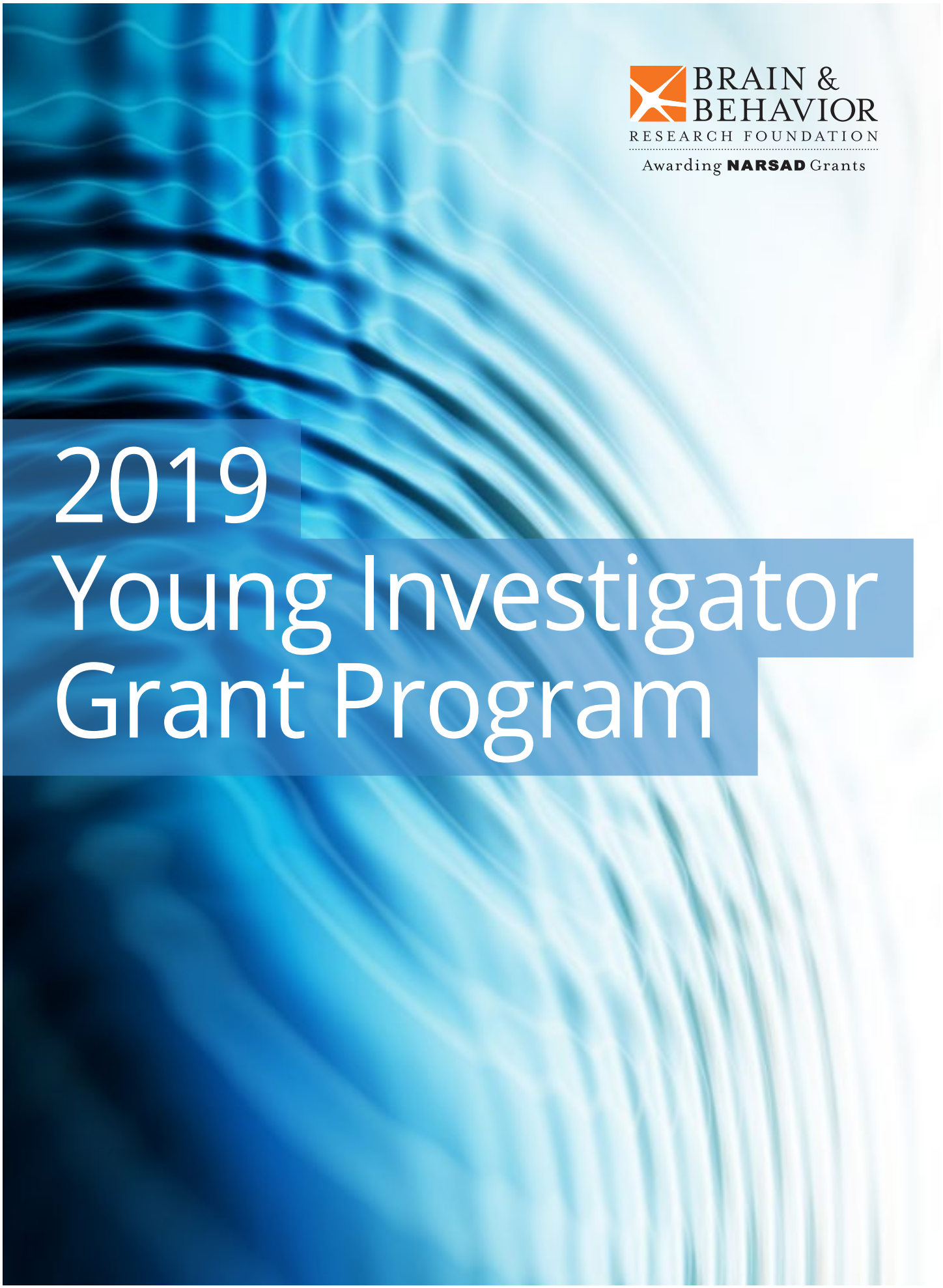

BRAIN &
BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants
2019
Young Investigator
Grant Program

"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 2019

We are pleased to present to you the 2019 Brain & Behavior Research Foundation Young Investigator Grantees. This extraordinary group of scientists represent a broad range of the best ideas in innovative brain research.

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 opportunities and supports basic, translational, and clinical researchers.

This year, the Foundation's Scientific Council, led by Dr. Herbert Pardes and comprised of 184 world-renowned scientists with expertise in every area of brain research, reviewed more than 900 applications and selected the 200 meritorious research projects summarized in the pages that follow.

Continuing our scientific growth strategy, many of our Young Investigator grantees are pursuing basic research projects. Others are specifically focusing on novel ideas for therapies, diagnostic tools, and new technologies. These research projects will provide future insights and advances that will help move the fields of psychiatry and neuroscience forward.

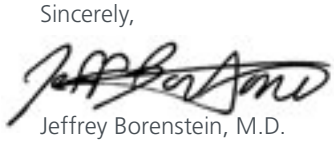
As in past years, the Scientific Council's selection of Young Investigator grantees reflects our mission of advancing "the best science possible." These 200 projects, taken together, call attention to areas of great promise, in which new insights are making possible explorations that could not have been made just a few years ago. For example, it is important to note how advances in technologies that stimulate the brain, non-invasively, are being employed by this year's grantees in a wide range of disorders including ADHD, PTSD, schizophrenia, suicide prevention, as well as new applications in depression, in which Foundation grants in the late 1990s first hinted at this technology's great potential.

Basic Research that has importance in multiple disorders is also very much in evidence. Some examples include research focusing on the impact of early-life stress; ways of treating cognitive deficits; understanding the circuitry that gives rise to anhedonia (the inability to experience pleasure); the workings of biological "clocks" that may underlie sleep disturbances; and the possible involvement of glia and astrocytes—long thought mere "helpers"—in malfunctioning brain circuits and networks across disorders.

We are proud to report that since 1987 we have provided more than $408 million in research grants to 4,896 scientists globally.

BBRF is a collaboration between generous donors and scientists. A grant to a Young Investigator not only funds an innovative research project, it is an investment in the career of a promising young scientist. **100% of every dollar donated for research is invested in our research grants. Our operating expenses are covered by separate foundation grants.** With your help we can continue to support scientists in the search for new treatments, cures, and methods of prevention so more people can live full, happy, and productive lives.

Sincerely,



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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 disorders."

Herbert Pardes, M.D.

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SINCE 1987

AWARDED
5,900+
GRANTS

FUNDED
$408M+
GRANTS

THE 2019 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $13.8 million in 200 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

943
YOUNG INVESTIGATOR APPLICATIONS

200
YOUNG INVESTIGATOR GRANTS AWARDED

$13.8
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (137 Grants)
To understand what happens in the brain to cause mental illness

Diagnostic Tools/Early Intervention (29 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

Next Generation Therapies (27 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

About 69 percent of the projects funded are **basic research**, the wellspring of innovation in brain research as in all sciences.

About 15 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 3 percent of projects fund the development of **new technologies** that will power both basic research and new developments in the clinic.

About 14 percent of the 2019 grants fund projects that specifically aim to develop **next-generation therapies.**

About 80 percent of grantees are from the United States (161 grantees). Twenty percent of grantees come from 16 other countries: Canada, the UK, Germany, The Netherlands, Switzerland, Italy, France, Brazil, Australia, Japan, Ireland, Spain, Argentina, Austria, Sweden, and the People's Republic of China.

INVENTORY OF PROJECTS: 2019 GRANTEES

(sorted by category; some projects are relevant in multiple categories)

ADDICTION / SUBSTANCE-USE DISORDERS

ATTENTION-DEFICIT HYPERACTIVITY DINSORDER (ADHD)

ANXIETY DISORDERS

AUTISM SPECTRUM DISORDER (ASD)

BIPOLAR DISORDER

BORDERLINE PERSONALITY DISORDER

DEPRESSION

EATING DISORDERS

OBSESSIVE-COMPULSIVE DISORDER (OCD)

PSYCHOSIS

POST-TRAUMATIC STRESS DISORDER (PTSD)

SCHIZOPHRENIA

SUICIDE PREVENTION

BIOLOGY OF THE BRAIN

These projects focus on how the brain works.

ALL DISORDERS

These projects pertain broadly to all disorders.

OTHER DISORDERS

Alzheimer's Disease

Angelman Syndrome

Epilepsy

Fragile X Syndrome

Parkinson's Disease

THE 2019 BBRF YOUNG INVESTIGATOR GRANTEES
(in alphabetical order)

Rany Abend, Ph.D., National Institute of Mental Health, NIH, seeks to elucidate cognitive behavioral therapy (CBT) treatment mechanisms. CBT is first-line treatment for pediatric anxiety, but shows substantial variability in treatment response, leaving many patients affected and underscoring the need to improve outcomes. The project aims to integrate translational neuroscience and clinical research to identify a brain-based biomarker of pediatric anxiety treatment response. Establishing such a biomarker is an important step in understanding CBT treatment mechanisms and promoting clinical neuroscience research toward improving treatment for pediatric anxiety disorders.

Diagnostic Tools/Early Intervention

Jessica Ables, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, seeks to determine the effect of increased blood sugar on vulnerability to stress, gene expression, structure and function of neurons in the striatum, habenula and midbrain in a mouse model of diabetes. These brain areas have been shown to be key in regulating mood and anxiety. Dr. Ables will look at specific cell types within each area, which is more informative than analyzing gene expression in the region as a whole, hoping that by sequencing and targeting specific cell types, it may be possible to identify a vulnerable population or specific pathway that may be targeted to develop new treatments for depression and anxiety.

Basic Research

Ream Al-Hasani, Ph.D., St. Louis College of Pharmacy and Washington University, will investigate how opioid peptide levels respond and adapt to natural rewards and threats. This will provide insight on how peptide modulation is altered in disease states, which in turn can inform alternative therapeutic approaches to addiction. The team will focus on how dynorphin, the endogenous peptide for the kappa opioid receptor, is involved in the modulation of natural reward- and threat-like behaviors.

Basic Research

Mariam Aly, Ph.D., Columbia University, will explore why individuals with ADHD and PTSD are at greater risk for nicotine dependence, testing the hypothesis that nicotine may restore a disrupted balance between processes in the brain that attend to internal states and the external world. Dr. Aly will examine the effects of cholinergic modulation on the hippocampus, a brain region involved in both the retrieval of internal memories and attention to the external world, and which shows abnormalities in ADHD and PTSD. This will involve fMRI scans of healthy participants who will take part in two sessions, one in which they abstain from nicotine (a cholinergic agonist) for at least 12 hours and another in which they ingest nicotine just prior to the session.

Basic Research

Azmeraw Tayelgn Amare, Ph.D., University of Adelaide, Australia, is exploring genes associated with treatment response in patients with mood disorders, using artificial intelligence (machine learning) methods to develop algorithms that can be used for personalizing treatment. To investigate the overlapping genetic mechanisms underlying multiple drug response, Dr. Amare will perform a bivariate genome-wide association study, followed by functional pathway and network analysis to uncover overlapping genes, biological pathways, and molecular networks involved in response to lithium and antidepressant treatments.

Basic Research

New Technologies

Lauren Asarnow, Ph.D., Stanford University, will study cellular markers of inflammation collected from 34 youth with sleep disturbances at high risk for internalizing disorders who are enrolled in a pilot trial examining the effectiveness of a mobile phone-based app designed to improve sleep health. Relevant disorders include anxiety, depression and eating disorders, in all of which individuals internalize their problems. The aim is to determine whether improving sleep positively impacts markers of inflammation. The study thus provides a framework for preventing internalizing disorders in youths, with the hope of better understanding biological pathways that may be contributing to risk.

Next-Generation Therapies

Maxime Assous, Ph.D., Rutgers University, will investigate the role of dopamine modulation of a group of inhibitory neurons in the striatum—tyrosine hydroxylase-expressing interneurons (THINs). She hypothesizes that they are involved in mediating the effects of dopamine in physiological, goal-oriented behavior and in response to psychostimulants. Past results point to a critical role of THINs in contributing to the effect of dopamine in striatal circuitry; the new research could contribute to a better understanding of the cellular mechanisms of action of psychostimulants in the striatum and their relation to addiction.

Basic Research

Jennifer Barredo, Ph.D., Brown University, seeks to identify functional circuits involved in symptom response to transcranial magnetic stimulation (TMS), a noninvasive brain stimulation intervention to prevent suicide. Dr. Barredo hypothesizes that TMS modulation of activity in the brain's dorsolateral prefrontal cortex will alter functional connectivity in fronto-striatal circuits and that these changes will be correlated with severity of suicide risk. Further, she anticipates that the strength of this correlation will predict suicide outcomes at 3-, 6- and 12-months. TMS will be given to 60 veterans recruited from the psychiatric in-patient unit at Providence VA Medical Center.

Next-Generation Therapies

Gerard Beaudoin, III, Ph.D., Trinity University, notes that different drugs of abuse have been shown to cause changes to excitatory synapses on midbrain dopamine neurons. Dopamine release is thought to induce changes in synapses in diverse brain structures to encode memories of drug-taking events. The activity of dopamine neurons are regulated by a large number of diverse neurons, in turn, so it has been unclear whether drugs of abuse cause changes to all or some of the excitatory inputs. This project addresses the question of what cocaine changes at one specific excitatory synapse. Dr. Beaudoin hopes to discover molecular mechanisms that can block changes at key synapses, reasoning that this may lead to a treatment to block relapse, a major barrier to success in addiction treatment.

Basic Research

Andre Berndt, Ph.D., University of Washington, who is interested in ASD and other developmental disorders, will use a novel optogenetic approach to study chloride-mediated signaling in intact brain circuits in early development, in zebrafish. The goal is to reveal the physiological determinants under which permanent neuropathological states emerge. The team hypothesizes that impaired chloride-mediated signals can permanently alter brain states depending on timing, frequency, length, and cell-type specificity of the stimulation. They aim to restore function in animals with impaired brain states through pharmacological applications to provide comprehensive insights for possible intervention mechanisms in people.

Basic Research

Michele Bertocci, Ph.D., University of Pittsburgh, notes the possibility that abnormal lactate concentrations (i.e., abnormal energy use) in key brain regions may be a mechanism for elevated-energy behaviors and reduced-energy behaviors related to bipolar disorder. She will study the oft-neglected area called the precuneus, which is engaged when the brain is at rest and in paying attention when we are performing mental tasks. The team will use magnetic resonance spectroscopy imaging (MRSI) to test the mediating role that lactate concentrations play in the relationship between precuneus activity/functional connectivity and self-reported feelings of mania and depression in a group of adults with pediatric onset bipolar disorder.

Basic Research

Venkat Bhat, M.D., M.Sc., FRCPC, University of Toronto, Canada, notes that currently approved non-invasive brain stimulation treatments for depression such as TMS are focused on superficial brain regions, leaving deeper targets such as the subgenual cingulate cortex (SCC) out of reach. Major depressive disorder has been associated with increased level of activity in the SCC, which is the most frequently targeted site for deep brain stimulation in treatment-resistant depression. This clinical study will use temporal interference (TI), a new technique that allows for focal neural stimulation to reach deep structures in the brain. To be tested in patients, TI will be performed concurrently with functional imaging to test its ability to reach targets in SCC.

Next-Generation Therapies

New Technologies

Tim Bigdeli, Ph.D., State University of New York, Downstate, notes 30% of patients diagnosed with schizophrenia will fail to respond to two or more antipsychotic medicines and thus meet criteria for treatment-resistant schizophrenia (TRS). His team seeks to identify TRS and non-TRS cases among the 3,942 study participants in an existing clinical study. The aim is to validate automated predictions of TRS based on rule-based decision trees. Among identified TRS cases, they will test for association between treatment resistance and genome-wide risk scores for schizophrenia, the presence of copy number variants, as well as common variants in genes encoding known antipsychotic metabolism enzymes. They hope results will inform future development of a multivariate prediction model for TRS, which could be validated in future studies.

Diagnostic Tools/Early Intervention

Jeremy Borniger, Ph.D, Stanford University, is interested in sleep problems prevalent across many cancer types, which are intimately related to cancer-associated mood disorders and cognitive impairments. Using mouse models, the team is focusing on mechanisms driving sleep disturbance in cancer. The aim is to construct a brain effector map detailing how tumors disrupt discrete neural circuits and how these changes are temporally related to one another, tumor growth, and changes in sleep/wake states. This will inform optogenetic and chemogenetic studies to stimulate and inhibit these circuits during tumor growth. The hope is to identify discrete neural populations altered by cancer in the periphery, and

reciprocally, how manipulation of neural firing can combat sleep/wake abnormalities and cancer itself.

Basic Research

Urs Andreas Braun, M.D., University of Pennsylvania, is studying how alterations in the prefrontal area of the brain give rise to a broad range of negative and cognitive symptoms in schizophrenia, how they relate to expression of symptoms in everyday life, and how are impacted by currently prescribed antipsychotics. The team seeks precise assessment of the stability and flexibility of prefrontal activity patterns elicited by four imaging tasks spanning working memory, reward anticipation, social interaction and emotion processing--core processes impaired in schizophrenia. To validate the importance of prefrontal stability as a unifying neural substrate of many cognitive and negative symptoms, they will link these imaging features to measures of cognitive and negative symptoms captured in daily life using ambulatory assessment.

Basic Research

Catherine Brownstein, Ph.D., M.P.H., Harvard University/Harvard Medical School, is examining the youngest children presenting with psychosis and symptoms of schizophrenia to find genes of large effect. Having discovered that de novo mutations in a gene called TRRAP can result in major depression with psychotic features, the team will perform experiments on mice with the TRRAP mutation seen in a patient to better understand how it results in major depression with psychotic features. They will analyze the behaviors of the TRRAP mice and determine how they are different from unaffected mice. They will also administer a medication (Prozac) that appears to improve the major depression and psychosis in a TRAAP patient, and test for how it affects the brain and behavior of the TRRAP mouse.

Basic Research

Benjamin Buck, Ph.D., University of Washington, notes that persecutory ideation (PI)—the feeling experienced by many patients with psychosis that they are being threatened—is not static, but varies in frequency and severity and involving different sets of contextual factors. Dr. Buck aims to understand factors that contribute to, maintain, exacerbate, or mitigate PI, to inform early detection and intervention approaches to improve outcomes. To do so, his team will invoke recent developments in mobile technology to make possible what they hope will be a real-time, real-place window into the dynamic emergence of PI. They will recruit 50 individuals with clinically significant persecutory ideation to carry and engage with an integrated mobile health assessment system for one month.

Diagnostic Tools/Early Intervention

Shelly Buffington, Ph.D., University of Texas Medical Branch at Galveston, noting recent evidence that the gut microbiome can regulate a person's neurophysiology and behavior and that offspring gut microbiota are acquired from the mother, seeks in this project to test a hypothesis concerning two mouse models of ASD, called the maternal high-fat diet (MHFD) and maternal immune activation (MIA) models: that the ultimate insult driving social deficits in both models converge onto a common pathway. The team also seeks to determine whether bacterial species they previously identified that restore social behavior in MHFD offspring also rescue social behavior in MIA offspring. This study has the potential to identify a new, cost-effective treatment for maternal infection-induced mental health disorders and reveal underlying molecular and neurophysiological mechanisms mediating maternal obesity-induced neuropsychiatric conditions.

Basic Research

George Buzzell, Ph.D., University of Maryland, will explore the notion that inadequate development in a brain area called the ventromedial prefrontal cortex (vmPFC) affects the ability to integrate affective signals with control functions, contributing to the emergence of social anxiety (SA) during adolescence. He hypothesizes that sufficient change in vmPFC connectivity strength will moderate relations between pre-adolescent SA risk and the emergence of clinically significant SA symptomology. To test these ideas, he will collect fMRI data and conduct longitudinal analyses of how functional connectivity between vmPFC and affective/control regions changes during adolescence. Success might lead to reconceptualizing how we think about the development of SA and inform the design of developmentally appropriate, targeted interventions.

Basic Research

Michael Cahill, Ph.D., University of Wisconsin-Madison, studies sleep disordered breathing (SDB), which is characterized by recurring breathing cessations during sleep causing intermittent oxygen deprivation up to hundreds of times per night. SDB is present in 15% of pregnant women as compared to 2%-4% of non-pregnant women of childbearing age. The team's mouse model of the condition revealed that male, but not female, juvenile offspring of mothers subjected to intermittent hypoxia during pregnancy exhibit deficits in several autism-relevant behaviors. Now the team seeks to determine if the ability of brain cells called microglia to engage in synaptic pruning is selectively impaired in male, but not female, offspring, as a result of SBD—a possible cause of the autism-related symptoms. They will also seek to restore microglial function in male offspring and determine the potential for alleviation of pathology.

Basic Research

Weidong Cai, Ph.D, Stanford University, proposes to develop a multi-component framework involving cognitive, computational, and clinical dimensions to test theoretical models of ADHD by examining dynamic circuits connecting the cortex and basal ganglia—circuits associated with deficits in cognitive control in children with ADHD. To accomplish this, Dr. Cai plans to detect dynamic latent brain states and circuits underlying human cognition. The research will use data being collected in the NIMH's longitudinal Adolescent Brain and Cognitive Development (ABCD) project involving many thousands of young people.

Basic Research

Erin Campbell, Ph.D., Florey Institute of Neuroscience and Mental Health, Australia, notes that those who try to abstain from drinking in alcohol-use disorder often show a propensity to relapse, despite knowledge of likely adverse consequences including health complications. Dr. Campbell has developed a rodent model in which susceptible rats recapitulate this behavior; the aim is to use the model to characterize brain circuits involved in relapse. The focus will be to address unresolved questions about how the anterior insular cortex drives relapse in a circuit-specific manner, based on the hypothesis that the anterior insular cortex drives the propensity to relapse following extended abstinence.

Basic Research

Nadia Cattane, Ph.D., IRCCS Centro San Giovanni di Dio Fatebenefratelli, Italy, is studying the gene FoxO1 and its protein product, following up on research suggesting its involvement when early-life stress or other environmental insults combine to raise risk of depression. In this study using rodents, Dr. Cattane and colleagues hope to dissect the molecular mechanisms through which FoxO1 may mediate the early-life stress-related vulnerability for depression; demonstrate the causal relationship between FoxO1 expression levels and the development of depressive behaviors; and test FoxO1-related signatures as possible biomarkers for early identification of people vulnerable to depression.

Basic Research

Simon Chamberland, Ph.D., New York University, is studying cannabidiol (CBD) and its potential for use as an antipsychotic agent. In this study he seeks to understand how CBD acts on specific molecules in the endocannabinoid system to mediate antipsychotic effects. The team will leverage a unique combination of electrophysiological approaches in postmortem brain samples and in a mouse model of schizophrenia to understand how CBD modulates brain network activity and decreases psychotic symptoms.

Next-Generation Therapies

New Technologies

Robin Chan, Ph.D., Virginia Commonwealth University, is studying a mechanism through which cells routinely modify the expression, or activity, of genes. Called methylation, it is one of several modes of what scientists call epigenetic regulation of genes—which involve the attachment of removal of molecular tags to DNA which affect their activation. Evidence suggests that the effects of psychosocial factors, development, and aging may be registered in our genes via methylation. This project studies how DNA methylation functionally impacts gene regulation and contributes to disease pathways in major depression. Methylation marks are potential treatment targets, Dr. Chan notes, because they themselves can be modified. Hence this research has implications for developing new forms of treatment for depression.

Basic Research

Natali Chanaday Ricagni, Ph.D., Vanderbilt University, is studying the mechanism of action of the rapidly acting antidepressant ketamine. Specifically, Dr. Ricagni will study a poorly understood phase in ketamine pathway, involving the first minutes to hours after ketamine treatment, when it generates dramatic relief from depression symptoms in many patients. The team will dissect the roles of presynaptic versus postsynaptic signaling in neurons affected by the drug, correlating these with the resulting antidepressant effects. The findings could increase understanding of the molecular mechanisms underlying ketamine's beneficial effects in depression and provide a basis for even more specific and efficient treatments in the future.

Next-Generation Therapies

Chandramouli Chandrasekaran, Ph.D., Boston University, seeks to understand neural circuit dynamics in cortical and subcortical brain regions involved in decision-making. A detailed understanding, when combined with tools for precise circuit manipulation and machine-learning techniques, could pave the way for the development of circuit-level therapeutics and brain–machine interfaces for individuals with psychiatric and neurological disorders. This project aims to provide a detailed description of circuit dynamics in decision-related brain regions in a primate, studying circuit dynamics in four clinically relevant brain regions.

Basic Research

New Technologies

Alicia Che, Ph.D., Weill Cornell Medical College, notes that the sense of touch contributes powerfully to parent-infant interactions fundamental for early social development. Among the most developed sensory modalities when infants are born, it continues to play a critical role in communication and social interaction throughout development and adult life. Abnormalities in tactile perception are prevalent features in

individuals with ASD, exacerbating the core social deficits. Dr. Che aims to understand how social features are encoded alongside early tactile sensory inputs—information that can provide insights into emerging circuits that integrate primary sensory processing and higher-order cognitive features such as social behaviors. These convergent circuits, she proposes, could hold a key to understanding the commonality among the seemingly independent behavioral symptoms of autism spectrum disorder.

Basic Research

Yao Chen, Ph.D., Washington University School of Medicine, is focusing on two genes associated with schizophrenia, Disc1 and Pde4b, both affecting the activity of the enzyme phosphodiesterase 4B (PDE4B). In addition to the genetic evidence, inhibitors of PDE4 have effects on depression, cognition, and memory. This project will explore the hypothesis that schizophrenia associated with PDE4B disruption may result from misinterpretation of neuromodulator signals. Noting that the spatial, temporal, and amplitude characteristics of intracellular signals are among the most important features that determine neuromodulator function, Dr. Chen proceeds on the thesis that understanding how PDE4B alters these features is critical to gaining insight into schizophrenia.

Basic Research

Kimberly Chiew, Ph.D., University of Denver, notes that investigations of reward incentives on cognitive performance in ADHD have yielded mixed results. Dr. Chiew aims to clarify this issue by investigating the effects of reward motivation on cognitive control performance within a theoretical framework called Dual Mechanisms of Control, which characterizes cognitive control in terms of temporally distinct, proactive, and reactive control mechanisms, each of which has advantages and disadvantages for performance outcomes. The team will characterize motivational modulation of cognitive control performance in a sample of children (8–12 years old) with and without ADHD from an ongoing government study of ADHD and learning disorders.

Basic Research

Daniel Christoffel, Ph.D., Stanford University, observes that in patients with binge eating disorder, eating behavior is accompanied by feelings of shame, disgust, and a desire but inability to stop binging; and that almost a third of patients have a co-morbid substance use disorder. He will explore the possibility that there is a common neurobiological mechanism, proceeding from the theory that the neural circuits that regulate motivation to obtain food are broadly similar to those "hijacked" by drugs of abuse. He will focus on the brain's nucleus accumbens (NAc), a primary hub of circuitry regulating motivation for food and involved in disorders with disordered reward processing including depression and addiction. How does chronic intake of palatable food alter specific cell types and circuits to regulate future feeding behavior? This research will identify excitatory inputs to the NAc altered by chronic high-fat intake and establish how modulation of NAc inputs and neuronal subtypes regulate the intake and motivation to obtain fatty nourishment.

Basic Research

Luis Colon-Perez, Ph.D., University of California, Irvine, seeks to understand substance use disorders (SUD) and addiction by developing and validating sensitive, predictive neuroinflammatory in vivo markers. The proposed studies, focusing on morphine, involve developing early clinical MRI imaging markers of SUDs and their relationship over time to the neuroinflammatory process. MRI markers generated by these studies and validated with methods of determining brain changes due to drug use could determine the level of neuroinflammatory activity in patients and eventually improve the lives of those with addictions.

Diagnostic Tools/Early Intervention

Gregory Corder, Ph.D., University of Pennsylvania, notes that pregnant women who misuse opioids may give birth to an infant suffering from neonatal opioid withdrawal syndrome (NOWS). NOWS infants receive opioid supplementation to taper withdrawal, which is associated with potential neurodevelopmental delay, cognitive impairments, and psychiatric disorders, such as anxiety. Non-opioid withdrawal treatments are urgently needed. A critical first step in developing novel targets for NOWS treatments is to identify the specific brain circuits that express the mu-opioid receptor (MOR), the molecular target of opioids. Dr. Corder will use imaging to assess the pathological activity dynamics in adolescent mice modeling NOWS during behavioral anxiety assays and will test a novel non-opioid therapy designed to effectively erase the neurodevelopmental pathology of NOWS that primes adolescents for anxiety.

Basic Research

Emmanuel Cruz-Torres, Ph.D., New York University, is interested in non-neuronal brain cells called astrocytes that play critical roles in learning and memory, and the possibility that dysregulation of astrocytic metabolism is involved in neurodevelopmental disorders such as Angelman syndrome. This project will investigate the role of astrocytic lactate metabolism in long-term memory formation during development and its regulation in Angelman Syndrome. He will investigate whether astrocytic lactate metabolism is dysregulated at young and old ages using a well-established mouse model of Angelman syndrome.

Basic Research

Alexis Cullen, Ph.D., King's College London, UK, is interested in the contribution of psychosocial stress to psychotic disorders such as schizophrenia. Dr. Cullen will use smartphone apps and wearable devices to accurately capture exposure to stress in the natural environment. The Urban Mind app developed by the team is designed to assess the impact of the urban environment (e.g., city living and crime exposure) on mental wellbeing. In this project, they will modify the Urban Mind app to produce a smartphone-based tool that combines passive and active stress measurement with the ability to prompt individuals to collect stress biomarker samples immediately following stress exposure. The intention is to try the tool on a pilot basis in a sample of psychosis patients.

New Technologies

Federico Daray, M.D., Ph.D., M.Sc., University of Buenos Aires, Argentina, will focus on detecting the different subsets of cells in patients suffering a major depressive episode. He is pursuing theories regarding the possible role of the innate and adaptive immune system in the development and maintenance of depression, specifically, monocyte-macrophage lineage cells found throughout the body. The hope is to characterize the profile of activation of monocytes and macrophages in participants with depression and determine if it is different from that of healthy controls and those in remission.

Basic Research

Senthilkumar Deivasigamani, Ph.D., European Molecular Biology Laboratory, Germany, is studying axonal pruning, the process by which the brain removes excess synaptic connections prior to birth. A recent study found that people carrying certain genetic variants of a molecule called complement factor C4 are at increased risk of schizophrenia. The gene that encodes C4 has been shown to affect the refinement of connections in the visual system of mice, and offers for the first time a potential causal link between aberrant pruning and schizophrenia. This research seeks to learn whether C4 mutations affect axonal pruning generally across the brain, or in some other way.

Basic Research

Johannes de Jong, Ph.D., University of California, Berkeley, will study what happens in the brain when individuals—(mice, for research purposes)—exert self-control, and what happens when they fail to do so. After teaching a task that earns the animals a reward, he will induce a stimulus that predicts a mild punishment. When mice are exposed to both of these stimuli at the same time, conflict is evoked. The team will monitor if the mice fail to be inhibited by the aversive stimulus or refrain from reward-seeking (i.e., display self-control). The team will record activity in the nucleus accumbens (NAc), known to play an important role in action selection and reward seeking. This and other experiments will contribute to a detailed description of the circuits underlying self-control within different sub-areas of the NAc, data that can inform new treatment approaches.

Basic Research

Kristen Delevich, Ph.D., University of California, Berkeley, will use a newly developed fluorescent dopamine sensor called nIRCat (near infrared catecholamine nanosensor) to visualize dopamine release, diffusion and reuptake in striatal brain tissue across the juvenile-to-adult transition in mice. Her team will determine whether there are age-dependent changes in striatal dopamine transmission and examine how drugs including antipsychotics that target D2 receptors regulate dopamine release, testing whether sensitivity to these drugs changes in an age-, sex-, or puberty-dependent manner. These experiments could inform the discovery of mechanisms that predispose individuals to dopamine system dysregulation during adolescence.

New Technologies

Laura DeNardo, Ph.D., University of California, Los Angeles, notes that circuits in the medial prefrontal cortex (mPFC) are uniquely vulnerable to early-life insults, and likely are involved in translating early adversity into long-term behavioral changes. Her team seeks a mechanistic understanding of how prefrontal circuits form and are modified by early-life stressors to produce maladaptive behaviors in adults. To elucidate the causal relationship between infant and adult memory circuits, Dr. DeNardo will perform experiments with engineered mice to reveal mPFC circuit nodes that are plastic during development, analyzing the impact of stress on the connectivity and behavioral function of mPFC circuits.

Basic Research

Yael Deri, Ph.D, Stony Brook University, notes that treatment with non-steroidal anti-inflammatory drugs has reduced both pro-inflammatory cytokine levels in the hippocampus and the behavioral symptoms in some people with PTSD. Dr. Deri hope to examine the relationship between neuroinflammation, chronic PTSD symptoms, and brain signatures obtained via MRI imaging. The team will investigate to what extent neuroinflammation is evident in chronic PTSD using a subset of 10 World Trade Center responders with PTSD compared to 10 age- and sex-matched responders without PTSD.

Basic Research

Emily DiBlasi, Ph.D., University of Utah, observes that genetic studies have greatly improved our understanding of the biological basis of suicide risk yet only a fraction of genetic variation influencing suicide risk has been accounted

for. This project will test the hypothesis that rare structural variants contribute to risk of suicide death using the large and unique genetic dataset and resources available in the Utah Suicide Research Study (USRS), comparing these data to a recent, very large control resource for over 10,000 structural variants matched for ancestry.

Basic Research

Sarah DuBrow, Ph.D., University of Oregon, notes that we can make false attributions, such as overgeneralizing outcomes from one situation to many (under-segmenting) or attributing each event to a completely new cause (over-segmenting). Deficits in "latent cause inference" are thought by some to be involved in misperceptions and false beliefs common in psychosis. This project will use a large-scale online trial to the hypothesis that positive symptoms of psychosis are correlated with over-segmentation. This will lay the groundwork for developing a domain-general framework by which to understand the mechanisms underlying symptoms of psychosis.

Basic Research

Julien Dupuis, Ph.D., Interdisciplinary Institute for Neuroscience - CNRS / University of Bordeaux, France, is studying the mechanisms through which ketamine exerts rapid antidepressant effects. Ketamine is known to engage a neurotransmitter receptor called the NMDA receptor (NMDAR), which is a vital actor in brain development and functioning. However, how the binding of ketamine to the NMDAR can translate into antidepressant action is not well understood. To tackle this challenging question, the team will use new high-resolution single-molecule imaging technologies to explore with unprecedented resolution if and how ketamine changes the location of NMDARs on the surface of neurons, perhaps to restore brain functions.

Next-Generation Therapies

Natalia Duque-Wilckens, D.V.M, Ph.D., Michigan State University, wants to know more about mechanisms by which stress initiates persistent inflammatory responses leading to depression. She will study the role of mast cells (MCs) in early-life adversity programming of adult vulnerability to depression-like symptoms and behaviors. MCs are highly activated in response to psychological stress, release a myriad of mediators that can initiate, amplify, and prolong inflammation, and are distributed throughout the body, including the brain. This project will proceed from prior experiments suggesting MCs are permanently, epigenetically programmed by early-life adversity, a major risk for major depressive disorder, in a sex-specific fashion.

Basic Research

Roman Dvorkin, Ph.D., Cold Spring Harbor Laboratory, will test the hypothesis that aspects of social anxiety are mediated by stress-induced changes in a brain region called locus coeruleus (LC). LC is a small, deep-brain area, and serves as the brain's primary source of the neurotransmitter noradrenaline. The locus coeruleus-noradrenaline system (LC-NA) has a well established role in arousal and attention, and is believed to be an important regulator of social behavior. It is also one of the principal brain systems activated during stress. The team will record and manipulate activity in LC neurons in female mice following adolescent social isolation, research that may elucidate the interaction of social stress with social motivation and social memory signaling in LC and form the basis of a better understanding of the unique neural circuit mechanisms of social anxiety.

Basic Research

Dawn Eichen, Ph.D., University of California San Diego, will develop and test a method of training executive function for people who have binge eating disorder plus a mood or anxiety disorder. Executive function is impaired in binge eating disorder, and therapies like cognitive behavior therapy depend on strong executive function to be successful. Dr. Eichen's method will be evaluated in 32 patients for its ability to reduce binge eating when provided in addition to the current gold-standard treatment. The novel executive function training will be adapted from a compensatory cognitive training program that has successfully improved executive function in patients with several psychiatric disorders and significant cognitive impairments.

Next-Generation Therapies

Hanan El Marroun, Ph.D., Erasmus University Medical Center, Netherlands, is testing a "double-hit hypothesis" that exposure to substances during pregnancy may lead to subtle alterations in brain development making the child vulnerable to stressors which lead them to begin using substances. This study will use a large population cohort in the Netherlands, the Generation R study, in which children and their parents have been followed from early pregnancy onward. Neuroimaging will be used to examine the long-term effects of prenatal cannabis exposure—the first hit—and substance use in adolescence and other stressors—the second hit—on neurodevelopmental trajectories of brain structure and connectivity.

Basic Research

Claudia Espinosa-Garcia, Ph.D., Emory University, will test the hypothesis that high levels of stress suppress autophagy in microglia, leading to excessive brain inflammation associated with depressive-like behavior. Autophagy is an essential process in which damaged cells remove dysfunctional components.

Microglia are important non-neuronal cells in the brain. This research seeks to determine if stress compromises autophagy in microglia. It will also evaluate the therapeutic effectiveness of allopregnanolone, a neurosteroid with antidepressant effects, to stimulate autophagy in microglia. This work will be conducted in rodents.

Basic Research

Gilad Evrony, M.D., Ph.D., New York University School of Medicine, observes that much of what we know about brain development is based on animal studies. This is because a central tool of developmental biology, lineage tracing, could not be performed in humans. In lineage tracing, cells are labeled with viruses or special proteins as the brain develops, allowing researchers to track those cells and all their progeny to watch which cell types and brain structures they create. It is much like learning about a person by studying their family tree. This research seeks to develop a technology called TAPESTRY that will allow lineage tracing to be performed systematically in humans for the first time.

New Technologies

Antonio Fernandez-Ruiz, Ph.D., New York University, notes that a key symptom in schizophrenia patients is altered functional connectivity between the prefrontal cortex and the hippocampal formation, which may be related to memory deficits. Dr. Fernandez-Ruiz works with a mouse model that captures these alterations and cognitive deficits. He will perform high-density electrophysiological recordings during learning to better understand certain relevant neural circuits. He will also use optogenetics to stimulate hippocampal cells using light beams to potentially enhance processes involved in learning. His hope is that this manipulation can improve spatial working memory in individuals with altered functional connectivity.

Basic Research

Courtney Filippi, Ph.D., National Institute of Environmental Health Sciences, NIH, seeks to identify biomarkers that reveal risk for anxiety disorders very early in life. This project will search for brain networks in infancy that predict negative reactivity and behavioral inhibition—temperaments that predict the development of anxiety. The hypothesis is that aberrant development of the amygdala and salience network emerges in infancy and is central to both negative reactivity and behavioral inhibition. Dr. Filippi will conduct behavioral assessments of reactivity, magnetic resonance imaging, and electroencephalography during a novelty detection task to examine temperament, brain structure and function in infants at 4 months. At 12 months, she will evaluate infants for behavioral inhibition and then conduct extensive analysis of the results in search of potential biomarkers.

Diagnostic Tools/Early Intervention

Emily Finn, Ph.D., National Institute of Mental Health, NIH, notes that people with depression are more likely to attend to negative information and to interpret neutral stimuli as negative, especially when the stimulus is social. But different people respond differently—perhaps on a spectrum in which only those with the most pronounced version of this trait become depressed. Dr. Finn will conduct an fMRI study in both healthy and depressed individuals, allowing characterization of heterogeneity in spatiotemporal patterns of brain activity evoked by ambiguous stimuli. The goal is better understanding of how the brain responds to complex, ambiguous social stimuli, as well as to take the first steps toward a standardized neuroimaging challenge, or psychiatric "stress test," with diagnostic or prognostic value for depression.

Diagnostic Tools/Early Intervention

Kyle Flippo, Ph.D., University of Iowa Hospitals and Clinics, is interested in the endocrine hormone fibroblast growth factor 21 (FGF21), known for its potent metabolic effects; it has been shown to significantly reduce alcohol consumption in mouse studies. Dr. Flippo hypothesizes the direct target of FGF21 in the brain that regulates alcohol consumption may be excitatory neurons which reside in the BLA (part of the amygdala) and project to the NAc (nucleus accumbens). This research aims to manipulate specific cell populations, and will observe neuron activity to determine how FGF21 inhibits alcohol consumption through signaling to the brain.

Basic Research

Gregory Fonzo, Ph.D., Dell Medical School, University of Texas at Austin, seeks to understand how reaction to threat influences brain, behavioral, and reward-related information-processing responsible for the generation, maintenance, and expression of positive affect in individuals with post-trauma psychopathology (PTP). He will test the hypothesis that threat reactivity in PTP maladaptively and abnormally influences reward-processing behavior and disrupts reward-related information processing and circuitry function. To do so, 45 trauma-exposed individuals with and 45 without PTP will undergo fMRI while completing reward processing paradigms under two contexts of interest: a threat-free—safe—context and under threat of shock.

Basic Research

Michael Francis, M.D., Indiana University School of Medicine, notes that there are no effective treatments for impairment of cognitive control (CC), a process commonly impaired in schizophrenia, due in part to a gap in knowledge regarding the neural mechanisms of cognitive dysfunction in schizophrenia. This study seeks to provide evidence that rTMS, a form of non-invasive brain stimulation, in two cortical areas will modulate activity in a third, called the

ACC, as well as connectivity between these three CC-relevant structures. The central hypotheses are that rTMS will result in increased functional activation in the ACC and lead to increased functional connectivity between the three cortical areas.

Next-Generation Therapies

Bharathi Gadad, Ph.D., Texas Tech University Health Sciences Center, is interested in microglia, pathogen-eating macrophages in the brain that integrate stress-induced neuroimmune signals leading to behavioral consequences. This project will study neuron-microglia interactions. These are modulated by several molecular and cellular pathways, dysregulation of which can have neurobiological consequences. To look at these interactions Dr. Gadad seeks molecular and functional characterization of neuron-microglial-specific markers. By utilizing a novel bioengineering method, neurons and microglia will be co-cultured from postmortem brains to understand the role of diffusing factors thought to be involved in dysfunction. The brains studied will be from people who suffered from major depression.

Basic Research

New Technologies

Damien Gallagher, M.D., University of Toronto, Canada, wants to better understand the relation between persistent inflammation and cognitive impairment in depression. Inflammation can exacerbate cognitive deficits, and is associated with persistent depressive symptoms, reduced response to antidepressant treatment, and increased risk of dementia. One possible contributor may be reduced integrity of the gut barrier, resulting in increased exposure to gut microbes, which may stimulate inflammation. Using blood samples from a study of patients with heart disease, Dr. Gallagher will determine if adults with depression have increased blood levels of proteins (biomarkers) associated with gut barrier function, and if these are associated with markers of inflammation; then he will determine if these markers are associated with severity of depressive symptoms and cognitive function. He will also examine if exercise or omega-3 supplementation can have a positive impact upon markers of gut barrier integrity and inflammation.

Diagnostic Tools/Early Intervention

Karina Genaro, Ph.D., University of California, Irvine, studies Fragile X syndrome (FXS), a neurodevelopmental disorder caused by silence of the FMR1 gene and a deficiency of Fragile X mental retardation protein (FMRP). A component of a receptor for the inhibitory neurotransmitter GABA is a possible drug target. This project, using an animal model of FXS, will test if a potential drug developed in Dr. Genaro's lab—a so-called PAM (positive allosteric modulator) of a portion of the GABA-A receptor—has therapeutic potential in FXS or other neurological disorders.

Basic Research

Supriya Ghosh, Ph.D., University of Chicago, notes that individuals with ADHD commonly suffer from deficits in selective attention, maintaining attention over prolonged periods, and flexibly switching tasks. Dr. Ghosh proposes a new conceptual experimental framework to delineate attentional effort from selective attention and characterize the underlying circuitry and neuronal processing that support these distinct processes. Through experiments with rhesus monkeys and analysis with computer models, the aim is to identify neural substrates in the primate brain that are critical to attentional effort and how contextual attributes influence its transitions. Mechanistic insights may expedite efforts to better classify ADHD and might provide potential therapeutic targets.

Basic Research

Gabrielle Girardeau, Ph.D., Sorbonne University, France, seeks to define how the hippocampus and the amygdala coordinate their activity during sleep to sustain the formation of aversive memories in normal and pathological conditions. Those two brain regions are required to establish associations between a threat and a physical location, yet little is known about the physiology of the interactions. In optogentically manipulated rats she will study the role of emotional memory in different sleep phases and their associated oscillatory brain-wave activities. A rodent model of post-traumatic stress disorder (PTSD) will be used to investigate how these consolidation processes are disturbed in pathological emotional memories.

Basic Research

Matthew Girgneti, Ph.D., Yale University School of Medicine, seeks to dissect the molecular basis of PTSD by measuring the activity of genes in particular cell types. Because women are twice as likely as men to develop PTSD he deems it critical to determine the molecular characteristics that differentiate females from males with PTSD and will therefore analyze RNA output of cells from postmortem cortical tissue from females with PTSD and matched controls, generating single cell-type transcriptomic profiles to aid in identifying the molecular determinants of PTSD pathology. Another part of the project aims to unravel specific molecular differences between subjects with PTSD and those that are comorbid for PTSD and major depression.

Basic Research

Felicity Gore, Ph.D., Stanford University, is pursuing clues that the orbitofrontal cortex may play a central role in

value-based decision-making. She seeks to better understand how the orbitofrontal cortex interacts with other brain regions to compute and execute choice. Determining how value-based decisions are computed and executed is critical, as this process is disrupted in psychiatric disorders including addiction, anorexia nervosa, and depression. This study focuses on how the orbitofrontal cortex interacts with downstream brain regions to mediate value-based decision-making in rats.

Basic Research

Adam Gorka, Ph.D., National Institute of Mental Health, NIH, uses experimental and pharmacological manipulations to understand the function of neural circuits relevant to the processing of threat and anxiety. His central theory is that effective anxiolytic agents reduce neural and behavioral markers of anxiety. He will test the hypothesis that acute ketamine application will reduce a type of connectivity between the hippocampus and medial prefrontal cortex and will attenuate the increased startle response to an unpredictable threat. He will use a double-blind procedure to measure the impact of acute ketamine on neural and behavioral markers of anxiety. Healthy participants will complete two study visits involving a resting-state sequence and the threat of predictable and unpredictable aversive events paradigm to elicit an anxious state. This could inform clinical research by identifying biomarkers predicting which individuals may successfully respond to ketamine's anxiolytic effects.

Next-Generation Therapies

Diagnostic Tools/Early Intervention

June Gruber, Ph.D., University of Colorado, Boulder, wants to identify pathophysiological processes that may aid in accurate diagnosis and detection of individuals at risk for developing bipolar disorder. Here she will examine markers of bipolar disorder risk in a not-yet-diagnosed emerging adult sample among college freshmen during the transition to college. She will investigate the neural and behavioral mechanisms underlying increased positive emotion reactivity and regulation in emerging adults at high versus low risk for bipolar disorder; and investigate the potential prospective clinical utility of reward-related neural and behavioral responses to predicting clinical symptoms and functioning difficulties during the transition to college in the high-risk bipolar disorder group.

Diagnostic Tools/Early Intervention

Danella Hafeman, M.D., Ph.D., University of Pittsburgh, notes that bipolar disorder is characterized by dramatic fluctuations in mood and energy. She seeks brain-based markers with adequate sensitivity and specificity to be useful to predict mood switch in individual patients. Her team will assess person-level fluctuations in functional neural circuits previously implicated in mood switches in bipolar disorder. This will involve scanning 10 adolescents and/or young adults with symptomatic bipolar disorder four times over a period of 6 weeks to 9 months, triggered by changes in mood/energy. Each scan will provide enough data to build a person-level connectomic portrait, changes in which will be tracked with fluctuations in mood/energy. This may reveal if symptomatic bipolar disorder patients show more fluctuations in functional brain networks than healthy individuals and if these track with changes in mood and energy.

Diagnostic Tools/Early Intervention

Hanne Hansen, Ph.D., Harvard University/Massachusetts General Hospital, seeks to learn about how the drug psilocybin acts on the brain. Psilocybin is a non-selective drug that mediates its psychedelic effect by binding to the serotonin 2A receptor (5-HT2AR). Psilocybin, like the drug ketamine, is currently being investigated for their treatment potential in not only major depression disorder but also other psychiatric disorders. It is not known if the hallucinogenic experience is necessary for the observed treatment effects. In non-human primates, Dr. Hansen will compare the brain's response to psilocybin to that of three other 5-HT2AR agonists: LSD, 25CN-NBOH and lisuride.

Next-Generation Therapies

Kristen Haut, Ph.D., Rush University Medical College, notes that disruptions in the neural network underlying cognitive control of emotion are fundamental to key symptoms of bipolar disorder, including emotional lability, extreme mood states, and disinhibited behavior. Using diffusion tensor imaging (DTI), which quantifies structural connectivity via the integrity of large white matter tracts, Dr. Haut seeks to identify structural disconnectivity in cognitive control of emotion networks in individuals with bipolar disorder and subsequently to provide quantifiable evidence of structural neuroplasticity between cognitive control and emotion networks. This could support improved early intervention and treatment for bipolar and other disorders.

Basic Research

Matthew Hearing, Ph.D., Marquette University, notes that major depression, OCD, schizophrenia, and addiction exhibit a number of overlapping behavioral symptomologies, including impaired cognitive performance, that are also observed in individuals with chronic psychosocial or self-perceived chronic stress. This project focuses on circuits in the prelimbic region (PrL) of the medial prefrontal cortex that encode high-order functions, including cognitive flexibility. Behavioral experiments will be performed with rodents to assess cell- and pathway-specific alterations in PrL synaptic regulation of specific circuits connecting the cortex, nucleus accumbens and thalamus.

Basic Research

Alexander Herman, M.D., Ph.D., University of Minnesota, is studying cognitive control and the importance of cognitive effort: the volitional allocation of cognitive resources during challenging tasks or decisions. His team is working to develop new interventions that directly augment cognitive effort, with reference to ideas in cognitive neuroscience and neuroeconomics that have recently demonstrated that cognitive control-related impairments in addiction result in part from the over-discounting and diminishment of cognitive effort. This research will test the hypothesis in human subjects that microstimulation of the dorsolateral prefrontal cortex will facilitate working memory-based decision making.
Next-Generation Therapies

Melissa Herman, Ph.D., University of North Carolina at Chapel Hill, aims to better understand underlying cellular actions and brain region-specific effects of the hallucinogenic drug psilocybin, which has recently been shown to significantly reduce anxiety and depression in multiple clinical trials. Dr. Herman will use wild-type and 5-HT2A transgenic mice to examine the cellular and circuit effects of the active metabolite psilocin in the central amygdala and the role of 5-HT2A receptors in that brain area in the behavioral consequences of psilocybin/psilocin exposure. This will inform assessment of potential therapeutic use of psilocybin and assist in the development of novel therapeutics based on the targeted actions of psilocybin in relevant brain regions.
Next-Generation Therapies

Andrea Hobkirk, Ph.D., Pennsylvania State University, notes that fMRI scans are beginning to elucidate functional brain mechanisms involved in reward and inhibitory control brain circuitry predictive of sustained recovery for substance users. But fMRI is too expensive to use with all patients in real-world treatment settings. This project addresses the critical need for inexpensive non-invasive methods of measuring neurobiological changes during treatment recovery. Dr. Hobkirk will test the feasibility of using saliva analysis to measure dynamic neurobiological information through the expression of non-coding genetic markers. This project will measure changes in salivary microRNA expression and brain function while smokers reduce their dependence on nicotine with very low-nicotine cigarettes.
Diagnostic Tools/Early Intervention

Ann Hoffman, Ph.D., University of California, Los Angeles, aims to inform translational research on the underlying contributing mechanisms of post-traumatic stress after traumatic brain injury (TBI). She notes that connectivity between sensory and emotional neural networks is highly conserved across species and is vulnerable to traumatic brain injury. Alterations in these connections may affect sensory processing after TBI and result in altered perception of auditory and somatosensory stimuli. Some neutral stimuli may seem threatening, leading to the intensification of perception and encoding of traumatic memories. Dr. Hoffman will test this hypothesis using auditory fear conditioning in rodents.
Basic Research

Philipp Homan, M.D., Ph.D., Feinstein Institute for Medical Research/Northwell Health, seeks to discover prognostic biomarkers to improve individual treatment decisions in patients with schizophrenia and other psychotic disorders. He has been studying a candidate marker called the striatal connectivity index, which captures the connectivity between the striatum and the cortex, to differentiate poor responders from robust responders to antipsychotic treatment. All antipsychotics act on receptors in the striatum. However, there is strong evidence that the biomarker might also be sensitive to the effects of lorazepam, a short-acting benzodiazepine that is widely used in the treatment of psychosis. This project will thus systematically study the effects of lorazepam on the striatal connectivity index.
Diagnostic Tools/Early Intervention

Suk Jun Hong, Ph.D., Child Mind Institute, is studying brain mechanisms underlying abnormal perceptual processing and their relationship to high-order cognitive deficits in individuals with ASD. Dr. Hong seeks to develop a computational framework to assess whole-brain semantic space in individuals with ASD based on fMRI data gathered while affected individuals aged 5 to 17 watch a movie. The aims are to discover which brain areas display different extent and magnitude of functional activation to given stimuli, and whether these alterations are related to perceptual status in ASD; whether patterns of semantic space in ASD reveal subtypes; and whether the semantic brain map predicts clinical symptoms.
Basic Research

James Howard, Ph.D., Northwestern University, is interested in prediction error signals, which is how the brain computes the difference between expected and experienced rewards. Aberrant functionality within the midbrain circuit composed of dopamine neurons has a profound negative impact on motivated behavior, in schizophrenia among other conditions. His recent research raised the possibility that some symptoms of schizophrenia are related to abnormal reward identity prediction error signaling. To generate testable hypotheses in clinical populations, this project seeks a more definitive understanding of the role of the orbitofrontal cortex (OFC) and dopamine in model-based identity learning in healthy subjects. Accordingly, the team will test for causal roles for OFC and dopamine in identity prediction error signaling in humans.
Basic Research

Hailiang Huang, Ph.D., Harvard University/Massachusetts General Hospital, is studying the possible relation between genetic variations in the major histocompatibility complex (MHC) and schizophrenia risk. The genome location where MHC proteins are encoded—called the MHC locus—is the site of the strongest genetic associations with schizophrenia in genome scans of European populations. Dr. Huang will now study this relationship in East Asian populations, by sequencing 100 schizophrenia cases and 100 healthy controls. This will provide insights into how a critical schizophrenia genetic factor is applicable across populations and may reveal additional genetic factors that have been missed in previous studies focusing mainly on European populations.

Basic Research

Nicholas Hubbard, Ph.D., Massachusetts Institute of Technology, will use multimodal brain imaging and machine learning to predict the development of depressive symptoms in adolescence; and to understand adolescent neurodevelopmental factors specifically associated with risk. The project will add to an ongoing Human Connectome Project grant that compares brain function and structure in adolescents (aged 14 to 16) with major depressive disorder and those without it. The overall aim is to elucidate the neural substrate of intergenerational risk for depression, as well as provide specific biological markers for identifying those who will eventually develop depressive symptoms.

Diagnostic Tools/Early Intervention

Rainbo Hultman, Ph.D., University of Iowa, has developed a rodent model of depression in which she has identified a novel measure that reliably predicts which animals will later show depressive behaviors following chronic stress. This measure is based on local field potential recordings, which are similar to electroencephalogram (EEG) measures. In this research Dr. Hultman will conduct genome-wide, cell-type specific, molecular profiling based on the neural-circuit vulnerability measure to identify the cellular and molecular mechanisms contributing to the vulnerability. To do this, she will implant mice with microwire electrodes in five brain regions, monitor their brain activity during a task designed to elicit a negative affect response, and analyze harvested brain tissue. This work may open up possibilities for understanding early causal contributors to depression.

Basic Research

Muhammad Husain, M.B.B.S, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, is following evidence identifying inflammation as a potential therapeutic target in bipolar disorder. Postmortem brain tissue of BD patients show increased microglial activation and paradoxically, reduced astroglial activation; in-vivo studies have shown peripheral measures of inflammation to be elevated in patients with bipolar disorder. This study will use positron emission tomography (PET) to evaluate neuroinflammation in patients with bipolar disorder to extend the findings of postmortem studies and identify surrogate markers for clinical trials. The trial will include 20 patients and data from 40 controls.

Basic Research

Jacque Pak Kan Ip, Ph.D., Massachusetts Institute of Technology, is studying Fragile X syndrome (FXS). Mutations of the FMR1 gene encoding for the fragile X mental retardation protein (FMRP) lead to FXS, an autism-related disorder that causes a range of developmental problems including learning disabilities and cognitive impairment. This project will test whether locally coordinated synaptic plasticity that modifies excitatory and inhibitory synapses is altered in a mouse model of FXS. The experiments may reveal a unifying mechanism that coordinates local synaptic potentiation and weakening. Such a mechanism could provide a framework to understand the pathophysiology of neurodevelopmental disorders including FXS.

Basic Research

Jesse Jackson, Ph.D., University of Alberta, Canada, notes that researchers have made extensive efforts to decipher how the outputs of the prefrontal cortex control activity in the hypothalamic-pituitary- adrenal (HPA) axis to modulate stress and anxiety-related behavior. Yet the prefrontal cortex also receives long-range inputs from other brain regions, and Dr. Jackson wants to know more about the role of these input pathways in generating anxiety. He will focus on one of the largest inputs to the prefrontal cortex, which arises from a brain region called the claustrum. Based on his team's ability to rapidly and powerfully control the prefrontal cortex, Dr. Jackson predicts that the claustrum plays a role in controlling the prefrontal cortex during the processing of anxiogenic brain states and behavior.

Basic Research

Mohsen Jamali, M.D., Ph.D., Harvard University/Massachusetts General Hospital, is interested in "theory of mind": the capacity to infer another's beliefs, thoughts, or desires and recognize that others may have different beliefs than one's own. This capacity forms early during human development, reaching maturity at 9 to 11 years of age. Disruption of the cognitive processes that make this ability possible may play a critical role in deficits observed in social behavior disorders such as bipolar disorder, schizophrenia, and perhaps most of all, ASD. This project seeks to reveal the underlying biology of theory of mind. Dr. Jamali will use single-neuron recording techniques in humans during a planned awake neurosurgical procedure to test specific hypotheses about whether and

how cortical neurons encode core features defining theory of mind.

Basic Research

Magdalena Janecka, Ph.D., Icahn School of Medicine at Mount Sinai, is exploring the theory that risk for ASD is partly influenced by changes in DNA methylation, an epigenetic process in which molecules (methyl groups) bind to DNA, effectively switching particular genes on and off. This project seeks to discover and understand the functional significance of rare "epimutations" in ASD—changes in DNA methylation that have severe effects on genes that influence autism risk. After discovering epimutations, the team will explore whether they are linked to changes in the genetic code; and investigate the characteristics of the genes with the epimutations, which will highlight the impact they may have on a developing baby.

Basic Research

Paul Jenkins, Ph.D., University of Michigan, has identified a variant of the ANK3 gene that causes a striking loss of forebrain inhibitory synapses. The team is now examining the cellular, electrophysiological, and behavioral manifestations in mice to understand how ANK3 mutations may contribute to symptoms of bipolar disorder. The development of personalized care for patients carrying unique mutations that contribute to disease necessitates a detailed understanding of the molecular underpinnings and a comprehensive examination of the genetic architecture of these diseases such as will be undertaken in this project.

Basic Research

Danique Jeurissen, Ph.D., Columbia University, notes that neural activity patterns after treatment are not the same as the patterns seen in control subjects. Therapy, for instance in schizophrenia, may help patients compensate for disrupted neural activity by up- or down-regulating activity in various brain regions. This project seeks to address the lack a detailed understanding of the neurobiological basis for compensatory mechanisms that can help relieve symptoms in psychiatric disorders. The proposed research will study compensatory mechanisms of impaired decision-making. The team will modify neurons in parietal cortex in rodents so that they can be selectively inactivated by systemic administration of the drug clozapine. To understand how the brain can compensate for lost functions, they will inactivate a selected group of neurons while recording from other brain areas known to exhibit similar decision-related activity. They will test the hypothesis that other areas within the same circuit will change their activity to compensate for the disturbed computations in the affected area.

Basic Research

Daniel Joyce, Ph.D., Stanford University, states that depression is a reported symptom of a variety of mental disorders including seasonal and non-seasonal depression, bipolar disorder, and schizoaffective disorder. He suggests there may be a common brain pathway that is faulty in these disorders, which causes similar depressive symptoms in all of them. This project explores a candidate pathway discovered in animals, a "non-image forming" (NIF) pathway that links light captured by the eye (but that is not consciously perceived) with brain areas that control pupil size, sleep, circadian rhythms, alertness, cognition, and, importantly, mood. Experiments will be conducted with LED-based light exposure in people with seasonal and nonseasonal depression, bipolar disorder and schizoaffective disorder, as well as healthy people. The team will precisely control light to activate the NIF pathway to different levels in the hope of finding a way ("photoceuticals") to alleviate depression symptoms across multiple disorders.

Next-Generation Therapies

New Technologies

Erica Jung, Ph.D., University of Illinois at Chicago, observes that acute hunger can be driven by the activation of a subgroup of neurons in the arcuate nucleus of the hypothalamus that express Agouti-related peptide (AgRP). She postulates that AgRP neurons are a good candidate to explore for the development of effective treatments to suppress drug craving in addicted individuals. This project seeks to determine the effect of AgRP neuronal excitability on drug-seeking behavior. Dr. Jung, using zebrafish larvae as an animal model, seeks to understand how such behavior is intensified by hunger driven by the activation of AgRP neurons.

Basic Research

Yuki Kageyama, M.D., Ph.D., Weill Cornell Medical College, seeks to discover circuit-level mechanisms linking oxidative stress and depression-induced behavioral change. This project will test the hypothesis that accumulating oxidative stress in cells in the medial prefrontal cortex and nucleus accumbens (mPFC and NAc) disrupts effort valuation and adaptive reward-seeking behavior by interfering with the encoding of reward-predictive cues. This could provide important new insights concerning the prefrontal circuit-level mechanisms that mediate the spontaneous induction and remission of anhedonic behavioral states and their relationship to mitochondrial oxidative stress, and make possible evaluation of whether similar mechanisms may be involved in conventional chronic stress models, thus perhaps also revealing new targets for treatments for depression.

Basic Research

Lana Kambeitz-Ilankovic, Ph.D., Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU, Germany, seeks to establish "neuro-cognitive preci-

sion medicine" for patients with recent-onset psychosis. The team hopes to create a machine-learning engine capable of tailoring interventions to optimize recovery according to the neurobiological and neurocognitive characteristics of individual patients—pivotal for developing personalized treatment in psychiatry. Using machine learning to predict treatment response based on neurocognitive and neurobiological characteristics would optimize not only recovery, but would also speed up and facilitate administration of interventions to patients most likely to benefit.

Diagnostic Tools/Early Intervention

Annie Kathuria, Ph.D., Harvard University/Massachusetts General Hospital, says that about 50% of patients with treatment-resistant schizophrenia (failure to respond to two or more treatments) do respond well to the antipsychotic clozapine over a span of 6 months. Clozapine use is complicated by increased risk of agranulocytosis, metabolic syndrome, and myocarditis. While these risks are often worth taking for patients who have a clearly positive response, there is no way to know in advance who the clozapine responders will be. Using reprogrammed stem cells, Dr. Kathuria will examine the effect of clozapine in specific cortical neuron subtypes implicated in disease biology in hope of delineating cellular-molecular features that distinguish neurons from clozapine responders from those of non-responders.

Diagnostic Tools/Early Intervention

Tae Hyun Kim, Ph.D., Case Western Reserve University, is interested in the possibility of chromosome therapy to correct errors that can cause ASD. Aberrations such as copy number variants (CNVs) in a genome region called 16p11.2 that lose (deletions) or gain (duplications) genes are one of the most common genetic associations with ASD. The abnormal chromosome containing the 16p11.2 deletion/duplication will be induced to form a ring chromosome that will be eliminated and replaced with a typical, duplicated normal chromosome in induced pluripotent stem cells (iPSCs). These cells can be grown in culture to more accurately assess the role of the deletion and duplication of genes in neuronal cells within these regions and how they may be related to ASD symptoms.

Basic Research

Benjamin Kleaveland, M.D., Ph.D., Whitehead Institute for Biomedical Research, seeks to systematically define the role of the Fragile X mental retardation protein (FMRP) in processes that may be crucial in Fragile X syndrome (FXS). The FMRP protein is important for the development and remodeling of synapses, the connections between neurons critical for learning and memory. This study seeks to determine its role in a process called miRNA localization. A subset of microRNA molecules localize to synapses and some of these miRNAs are known to regulate synapse development or remodeling.

Basic Research

Janine Knauer-Arloth, Ph.D., Max-Planck Institute of Psychiatry, Germany, is studying the relation between dysfunctions in the immune system and symptoms and brain circuit activation patterns in people with depression. This study will draw upon data collected in the Biological Classification of Mental Disorders (BeCOME) study, involving over 450 subjects. The hypothesis is that specific immune signatures in depression exist and are characterized by different psychiatric symptoms, gene expression and neuroimaging patterns. The team will capture a comprehensive picture of the immune function by focusing on a wide range of inflammatory markers in 300 subjects (50 controls and 250 depressed patients) to generate a multi-layer classifier of immune depression.

Diagnostic Tools/Early Intervention

Christoph Kraus, M.D., Ph.D., Medical University of Vienna, Austria, will use deep brain stimulation (DBS) to treat patients with OCD. Recent research has shown remarkable success rates for DBS in refractory OCD, yet the mechanisms involved in how neuronal networks are changed are unknown. Dr. Kraus hope to explain why some OCD patients do and do not benefit from DBS treatment, and extend the results if possible to Parkinson's disease, dystonia, and epilepsy, in which DBS treatment is an established option for severest clinical forms, as well as depression, in which is it experimental.

Next-Generation Therapies

Munir Kutlu, Ph.D., Vanderbilt University, hopes to improve our understanding of the neurobiological mechanisms determining how we respond to aversive situations, a common problem for all affective disorders including anxiety and stress disorders as well as depression and bipolar disorder. The team will follow upon past results suggesting that dopamine input into the medial prefrontal cortex (mPFC) is critically involved in encoding aversive stimuli in a context-specific fashion. The purpose of this project, to be conducted in mice, is to clarify how the dopaminergic regulation of cortical projections mediates formation of cue-aversive stimulus associations and how these signals guide avoidance of aversive outcomes in real time.

Basic Research

Madeleine Kyrke-Smith, Ph.D, University of Utah, is trying to understand more about difficulties people with schizophrenia have in interpreting social cues, faces, and emotions—due to impaired processing of visual stimuli within

the visual cortex of the brain. This project is concerned with how synaptic pruning is regulated and how it may go awry in schizophrenia. At the focus is a gene called Arc that regulates synaptic pruning and whose activity is decreased in patients. She will study the structure and function of visually responsive neurons and their synapses in animals in which the Arc gene has been knocked out, comparing results with their wild-type littermates, which serve as controls.
Basic Research

Johannes Larsch, Ph.D., Max-Planck Institute of Neurobiology, Germany, is studying the neural basis of social affiliation, a behavior that is impaired in people with ASD and schizophrenia. He will use zebrafish, an ideal vertebrate model because they display spontaneous social behavior with robust individual variability. It is possible to characterize behavior in hundreds of animals and to record whole-brain neural activity at cellular resolution. Studies of the neural basis of vertebrate social behavior have implicated the "social behavior network," a set of evolutionarily conserved brain areas. This project seeks to determine its exact circuit components, and how each contributes to behavior.
Basic Research

Rachel Lean, Ph.D., Washington University School of Medicine, wants to know when, during child development, brain networks are disrupted, altering the very early development of self-regulation, executive attention, and cognitive flexibility—building blocks for later emergence of executive function, which is impaired in many brain disorders including ADHD. Dr. Lean focuses on dysfunctional parenting in early mother-infant interactions, a strong predictor of impaired executive function and brain development. She will access an infant population undergoing multimodal neuroimaging, parent-child observations, and developmental assessments, hoping to inform early parent-child interventions that enhance infant brain connectivity during a sensitive period of brain plasticity by targeting dysfunctional parenting to reduce risks of executive dysfunction and subsequent psychopathology in childhood.
Basic Research

Pierre Le Merre, Ph.D., Karolinska Institute, Sweden, is studying impairment of auditory working memory as a possible model for pathology in schizophrenia. The project will investigate a connection between cortical interneurons that express a peptide called somatostatin (SST), specific oscillatory patterns, and impaired working memory, the latter being a cognitive deficit observed in schizophrenia. Recent findings in mice implicate that intact SST interneuron functioning in the PFC is of importance to working memory. Dr. Le Merre will obtain data through an auditory working memory task for mice that he has developed.
Basic Research

Felix Leroy, Ph.D., Columbia University, is studying the neural circuitry involved in negative symptoms in schizophrenia such as impaired social cognition and memory. Dr. Leroy will examine the neural circuit mechanisms of altered social cognition, hoping to provide critical insights into novel neural circuit targets for future therapeutic interventions. He will focus on damage to the CA2 subfield of the hippocampus that causes impairments in plasticity, which may be critically important for producing the social impairments observed in schizophrenia. This area's unique molecular properties makes it a promising selective therapeutic target to treat abnormal social behaviors (including social memory and aggression) also associated with other neuropsychiatric illnesses.
Basic Research

Daniel Levey, Ph.D., Yale University, will investigate genetic overlap between anxiety, depression, and suicide in three phases. First, his team will look at overlapping common and rare genetic variation between anxiety and depression using cohorts from the Million Veterans Program (MVP), Psychiatric Genomics Consortium (PGC), and UK Biobank. Second, they will see to what extent rare genetic variants, polygenic risk scores from common variants, and available clinical risk factors may be able to identify individuals at greatest risk for suicide attempt in the independent Yale-Penn cohort. Third, they will investigate cell-type and tissue-specific gene expression consequences of common genetic variation associated with anxiety, depression, and suicide to identify novel biological targets for treatments.
Diagnostic Tools/Early Intervention

Laura Lewis, Ph.D., Boston University, notes that depressed mood is accompanied by low energy and altered sleep patterns. Remarkably, inducing acute sleep deprivation (for example, by asking patients to stay awake all night) causes symptom relief and improved mood in approximately half of patients. But when patients eventually sleep, they rapidly relapse and their emotional state returns to baseline. This potent effect of manipulating sleep suggests to Dr. Lewis that important biological mechanisms jointly modulate both arousal and emotional states in depression. This project seeks to uncover neural mechanisms underlying these linked emotional and arousal states, using new neuroimaging approaches ("fast neuroimaging") that can measure neural dynamics associated with sleep throughout large-scale brain networks in humans.
Basic Research
New Technologies

Jessica Lipschitz, Ph.D., Harvard University/Brigham and Women's Hospital, proposes that outcomes in patients with bipolar disorder are diminished owing to wide variation in illness characteristics and course from patient to patient, along with insufficient methods for classifying patients with homogeneous disease trajectories. Her team will use smart devices to track biobehavioral markers of bipolar disorder as well as data on mood variability and cognitive functioning in 40 individuals over 9 months. The team will apply machine learning to understand the relationship between longitudinal 9-month data and clinical outcomes and determine if clusters within smart device data patterns meaningfully differentiate individuals on important clinical outcomes.

Diagnostic Tools/Early Intervention

New Technologies

Elizabeth Lucas, Ph.D., North Carolina State University, notes that women are twice as likely as men to experience fear-based psychiatric conditions, and that greater symptom severity leads to poorer quality of life in women with these illnesses. Why are women more susceptible? By understanding how females encode and express fear memories differently than males, Dr. Lucas hopes to pinpoint sex-specific mechanisms and treatment strategies for fear-based psychiatric disease. This project will investigate in animal models the cellular- and circuit-based mechanisms underlying this divergent vulnerability by examining the role of a brain region called the lateral septum (LS) in sex-specific fear memory storage and expression.

Basic Research

Claudia Lugo-Candelas, Ph.D., Columbia University/Research Foundation for Mental Hygiene, Inc. / NYSPI, studies the relation between maternal sleep deprivation during pregnancy and its impact on offspring, especially its connection with risk to the child of developing ADHD. The project involves measuring the influence of objectively measured prenatal maternal sleep duration on frontostriatal circuits (ventral striatum-orbitofrontal cortex) in offspring as measured by resting fMRI at infancy (~4 weeks) and again at toddlerhood (~12 months); the influence of maternal sleep on toddlers' inhibitory control abilities; and whether the influence of maternal sleep on offspring neurodevelopment is mediated by maternal prenatal inflammation. The subject is particularly relevant within Latin populations, in which there is a disproportionate burden of pregnancy complications, shorter reported prenatal sleep duration, and disproportionate increases in ADHD diagnoses over the last 15 years.

Basic Research

Amanda Lyall, Ph.D., Harvard Medical School, hypothesizes that the relationship between cortical glutamate levels and the expression of mGluR5 receptors in the brain is aberrant in patients with bipolar disorder. This project seeks to provide foundational evidence to assist in the development of more effective therapeutic interventions focusing on metabotropic glutamate receptors. The team will access the large population of well-characterized patients with bipolar disorder who have already been recruited by the Human Connectome Project for Early Psychosis. The plan is to collect two types of advanced imaging data (GluCEST and MR-PET) specific to the assessment of glutamate in 10 patients with early-course bipolar disorder.

Basic Research

Angela Mabb, Ph.D., Georgia State University, aims to provide a temporal map of the proteins that are expressed in groups of neurons called neural ensembles that are associated with flexible behaviors. The identified molecular signatures of behavioral flexibility will help inform understanding of our ability to switch between mental processes to generate appropriate behavioral responses. This ability is impaired in early-onset and psychiatric disorders such as autism spectrum disorder, schizophrenia, post-traumatic stress disorder, depression, and anorexia may lead to the identification of molecular targets to treat mental health conditions associated with diminished cognitive flexibility.

Basic Research

Erika Manczak, Ph.D., University of Denver, seeks to test a social-immunological model of depressive symptoms in adolescents and their parents that offers an explanation for how salient environmental experiences can become biologically embedded to confer risk. Specifically, Dr. Manczak proposes that maladaptive features across multiple types of specific social relationships (e.g., with parents or friends) lead to inflammatory cascades reflected in the expression of pro-inflammatory and anti-viral genes and higher levels of circulating pro-inflammatory molecules called cytokines in peripheral blood, which in turn promote depressive symptoms. This will be explored through repeated assessments of social relationships, molecular and protein markers of inflammation, and depressive symptoms in 100 adolescent and parent dyads.

Basic Research

Merry Mani, Ph.D., University of Iowa, notes that about half of antidepressant-resistant patients respond favorably to the non-invasive brain stimulation method called transcranial magnetic stimulation or TMS with a reduction in symptoms of 50%. Yet since it is not yet clear how TMS exerts its beneficial effects, it is also not known why it does not provide these benefits in the other 50% of treatment-resistant patients. Dr. Mani will use two types of imaging to study 20 people

with major depression who are initiating a clinical course of high-frequency rTMS. The aim is to identify imaging-based biomarkers that can inform target engagement at the onset of treatment.

Next-Generation Therapies

Devanand Manoli, M.D., Ph.D., Gladstone Institutes/University of California, San Francisco, is working with prairie voles—small rodents that display strong social attachment behaviors between peers and develop enduring pair bonds between mates—to study social behaviors and their disruption in anxiety- and depressive-like behaviors. Pioneering work in the prairie vole has identified vasopressin and oxytocin as critical mediators of pair bonding, as well as social cognition and attachment behaviors in humans. This project seeks to determine the changes in neural activity and gene expression that underlie deficits in attachment in voles that carry mutations in genes that have been implicated in neuropsychiatric disorders.

Basic Research

Joanna Martin, Ph.D., Cardiff University, UK, notes there are striking sex differences in the prevalence of ADHD, depression, and anxiety, with a male bias in ADHD and a female bias in depression and anxiety. The aim of this project is to comprehensively characterize the sex-specific impacts of genetic risk variants on clinical diagnoses of ADHD, depression, and anxiety, in children and adults. She will use data from patient case-control samples of diagnosed individuals, as well as a sample of 75,000 children assessed in mental health clinics for a variety of psychiatric problems. She will test the hypothesis that ADHD genetic risks are more strongly associated with depression and anxiety in females than in males; and whether depression and anxiety genetic risks are more strongly associated with ADHD in males.

Basic Research

Pierre Mattar, Ph.D., Ottawa Hospital Research Institute, Canada, has discovered that two genes prominently associated with ASD and intellectual disability form a protein complex in the developing brain. This suggests they may regulate the production of neurons and glia during the generation of the cerebral cortex. In this project he proposes to determine whether and how these genes cooperate to regulate brain development. Specifically he hopes to shed light on whether and how protein complexes that participate in chromatin remodeling regulate the production of neurons and glia during the development of the cerebral cortex.

Basic Research

Jordan McCall, Ph.D., Washington University, observes that prior studies on the brains of suicide victims have revealed major disruption of genes and proteins associated with excitatory neurotransmission in a brain area known as the locus coeruleus. This project seeks to understand how two critical brain structures, the ventral tegmental area and the locus coeruleus, communicate during stress. In particular, Dr. McCall hypothesizes that the brain circuit between these two structures is enhanced in during chronic stress, perhaps contributing to the negative behavioral consequences of stress. This will be investigated in animal studies.

Basic Research

Philipp Mews, Ph.D., Icahn School of Medicine at Mount Sinai, is exploring the hypothesis that permanent changes in chromatin structure—the complex bundle in which our DNA is packaged in the cell—underlie the dysregulation of gene activation patterns characterizing drug addiction. There is currently no direct link between drug-induced alterations in chromatin and the aberrant gene regulation observed during relapse. Dr. Mews seeks to determine which neuronal subtypes are responsible within the nucleus accumbens, which is composed of two opposing types of medium spiny neurons, the D1 and D2 dopamine receptor-expressing subtypes. These exhibit dramatic differences in activity and effects on drug reward. This project aims to identify the precise epigenetic mechanisms that establish and preserve the molecular pathology in these distinct striatal subpopulations.

Basic Research

Jacquelyn Meyers, Ph.D., State University of New York, Downstate, is interested in EEG coherence—the degree of synchrony in brain oscillatory activity between neural networks in two brain regions. Coherence has been particularly useful in the study of normal brain development and disorders such as schizophrenia. The team will draw upon the Collaborative Study on the Genetics of Alcoholism, with longitudinal EEG data (14,495 total assessments) in addition to GWAS data, available on 3,911 offspring aged 12 to 32 from families densely affected with Alcohol Use Disorders as well as community comparison families. The team will examine whether genetic risk for schizophrenia is reflected in individual differences in neural connectivity among unaffected male and female adolescents and young adults throughout a key period of risk for the onset of psychotic illness (ages 12-32), and how this is influenced by substance use behavior (alcohol, nicotine, and cannabis use and DSM-5 disorder). Importantly, they will examine how these associations differ among males and females and by age.

Basic Research

Giorgia Michelini, Ph.D., Stony Brook University, seeks to identify EEG signatures of risk for depression in adolescence. Several atypical EEG patterns can be observed in people

with depressive disorders, but we still do not know whether these alterations predate the development of depression and can predict future first onsets before people start showing symptoms. This research seeks to identify EEG signatures of risk for depressive disorders using cutting-edge analytic tools, and examine whether they help improve our ability to predict first onsets of depressive disorders. This project will be conducted on available data from a community sample of 550 teenage girls followed up into young adulthood, using the ADEPT study.

Diagnostic Tools/Early Intervention

Kai Miller, M.D., Ph.D., Mayo Clinic College of Medicine, Minnesota, notes that the ventral striatum (VS) is a region deep in the brain where motivational inputs from many areas converge. Within the VS, the nucleus accumbens (NAc) has been a target for deep brain stimulation (DBS) to treat OCD since its inception nearly 20 years ago. Dr. Miller will record electrophysiology data from the ventral striatum in patients who are undergoing DBS treatment for OCD. The aim is to characterize the fine-structural neurophysiology of the ventral striatal region and the brain network it is part of. This may help explain why some patients respond to DBS therapy and others do not. The goal is to develop neurosurgical approaches for DBS using biomarkers to trigger selective stimulation, with the goal of retraining aberrant brain networks.

Next-Generation Therapies

Jean-Philippe Miron, M.D., University of Toronto, Canada, seeks to validate in a pilot test a new, cost-effective way of delivering non-invasive brain stimulation called rTMS for depression. Its widespread adoption has been impeded by its complexity and high acquisition and operational costs compared to medication, says Dr. Miron. This Phase I study in 60 unipolar depression patients, to be conducted in a clinical setting, will test a novel rTMS protocol optimized for maximal safety, tolerability, fault-tolerance, and cost-effectiveness, using techniques simple enough to enable self-administration. Since home use would enable multiple daily sessions, the protocol employs an initial 6-times-daily 5-day phase followed by a conventional 25-day once-daily extension course of treatments.

Next-Generation Therapies

Stephanie Moon, Ph.D., University of Colorado, Boulder, notes that the cellular and molecular processes that allow white matter to form and function are not well understood. She is focusing on the molecular pathway for protein biosynthesis, which appears particularly important for the formation and function of the white matter. Dr. Moon seeks to determine how protein biosynthesis occurs in oligodendrocytes and neurons. The research, using reprogrammed stem cells (iPSCs), will allow direct examination of whether and how protein biosynthesis is compartmentalized to support the formation and function of cells of the white matter. By introducing mutations in the iPSCs in genes involved in protein biosynthesis, it may be possible to see how defects in the protein biosynthesis pathway interfere with the function and formation of oligodendrocytes and neurons.

Basic Research

Laurel Morris, Ph.D., Icahn School of Medicine at Mount Sinai, has developed an ultra-high field MRI procedure that provides much improved images of the ventral tegmental area (VTA), a brain area linked with the problem of motivation in depression. This project will consist of a randomized controlled trial to train individuals with major depressive disorder to modulate their own VTA activity during an ultra-high field MRI scanning session. Previous studies have shown that the activity of the VTA can be changed in healthy volunteers if they are trained to use certain thought patterns while watching their own VTA activity in real-time. The hope is that such biofeedback training is feasible in patients with major depressive disorder.

Next-Generation Therapies

Fabian Munoz Silva, Ph.D., Columbia University, notes that for certain disorders, a promising alternative to treatment with deep brain stimulation, which involves surgery, is to use DREADDS (designer receptors exclusively activated by designer drugs) to modulate neural activity pharmacologically in targeted brain regions. Unfortunately, DREADDS also require invasive methods to deliver the genes that express the receptor. This project attempts to modulate neural circuits non-invasively via focused ultrasound (FUS), which sends an ultrasound beam through the skull to reach deep brain structures and directly stimulate or inhibit neurons in the targeted region. Combined with lipid microbubbles, focused ultrasound can be used to open the blood-brain barrier in precisely targeted brain regions. It will be tested in non-human primates directed to perform a reward-based decision-making task.

Next-Generation Therapies

New Technologies

Ciaran Murphy-Royal, Ph.D., University of Calgary, Canada, will investigate the role of a family of non-neuronal brain cells, astrocytes, in a rodent model of depression. These cells play key roles in maintaining many aspects of normal brain function. Preliminary data suggests that astrocyte function is impaired by a single bout of acute stress, yet there is little evidence of the effects of chronic stress on astrocytes and whether this impacts neural transmission. Using an animal model of depression, the team will investigate the

cumulative effects of stress on astrocyte structure, function, and impact on neural transmission and plasticity. They also plan to specifically target astrocytes, seeking to alleviate stress and depression-like behaviors in mice.

Basic Research

Carla Nasca, Ph.D., The Rockefeller University, aims to provide a precision medicine model of diagnosis and treatment of a metabolic subtype of major depressive disorder by validating a novel biomarker of brain plasticity. Specifically, the project will help to identify central and peripheral mechanisms of insulin action in relation to acetyl-L-carnitine (LAC) in 50 patients with major depression as compared to a group of 50 non-diabetic age and sex-matched subjects without psychiatric disorders. Greater understanding of the reciprocal link between LAC and insulin action in major depressive disorder could be instrumental in uncovering novel targets to regulate brain plasticity and ultimately lead to personalized medicine strategies.

Diagnostic Tools/Early Intervention

John Naslund, Ph.D., Harvard Medical School, seeks to leverage digital technology to support training and development of clinical skills among community health workers for early detection and referral of severe mental disorders in primary care settings in rural India. The objective is to develop and pilot-test the feasibility, acceptability, and initial impact of a digital intervention for training community health workers, called ASHAs (Accredited Social Health Activist), in the detection and referral of severe mental disorders. The team will measure initial program impact using pre/post assessments of knowledge and skills and general attitudes about severe mental disorders. They will also employ qualitative focus group discussions to ascertain feasibility and acceptability of the digital training, and to elicit feedback from community health workers for improving the course design and content.

Diagnostic Tools/Early Intervention

Ralda Nehme, Ph.D., The Broad Institute of MIT and Harvard University, is studying a vulnerable location in the human genome called 22q11.2, where a deletion in chromosome 22 is associated with increased risk of psychiatric disorders, and is the highest known genetic risk factor for schizophrenia. Despite its high prevalence, little is known about the molecular mechanisms that lead to psychiatric symptoms in a subset of those who carry the mutation. This project will test the hypothesis that 22q11.2 deletion alters genome organization in neuronal cells, modulating expression of psychiatric risk genes. To test the hypothesis, Dr. Nehme will investigate the effects of 22q11.2 deletion in neurons derived from human induced pluripotent stem cells (hiPSCs). The research could provide mechanistic insight into disease causation at the molecular level, bridging the role of rare and common genetic variants associated with various disorders.

Basic Research

Daniela Neuhofer, Ph.D., Medical University of South Carolina, studies cannabis use disorder (CUD), characterized by tolerance, difficulties to control use, craving, and withdrawal symptoms after discontinued use. She seeks to characterize and understand neuroadaptations in reward circuitry that might contribute to CUD, as well as anxiety and depressed mood associated with cannabis withdrawal. In rodents, she hopes to reveal a circuit-based mechanism underlying cannabis craving and withdrawal-related emotional symptoms of CUD that could help to open a biological strategy for future possibilities in drug development for treating cannabis addiction.

Basic Research

Tan Hoang Nguyen, Ph.D., Virginia Commonwealth University, has developed a multi-trait method (multi-trait Transmission And De novo Association test, mTADA) to perform pairwise analyses of six neuropsychiatric disorders using family data, and single-trait methods that integrate rare variant, gene-expression, and pathway information for deeper analysis of each disorder in isolation. The aim in this project is to perform joint analysis of multiple traits, allowing for identification of both shared and unique components of genetic risk, and with great potential to 1) increase statistical power for the identification of risk loci and 2) further elucidate the genomic etiologies of the tested traits. Existing large rare-variant datasets from autism and schizophrenia cohorts provide the basis for this research.

Basic Research

Jason Nomi, Ph.D., Miami University, aims to introduce a new approach for characterization of ASD neurobiology inspired by computational neuroscience that relies on measures of brain signal variability. Previous research in typical individuals has shown that increased brain signal variability is more prevalent in younger individuals and those who perform better on tasks of flexible cognition. This makes brain signal variability a promising new measure of development and flexible cognition that can be used to investigate the neurobiology of ASD and associated inflexible behaviors that characterize the disorder (e.g., restrictive and repetitive behaviors).

Basic Research

Agnes Norbury, Ph.D., Icahn School of Medicine at Mount Sinai, wants to test new theories suggesting that people only use new information to update an older fear memory if they think that the same causes are responsible for events during

both the original fear memory and current learning episode. In other words, new learning that an object or situation is safe may fail to update an older memory of that object or situation being harmful if the individual reasons that the difference in context across these events means that is unlikely that they are the result of the same underlying factors. The team will test if this new theory can explain excessive avoidance behavior in individuals with an anxiety disorder or PTSD, using an online game to test how they learn about negative events.

Basic Research

Kieran O'Donnell, Ph.D., Douglas Mental Health University Institute, Canada, notes growing evidence implicating maternal hormonal sensitivity and increased risk for postpartum depression. This project aims to build on such findings to develop a simple blood test, using a novel blood collection system that will directly assess maternal hormonal sensitivity as described by computational modelling of dynamic change in hormone-sensitive gene expression. The team will combine biological measures of hormonal sensitivity with existing known psychological and social risk factors to determine if this molecular screen helps to better identify women at risk for postpartum depression than is currently possible.

Diagnostic Tools/Early Intervention

Won Chan Oh, Ph.D., University of Colorado, Denver, who is studying autism-like social deficits, will examine the neural circuit mechanisms of mesoprefrontal VTA dopamine neurons, one of the major components of stress/reward circuitry underlying asocial behavior elicited by early-life stress. The goals are to define how exposure to early-life stress affects PFC-projecting VTA dopamine neurons; to determine structural and functional changes of layer 2/3 pyramidal neurons in the PFC following early- life stress; and to define projection-specific roles of VTA dopamine neurons in asocial behaviors induced by early-life stress using viral-mediated gene delivery and chemogenetics. The larger aim is to identify novel targets and avenues for future treatment strategies to manage ASD.

Basic Research

Jason Oliver, Ph.D., Duke University, is interested in the way anhedonia—the loss of interest in pursuing pleasure or engaging in pleasurable activities—affects human activity patterns. Dr. Oliver will use GPS technology to identify the activity pattern signatures associated with anhedonia. This may provide important insight into factors that cause or perpetuate anhedonia (e.g. lack of time spent outside the home, limited number of fixed activity points). Long-term, it could lead to the development of digital health approaches for detecting the presence of anhedonia or other psychopathology using GPS traces drawn from mobile phones or wearable devices. It could also make possible determination of the effects of psychotherapy on activity patterns, information that might inform intervention goals (e.g. should participants simply increase their time spent outside home? Spend time in novel locations? Spend small amounts of time in many different locations?)

New Technologies

Jocelien Olivier, Ph.D., University Medical Center Groningen, Netherlands, notes that the human gut contains 95% of the body's serotonin and that there is clear evidence that the microbiome interacts with serotonin maintenance in the body. This project seeks to investigate how alterations in the gut microbiome due to maternal antidepressant treatment are transmitted from the mother to the offspring. A second goal is to elucidate how altered metabolites cross the blood-brain barrier in rats and in human cells. By assessing the microbiome, metabolites, and the behavioral outcome of offspring, the research could deliver insights on risk factors in developing offspring. It will also explore possible interventions (metabolite alterations) with the aim of developing new leads for depression treatment during pregnancy and the postnatal period.

Basic Research

Alexey Ostroumov, Ph.D., University of Pennsylvania, seeks to understand the role of midbrain inhibitory GABAergic circuitry and identify potential new targets for treating major depressive disorder. He will use a rat model of anhedonia, seeking to determine if pharmacological or molecular manipulation of a protein called KCC2 will influence depression-like behaviors. KCC2 is involved in regulating inhibition at synapses. Preliminary data in rats indicates that stress dysregulates midbrain inhibitory circuitry via decreased function of KCC2, located in VTA GABA neurons. KCC2 dysfunction impairs GABAA receptor-mediated inhibition leading to increased midbrain GABAergic circuit excitability. This in turn attenuates dopamine signaling, which is commonly associated with blunted behavioral reward sensitivity. Dr. Ostroumov hopes to test the therapeutic potential of several drugs that boost KCC2 function or compensate for its loss.

Basic Research

Thomas Papouin, Ph.D., Washington University School of Medicine, aims to better understand the molecular and cellular underpinnings of cognition in brain disorders such as schizophrenia, and has become particularly interested in the role played by astrocytes in this process. Astrocytes are a subclass of glial "helper" cells that are often overlooked in research. The team will study the role of the alpha-7 nicotinic receptor expressed by astrocytes in cognition and cognitive deficits, including their role in the pro-cognitive effect of

cholinergic therapeutics. Enhancement of this receptor has become a major approach to ameliorate cognitive deficits associated with schizophrenia and Alzheimer's disease. Though the receptor is expressed by all cell types in the central nervous system, its role has not been systematically studied.
Basic Research

Johannes Passecker, Ph.D., Columbia University, is interested in identifying sex differences in neurodevelopment that bear upon cognitive deficits in neuropsychiatric disorders like schizophrenia. Working with a mouse model of the 22q11.2 human microdeletion syndrome, which is characterized by pronounced age and sex-related disturbances in cognitive tasks that depend on the hippocampus and prefrontal cortex, including working memory, Dr. Passecker seeks to test sex-specific rescue of working memory deficits and neurophysiology in his rodent model by selective manipulation of versions of a protein kinase called GSK3. These experiments combine sex-specific circuit level investigation with neurodevelopmental rescue to determine the efficiency of novel pro-cognitive therapeutic interventions for neuropsychiatric disorders.
Basic Research

Rui Peixoto, Ph.D., University of Pittsburgh, is addressing the question of how dopamine (DA) signaling is regulated during early development and how it influences the maturation of circuits in the striatum. Dr. Peixoto will take advantage of two new technological advances to establish a new experimental paradigm to monitor striatal DA levels and DA-induced signaling in freely behaving developing mice. This will make it possible to characterize early dynamics of striatal DA release in response to stimuli and determine how it modulates a signaling mechanism that is critical for the development of synapses in striatal neurons. This work could help determine how different genetic and environmental insults affect early DA signaling and normal brain development.
Basic Research
New Technologies

Catherine Pena, Ph.D., Princeton University, notes that early-life stress alters brain development, yet the resulting molecular changes in the brain that may mediate altered response to antidepressant drugs have not been systematically studied. She will use a combination of bioinformatic analyses and pharmacological testing in a mouse model to better understand why early-life stress is associated with poorer antidepressant treatment outcomes. She has validated a "two-hit" mouse model of early-life and adult stress in male and female mice, wherein mice exposed to early-life stress in a postnatal- sensitive window have increased sensitivity to stress in adulthood and higher rates of depression-like behavior, akin to human clinical findings.
Basic Research

Greg Perlman, Ph.D., Stony Brook University School of Medicine, observes that drug addiction is associated with low levels of dopamine release in the striatum, the brain's reward center. Many prominent features of addiction stem from low dopamine release, including reduced salience of non-drug rewards. Studying the origin of low dopamine function in chronic drug users may hold the key to finding new strategies for treatment and prevention. He will use a novel imaging technique called NM-MRI to measure the accumulation of neuromelanin (a dark pigmented deposit) in the substantia nigra in eighty 18-year-olds with a history of drug use. Neuromelanin is a byproduct when dopamine is made. One aim is to establish a definitive link between NM-MRI level and cumulative adolescent drug use.
Diagnostic Tools/Early Intervention
New Technologies

Roseann Peterson, Ph.D., Virginia Commonwealth University, begins with the premise that a deeper understanding of causal processes in depression will require novel approaches incorporating multiple data types: environmental, clinical, neuroimaging, and genomic. This project seeks to leverage the "phenome"—the sum total of traits expresses by a cell—and genome sequencing to identify genetic variants conferring depression risk, specific subtypes and symptoms, and correlated traits. The idea is to move beyond phenotype–genotype association toward greater understanding of underlying causal processes between major depression and psychological and medical conditions, environmental risk, and brain region and cell types.
Diagnostic Tools/Early Intervention

Mu Qiao, Ph.D., California Institute of Technology, will apply computational models of decision-making and its underlying neuronal dynamics to understand neural mechanisms of decision-making and decision-making deficits in psychiatric disorders. The project aims to understand how a mouse weighs current sensory input and prediction from previous experience for decision-making, to identify neural computation underlying the balance of the two, and to determine how this process is altered in mouse models of ASD and schizophrenia.
Basic Research

Brian Rash, Ph.D., Yale University, is interested in the gyrus—the ridges that characterize the outward appearance of the cerebral cortex. Abnormalities of gyral size and pattern have been reported in neuropsychiatric diseases ranging from autism spectrum and bipolar disorders to schizophrenia. He

seeks to understand the mechanisms behind the formation of cortical convolutions, which increase the surface area of the cerebral cortex and hence enable our higher cognitive abilities. In research with macaque monkeys, he aims to assess two current theories of how these features are generated in the developing brain.

Basic Research

Juliet Richetto, Ph.D., Brain Research Institute, University of Zurich, Switzerland, will use a mouse model to determine whether underlying maternal depression or exposure to antidepressants has greater influence on the risk of neurodevelopmental disorders in offspring. She hopes to assess the biological correlates that mediate the link between prenatal depression (and/or antidepressant exposure) and altered brain and behavioral functions in the progeny. The working hypothesis is that prenatal depression leads to genome-wide, stable alterations in DNA methylation and gene expression in the offspring's brain, which in turn may lead to altered function of pathways and neuronal systems that underlie behavioral functioning.

Basic Research

Mina Rizk, M.D., Columbia University, will study, in detail, opioid-use disorder patients at significant risk for suicidal behavior. Several animal and human studies show that activation of kappa opioid receptors, a class of brain opioid receptors, may be underlying the negative emotional states experienced by opioid-use disorder patients. Buprenorphine, a treatment for opioid-use disorder, has recently shown promise in the treatment of depression and suicidal ideation. To investigate the mechanism of the anti-suicidal effects the team will examine its effect on suicidal ideation compared with naltrexone, which blocks both mu and kappa receptors and is also used for opioid-use disorder treatment. If the efficacy of naltrexone is equivalent to that of buprenorphine, this would suggest that their anti-suicidal effects are mediated via common kappa-antagonism properties. Conversely, if naltrexone does not work, it would suggest that buprenorphine acts through its mu receptor properties.

Basic Research

Christopher Rodgers, Ph.D., Columbia University, will use a combination methods to reveal the flow of information across the layers of cortex during object recognition. Humans and other animals can identify objects by active touch-coordinated exploratory motion and tactile sensation. The brain must integrate exploratory motor actions with tactile signals in order to form a holistic representation of object identity. Impairments in object manipulation are visible in 6-month-old infants with ASD, long before other symptoms appear. A greater understanding of these sensorimotor processes, both in health and in ASD, could lead to earlier interventions and eventually therapeutics.

Basic Research

David Root, Ph.D., University of Colorado Denver, wants to contribute to research establishing that the activation of dorsal raphe serotonin neurons is responsible for the social and fear-related consequences of inescapable stress. Dorsal raphe serotonin neurons are divided into two genetically distinct cell-types. Some solely release serotonin (serotonin-only neurons) while others co-release serotonin with the excitatory neurotransmitter glutamate (glutamate-serotonin neurons). Dr. Root proposes to identify 1) which type of genetically distinct dorsal raphe serotonin neuron is activated by inescapable stress and 2) which type of genetically distinct dorsal raphe serotonin neuron is necessary for the social and fear-related consequences of inescapable stress.

Basic Research

Can Ruan, Ph.D., Capital University of Medical Sciences, Beijing Anding Hospital, People's Republic of China, will study a population of patients for a genetic predisposition to poor breakdown of the antipsychotic medicine clozapine. Although very effective in controlling psychotic symptoms, clozapine has dangerous side effects which have restricted its use, in many places, to patients who are not helped by other medicines. This research will involve recruitment of some 1,000 Chinese inpatients on clozapine, with the hope of identifying 40 "poor metabolizers" of clozapine who will have their DNA sequenced to discover variations that may affect clozapine breakdown in the body. The aim is to optimize clozapine administration.

Diagnostic Tools/Early Intervention

Tomas Ryan, Ph.D., Trinity College, Dublin, Ireland, suggests that if we understood how to control the brain's normal access to specific memories, then we may be able to design treatments that modify targeted memory access in traumatic circumstances. Toward this end, he wants to learn from the biology of amnesia and memory loss. He will probe how memories are stored in development by integrating recently developed engram-labelling technology with various rodent models of infantile amnesia. Engrams are biochemical units within which it is proposed that memories are stored. He will study the effect of engram-cell manipulation on memory retrieval. This may shed light on the persistence and functionality of infant memories in adults, and could advance efforts to find ways of reinstating normal access to these engrams by the induction of new plasticity.

Basic Research

Marcos Santoro, Ph.D., Universidade Federal de Sao Paulo, Brazil, is intrigued by exosomes—small bubble-like containers floating outside cells that are found in body fluids like CSF, serum, saliva, and urine. The exosome represents the cell of its origin, with its specific membrane markers and intracellular content, including microRNAs. Their tiny size enables them to cross the blood-brain barrier, and thus, some exosome studies have targeted neuropsychiatric disorders to identify potential biomarkers. Dr. Santoro hopes to identify potential biomarkers of transition to psychiatric disorders and improve currently available tools for prediction, by evaluating microRNA expression from serum exosomes of adolescents before and after the transition to psychiatric disorders.

Diagnostic Tools/Early Intervention

Anindita Sarkar, Ph.D., Salk Institute for Biological Studies, points out that sensors of environmental stress are not well understood, although detection of such stress likely involves a complex interaction of genetic and environmental factors that alter neural function. Dr. Sarkar is interested in segments of DNA that jump around in the genome, called LINE-1 or L1 elements. Dr. Sarker wonders if aberrant L1 activity could be a maladaptive response to environmental challenges and contribute to neurological disorders by jumping into new genome regions while neurons are being born. Depending on the insertion site, they may alter gene expression, and lead to changes in neuronal function. This research will explore that possibility.

Basic Research

Shogo Sato, Ph.D., University of California, Irvine, is investigating molecular implications in the circadian clock of depression and antidepressant treatment. The circadian clock is the biochemical time-keeping mechanism in our cells that orients us to the 24-hour cycle. Dr. Sato's lab regards the circadian clock as a key operator in the onset of depression and the action of antidepressant treatments such as rapidly acting low-dose ketamine. To further this work, they will profile the activity of circadian genes across the genome at different times of day, using cells harvested postmortem from prefrontal cortex of mice with depression-like behaviors generated by chronic social-defeat stress.

Basic Research

Lindsay Schwarz, Ph.D., St. Jude Children's Research Hospital, is interested in aberrant norepinephrine signaling, which is thought to promote depression, anxiety, and posttraumatic stress disorder. This implicates a brain area called the locus coeruleus (LC), a crucial arousal center in the brain and an important source of norepinephrine. Dr. Schwarz recently identified a population of LC neurons that co-express NE and the opioid peptide precursor gene prodynorphin. This project explores the hypothesis that Pdyn+ LC neurons are important mediators of stress response, and that dysfunction within this neural circuit may be an underlying contributor to chronic stress disorders.

Basic Research

Helen Schwerdt, Ph.D., Massachusetts Institute of Technology, aims to characterize—at multiple levels of neurochemical and neural electrical activity across basal ganglia and cortical sites—the neural sources of key behavioral variables that are compromised in mood disorders. She makes a critical first step: to examine corticostriatal pathways and striatal dopamine signals simultaneously, given the strong connection of these fundamental brain processes in mood disorders. She will use tools that probe rapid extracellular dopamine fluctuations concurrently with neural electrical activity from a wide distribution of sites in the striatum of behaving nonhuman primates. The hope is that these types of multi-modal measurements will contribute to development of improved diagnostics and treatments.

Basic Research

Samantha Scudder, Ph.D., University of California, Santa Barbara, will probe the underlying circuitry supporting alcohol-seeking behaviors. The focus will be the molecular determinants of alcohol-evoked changes on plasticity at specific inputs to the bed nucleus of the stria terminalis (BNST), a region deep in the brain which integrates widespread input from across the brain and sends projections to multiple downstream areas that control behavior and emotional states. As this region is also known to be a key regulator of stress responses and anxiety-related behavior, knowledge of the baseline wiring of inputs and outputs of the BNST will additionally inform understanding of how this region promotes or reduces anxious states.

Basic Research

Andrey Shabalin, Ph.D., University of Utah, is studying how methylation—a form of epigenetic modification of gene expression—may impact suicide risk. Since increased risk for suicide death has been well documented in schizophrenia, bipolar disorder, depression, and PTSD, and has strong links to environmental exposures, she argues that suicide death is a prime phenotype for a methylation study. This project is a well-powered pilot methylome-wide association study of population-ascertained suicide death, testing for differential methylation in both bulk blood tissue and within diverse blood-cell types. Results will be compared with those in schizophrenia and depression. Methylation markers may point to biological mechanisms and processes otherwise undetectable.

Basic Research

Yasuyuki Shima, Ph.D., RIKEN Brain Science Institute, Japan, is working with animal models that recapitulate both genetics and phenotypes of people with bipolar disorder. This project will apply single-cell analyses to detect the pathophysiology of BD with high sensitivity by accessing individual BD-responsible neurons in the brain of a BD animal model. The work will address how bipolar disorder-responsible neurons behave differently from healthy neurons in the polg mouse model, a transgenic mouse line expressing a mutant polg gene that develops mitochondrial DNA deletions in neurons and expresses depression-like behaviors.

Basic Research

Shan Siddiqi, M.D., Harvard Medical School, aims to better understand how distinct brain circuits can be mapped and selectively stimulated with non-invasive transcranial magnetic stimulation (TMS) to treat different symptoms of major depression. This project seeks to personalize TMS targets based on a patient's specific symptoms and their specific pattern of brain connectivity. Dr. Siddiqi will test this hypothesis by using the human connectome to map the connections responsible for improvement in individual depressive symptoms using TMS. Prior results, which identified yielded two distinct circuits responsible for improvement in dysphoric vs. anxiosomatic symptom clusters, will here be rigorously replicated and validated across multiple datasets.

Next-Generation Therapies

Sandeep Singh, Ph.D., Virginia Commonwealth University, is studying the molecular mechanisms that govern astrocyte-synapse interactions in the central nervous system (CNS). How do neurons and astrocytes interact to orchestrate synaptic circuit assembly? What are the molecular signals that mediate cross-talk between astrocytes and neurons in CNS development and disease? These are the fundamental questions to be addressed in this project. One focus is hevin/SPARCL1, a protein secreted by astrocytes that induces neuronal connectivity, dictates synaptic adhesion, and is required for developmental synaptic plasticity. Expression of SPARCL1 is reduced in depressed individuals and suicide victims. However, the role of SPARCL1 in resilience to social stress is currently unknown.

Basic Research

Tarjinder Singh, Ph.D., Harvard University/Massachusetts General Hospital, is trying to better understand the significance of sequencing studies for schizophrenia that have implicated individual risk genes using ultra-rare coding variants, e.g., the Schizophrenia Exome-Sequencing Meta-Analysis (SCHEMA). While some identified alleles have individually large effects, whether or not they are sufficient in conferring risk for schizophrenia in the absence of common polygenic risk remains unknown. This project will use the genetic data generated by large sequencing efforts like the SCHEMA consortium and the UK Biobank to clarify the contributions of common polygenic risk in the presence of ultra-rare protein-coding variation.

Basic Research

Steven Sloan, M.D., Ph.D., Emory University, notes that glia actively coordinate neural circuit formation during development, and asks whether aberrant glial development underlies circuit dysfunction in disorders like autism and schizophrenia. To answer these questions, his team uses genome engineering, next-generation sequencing, stem cell biology, imaging, and neurobiological approaches to understand how glia develop and interact with neurons in the lab's 3D human brain organoid culture system. This platform also allows them to study brain organoids derived from patients who have a clear genetic basis for their diagnosis of neuropsychiatric disorders, which can then be studied at a close cellular and molecular level that was previously inaccessible.

Basic Research

Adam Snyder, Ph.D., University of Rochester, notes that the interactions of many tiny neurons give rise to large patterns of activity, but also that large-scale states influence how small groups of neurons compute. The project is about how multi-scale brain function unfolds. The focus will be attention, which is disrupted in nearly every mental disorder. It involves large-scale coordination between brain areas representing things such as our goals and priorities with other brain areas processing sensory information. Within sensory areas, the fine-scale activity patterns of neurons changes depending on our attention states. The aim here is to better understand the moment-to-moment relationship of how these two processes unfold in tandem.

Basic Research

Maite Solas, Ph.D., University of Navarra, Pamplona, Spain, is studying insulin action on the brain, which may modulate processes including cognition and mood. Evidence has indicated that insulin-signaling disturbances in the central nervous system are present in neurodegenerative diseases and may also be implicated in cognitive deficiencies observed in many mental disorders. Mice lacking the insulin receptor (IR) in neurons display metabolic abnormalities; this research will focus on insulin action on another brain cell type, the astrocytes, which are imperative for proper brain homeostasis. The ultimate aim of the research is to explore the possibility of targeting the astrocytic insulin receptor to treat neuropsychiatric disorders.

Basic Research

Andre Sousa, Ph.D., Yale University, aims to reveal functional regulatory elements that govern human-distinct features of brain development and disease. The focus will be to uncover the regulatory mechanisms that govern human-specific gene expression changes that are heterochronic, i.e., occur in different temporal sequence in humans, during prenatal development. To do so, Dr. Sousa will simultaneously assess the regulatory potential of all areas of the human genome, in single neurons, glia, and other cell types. The aim is to reveal genome regions whose regulatory potential may explain differences in gene expression observed between species.

Basic Research

Colenso Speer, Ph.D., University of Maryland, notes that photosensitive retinal ganglion cells (ipRGCs) in the retinae transmit luminance information to subcortical targets in the brain to adjust neural circuits to the light cycle. Despite the importance of ipRGC circuits for regulating mood, circadian physiology, and sleep, little is known about the synaptic organization and activity-dependent plasticity of ipRGC connections. Dr. Speer is investigating the molecular and structural mechanisms regulating the formation and function of a visual system pathway that drives circadian rhythms in the mammalian brain; it is called the retinohypothalamic tract (RHT). He will use a platform that can also be used to study molecular changes in circuit-specific synapse development and plasticity in animal models of various human brain diseases.

Basic Research

Louisa Steinberg, M.D., Ph.D., Columbia University, will conduct functional quantification of auditory responses with functional magnetic resonance imaging (fMRI) and measurement of cortical GABA levels by magnetic resonance spectroscopy (MRS) to determine whether these measures in a group of patients with major depressive disorder can predict treatment response to SSRI antidepressants. The team will recruit 20 participants with major depressive disorder currently in a major depressive episode who are unmedicated. They will undergo two MRI sessions, at baseline while medication-free and after 6–8 weeks of medication treatment.

Diagnostic Tools/Early Intervention

Adele Stewart, Ph.D., Florida Atlantic University, notes the need for genetic models that demonstrate a functional impact of sexual difference in the dopamine (DA) system relating to neurodevelopmental disease susceptibility. Such models would inform efforts to identify penetrant genetic changes in DA signaling that drive risk for ADHD, and generate improved animal models of the disorder. She will work with a model based on the DAT Val559 mutation to gain a more complete picture of how it influences presynaptic DA neurotransmission in distinct dopaminergic circuits of male and female mice and probe the corresponding impact on behavior.

Basic Research

Benjamin Suarez-Jimenez, Ph.D., Columbia University/ Research Foundation for Mental Hygiene, Inc. / NYSPI, is interested in the hypothesis that PTSD is mediated by dysfunctional discrimination and reward processing, involving the hippocampus, nucleus accumbens, amygdala, and prefrontal cortex. This research will investigate brain activity differences between patients with PTSD (n=30; half with major depressive disorder), and trauma-exposed controls (n=30). fMRI and a VR paradigm will be used to clarify the neural mechanisms underlying reward learning and discrimination processing across PTSD, and whether it differs from PTSD-major depressive disorder. The work can shed light on the specific role of brain areas needed for discrimination learning within an environment, thus informing the development of diagnostics and treatments for PTSD and other psychopathologies.

Basic Research

Karuna Subramaniam, Ph.D., Gladstone Institutes/ University of California, San Francisco, notes that patients with schizophrenia suffer from severe cognitive impairments such as impaired reality-monitoring. Reality-monitoring is the ability to distinguish internally self-generated information from outside reality. This project will test the assumption that the medial prefrontal cortex (mPFC) is central in both mood and reality monitoring; if so, then modifying its activity with non-invasive brain stimulation method TMS could reveal the mechanisms through which TMS targeting of the mPFC may causally impact mood and higher-order cognition, both in controls and in schizophrenia patients.

Next-Generation Therapies

Anne Takesian, Ph.D., Harvard Medical School, notes that while ASD is characterized by deficits of communication and social interaction, surprisingly little is known about the neurobiological underpinnings of the auditory sensory symptoms of the disorder. Dysregulation of neural circuits within the auditory cortex may be particularly disruptive in ASD, as these circuits provide the foundation for language and social learning. Alterations within these cortical circuits may also underlie the auditory perceptual hypersensitivity often seen in ASD. This research aims to harness the brain's inherent plasticity mechanisms to promote recovery of pathological auditory cortical circuits. The goal is to find ways of activating a subset of interneurons within layer 1 (L1) of the auditory cortex, which past work has identified as hubs of

plasticity that promote the re-wiring of connections.

Basic Research

Next-Generation Therapies

Sunny Tang, M.D., University of Pennsylvania, proposes that in order to target interventions in schizophrenia and related psychotic disorders early in the course of illness, particularly during the prodromal phase, we need a sensitive and efficient way of tracking disease-related changes in the brain. Suggesting that language provides an optimal avenue for tracking psychosis, the team will use automated linguistic analyses in young people with psychosis symptoms to measure language features including fluency (speech rate), complexity (proportion of unique words), prosody (changes in tone during speech), semantic coherence (how sequencing of words conform to expected patterns), and acoustic accommodation (how speech between conversation partners become more similar over time). They will test whether these features meaningfully reflect clinical symptoms, cognition, and functioning, and whether they help predict how psychosis symptoms change over time. The linguistic features will also be compared with observable psychosis-related changes on magnetic resonance imaging (MRI).

Diagnostic Tools/Early Intervention

Ashwini Tiwari, Ph.D., McMaster University, Canada, notes that past studies have shown disruptions in functioning across the major neuroendocrine stress system, the hypothalamic pituitary adrenal (HPA) axis, as well as the sympathetic nervous system (SNS), and parasympathetic nervous system (PNS) among child populations exposed to early trauma. This project focuses on related physiological or psychophysiological outcomes among youth victims of child sexual abuse enrolled in trauma services, with an eye to their utility in predicting how youth victims progress through treatment. The aim is to examine effects of treatment on HPA axis and psychophysiological markers for SNS and PNS functioning. The team will also explore whether regulation differs by gender, and between youth responders and non-responders to trauma treatment. Assessments will be made at three time-points: prior to treatment, following treatment, and at a 3-month follow up.

Diagnostic Tools/Early Intervention

Jorien Treur, Ph.D., University of Amsterdam, Netherlands, wants to better understand the relation between schizophrenia and cardiovascular disease, specifically the causes of increased rates of death in patients that are due to heart disease. This project will test several theories. First, by analyzing data from a large cohort study of ~167,000 participants who are followed up longitudinally and who have completed extensive questionnaires on their mental health, medication use; and by applying Mendelian randomization (MR) to test the causal nature of associations between liability to schizophrenia and cardiovascular disease risk. MR uses one or more genetic variants that are robustly predictive of a certain risk variable (for instance, schizophrenia) as an instrument, or proxy, to test causal effects on a certain outcome variable (for instance, cardiovascular disease).

Basic Research

Chelsea Vadnie, Ph.D., University of Pittsburgh, will address whether circadian disturbances are simply co-occurring symptoms or are involved in the etiology of depression and anxiety. Animal studies suggest they have a causal role in mood and anxiety disorders, but the underlying mechanisms are unclear. Her team has uncovered a role for the suprachiasmatic nucleus (SCN), the pacemaker in the brain, in the regulation of depressive and anxiety-like behavior. This project seeks to determine whether SCN neural activity rhythms regulate psychiatric-related behaviors, though use of optogenetics to manipulate SCN firing. This will allow determination of the specific impact of the SCN on mood, cognitive, and anxiety-related behaviors. It could help determine the feasibility of treatment strategies that target the SCN or clocks in other brain regions.

Basic Research

Matilde Vaghi, Ph.D., University of London/University College London, UK, observes that little is known about the role of mood in regulating successful behavior. The goal of this project is to determine whether abnormal mood responses to positive and negative outcomes in depression explain deficits in adapting to environmental changes. She will use a combination of computational modeling, online- and smartphone-based data collection, and longitudinal resting-state functional magnetic resonance imaging (fMRI) brain scans in adolescents with clinical and subclinical depression. She will test the hypothesis that abnormal mood responses precede changes in both functional brain connectivity and depressive symptoms.

Basic Research

Leandro Valiengo, M.D., Ph.D., Universidade de São Paulo, Brazil, will perform a randomized, controlled, double-blind clinical trial to evaluate the efficacy of theta-burst rTMS in the treatment of major depressive disorder in the elderly. A sample of 108 subjects will be randomly assigned to receive either a TBS treatment (called TBS group) or a placebo treatment (called sham group). The hope is that TBS stimulation in patients 60 and over will prove to be a safe, well-tolerated and effective intervention for the treatment of major depression and become a therapeutic option, particu-

larly useful for patients with poor response or contraindications to the use of antidepressants.

Next-Generation Therapies

Stefon van Noordt, Ph.D., McGill University, Canada, asks: are there distinct patterns of brain activity during infancy that reliably predict future autism outcomes? He proposes that the dynamics of the brain in early infancy can serve this function. The team will integrate data collected in the three largest autism cohorts in the world, resulting in over 1400 EEGs (electroencephalograms) from more than 400 infants. This EEG repository includes infants who are at low risk or high familial risk because an older sibling has received an autism diagnosis. The team will apply techniques that capture subtle dynamic patterns in brain activity, resulting in profiles, detectable as early as 3 months. These suggest that very early EEG markers reflect altered functional brain states that map onto diagnostic outcomes, a supposition that will be tested in this project.

Diagnostic Tools/Early Intervention

Alessandra Vergallito, Ph.D., University of Milano Bicocca, Italy, seeks to combine two fields apparently independent, neuroscience and clinical psychology, in order to increase the effectiveness of a short psychotherapeutic intervention. She will test an integrated approach which combines the noninvasive brain stimulation called transcranial direct current stimulation (tDCS) with an evidence-based psychotherapeutic intervention called metacognitive therapy (MCT). Patients will be invited to take part in an experimental protocol treatment; symptomatology will be tested at four different times to evaluate the effectiveness of the integrated treatment. She will start with a representative project focused on patients with major depressive disorder, the clinical sample in which both MCT and tDCS have proven to be effective. The protocol, however, could be experimentally extended to other disorders such as anxiety and craving.

Next-Generation Therapies

Thomas Vierbuchen, Ph.D., Memorial Sloan-Kettering Cancer Center, will use stem cell technology to study neuronal pathologies related to neurodevelopmental (e.g. intellectual disability, autism) and psychiatric (e.g. schizophrenia, bipolar disorder) conditions. These experiments are designed to characterize the function of a gene, called Arid1b, which is among the most frequently mutated in children with intellectual disability/autism. Arid1b is a component of a specific molecular machine called the BAF complex, which is involved in the process of turning specific genes on and off in cells throughout the body. Preliminary research suggests the BAF complex is especially important for regulating a specific subset of genes that are activated by signals from the environment.

Basic Research

Lu Wang, Ph.D., University of California San Diego, will create human brain organoids, generated from patients with mutations in a gene called ACTL6B, to understand its role in neurodevelopment and the pathogenesis of ASD. The lab has already clinically characterized 253 families having at least one child diagnosed with ASD, in six of which, variants in ACTL6B encoding BAF53b were associated with ASD. The working hypothesis is that functional loss of ACTL6B leads to a dysfunction of activity-dependent chromatin accessibility during brain development, causing altered expression of ASD-related and/or dendrite-genesis related genes, ultimately perturbing cellular fate.

Basic Research

Allison Waters, Ph.D., Icahn School of Medicine at Mount Sinai, notes that advances in white matter imaging have provided maps of the brain whose great detail help explain the difficulty of precision-targeting a treatment like deep brain stimulation (DBS), a method that involves surgically implanting electrodes deep within specific brain areas such as a large and complex white matter fiber bundle called the anterior limb of the internal capsule (ALIC), a promising target for DBS to treat OCD. This project seeks to develop a patient-level, electrophysiological read-out of the cortical response to DBS at specific white matter targets within the ALIC. The probe is to be validated on the level of individuals, which could allow for individualized DBS "tuning."

Next-Generation Therapies

Yi-Lan Weng, Ph.D., Houston Methodist Research Institute, seeks to advance our understanding of epitranscriptomic regulation in the brain as it may inform neurodevelopmental disorders such as ASD. This layer of regulation refers to the complete set of chemical changes that impact the transcriptome, which is the total set of "messages" generated by activated genes. Dr. Weng's goal is to understand how DDX3X and m6A residues engage neuronal mRNAs and whether this modulates synaptic function. The team's main approach will be to utilize cutting-edge human induced pluripotent stem cell models to focus on defining the roles of m6A-DDX3X signaling axis on neuronal function.

Basic Research

Corinde Wiers, Ph.D., National Institute on Alcohol Abuse & Alcoholism, NIH, explains that a ketogenic diet (KD; high in fat and low in carbohydrates) increases ketone bodies including acetoacetate, acetone and beta-hydroxybutyrate (BHB) in plasma and brain (i.e., a state of metabolic ketosis). KD has been proposed as a therapeutic intervention for psychiatric disorders, including mood disorders and epilepsy. In rat models of alcohol dependence, a KD has been shown to improve withdrawal symptoms during alcohol detoxification,

and reduce alcohol intake. This project is a pilot intervention study with a one-dose ketone ester (KE), a nutritional supplement, and a randomized two-way crossover design in non-treatment-seeking heavy drinkers with alcohol use disorder to explore this possible therapeutic avenue.

Next-Generation Therapies

Leena Williams, Ph.D., University Hospital of Geneva, Switzerland, hopes to gain an understanding of neuronal network function and plasticity in the somatosensory cortex (S1) of a mouse model for ASD. Dr. Williams will explore the hypothesis that GABAergic dysfunction may translate into altered synaptic plasticity, a phenomenon that strongly depends on GABAergic interneuron function. The excitatory synapse scaffolding protein SHANK3 has been implicated in some forms of autism, and some autistic symptoms are reproduced in animal models carrying a homozygous mutation for SHANK3. Such a mouse model will be used in this project, to reveal how ASD-implicated SHANK3 downregulation alters underlying GABAergic-dependent LTP mechanisms in S1.

Basic Research

Ross Williamson, Ph.D., University of Pittsburgh, will conduct experiments addressing questions about the flow of information from the auditory cortex to the striatum, to provide a better understanding of the neural mechanisms underlying auditory deficits in schizophrenia. The striatum receives long-range input from two main cell-types in the primary auditory cortex: intratelencephalic (ITN) and sub-cerebral (SCN). This research will test how known biomarkers of behavioral state can modulate distinct corticostriatal cell-types; and describe how distinct populations of corticostriatal cell-types contribute to goal-directed auditory behavior.

Basic Research

Jon Willie, M.D, Ph.D., Emory University/Emory University Hospital, notes functional imaging results suggesting that amygdala hyper-reactivity predicts development and maintenance of PTSD symptoms and treatment non-response. In a collaboration between one of the largest epilepsy surgery programs in the country and an established PTSD research group at Emory University Hospital, Dr. Willie aims to characterize neurophysiological responses in the human amygdala and hippocampus during a fear acquisition and extinction task in patients with PTSD, and to test for the first time whether direct electrical stimulation (DES) of the amygdala can enhance fear extinction in PTSD.

Next-Generation Therapies

Zachary Wills, Ph.D., University of Pittsburgh, has developed means to simultaneously image the enzyme GTPase and calcium sensors in developing neurons, offering a means of characterizing the function of GTPase regulators and calcium modulators. This technological advance enabled his team to uncover a novel function for the GTPase RhoA in dendrites of pyramidal neurons. This project will use this sensor imaging-based approach to characterize the function of three GTPase activators, guanine nucleotide exchange factors (GEFs) Kalirin 7, 9 and Trio, whose encoding genes are linked by GWAS studies to schizophrenia. The ultimate aims are to uncover cellular origins of schizophrenia and identify potentially novel pharmacological targets to reverse disease pathology.

New Technologies

Christian Wozny, M.D., Ph.D., University of Strathclyde, Scotland, UK, is studying an overlooked part of the hippocampal formation called the subiculum (SUB). Patients suffering from depression show a significant reduction in the volume of the SUB. Dr. Wozny and colleagues will address the SUB as a potential target for intervention in depression. They hypothesize that the connections of the SUB to downstream brain regions are altered in depression and that strengthening and restoring these connections might alleviate symptoms. This will be explored in animal models of depression.

Basic Research

Matthew Wright, M.D., Ph.D., Stanford University, notes that the dorsal raphe nucleus (DRN), the main source of forebrain-projecting serotonin neurons, is thought to be a central node in coordinating coping responses to stress, based on multiple lines of basic and clinical evidence. However, the cell types which drive coping responses within the DRN, a complex and heterogeneous nucleus containing many neural subtypes, remain to be elucidated. Dr. Wright plans to dissect the causal roles of DRN glutamatergic, serotonergic, and GABAergic neurons in driving active coping responses as well as the local and long-range circuit architecture arising from the DRN which modulates coping responses.

Basic Research

Yao Wu, Ph.D., Children's National Medical Center/Children's Research Institute, is studying the impact of pregnancy-related stress on maternal and child health outcomes. Dr. Wu's pilot studies in pregnant women with a fetal diagnosis of coronary heart disease (CHD) suggest an alarmingly high prevalence (>60%) of prenatal psychological distress. Survivors of CHD experience long-term learning and social-behavioral difficulties despite successful neonatal cardiac repair. Evidence suggests neurobehavioral dysfunction in CHD may begin in the fetal period. Dr. Wu's team has pioneered advanced non-invasive fetal magnetic resonance

imaging (MRI) techniques to study in utero brain development. In this pilot study the team aims to examine the impact of a prenatal cognitive behavioral therapy intervention on psychological distress reduction in pregnant women carrying fetuses with a diagnosis of CHD; and to examine the impact of this intervention on brain growth in CHD fetuses using advanced 3D volumetric MRI.

Next-Generation Therapies

New Technologies

Yuanzhong Xu, Ph.D., University of Texas Health Science Center at Houston, who is studying eating disorders, takes a lead from recent studies which have suggested that a common neural pathway in the brain regulates feeding and anxiety disorders: the paraventricular nucleus of hypothalamus (PVH), a brain region important in homeostatic regulation, including feeding and physiological adaptions for survival; and the lateral septum (LS), implicated in relevant psychiatric disorders, including anxiety disorders and stress. This project, in an animal model, tests the hypothesis that the glutamate-releasing PVHMC4R-LSv neurocircuit is a novel shared neural pathway for controlling feeding and anxiety-related emotional states.

Basic Research

Jingqi Yan, Ph.D., Albert Einstein College of Medicine, notes that during the critical period of brain development, sensory stimuli induce remodeling of cortical synapses by eliminating some synapses while strengthening others. Deficits of sensory-dependent synaptic remodeling are thought to underlie the delayed maturation of synapses, hypersensitivity to sensory stimuli in adulthood, seizure, and deficits in social behaviors associated with autism, schizophrenia, and other neuropsychiatric disorders. Dr. Yan wants to understand how sensory input induces synaptic remodeling. This project will test whether autophagy—the process in which cells eliminate dysfunctional components—is involved in sensory experience-dependent synapse remodeling; and examine whether impaired autophagy is causally related to hypersensitivity to sensory stimuli and social deficits in mice that model Fragile X syndrome, a genetic disorder with some similarities to autism spectrum disorder.

Basic Research

Kun Yang, Ph.D., Johns Hopkins University School of Medicine, will test the hypothesis that treatment resistance (TR) in psychotic disorders is associated with epigenetic mechanisms and that a genome-wide epigenetic study using neurons from TR patients in comparison with those from non-TR patients and healthy controls may be an effective approach to address this question. Taking advantage of the Johns Hopkins Schizophrenia Center (JHSZC)'s longitudinal cohort of recent-onset psychosis patients (ROP), the team will study how epigenetic signatures identified via whole-genome analysis of olfactory neuronal cells sampled from TR patients correlate with clinical manifestations of psychosis. This will be the first step toward identifying biomarkers to quantitatively assess treatment-resistant psychosis.

Basic Research

Hideaki Yano, Ph.D., National Institute on Drug Abuse, NIH, is focusing on synthetic cannabinoids (sCBs) which have emerged as a major problem leading to a high occurrence of emergency room visits, particularly among young people. sCBs are categorically different from phytocannibinoids like cannabis and cause an array of undesired symptoms rarely triggered by cannabis, including hallucinations, disorientation, hypothermia, catalepsy, coma, and even death. Some of the adverse effects observed in patients resemble serotonin (5-HT)-mediated effects. This project will address the 5-HT1A receptor (5-HT1AR) interaction in particular since hypothermia and catalepsy are the hallmarks of 5-HT1AR-mediated effects. Dr. Yano will also evaluate structurally discrete sCBs for canonical and non-canonical receptor targets in vitro and for commonly reported physiological effects (i.e., cardiovascular and hallucinogenic activities) in vivo.

Basic Research

Zeynep Yilmaz, Ph.D., University of North Carolina at Chapel Hill, is focusing on the intersection of anorexia nervosa, an eating disorder, and obsessive-compulsive symptoms. Recent research has uncovered eight genetic risk variants for anorexia nervosa. Converging lines of evidence suggest that anorexia nervosa patients with high levels of obsessive-compulsive symptoms and perfectionism could be a clinically distinct group, and the goal of this study is to examine the genetic architecture of obsessive-compulsive and perfectionism symptom dimensions in patients with anorexia nervosa to determine whether these symptoms also form a biologically distinct subgroup within anorexia nervosa. Dr. Yilmaz will leveraging existing genetic data from the Psychiatric Genomics Consortium Eating Disorders Working Group (~17,000 patients with anorexia nervosa and ~56,000 controls), and a separate dataset comprising 1,374 anorexia nervosa patients.

Basic Research

Jun Yokose, Ph.D., University of Texas Southwestern Medical Center at Dallas, is interested in observational learning, the ability to learn through observing others' experience. Previous human studies suggest that individuals with ASD have difficulty in processing the information between specific actions performed by the self and observing the matching actions performed by others. This project tests the hypothesis

that a dysfunction of neuronal representations may result in an impairment of cognitive observational learning in ASD individuals. Dr. Yokose seeks to identify neuronal populations active during both self-grooming and observational grooming in control and ASD model mice, and to artificially activate implicated cells in the hope of rescuing the behavioral impairment in ASD mice.

Basic Research

Sangjin Yoo, Ph.D., California Institute of Technology, is testing technology for noninvasive control of neural circuits using ultrasound and sonogenetics. Ultrasonic neuromodulation (UNM) has the potential to provide non-invasive control of neural activity in deep-brain regions with millimeter spatial precision. This project seeks to understand its mechanism of action in the brain. Dr. Yoo seeks to optimize ultrasound stimulation parameters and introduce sonogenetic receptors to sensitize specific neuronal populations to ultrasound. The notion of sonogenetic receptors follows from the hypothesis that sensitivity to ultrasound may be substantially enhanced by genetically modifying neuronal receptors. This hope in this work is to provide key guidelines for human applications.

New Technologies

Katherine Young, Ph.D., King's College London, UK, is studying a new treatment for anhedonia—the loss of interest in the pursuit of pleasure and reward, a prime symptom of depression and schizophrenia—that aims to "upregulate" aspects of the brain's reward systems, including how people anticipate and experience positive events. In adolescence, these reward systems are still maturing, offering an optimal period to intervene and generate long-lasting effects. This project aims to explore whether one component of this novel treatment for anhedonia changes how the brain reacts to rewards. Dr. Young will use fMRI to examine whether savoring of a positive stimulus enhances activation and connectivity in brain reward circuitry. She will also investigate whether anhedonia symptoms in adolescence impact the ability to alter brain reactivity to reward using savoring, and how this relates to future symptoms of depression, anxiety and psychosis.

Next-Generation Therapies

Sanghee Yun, Ph. D., University of Pennsylvania/ Children's Hospital of Philadelphia, has found that found stimulation of a neural circuit called Ent-DG, connecting the entorhinal cortex (Ent) and the hippocampal dentate gyrus (DG)—is antidepressive in both male and female mice, normalizing avoidance behavior and neophobia. Dr. Yun's team will address knowledge gaps about this novel circuit stimulation-induced improvement in cognitive and negative valence systems. They will test the theory that chronic, but not acute, Ent-DG circuit stimulation modulates the synaptic connectivity between Ent inputs and their postsynaptic outputs (new neurons vs. mature DG granule cells). The overall aim is to learn how to promote antidepressive effects and to avoid counterproductive hippocampal circuitry "recalibaration."

Basic Research

Xian Zhang, Ph.D., Cold Spring Harbor Laboratory, aims to elucidate neural circuit mechanisms underlying the processing of negative feedback and reward information, and determine how these circuits are disrupted in depression. The focus is on the basolateral amygdala (BLA), which plays an essential role in regulating behaviors driven by aversive and rewarding stimuli. A major aim is to overcome the challenge in studying the BLA, which contains functionally heterogeneous populations of neurons, each of which may differentially contribute to behavior or disease conditions. Dr. Zhang will concentrate on two distinct populations of BLAFezf2 neurons, one activated by appetitive stimuli and the other by aversive stimuli. The hypothesis is that an imbalance between the two contributes to the generation of depressive states.

Basic Research

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