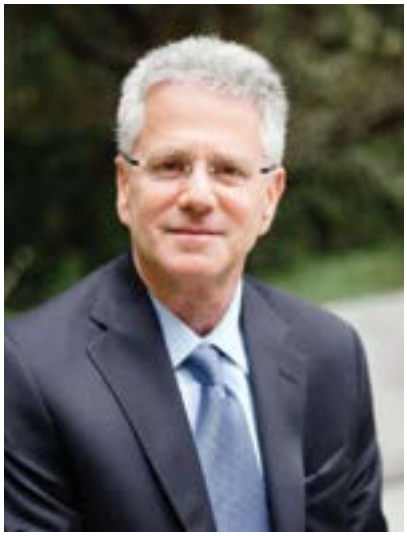
BRAIN & BEHAVIOR RESEARCH FOUNDATION

2020 Young Investigators

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



"BBRF Young Investigators represent a new generation of researchers who will pioneer breakthroughs in mental health research. These grants enable outstanding scientists to pursue bold new ideas to answer important questions or help identify potentially game-changing targets for treatment. The awards function as seed funding for new directions which would otherwise be highly unlikely."

September 2020

We are pleased to present to you the 2020 Brain & Behavior Research Foundation Young Investigator Grantees. This extraordinary group of scientists represents 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 181 world-renowned scientists with expertise in every area of brain research, reviewed more than 1,000 applications and selected the 150 meritorious research projects summarized in the pages that follow.

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.

From BBRF's earliest days, the Scientific Council has sought to support "the best science possible" in selecting Young Investigator grant projects. This year is no different. Many of the new projects focus on brain biology underlying a range of psychiatric disorders—for example, imbalances between excitation and inhibition in the brain; or brain circuitry that is engaged when we form memories, including fear memories when we are exposed to threats or trauma. A number of grantees are exploring tiny changes in the way the vast human genome is densely packaged in the nucleus of each cell—changes that can alter the expression of genes thought to contribute to illnesses such as schizophrenia and autism.

Several projects seek to grasp how immune cells in the brain called glia and microglia, as well as microbes living in the human gut, may be contributing to vulnerability to mental illnesses, notably depression and stress-related disorders.

Other 2020 grantees are trying to understand the mystery behind gender differences in susceptibility to depression and anxiety disorders, as well as ADHD and autism. Three projects are using machine learning and other analytical methods in an effort to coax hidden clues about illness risk from masses of data encoded in electronic health records. Several grantees want to know more about how cannabis use during pregnancy affects biology impacting the child's mental health: in the placenta, and in young people who were exposed during gestation. These are just a few of the many exciting new projects that our grantees will be working on.

We are proud to report that since 1987 we have provided more than $418 million in research grants to more than 5,000 scientists globally.

BBRF is a collaboration between our donors and scientists. A grant awarded to a Young Investigator not only funds an innovative research project, but is also 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 support we can continue to fund scientists on the path to discovery for better treatments, cures, and methods of prevention for psychiatric illness so that more people can live full, happy, and productive lives.

Sincerely,

Jeffrey Borenstein, M.D.
President & CEO

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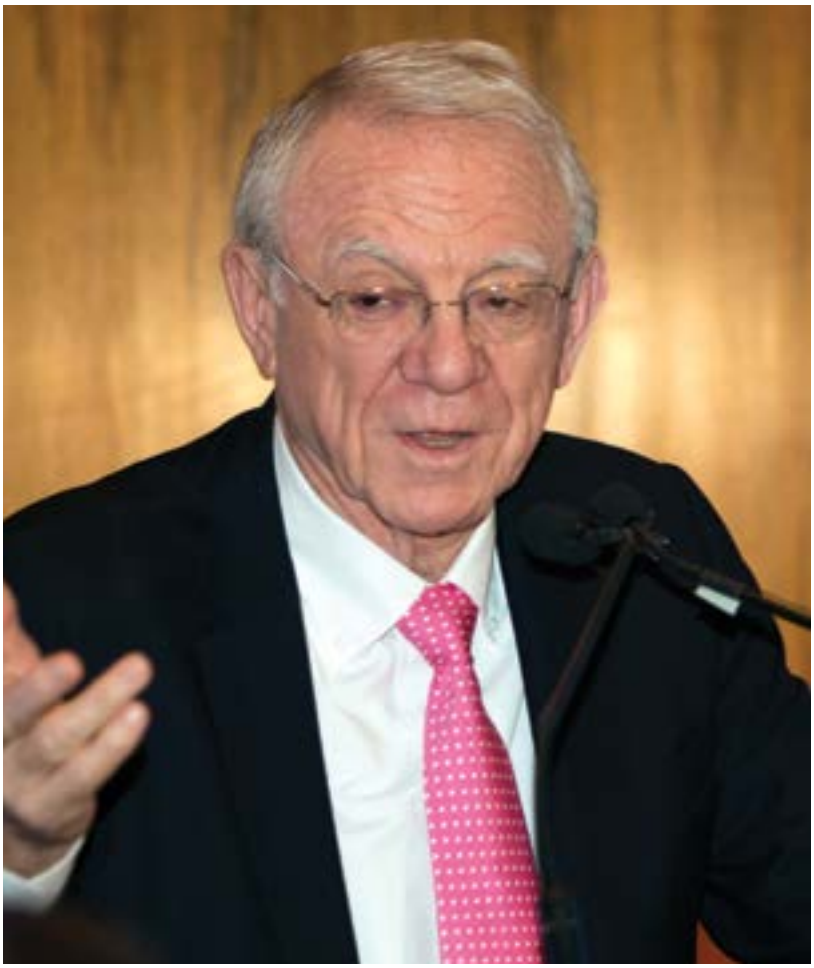

"BBRF Young Investigator Grants have led to groundbreaking and important new research that has improved the lives of people living with mental illness, through enhanced treatments and therapies, and a better understanding of the causes of mental illness. These early-career scientists are making great strides in basic research, new technologies, next-generation therapies and early intervention techniques. This is the kind of out-of-the-box research that will offer the best hope for change."

Herbert Pardes, M.D.

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SINCE 1987

AWARDED
6,000+
GRANTS

FUNDED
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GRANTS

THE 2020 YOUNG INVESTIGATOR GRANTEES

The Foundation is pleased to announce over $10.3 million in 150 new two-year grant awards to support the work of promising young scientists with innovative ideas in mental health research.

1,012
YOUNG INVESTIGATOR APPLICATIONS

150
YOUNG INVESTIGATOR GRANTS AWARDED

$10.3
MILLION AWARDED IN YOUNG INVESTIGATOR GRANTS

RESEARCH CATEGORIES

Basic Research (121 Grants)
To understand what happens in the brain to cause mental illness

Next-Generation Therapies (18 Grants)
To reduce symptoms of mental illness and ultimately cure and prevent brain and behavior disorders

Diagnostic Tools/Early Intervention (8 Grants)
To recognize early signs of mental illness and treat as early as possible

New Technologies (3 Grants)
To advance or create new ways of studying and understanding the brain

About 81 percent of the projects funded are **basic research**, the wellspring of innovation in brain research, as in all sciences.

About 12 percent of the 2020 grants fund projects that specifically aim to develop **next-generation therapies.**

About 5 percent of the projects funded are **diagnostic tools/early intervention** that aim to prevent brain and behavior disorders.

About 2 percent of projects fund the development of **new technologies** that will power both basic research and new developments in the clinic.

About 71 percent of grantees are from the United States (107 grantees). Twenty-nine percent of grantees come from 16 other countries: Canada, Australia, the Netherlands, France, the UK, Germany, Israel, Brazil, Sweden, Norway, Belgium, Denmark, Portugal, Switzerland, Uganda, and China.

INVENTORY OF PROJECTS: 2020 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

Encephalitis

Epilepsy

Parkinson's Disease

THE 2020 BBRF YOUNG INVESTIGATOR GRANTEES
(in alphabetical order)

Gulcan Akgul, Ph.D., Physiology and Neurobiology Department/University of Connecticut, will use the gene-editing tool CRISPR to engineer a line of mice that model specific non-inherited genetic variants associated with schizophrenia that have been seen in postmortem brains. The aim is to study if and how they alter connectivity and function of circuitry in the prefrontal cortex. The study could serve as a bridge between postmortem genetic investigations on patient tissue and fMRI studies in live individuals and offer specific neuronal circuits as the targets for therapeutic interventions.
Basic Research

Matthew Albaugh, Ph.D., University of Vermont, seeks to characterize presumed ties between internalizing psychopathology and age-related brain changes, using longitudinal data from the Adolescent Brain Cognitive Development (ABCD) study. The ABCD study of 11,872 youths is an ongoing NIH project that aims to track adolescent neurodevelopment. Internalizing problems during childhood and adolescence predict an array of mood and anxiety disorders in adulthood. Dr. Albaugh proposes that developmental trajectories of internalizing psychopathology may be linked, in part, to the maturation of neural circuitry involving portions of the prefrontal cortex, limbic structures such as the amygdalae, and fiber pathways serving to connect these brain areas.
Basic Research

Christoph Anacker, Ph.D., Columbia University Medical Center, is exploring the role of the ventral dentate gyrus as a mediator of the effects of early-life stress, which is a major risk factor for depression, anxiety, and other mood disorders. Ventral dentate gyrus hyperactivity precedes the development of behavioral abnormalities in adulthood, making it a potentially promising target for early intervention. Dr. Anacker will use hM4Di, a DREADD (Designer Receptor Exclusively Activated by Designer Drug), to functionally inhibit the ventral dentate gyrus in adolescent mice that experienced early life stress, to see if inhibition can protect against development of behavioral impairments later in life. He will also investigate the role of serotonin 1A receptors in the dentate gyrus as potential targets to inhibit hippocampal hyperactivity.
Basic Research

Paul Anastasiades, Ph.D., University of Bristol, UK, notes that cerebellar damage is a strong predictor of developing autism symptoms, particularly if damage occurs during early development. He will test the hypothesis that cellular abnormalities in the cerebellum propagate to the prefrontal cortex (PFC), disturbing prefrontal network formation. He will try to uncover, in mice, when and how PFC circuits are impacted during development. Understanding the influence of the cerebellum over disparate brain regions is important for uncovering the cause of ASD, and for its treatment: if localized deficits can drive global changes throughout the brain, then localized therapy might lead to brain-wide rescue. He will address this by identifying periods of heightened prefrontal plasticity, which may indicate periods of maximal therapeutic benefit.
Basic Research

John Anderson, Ph.D., University of Toronto/Centre for Addiction and Mental Health, Canada, is interested in treatment-resistant, late-life depression, which escalates the risk for significant cognitive decline by as much as 33%. This project studies the possible impact of cognitive reserve (CR)—lifestyle factors such as exercise, education, challenging jobs, and language learning which may extend the amount of time a person can cope with Alzheimer's-related degeneration. Does having higher CR allow people with resistant late-life depression to recover faster or avert conversion to cognitive decline? He will assess the impact of CR on cognitive ability and memory in older adults with resistant depression across time through the course of novel drug treatments.
Next-Generation Therapies

Madeline Andrews, Ph.D., Gladstone Institutes/University of California, San Francisco, studies outer radial glial (oRG) cells, which develop into many different types of neurons of the mature brain. oRG cells turn on genes that regulate the signaling of a protein called mTOR. Mutations in genes that regulate mTOR signaling occur in several disorders, including autism. Using living 3D cultures of brain cells called organoids, she seeks to determine if mTOR signaling is needed for oRG formation by blocking mTOR signaling and will assess whether an increase in mTOR signaling is sufficient to increase oRG numbers. She will then explore how changes in mTOR signaling affect the way oRG cells divide, whether it shifts their identity to other stem cell types, or whether there is an increase the number of neurons indicating inappropriate maturation of these cells.
Basic Research

Yuen Siang Ang, Ph.D., Harvard University/McLean Hospital, is studying neural mechanisms underlying anhedonia in major depressive disorder (MDD)—the often debilitating loss of interest in seeking pleasure. Dr. Ang is espe-

cially interested in dysregulation of motivation to exert cognitive (as opposed to physical) effort for rewards. Dr. Ang will collect fMRI imaging data from 40 healthy individuals and 40 MDD patients while they perform a task. The expectation is that parts of the brain called the vmPFC and VS will process cognitive effort valuation and that MDD patients will exhibit reduced activation in these regions compared to controls. The study, if successful, could lead to greater diagnostic precision in classifying anhedonia and contribute to the development of personalized treatment for patients with anhedonia.

Basic Research

Diagnostic Tools/Early Intervention

Melody Atkins, Ph.D., INSERM, France, studies a small, dynamic structure called the primary cilium (PC) that extends like an antenna from the cell surface and is required during brain development for accurate migration of inhibitory cortical interneurons (cINs) to the cortex. There is evidence that there are a reduced number of inhibitory GABAergic cortical interneurons in patients with schizophrenia and autism. Her team will study signaling pathways involved in cellular and molecular mechanisms by which PC could regulate cIN migration. This could shed new light on the physiopathology of psychiatric disorders such as autism and schizophrenia.

Basic Research

Pragathi Priyadharsini Balasubramani, Ph.D., University of California, San Diego, seeks to develop a next-generation rTMS brain stimulation protocol for depression. Dr. Balasubramani will use electroencephalographic brain recordings (EEG), measured during active cognitive states, to identify dysfunctional brain circuits in a subject-specific manner; measure the efficacy of stimulation in driving plasticity in brain circuits; and develop and test a targeted, phase-locked rTMS stimulation protocol based on these measurements. The work is based on the hypothesis that treatment efficacy will improve if it is more finely calibrated with specific cognitive states that occur in depression.

Next-Generation Therapies

Sonia Bansal, Ph.D., University of Maryland/Maryland Psychiatric Research Center, studies the abnormal perceptions, skewed conception of reality and array of emotional and cognitive impairments involved in schizophrenia that give rise to "agency-related symptoms": the patient's inability to correctly attribute their own thoughts, internal speech, or covert or overt actions to themselves. This project seeks to develop detailed information on the contribution of disruptions in a neural mechanism called corollary discharge to psychosis symptoms. Utilizing a behavioral assessment, in combination with evaluations of positive psychotic symptoms and electrophysiology across two sensory modalities, Dr. Bansal hopes to verify that corollary discharge disruptions are associated with the quantified abnormalities in agency-related symptoms.

Basic Research

Renata Batista-Brito, Ph.D., Albert Einstein College of Medicine, hopes to add to knowledge about how different types of inhibitory neurons contribute to behavioral and cognitive dysfunction in schizophrenia. The focus will be on determining the roles of SST/nNOS inhibitory cells in regulating brain network activity and cognition. These cells, which project over long distances and whose function is not well understood, have been found to be mis-localized in schizophrenia patients. Using a mouse model, she will ask how SST/nNOS cells impact brain activity and cognitive functions known to be disrupted in schizophrenia, part of a broad effort to study the role of inhibition in generating patterns of cortical activity and influencing the processing of sensory information in patients.

Basic Research

Laura Berner, Ph.D., Icahn School of Medicine at Mount Sinai, is studying deficits in cognitive control processes and alterations in the circuits that support those processes, which are thought to occur in the eating disorder bulimia nervosa (BN). She works from the hypothesis that cognitive control deficits depend in part on effort-cost computations—decisions about whether exerting control is worth the costly cognitive effort. She will try to assess such computations in BN to determine if episodic oscillations in control are related to binge eating and purging. Her team will compare responses of the "hunger hormone" ghrelin in 25 women with BN to those of 25 group-matched controls during a cognitive effort-discounting paradigm at two time points: after a 16-hour fast and again after a standardized meal. They hope the data will inform an explanatory model of BN that, for the first time, links altered gut-brain signals to cognitive control dysfunction.

Basic Research

Aaron Bornstein, Ph.D., University of California, Irvine, is interested in the phenomenon of relapse in substance abuse, having listened carefully to patients obsessed with "chasing the first high." He proposes that memories of early drug experiences—"episodic memories"—end up driving the decision to seek drugs, even after years of sobriety. Even after treatment, the memories remain. The project seeks to demonstrate that much of the individual differences in decisions can be explained by individual differences in the content of memories. A shift toward understanding addiction as a disorder of memory would dramatically expand the range of treatment

options available, and reduce the suffering of many thousands of people every year.

Basic Research

Vincent Breton-Provencher, Ph.D., Massachusetts Institute of Technology, seeks to better understand the neurobiology associated with attentional processes to enable better diagnostic accuracy and targeted treatments for ADHD and disruptive behavior. He will study noradrenaline (NA) dynamics in the locus coeruleus (LC) region, specifically LC-motor and LC-prefrontal cortex pathways, and their involvement in sustained attention and cognitive flexibility. The pathways will be observed via optogenetics and electrophysiology in NA neurons in mice trained on an attention-demanding task. This and other experiments will seek to determine how NA activity affects cortical computations in neurons during attention. This could help us better understand of the heterogeneity of ADHD dysfunctions.

Basic Research

Melissa Caras, Ph.D., University of Maryland, is focusing on perceptual learning, through which individuals can improve their ability to detect or discriminate sensory stimuli. It is critical for the acquisition of many complex behaviors, including speech and language, and is disrupted in individuals with autism spectrum disorder (ASD). Dr. Caras proposes that dopamine is a key mediator of the sensory cortical plasticity that underlies perceptual learning, and that abnormalities in dopamine transmission disrupt these plasticity mechanisms, impair perceptual learning, and give rise to the communication deficits observed in ASD. Through a variety of experiments in mice, she hopes to shed light on mechanisms underlying communication deficits in ASD.

Basic Research

Robin Cash, Ph.D., University of Melbourne, Australia, seeks ways to make repetitive transcranial magnetic stimulation (rTMS) more effective in depression patients who do not respond to current protocols. Dr. Cash notes research indicating that treatment outcome is associated with brain connectivity between the precise treatment site (in the dorsolateral prefrontal cortex, or DLPFC) and deeper limbic structures. She will use a novel targeting methodology to compare clinical outcomes from conventional targeting methodology and individually optimized connectivity-guided targeting. The team will also develop a fully integrated software tool (OptiStiM) which they would make freely available to enable routine application of their rTMS personalization methodology in the clinic.

Next-Generation Therapies

Flurin Cathomas, M.D., Icahn School of Medicine at Mount Sinai, notes evidence that psychosocial stress leads to profound changes in the immune system that can directly induce depression-relevant behaviors. The focus in this project is possible weakness in the blood-brain barrier (BBB): investigation of interactions between peripheral leukocytes and neurovasculature to better understand the etio-pathology of BBB disruption and stress-induced depression-relevant behavioral changes. The project is translational, involving mice and humans. It proposes a novel mechanism linking peripheral immune system dysfunction and central nervous system pathologies relevant to depression that could potentially serve as a novel therapeutic target.

Basic Research

Suheyla Cetin Karayumak, Ph.D., Harvard University/Brigham and Women's Hospital, notes that prenatal cannabis exposure, which has been linked with psychosis risk in adolescents, has been shown to negatively affect white matter microstructure related to a variety of cognitive functions, specifically working memory and attention networks. The team will study white matter in working memory and attention networks in large groups of adolescents who were prenatally exposed to cannabis, leveraging the NIH's ABCD clinical trial database of over 11,000 adolescents, with includes nearly 1,000 prenatally exposed youth. They will use machine learning to determine which white matter tracts and dMRI measures in these adolescents are predictive of potential risk for developing psychosis.

Basic Research

Yuan-Hsin Chao, Ph.D., University of Minnesota Duluth School of Medicine, focuses on the cerebellum, whose functions are associated with downstream neuronal circuits via the ventrolateral nucleus of thalamus (VL) and ventral tegmental area (VTA). These regions communicate with multiple parts of the cortex, which participate in multiple brain functions. It remains unclear that cerebellum-VL and cerebellum-VTA circuits generally or specifically influence sensorimotor, cognitive, emotional and social behaviors. This project proposes that understanding neurobiological mechanisms in cerebellum-connected circuits, *in vivo* using mouse subjects, could help uncover the cerebellum's role in a range of neuropsychiatric disorders, such as schizophrenia, depression, and autism spectrum disorder.

Basic Research

Ren-Chao Chen, Ph.D., Boston Children's Hospital, wants to learn more about an epigenetic factor called Setd1a, the gene for which is mutated in a subpopulation of schizophrenia patients. Setd1a can regulate gene expression by marking transcriptionally active chromatin regions of the genome. This

project seeks to clarify its role in postnatal brain development and function. Having made a mouse model of the mutation, Dr. Chen now intends to identify the cell population in the striatum that is involved in Setd1a mutation-related behavior phenotypes; and identify changes in the transcriptome and epigenome of striatal medium spiny neurons caused by Setd1a heterozygosity, which may reveal potential targets responsible for behavioral phenotypes in schizophrenia. This in turn could reveal novel molecular and cellular targets for future therapies.

Basic Research

Ritchie Chen, Ph.D., Stanford University, focuses on activity imbalance in the brain, which contributes to social deficits and other cognitive comorbidities. To address it, Dr. Chen hopes to employ optogenetics in living mice, aiming to overcome longstanding hurdles that have prevented the method from being translated to humans. The work involves developing viral targeting strategies to restrict expression of newly discovered red-shifted channel rhodopsins to therapeutically-relevant serotonin neurons in the dorsal raphe nucleus, followed by light delivery for transcranial optogenetic stimulation of these targets in mice. Noninvasive modulation of social circuits using beams of light would present new opportunities for the treatment of ASD and might be extended to manage other brain and behavioral disorders.

Next-Generation Therapies

Xi Chen, Ph.D., Harvard University/McLean Hospital, will extend past work suggesting that the relationship between neurotransmitter concentrations in the brain's default-mode network and activities of various functional networks breaks down in first-episode psychosis patients. Participants with first-episode psychosis will now receive fMRI/MRS scans, 4 years following a set of initial scans, to monitor how neurotransmitter concentrations, brain functions, as well as their relationships, change as the illness progresses and medications take effect. By generating new insights into abnormal brain neurotransmitter function and network activities, the project provides a potential path to novel treatment strategies and earlier interventions for psychosis.

Basic Research

Karmel Choi, Ph.D., Harvard University/Massachusetts General Hospital, wants to improve our ability to identify complex psychiatric conditions like PTSD from electronic health record (EHR) data. This would allow researchers to study predictors and consequences of the illness at scale. This project leverages 20 years of longitudinal EHR data in over 5 million individuals, to develop an EHR-based algorithm for PTSD using a state-of-the-art phenotyping approach that combines both structured (e.g., billing code) and unstructured (e.g., clinical note) data to ascertain PTSD cases, validating the algorithm against gold-standard clinician labels. The team also seeks to genetically validate their PTSD algorithm and to validate known health comorbidities and identify potentially novel associations for genomic and epidemiological follow-up.

Diagnostic Tools/Early Intervention

Coco Chu, Ph.D., Weill Cornell Medical College, notes that alterations in gut microbes can affect neurogenesis, myelination, and blood-brain barrier function, and can modulate social behavior, stress responsiveness, learning, and memory. Dr. Chu will test the hypothesis that microbial metabolites, through signaling mediated via the aryl hydrocarbon receptor (AHR), directly act on neurons and microglia to influence fear extinction learning behavior. The project will directly address these questions: What are the effects of microbiota-derived metabolites on neurons and microglia? Is AHR a cellular sensor of microbiota-derived metabolites within the CNS? The hope is to provide a road map for further exploration of intestinal microbiota and microbial metabolites as potential therapeutic targets for human neuropsychiatric disorders.

Basic Research

Hong-yuan Chu, Ph.D., Van Andel Research Institute, notes research indicating that dysfunction of the amygdala, a brain region showing particular vulnerability to α-synuclein pathology, underlies psychiatric symptoms such as anxiety and depression in Parkinson's disease (PD). This project seeks to define how pathology in α-synuclein—abundant in the brain and present in synapses—alters amygdala function at the cellular and neural-circuit levels. Such knowledge could help in the design of better treatments for the psychiatric symptoms in PD and other α-synucleinopathies.

Basic Research

Brian Corbett, Ph.D., University of Pennsylvania/Children's Hospital of Philadelphia, is using a social-defeat mouse model to identify novel neural substrates underlying stress vulnerability/resilience. This project builds upon past work showing that in the medial prefrontal cortex (mPFC), resilient rats express higher levels of sphingosine-1-phosphate receptor 3 (S1PR3), which regulates inflammation in peripheral tissue and neuron excitability in the brain. In resilient rats, S1PR3 expression is increased by glucocorticoid receptors (GRs), which regulate gene expression in response to stress. This project seeks to show that inhibiting the locus coeruleus-mPFC circuit will prevent stress-induced mPFC inflammation and network dysfunction and that these effects will be exacerbated in genetically modified mice.

Basic Research

Ana Covelo, Ph.D., INSERM, France, seeks to define the contribution of astrocytic CB1 receptors to synaptic plasticity in the nucleus accumbens (NAc) and their impact in amphetamine-induced behavior. This may help determine 1) whether astrocytes in the NAc express functional CB1; 2) how astrocytic CB1 regulates synaptic transmission and plasticity in the NAc; 3) how astrocytic CB1 impacts amphetamine-induced behavior; and 4) how astrocytic mtCB1 influences astrocyte activity, synaptic plasticity in the NAc, and behavior. Results will shed light on the involvement of astrocytes in reward through the endocannabinoid system, and could reveal astrocytes as potential targets for treatment of motivational disorders.

Basic Research

Giordano de Guglielmo, Ph.D., University of California, San Diego, aims to add to knowledge of the neuronal ensembles that are responsible for excessive opioid intake—information that would allow identification of neuronal circuits that causally contribute to opioid dependence. Following upon preliminary data showing that withdrawal from oxycodone self-administration in dependent rats leads to the activation of a neuronal ensemble in the central nucleus of the amygdala, this project seeks to characterize the role of this specific neuronal ensemble—activated during withdrawal—in the central nucleus of the amygdala.

Basic Research

Arthur de Jong, Ph.D., Utrecht University, the Netherlands, has developed novel gene editing technology to directly study ion channels with high-resolution single molecule fluorescence microscopy. This facilitates study of ion-channel distribution and nanodomain co-clustering in neurons with unprecedented precision. He has observed that dendritic spines, small neuronal protruberances that receive neuronal signals, have highly variable levels of calcium and potassium channels. This suggests that the presence of these channels is regulated locally within small subcellular structures, which would allow for precise tuning of excitability. This project seeks to investigate the applicability of these insights to autism, in experiments that may help explain how disturbances in the subcellular organization of ion channels lead to excitability defects in ASD.

Basic Research

Cesar de la Fuente, Ph.D., University of Pennsylvania, is studying neuropeptide Substance P (SP), a neurokinin, which has been implicated in the development of neuroinflammatory aspects of Parkinson's disease. He seeks knowledge about the process of activation of neurokinin receptors (NK) at the atomic scale. This is a novel comparative computational study of tachykinin receptors bound to natural and synthetic ligands, in the context of realistic cell membranes. The team's computational approach could reveal how structural changes in the receptor and neuropeptides interfere with their interactions. This detailed model will be used as a basis to design drugs that could provide improved therapeutic outcomes for Parkinson's disease.

Basic Research

Masoumeh Dehghani, Ph.D., Douglas Mental Health University Institute, Canada, will investigate alterations in cerebral metabolites and glucose metabolism as the result of mitochondrial dysfunction in individuals with bipolar disorder (BD) in the euthymic state. It is hypothesized that 1) individuals with BD will exhibit altered cerebral levels of glutamate, as well as altered TCA cycle and neurotransmitter flux rates; and that 2) the degree of altered glutamate levels will be associated with the degree of metabolic deficits, and with clinical severity. The study will recruit 15 type I bipolar patients in a euthymic state and 15 matched healthy control subjects. Results could lead to a better understanding of BD etiology and progression, and inform development of new therapeutic interventions.

Basic Research

Jessica Dennis, Ph.D., University of British Columbia, Canada, will use advanced statistical methods to test whether previously identified ASD and ADHD genetic risk factors affect genes in the placenta. She will also test how sex differences in the placenta relate to the higher rate of ASD and ADHD diagnoses in males compared to females. Few studies on the genetics of mental health have focused on the placenta, or on how it may relate to differences in ASD and ADHD symptoms in males compared to females. Findings could help us better understand the biology that connects genetic risk factors, the prenatal environment, and ASD and ADHD, an essential step toward bringing genetic discoveries closer to the clinic.

Basic Research

Lauren DePoy, Ph.D., University of Pittsburgh, will use a translational model of drug taking (intravenous self-administration in mice) to measure cocaine intake, motivation, and relapse-like behavior following environmental or genetic adolescent circadian disruption. Manipulating the light/dark cycle (environment) or core circadian "clock" genes (genetics) separately will allow identification of potential mechanisms: specifically, which brain regions might underlie the effects of adolescent circadian disruption upon reward. This will be the first study to use large-scale sequencing in brain tissue to understand how developmentally disrupted circadian rhythms enhance substance-use vulnerability later in life. These studies may lead to early identification of vulnerable populations, as well as novel drug targets.

Basic Research

Giannina Descalzi, Ph.D., University of Guelph, Canada, notes that while chronic pain is known to be associated with plasticity of neurons within the brain, new evidence indicates that other cell types, including glial cells, are also involved in these changes. This work builds on findings indicating that chronic pain increases astrocyte activity within the brain, including regions associated with anxiety and depression. Astrocytes are activated by numerous inflammatory cytokines that are increased in chronic pain states. Dr. Descalzi will test the hypothesis that astrocyte-neuronal lactate shuttling is critically involved in chronic pain, and is necessary for the development of comorbid anxiety and depression.

Basic Research

Pengfei Dong, Ph.D., Icahn School of Medicine at Mount Sinai, notes that little is known about how the physical conformation of chromatin—the way the genome is packaged—affects genetic variance and its impact in genome regions that have been identified as altered in schizophrenia. To learn more about how the packaging of DNA affects risk, the team will analyze whole genome sequencing (WGS), *in situ* Hi-C, cell-type-specific RNA-Seq and ATAC-Seq data in 50 schizophrenia and 50 control samples. Among other experiments, they will perform differential chromatin conformation analysis where altered chromatin structure reshapes the regulatory landscape and affects associated gene expression. They also seek to link regulatory elements and genetic variants with specific transcripts.

Basic Research

Jennifer Dwyer, M.D., Ph.D., Yale University, aims to develop connectome predictors of rapid antidepressant response in adolescents with treatment-resistant depression. (Nearly a third of adolescents with major depressive disorder fail to obtain relief from first-line treatments.) The team will employ novel connectome-based predictive modeling (CPM), developed to identify and validate predictive models of symptoms and behaviors based on functional connectivity data. They hope to identify pre-treatment connectome phenotypes, or "fingerprints," that predict rapid antidepressant responses to ketamine or to a control treatment. The aim is to validate the method for use in clinical trials, and ultimately to translate predictive neuroimaging into personalized psychiatric medicine.

Diagnostic Tools/Early Intervention

Christian Ebbesen, Ph.D., New York University School of Medicine, proposes that during healthy social interactions, oxytocin neurons in the hypothalamic paraventricular nucleus release oxytocin, modulating inhibitory transmission in sensory cortical areas to "decorate" incoming sensory signals with the appropriate "social significance." Thus oxytocin is therapeutically promising for many conditions in which there is abnormal processing of social stimuli. This project will ask: what drives the activity of oxytocin neurons, moment-to-moment, during naturalistic social interactions? (2) can we affect behavior during social interaction by modulating the oxytocin neuron activity optogenetically? Dr. Ebbesen will explore answers using a novel behavioral tracking system that combines 3D videography, deep learning, and physical modeling to track socially interacting mice during naturalistic interactions.

Basic Research

Juliet Edgcomb, M.D., Ph.D., University of California, Los Angeles, will apply machine-learning classification algorithms to an electronic health record (EHR) "training set" of 400 children and adolescents, to identify children and adolescents presenting with suicidal thoughts and behaviors. The aim is to identify the predictive variables best defining each pertinent phenotype and produce a predicted probability of each suicide-related phenotype for each child. The algorithm's performance will be evaluated by application to a separate validation set (N=200) and comparison to gold-standard clinician categorization. The hope is to develop a set of rules for clearly identifying children and adolescents with suicide-related presentations from within noisy and complex EHR data.

Diagnostic Tools/Early Intervention

Neir Eshel, M.D., Ph.D., Stanford University, has developed a "frustration paradigm" in mice, teaching them to exert effort for reward, and then thwarting them before they reach it. After omission of an expected reward, the mice tend to attack other mice. Dr. Eshel will now record from and manipulate the brains of these mice as they perform this task, seeking out the neural signature of frustration. The contribution of dopamine and serotonin will be scrutinized. Dopamine previously has been considered pro-aggressive and serotonin anti-aggressive, but no studies have actually recorded from dopamine or serotonin neurons during aggression. This project will fill that gap, tracking second-by-second how these neurons behave as mice respond to unexpected events.

Basic Research

Manoela Fogaça Ph.D., Yale University, will evaluate a novel hypothesis about how rapid-acting antidepressants result in long term behavioral changes, seeking to identify the contribution of GABAergic cellular and synaptic mechanisms underlying their rapid and sustained mechanisms. The hypothesis to be tested is that synaptic plasticity of glutamatergic inputs onto GABA neurons is responsible for restoring excitatory/inhibitory balance and maintaining the sustained antidepressant effects of rapid-acting agents. Dr. Fogaça will use cell type-selective methods to determine, among other objectives, whether cortical α5-GABAARs in

specific subpopulations of neurons contribute to sustained antidepressant effects and to synaptic changes induced by the medications ketamine and scopolamine.
Next-Generation Therapies

Daniel Fuerth, Ph.D., Cold Spring Harbor Laboratory, is exploring how long-term symbolic information transfer is achieved in face of the molecular turnover at the synapse. This project will apply a sequencing tool Dr. Fuerth has developed to an assay for investigating transfer of circular RNAs (circRNAs) across the synapse using the Drosophila Neuromuscular Junction (NMJ). One question to be answered is whether circRNAs are transferred from motor neurons across the synapse to muscle cells. Once specific circRNAs have been identified he will examine their functional role by using cell type-specific targeting of Cas13 enzymes to nick the splicing junction only present in the circular version of the transcript in either donor or acceptor cells.
Basic Research

Atsushi Fujimoto, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, is studying "the near-miss effect," in the context of gambling disorder (GD). This effect is thought to promote gambling in both healthy individuals and GD patients. This research aims to determine the neural basis of the near-miss effect at the brain-wide and single-cell levels. Dr. Fujimoto hopes to achieve this goal by developing a novel slot-machine task for macaque monkeys, and conduct fMRI and single-neuron recordings together with autonomic responses while monkeys experience near-misses. The hypothesis is that the anterior insular cortex and its functional connectivity to limbic areas plays a crucial role in the near-miss effect.
Basic Research

Janos Fuzik, Ph.D., Karolinska Institute, Sweden, notes that women have a two-fold higher risk of developing anxiety disorders and tend to develop more long-term and severe clinical symptoms. This project aims to understand the role of the hypothalamus, focusing on its communication with the lateral habenula, a brain region strongly affected by depression and chronic anxiety. The research aims to describe sex-specific changes in mice underlying the onset of chronic anxiety conditions, looking at the habenula-controlling hypothalamic neurons in both sexes. Discovery of sexual dimorphism in the organization and function of the hypothalamus-habenula circuit might reveal new molecular and cellular targets for developing new therapeutic strategies for the treatment of anxiety disorders.
Basic Research

Kirsten Gilbert, Ph.D., Washington University, St. Louis, will utilize data from an ongoing longitudinal study characterizing heightened performance monitoring and overcontrol (HPM/OC) in children. This phenomenon, related to an excessive need for control, is a risk factor in obsessive-compulsive disorder (OCD), social anxiety disorder (SAD) and anorexia nervosa (AN). Dr. Gilbert will examine the role of the parent, testing how neural markers of HPM/OC in parents and neural modeling in parents of HPM/OC (via parent-child neural synchronization) independently contribute to elevated psychiatric symptoms in children. The aim is to identify neural and behavioral characteristics that predict increased risk of child OCD, SAD and AN. This knowledge could help in developing interventions to lessen the severity, course and impairment of multiple child mental illnesses across the lifespan.
Basic Research

Fabiano Gomes, M.D., Ph.D., Queen's University, Australia, seeks to develop effective, safe, and affordable options targeting lifestyle and metabolic changes as a novel therapeutic approach to depression during menopause transition and midlife years in women. This project is a proof-of-principle study to investigate the efficacy and safety of a ketogenic diet (KD) for the management of depression in 30 women aged 45-55 years who are perimenopausal/early postmenopausal. KD is a high-fat, adequate-protein, low-carbohydrate diet that forces the body to use ketones from fat as the main energy source; preliminary evidence suggests it may help reduce depression symptoms.
Next-Generation Therapies

Andrea Gomez, Ph.D., University of California, Berkeley, seeks to understand how alternative RNA splicing—a naturally occurring mechanism that enables a single gene to encode multiple versions of a given protein—generates organizing signals that specify properties of the synaptic gaps across which neurons communicate. Dr. Gomez notes that synaptic dysfunction and aberrant splicing are causal factors in many neurological disorders, and she contends that deficits in our knowledge linking these mechanisms matches with our lack of clinical solutions for psychiatric conditions. She aims to learn how alternative RNA splicing programs specify synaptic properties and gain mechanistic insight into how these properties bias neuronal computation in health and in illness. The research is relevant to processes that may occur in autism, intellectual disability, and neurodegenerative disorders, among others.
Basic Research

Travis Goode, Ph.D., Harvard University/Massachusetts General Hospital, notes that human imaging work has revealed that abnormalities exist in how eating disorder patients process food-related cues, often at the level of the hippocampus, which is known to modulate feeding and food-seeking through its densely innervated subcortical target: the lateral septum (LS).

This project will test the theory that dorsal hippocampus-dorsal LS-lateral hypothalamus (LH) computations, mediated by a class of neurons called LS(PDYN+) neurons, critically govern food-associative memory. To do so, Dr. Goode will deploy *in vivo* calcium imaging and optogenetics in a food-location association task in mice to determine the contribution of a LS(PDYN+)-LH circuit in the contextual gating of feeding behavior.

Basic Research

Shulamite Green, Ph.D., University of California, Los Angeles, is studying sensory over-responsivity (SOR), an impairing condition marked by severe sensitivity to sensations such as scratchy clothing, loud noises, or stimulating environments. Dr. Green wants to develop treatments that could significantly improve quality of life for individuals with ASD, ADHD, anxiety, and schizophrenia. This study will examine the short-term effect of using the medication propranolol vs. placebo on behavioral, physiological, and neurobiological markers of SOR in 20 youth with ASD. The hope is that propranolol will reduce behavioral reactivity, physiological arousal, and amygdala over-activation in response to aversive sensory stimulation.

Next-Generation Therapies

Parthiv Haldipur, Ph.D., Seattle Children's Research Institute, seeks to determine the cellular and molecular characteristics of human cerebellar progenitor and neuronal subtypes implicated in autism. This project leverages Dr. Haldipur's cerebellar developmental expertise from model organisms and unique access to human cerebellar tissue. These studies could improve our view and understanding of the biology of both normal and abnormal cerebellar development, which could enable improved understanding and diagnosis of cerebellar defects. They should also provide new insight into brain evolution and human neurodevelopmental disorders.

Basic Research

Simone Haller, Ph.D., National Institute of Mental Health (NIH), suggests that the acute onset of the COVID-19 pandemic provides a rare opportunity to leverage clinical and neural data acquired before the pandemic to assess clinical and biological impacts once it is over. The focus is on young people, in whom the developing brain can be hypersensitive to stress. The study will involve youths aged 8–17 with anxiety- or irritability-related psychopathology (ADHD, disruptive mood dysregulation disorder, and anxiety disorders) and youths without psychopathology, who completed at least one pre-pandemic resting-state MRI scan (~N=230). A subset of these youth also completed a threat-processing fMRI task (~N=130). Dr. Haller will reassess participants using the same sequences and multiple clinical assessments over a 1-year period following the COVID-19 pandemic.

Basic Research

Henry Hallock, Ph.D., Johns Hopkins University/Lieber Institute for Brain Development, seeks to provide a thorough understanding at the systems and molecular levels of the neural circuitry underlying sustained attention and related behavior in the continuous performance tests (CPTs) commonly used to assess sustained attention in patients diagnosed with such disorders as schizophrenia, depression and ADHD. He will leverage genetic and circuit-specific tools to dissect the molecular and cellular underpinnings of sustained attention during a touchscreen-based rodent analog of the human CPT in mice. This research could provide potential avenues for anatomically and genetically localized therapeutic targeting in disorders featuring dysregulation of attention.

Basic Research

Oliver Harschnitz, M.D., Ph.D., Memorial Sloan-Kettering Cancer Center, notes that in a group of disorders collectively termed autoimmune encephalitis, cell-surface proteins are directly targeted by pathogenic autoantibodies, of which anti-NMDAR (N-methyl-D-aspartate receptor) antibodies are the most common. This can lead to long-term cognitive deficits and even death. His research seeks to determine what cell-nonautonomous signaling pathways drive the pathogenesis of NMDAR-encephalitis and generate long-term neurological deficits. A highly defined and controllable human stem cell-based disease model would offer a powerful tool for the neuroscience community which could lead to the discovery of new targeted treatment for autoimmune psychosis and encephalitis.

Basic Research

Keith Hengen, Ph.D., Washington University, St. Louis, is interested in how homeostatic mechanisms, which stabilize neural activity much like a thermostat stabilizes temperature, fail to rescue circuit dynamics in depression and anxiety. Chronic stress challenges circuits involved in mental well-being. In a subset of people, these circuits are incapable of mounting a sufficient compensatory response, resulting in depression and anxiety. This research seeks to understand how depression impacts the set-points governing neural networks in the ventral striatum, a key brain structure involved in affective regulation. Identifying the set-points that define healthy function and understanding how they are compromised in disease could present novel targets for intervention in depression and anxiety.

Basic Research

Jonathan Hess, Ph.D., State University of New York, Upstate Medical University, wants to know: What genes confer resilience to mental illness? Does genetic resilience transcend diagnostic boundaries? What phenotypes are to be expected among persons who possess genetic resilience? Dr. Hess will apply an

innovative statistical genomic method to identify resilience genes that moderate risk for schizophrenia and two related conditions that share genetic and clinical features—bipolar disorder and major depressive disorder. The team will use a new collection of genomic data from approximately 4,670 "resilient" control subjects and 20,424 risk-matched cases. This large sample will allow identification of new resilience genes and potentially uncover sex- and ancestry-related differences related to resilience.
Basic Research

James Heys, Ph.D., University of Utah School of Medicine, notes that fundamental cognitive processes such as learning and memory, inferring cause and effect, and decision-making, all depend critically upon the brain's ability to encode time. An intriguing possibility is that schizophrenia and perhaps other disorders result from disrupted temporal coordination and temporal processing within the brain. This project seeks to understand more about the neural basis for encoding time. Proceeding from previous work revealing that neurons in medial entorhinal cortex (MEC) can encode elapsed time, Dr. Heys will use various methods to uncover the circuit, cellular, and synaptic mechanisms that underlie temporal encoding that his team has observed in MEC.
Basic Research

Frankie Heyward, Ph.D., Harvard University/Beth Israel Deaconess Medical Center, notes the difficulty in studying the distinct cell populations implicated in depression. His interest is microglia, the brain's resident immune cells, which exhibit functional derangements during depression. It is thought that a breakdown in the ability of these cells to properly coordinate their gene expression may underlie their inappropriate level of activation in the illness. Dysregulation of the epigenetic processes that govern gene expression might also contribute to transcriptional dysfunction during depression, he suggests. This project uses a novel tool called ProCUT&RUN to isolate microglia in order to generate epigenomic profiles of microglia and microglia subtypes in human brain tissue, with an eye to their dysregulation in depression.
Basic Research

David Hildebrand, Ph.D., The Rockefeller University, is interested in social perception processes that contribute to social instability and mental illness. This is particularly apparent in the inability of many people with autism and schizophrenia to respond to facial expressions in others. By leveraging the marmoset monkey's smooth cortex, he developed an approach for imaging across populations of thousands of neurons while the monkey views different face and control stimuli. He is using this technique to determine how neuronal populations represent faces and to measure the putative connectivity between neurons by studying correlations in their activity. He aims to integrate this functional analysis of face areas with reconstruction of synaptic circuit structure using serial-section electron microscopy.
Basic Research

Ansel Hillmer, Ph.D., Yale University, notes that while stimulant medications effectively manage ADHD symptoms, their efficacy is diminished for improving long-term functional impairments. β2*-containing nicotinic acetylcholine receptors (nAChRs) in the brain are critically involved in working memory and executive function. These receptors have been proposed as targets for medications treating cognitive deficits in ADHD, but the relationship of β2*-nAChRs with cognitive impairments in ADHD remains unknown in humans. Dr. Hillmer seeks to close this knowledge gap by using positron emission tomography (PET) imaging to determine the relationship of β2*-nAChR levels in adults with ADHD with cognitive function.
Basic Research

Gil Hoftman, M.D., Ph.D., University of California, Los Angeles, will investigate the impact of cannabis use on novel neuroimaging indices (Morphometric Similarity Networks) in human subjects at clinical high risk for psychosis who subsequently converted to psychosis (n=62); those who did not convert during follow-up (n=491); and matched healthy controls (n=224). The aim is to arrive at a better understanding of the mechanisms by which cannabis use may increase risk for psychosis. The hypothesis is that cannabis use affects cortical morphometry measures on MRI and impacts the spatial relationship between MRI measures and endocannabinoid-, glutamate- and GABA-related transcripts in cortical regions affected in schizophrenia.
Basic Research

Sarah Hopp, Ph.D., University of Texas Health Science Center at San Antonio, is interested in mutations in the gene CACNA1C for the calcium channel Cav1.2, which have been associated with the development of several brain disorders, including schizophrenia, depression, bipolar disorder, and autism. Once inside the cell, calcium controls several different cell functions. It is important to control when and how much calcium enters cells. In this project, Dr. Hopp and team will remove Cav1.2 from microglia and examine how this changes their response to inflammatory stimuli that are risk factors for the development of neuropsychiatric illnesses. They ultimately hope to examine the role of microglia Cav1.2 in numerous brain disorders, in view of the fact that microglia function is disturbed in many brain disorders in which Cav1.2 mutations have been noted.
Basic Research

Helen Hou, Ph.D., Columbia University, studies the production of facial expressions, which is impaired in children with autism spectrum disorders (ASD), in which facial expressions are atypical in appearance, as well as in usage and timing during social interactions. She seeks to learn more about how emotions orchestrate the production of facial expressions, and how the process goes awry in neurodevelopmental disorders. This project will use mouse genetic tools to measure and perturb activity of select neuron and muscle groups, as well as quantitative behavioral analyses to establish a research program to study the control of facial expression using the laboratory mouse as a model. It will combine anatomical tracing and *in vivo* electrophysiology to dissect candidate pathways by which emotion commands coordinate facial muscle movement, among other objectives.

Basic Research

Wei-Hsiang Huang, Ph.D., McGill University Health Center Research Institute, Canada, notes that an increasing number of neuropsychiatric disorders, including autism spectrum disorders and schizophrenia, are caused by mosaic genetic mutations. Mosaic mutations only affect a small portion of cells in the brain but often cause symptoms just as severe as germline genetic mutations. This suggests that mutant cells affect the development and function of surrounding healthy cells. This project seeks to develop a working mouse model of how mosaic mutations have a brain-wide effect, focusing on the cerebellum, a brain area perturbed by genetic mutations linked with ASD.

Basic Research

Kathryn Humphreys, Ph.D., Vanderbilt University, will leverage an existing longitudinal dataset of pregnant women and their newborn offspring to examine the data collected from 125 women assessed during pregnancy who completed interviews to assess their exposure to stress. The aim is to study, at the dawn of life, the BNST (bed nucleus of the stria terminalis), a tiny brain region positioned within the threat network with direct projections to the hypothalamus and which drives the hypothalamic-pituitary-adrenal (HPA) axis response to stress. The team will collect additional information regarding infant affect and temperament, a well-established risk factor for anxiety disorders, at age 6 months. They hypothesize that BNST volume and connectivity mediate the associations between prenatal stress exposure and infant temperament.

Basic Research

Min Jee Jang, Ph.D., California Institute of Technology, aims to develop a new high-throughput method for *in situ* screening of genetic variant pools in the intact brain and use it to build expanded genetic toolkits for cell-type targeted gene delivery to the brain. In preliminary studies, Dr. Jang has developed an ultrasensitive sequential fluorescence *in situ* hybridization (useqFISH) method which produces a highly sensitive RNA signal, allowing for multiple rounds of hybridization, and enabling discrimination of a few genetic variants that share the same sequence but have a short-mutated region. This method allowed for detection of 10 variants, co-delivered to one animal, in the intact brain. The current project aims to improve useqFISH for larger pools and utilize it to attain the transduction profiling of recombinant adeno-associated virus (rAAV) pools in the intact brain. These would constitute new means to examine diverse genetic variants, including viral capsids, gene regulatory elements, or guide RNA sequences for CRISPR, in a high-throughput manner.

New Technologies

Jing Jiang, Ph.D., Stanford University, focuses on high negative-affect symptoms, which commonly co-occur across mood and anxiety disorders such as major depressive disorder, general anxiety disorder and PTSD. This project addresses the necessity of probing 1) the causal circuit map relevant for impairments in emotional and cognitive functions in patients with significant negative-affect symptoms and 2) how trauma exposure impacts pathways in the causal circuit map. Using data collected from ~200 individuals with four types of symptoms, Dr. Jiang hopes to provide the first comprehensive prefrontal causal connectivity map in healthy individuals, individuals with high negative-affect symptoms, and individuals with trauma exposure, laying a foundation for development of novel and precise neuromodulatory interventions.

Basic Research

Emma Johnson, Ph.D., Washington University, St. Louis, will use data being collected in an ongoing NIH-funded study of pregnant mothers who are using or not using marijuana during pregnancy (total anticipated N=400; 250 with neuroimaging; 50% prenatal users) to obtain placental tissue from mothers who regularly used marijuana during their pregnancy (n=40) and mothers who have a lifetime history of marijuana use, but did not use during their pregnancy (n=40). These data will be combined with ongoing data collection assessing adverse birth outcomes, newborn and infant cognitive and emotional development, as well as brain structure and resting state functional connectivity assessed using magnetic resonance imaging. The aim is to learn more about the impact of prenatal cannabis exposure on placental epigenetics—an important mechanism through which genes are regulated.

Basic Research

Anne Marije Kaag, Ph.D., Vrije Universiteit Amsterdam, the Netherlands, notes that while the prevalence of alcohol use disorder (AUD) is 2-3 times higher among men than women, this gap is quickly closing. Nonetheless, she says,

women are structurally ignored in AUD research, impeding the development of much-needed sex-tailored interventions. This project follows upon evidence that guanfacine lowers stress-induced arousal and craving, while improving cognitive control in women but not men with a substance-use disorder. To probe sex-dependent effects of the medication guanfacine, this project will use pharmacological magnetic resonance imaging (phMR) in which (task-related) brain activation in response to a novel drug is compared to response to a placebo.
Basic Research

Bashkim Kadriu, M.D., National Institute of Mental Health (NIH), aims at identifying the neurobiological mechanisms of two medications (ketamine and psilocybin) that show rapid, robust and sustained antidepressant efficacy. The goal is to investigate whether ketamine and psilocybin share a common downstream mechanism of enhanced neuroplasticity at the level of glutamatergic and GABAergic synapses. This mechanism is likely to be an important component of the enhanced antidepressant effects of these drugs in patients with treatment-resistant depression. Uncovering the mechanism could lead to the development of safer therapeutics with an improved side-effect profile.
Next-Generation Therapies

Allan Kalungi, Ph.D., Makerere University, Uganda, notes that findings from genetic studies undertaken in populations of predominant European ancestry may not be generalizable to non-European populations including those of African ancestry. He also notes that undertaking genetic studies on samples of African ancestry may unlock new understandings of the genetic architecture of major depressive disorder (MDD), since African genomes contain the highest genetic diversity due to the continent's longer population history. This project therefore aims to investigate the genetic risk associated with MDD among ethnically diverse samples of African ancestry from Eastern and Southern Africa (Uganda, Kenya, Ethiopia and South Africa) (N = 17,000).
Basic Research

Jonathan Kao, Ph.D., University of California, Los Angeles, is interested in a brainstem region, the dorsal periaqueductal grey (dPAG), which is implicated in panic attacks and exhibits different functional connectivity in PTSD patients. Understanding how cortical and brainstem areas, including dPAG, represent threat and anxiety is critical to developing therapeutic interventions for people with anxiety disorders. The goals of this research are to (1) understand the neural population dynamics in dPAG underlying threat and defensive behaviors, and (2) build an *in silico* recurrent circuit model of dPAG that predicts how interventions in dPAG activity affect threat level and defensive behaviors.
Basic Research

Florence Kermen, Ph.D., Norwegian University of Science and Technology, Norway, is interested in the inherent variability in individuals' ability to cope with stress. Because stress broadly affects regions that are highly distributed in the brain, it has been challenging to identify the key neural circuits that support resilience in humans and rodents. In addition, the molecular nature of the neurons remains elusive, which is hampering the search for new treatments. This research will use a small and transparent vertebrate, the zebrafish, in which the whole brain can rapidly be imaged at cellular resolution. Dr. Kermen will develop a model of chronic stress resilience in order to investigate the brain-wide neural adaptations taking place in resilient individuals.
Basic Research

Budhachandra Khundrakpam, Ph.D., Montreal Neurological Institute/McGill University, Canada, is interested in how substance use alters adolescent brain trajectories, and how these impact later health outcomes such as addiction and mental illnesses. This research aims to address the need for prospective, longitudinal assessment of adolescents' neuroimaging data, measures of substance use, and mental health to generate normative neurodevelopmental trajectories that can reveal the interactive relations between substance use, brain development and mental health outcome. To do so, the project will leverage the ongoing Adolescent Brain Cognitive Development (ABCD) study, which is collecting multimodal MRI, mental health measures, and substance use-module measures from 12,000 youth, as they transition into adolescence and young adulthood.
Basic Research

Juhyun Kim, Ph.D., Johns Hopkins University School of Medicine, notes that excitatory and inhibitory (E/I) imbalance followed by sensory processing abnormality in the cortex has been commonly observed in autism spectrum disorder (ASD). However, neither circuit mechanisms nor cell types responsible for the E/I imbalance in the disorder are clearly specified. This project focuses on layer 6b (L6b) neurons as a strong candidate for cortical inhibitory gain controller. Using optogenetics-based multiple whole-cell patch clamp recordings and *in vivo* axonal calcium imaging of deep-layer neurons, the project could provide a new conceptual understanding of dysregulated inhibition and sensory processing abnormality in ASD, by presenting L6b neurons as a key cortical gain controller.
Basic Research

Erica Korb, Ph.D., University of Pennsylvania, works at the intersection of neuroscience and epigenetics with the overarching goal of understanding how the epigenome affects neuronal function. Epigenetics is one of the principal means by which expression of our genes is regulated, sometimes in

response to the environment. Epigenetic mechanisms are critical to neuronal function, the creation of new memories, and contribute to a wide range of neurological and mental health disorders. Dr. Korb's focus is on chromatin, the complex of DNA and proteins called histones which package our DNA into organized structures and control access to our genes. This project will examine changes in chromatin modifications during the encoding and reactivation of a fear memory in mice. It will facilitate mapping the chromatin landscape that underlies fear learning.

Basic Research

Hakan Kucukdereli, Ph.D., Beth Israel Deaconess Medical Center, will examine, in the interest of making an animal model, the circuit basis underlying key aspects of anorexia nervosa, particularly the learning and willful performance of actions that maintain caloric restriction. The project will use a paradigm combining behavior and optogenetics in mice to study voluntary seeking of a hunger state in a stressful environment. Combined with deep-brain neural imaging methods that the team developed, the research will test whether willful seeking or maintenance of a hunger states attenuates activity patterns of amygdala neurons that respond to aversive cues and that become active under stressful conditions. This work will help elucidate the circuit-level interplay between hunger and anxiety, and may guide potential approaches for the development of new treatments for this devastating disorder.

Basic Research

Sophie Laguesse, Ph.D., University of Liège, Belgium, will use a mouse model of adolescent alcohol binge drinking to unveil how alcohol interferes with prefrontal cortex (PFC) maturation and leads to long-lasting behavioral defects. By using a multidisciplinary approach, the project aims at uncovering how alcohol modulates local translation of mRNAs in the PFC during adolescence, as well as identifying the targeted synaptic proteins, analyzing their involvement in altered synaptic plasticity underlying alcohol-dependent behaviors. Dr. Laguesse also hopes to shed light on the differential sensibility to alcohol's effects between males and females as well as related differences in structural, physiological and behavioral consequences.

Basic Research

Amber Leaver, Ph.D., Northwestern University, notes that in transcranial direct current stimulation (tDCS), a form of non-invasive brain stimulation for depression, electrodes are placed on the head without referencing the patient's underlying brain anatomy, which varies from person to person. This project seeks to improve targeting using focal high-definition (HD) tDCS, with electrode positions determined using patterns of brain-network connectivity as measured with fMRI. Noting that antidepressant response to another form of stimulation, rTMS, is related to connectivity between the dorsolateral prefrontal cortex (DLPFC) and subgenual anterior cingulate cortex (sgACC), Dr. Leaver will target a region of left DLPFC that is most strongly connected with sgACC as determined by pre-treatment MRI.

Next-Generation Therapies

Chang Hoon Lee, Ph.D., University of Texas Southwestern Medical Center at Dallas, will use genome-wide neuroinformatic approaches to shed light on mechanisms driving sleep disturbance in autism spectrum disorder. Following his prior work showing that orphan C/D box small nucleolar RNA (snoRNA)-dependent alternative splicing in the brain is aberrantly activated in ASD, this work seeks to demonstrate that ASD-risk snoRNAs also underlie sleep disorder in ASD and are possible novel therapeutic targets. To do so, he will identify expressed snoRNAs and assess their circadian rhythmicity from small non-coding RNA-sequencing datasets, and then prepare neuronal cell lines for analysis with individual snoRNA deletions using CRISPR/Cas9 gene editing.

Basic Research

Andrew Lee, M.D., Ph.D., Gladstone Institutes/University of California, San Francisco, notes the anterior insular cortex is a critical node within a larger corticolimbic "anxiety network," which mediates various dimensions of anxiety. He will use intracranial electrophysiological mapping with high-density recordings to study insular networks in the context of anxiety-related cognitive tasks and multimodal emotional assessments. These studies will be conducted in patients with medication-refractory epilepsy implanted with intracranial electrodes for the clinical purpose of identifying their seizure foci and pre-surgical planning. The hope is to identify novel insular biomarkers of anxiety and definitively demonstrate a causal role for these circuits in generating symptoms of anxiety.

Basic Research

Douglas Leffa, M.D., Ph.D., Federal University of Rio Grande do Sul, Brazil, has used transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, in a pilot study to show its feasibility for the treatment of inattention in adult patients with ADHD. In this study, his team will perform an add-on study in the context on an ongoing randomized, double-blinded clinical trial under development since 2019, called TUNED. 64 patients will be included and a home-based tDCS device will be used to stimulate the right dorsolateral prefrontal cortex (DLPFC), a region involved in attention and known to be less active in patients with ADHD. Patients will be treated for 3 months, receiving daily stimulation of 30 minutes during the first 4 weeks, 2 weekly stimulations for the next 4 weeks, and weekly stimulation over the last 4 weeks.

Next-Generation Therapies

Jonathan Levy, Ph.D., Interdisciplinary Center, Herzliya, Israel, has been following a cohort of individuals exposed to war conditions near the Gaza Strip for the last 10 years, looking at how chronic adversity, psychopathology and parenting impacts neural development of the social brain. This project will examine the same sample of preadolescents studied in the prior wave, who are now adolescents. Each will receive a whole-head magnetoencephalography (MEG) scan to evaluate how exposure to continuous war impacts the ability to evoke empathy and emotion regulation, among other things. Prior work led to discovery of a major developmental shift in the neural empathy response during the transition from preadolescence to adolescence. This work seeks to determine if chronic adversity impedes this shift and if so, the specific neural and mental processes affected, while considering how psychopathology and caregiving combine to shape this developmental phase.

Basic Research

Yadong Li, Ph.D., University of North Carolina at Chapel Hill, studies the relation of chronic pain-induced depression and memory deficiency. The dorsal hippocampus is a well-known region informing and storing spatial memories, while the ventral hippocampus is a region where important alterations in depressive disorders occur. Previous work found that hippocampal dentate gyrus (DG) granule cells (GCs) receive anterior cingulate cortex (ACC) inputs. As a crucial region for chronic pain regulation, ACC excitatory pyramidal neurons are activated in chronic pain mice and patients, and this project, using mouse models, aims to determine if ACC–DG projection regulates chronic pain-induced depression and spatial memory deficiency.

Basic Research

Yun Li, Ph.D., SickKids Research Institute, Toronto, Canada, notes that the majority of human cortical neurons are generated by human-specific precursors called outer radial glia that are almost entirely absent in the developing mouse cortex. Dr. Li's team uses new technologies that enable research to be conducted on brain cells differentiated from pluripotent stem cells. They have generated a platform to study the human outer radial glia and their neuronal progeny, which are particularly expanded in the human cortex compared to other mammals. This project will systematically investigate the function of autism spectrum disorder risk genes in human stem cell-derived 2D neural cells and 3D brain organoids, paying particular attention to the 10% of ASD genes that are specifically enriched in the outer radial glia. They will investigate how disruptions of their functions alter normal neurodevelopment, and whether these changes are reversible.

Basic Research

New Technologies

Sweyta Lohani, Ph.D., Yale University, focuses on cholinergic signaling, a key regulator of perceptual, cognitive, and behavioral state-dependent cortical processing. Dr. Lohani will use a combination of viral-genetic and widefield imaging methods to dissect the relationship between impaired cortical cholinergic signaling and long-range network connectivity disruptions in a mouse model of schizophrenia. Using the ketamine model for schizophrenia, the project aims to identify disruptions in cholinergic signaling and widespread network activity in the cortex. The hypothesis is that acute ketamine-induced psychosis is characterized by increased basal cholinergic levels but decreased phasic cholinergic responses to state transitions across the cortex, resulting in the loss of cortical state dependence and in impairment of sensory processing.

Basic Research

Tierney Lorenz, Ph.D., University of Nebraska-Lincoln, notes that survivors of sexual trauma have significantly higher risk for premenstrual dysphoric disorder (PMDD) and other cycle-related mental health disturbances. PMDD is itself a serious mental health condition that can increase risk for other mood disorders such as depression and bipolar disorders. Following past work showing elevated inflammation among sexual trauma survivors, Dr. Lorenz proposes a new explanation: sexual trauma survivors may have larger changes in inflammation across the menstrual cycle, particularly if they are sexually active. In this project the team will measure pro-inflammatory cytokines, reproductive and stress hormones, mood symptoms, and sexual activity across the menstrual cycle in 40 women age 19+ who self-report cycle-related mood symptoms.

Basic Research

David Lydon, Ph.D., University of Pennsylvania, seeks a more complete understanding of smoking withdrawal, with the potential to inform smoking cessation treatment, by considering the neurobiological context of withdrawal. This project will collect resting-state fMRI data from daily smokers during 5 days of smoking satiety and 5 days of a smoking cessation attempt. Capturing multiple fMRI measures will serve to match the cadence of fMRI data collection to day-to-day dynamics in withdrawal symptoms observed in experience-sampling studies. With this dataset, he will quantify the extent to which differences in functional brain organization are due to differences across people, across days, and across levels of smoking satiety. Findings will provide important information about the time-varying nature of large-scale functional brain organization across periods of smoking abstinence and the need to account for these fluctuations in future studies.

Basic Research

Rajtarun Madangopal, Ph.D., National Institute on Drug Abuse (NIH), notes that preclinical models of drug relapse have typically focused on how rats respond to cues known as conditioned stimuli (CSs) that were present when they took drugs. A second type of cue, the discriminative stimulus (DS), can also influence relapse, signaling whether or not drugs are available. Dr. Madangopal has found that the infralimbic subregion (IL) of the medial prefrontal cortex is critical for DS-controlled drug-seeking. Understanding how persistent DS-drug memories are encoded and maintained in the IL could help identify new strategies for preventing relapse. To identify neurobiological substrates of persistent maladaptive DS-drug memories, he will use two techniques to isolate DS-memory ensemble neurons within the IL and identify molecular alterations within them with greater temporal specificity than previously possible.

Basic Research

Behrang Mahjani, Ph.D., Icahn School of Medicine at Mount Sinai, seeks to identify biomarkers that precede symptom onset, convey prognostic information, or indicate disorder subtypes in children with neurodevelopmental disorders. He aims to determine the role of prenatal maternal depression and anxiety on the risk of ASD, ADHD, and OCD in the offspring and differentiate genetically and environmentally driven transcription differences involved in ASD, ADHD, and OCD to assess their association with prenatal maternal depression, anxiety, and inflammation during pregnancy. His hypothesis is that pathway-based transcriptomic biomarkers are informative as a diagnostic ASD, ADHD, and OCD classifier. He will make use of data from Swedish national population registers and maternal survey and RNA-seq data from the BASIC study, a longitudinal cohort of 6478 Swedish pregnancies.

Basic Research

Diagnostic Tools/Early Intervention

Moritz Mall, Ph.D., German Cancer Research Center, Germany, is studying the mechanistic role of specific transcription factors in ASD. The focus in this work is neuron-specific transcription factor (TF) Myt1l, one of the top 25 genes associated with high confidence to ASD. It is one of three TFs that are able to directly reprogram fibroblasts into functional neurons. His prior research identified that protein Myt1l acts as a transcriptional repressor to induce and maintain neuronal identity by actively repressing several non-neuronal programs, such as muscle and liver genes. This project will combine cell-fate reprogramming and genetically engineered human stem cells to investigate the possibility that patient-specific Myt1l mutations could cause mental disorders by impairing neuronal identity and function.

Basic Research

James Marshel, Ph.D., Stanford University, aims to reveal, in the context of perception in psychosis, fundamental circuit mechanisms that underly normal and artificially triggered visual perception. This will provide a unique view of the mechanisms that may be involved in generating hallucinations in psychosis and schizophrenia. The project will entail developing novel approaches for recording and manipulating neural activity with single-cell resolution across multiple cortical areas using optical methods in mouse models. Specific groups of neurons will be probed for their roles in visual perception, even in the absence of visual input. In this way, artificial visual percepts will be "written into" the cortex at various visual processing stages to determine their relative impact on perception.

Basic Research

Pietro Giuseppe Mazzara, Ph.D., Columbia University, notes that generating diverse neuronal subtypes, particularly those with features related to key aspects of psychiatric disease, largely relies on trial and error. Dr. Mazzara aims to develop an unbiased screen for reprogramming methods to identify a diverse and perhaps comprehensive set of combinations of neuronal transcription factors (TFs) to generate neurons. Results will directly link transcription factor and microRNA reprogramming factors to specific aspects of neuronal identity, enabling discovery of a variety of new methods to produce different human-induced neuronal subtypes. Efforts will follow to generate neurons involved in schizophrenia, particularly GABA-B receptor-expressing neurons found in the HPA axis.

New Technologies

Robert McCutcheon, M.D., Ph.D., Institute of Psychiatry/King's College London, UK, notes the delicate balance between excitation and inhibition (E/I balance) in the brain, which gives rise to patterns of larger-scale brain activity, called functional networks, that can be observed using brain scans and are related to normal cognitive function. Postmortem and animal studies suggest that E/I balance is disrupted in schizophrenia and ASD. In this project he hopes to assess the molecular and genetic underpinnings of E/I balance by measuring functional networks in over 30,000 individuals who have received brain scans and had their DNA sequenced. He will examine if genes associated with E/I balance are similar to genes associated with schizophrenia and autism, and look at biological pathways these genes are involved in, as well as look at precisely how the medication riluzole affects E/I balance.

Basic Research

Zayra Millan, Ph.D., The University of New South Wales School of Psychology, Australia, studies how behavior is organized in relation to learning and memory processes in

addiction. This project examines behavioral transitions—from wanting to taking—that occur during presentations of cues that signal reward. What are the brain circuits that control the switch? Are these circuits changed by chronic alcohol use? If so, how? Answers could provide insight into how cue-elicited craving is translated into taking and why this craving may persist. The studies use a cue-guided reward-seeking task where the transition from wanting to taking is marked by an inflection point in behavior: seeking is initially high in the presence of reward cues (wanting), then ceases following reward delivery (taking). Limbic-striatal circuits, including those involving the amygdala and nucleus accumbens, are well-placed to control this transition, which will be studied in drug-naïve and in alcohol-drinking rats.
Basic Research

Ali Mohebi, Ph.D., Gladstone Institutes/University of California, San Francisco, is developing a novel conceptual framework to explain, in the context of nicotine addiction, the reinforcing and motivational enhancing effects of dopamine. In this model, these dual effects reflect separate actions at midbrain dopamine cell bodies and their release sites in the forebrain nucleus accumbens (NAc). It has been posited that nicotine acts as a primary reinforcer by activating midbrain dopamine cells (DA) through nicotinic acetylcholine receptors (nAChR). But nicotine also affects behavior as a motivational enhancer of other reinforcers. The co-use of tobacco with other drugs such as alcohol has synergistic effects. The neural mechanism underlying the "dual nature" of nicotine effect on behavior has remained unknown. Experiments in this project seek to better understand nicotine addiction and will motivate several subsequent studies to further study the presynaptic regulation of dopamine release.
Basic Research

Juan Molina, M.D., University of California, San Diego, is trying to improve upon a method of cognitive remediation for people with schizophrenia called auditory targeted cognitive training (TCT). It is designed to promote cognitive recovery by stimulating plasticity in neural systems mediating auditory learning and memory, but individual responses vary considerably with up to 40% of patients showing little or no response. This project will test a platform for augmenting the benefits of TCT in antipsychotic-medicated schizophrenia patients with memantine, an FDA-approved medication for the treatment of cognitive dysfunction in Alzheimer's disease.
Next-Generation Therapies

Sarah Moore, Ph.D., University of British Columbia, Canada, aims to isolate sex-specific pathways of genetic regulation that link genetic and environmental risks to stress disorders. This project focuses on gene expression and epigenetic aging in a mouse model of early-life stress. Two genetic strains of mice, one stress-sensitive and one stress-resilient, undergo early-life stress or control conditions so that the effects of the environment can be explored at two levels of genetic vulnerability. Two gauges of gene regulation will be measured at four time points over the life course following early-life stress: gene expression and DNA methylation at specific genomic sites that are tightly correlated with age. Results will help to determine how males and females differ in their biological stress responses.
Basic Research

Carole Morel, Ph.D., Icahn School of Medicine at Mount Sinai, notes that while much attention has been devoted to understanding the neurobiological alterations underlying anxiety and depression, the shared or distinct mechanisms underlying these disorders and their comorbidity are still poorly understood. Her team will use the chronic social-defeat stress (CSDS) paradigm to model anxiety/depression (A/D) or anxiety (A) phenotypes in subgroups of mice. These same mice can be segregated into two subpopulations—those who are either susceptible (A/D mice) or resilient to depression (A mice). This preclinical model provides a unique opportunity to dissect the shared or distinct mechanisms regulating depressive- from anxiety-related behaviors, with attention to the dopamine circuit imbalances in areas of the brain implicated in the team's prior research.
Basic Research

Megan Mueller, Ph.D., Tufts University, notes a growing body of research finding that relationships with pets, or human-animal interaction (HAI), can be a particularly effective method of reducing anxiety. This study addresses the specific psychophysiological effects of interacting with pets on social anxiety in young people and aims to test the feasibility of a methodology for assessing physiological responses to pet interactions in real-life scenarios, using a wearable wristband device. Results will provide previously unavailable data on the psychobiological effects of interacting with an animal on physiological responses in the context of social anxiety and lay the groundwork for future longitudinal research focused on understanding how pet ownership may be a particularly cost-effective strategy for supporting resiliency for youths with social anxiety.
Next-Generation Therapies

Niamh Mullins, Ph.D., Icahn School of Medicine at Mount Sinai, will lead a large-scale genetic study of suicide attempts, drawing upon data in over 30,000 cases, obtained by combining data from research cohorts worldwide within the International Suicide Genetics Consortium (ISGC), which Dr. Mullins co-leads. Cases include individuals who have died by suicide or made a serious suicide attempt. Their genomes will be compared against those of participants who have not

made a suicide attempt, controls from the general population, and non-psychiatric controls. The aim is to detect genetic variants associated with suicide attempt across the genome. Follow-up analyses will be conducted to illuminate the genes, biological pathways and molecular mechanisms underlying suicide attempt. The study design may also allow the identification of genetic variants involved specifically in suicide attempt, versus those which also increase risk for associated psychiatric disorders.

Basic Research

Karly Murphy, M.D., Johns Hopkins University School of Medicine, states that it is imperative to study how implicit attitudes toward people with serious mental illness influences care. Prior work has shown that medical record notes may reflect providers' conscious and unconscious biases, misconceptions, and stigmatizing attitudes. Dr. Murphy's project seeks to understand whether negative attitudes are embedded in the medical record for people with serious mental illness and if these negative attitudes influence delivery of care within the primary care setting. This work will help to develop a more nuanced understanding of how clinicians deliver physical health care for patients with serious mental illness and serve as a foundation for future interventions aimed at reducing clinician bias.

Basic Research

Keely Muscatell, Ph.D., University of North Carolina at Chapel Hill, notes that black Americans are diagnosed with schizophrenia at twice the rate as white Americans, and have comparatively poorer functional outcomes. Dr. Muscatell will investigate the effects of race-related stress on neural processing and social cognitive functioning, recruiting 40 black Americans diagnosed with a schizophrenia spectrum disorder who either undergo a negative, social evaluative stress task in the presence of a "white evaluator" (race-related stress condition) or a "black evaluator" (general social stress condition) while they are scanned using fMRI. Following the scan, social cognitive function in participants will be assessed. The hypothesis is that race-related stress will be associated with poorer social cognitive task performance relative to general social stress, and associated with greater activity in brain regions involved in processing social rejection and negative emotions (e.g., dACC, anterior insula, amygdala) and greater activity in regions involved in thinking about others (e.g., DMPFC), compared to social stress.

Basic Research

Katherine Musliner, Ph.D., Aarhus University, Denmark, hopes to show that genetic information can improve our ability to predict which patients diagnosed with bipolar disorder in early life are most likely to have negative clinical and socioeconomic outcomes. She will use polygenic risk scores in combination with other known risk factors such as gender racial/ethnic background, family history of mental illness, age at bipolar onset, and prior psychiatric diagnoses to build prediction models for identifying patients diagnosed early who are most likely to experience frequent re-hospitalization, inability to complete education or to participate in the work force. The project will utilize a register of individuals born since 1981 in Denmark who were diagnosed with bipolar disorder through 2015 (N=3,819).

Diagnostic Tools/Early Intervention

Nicholas Neufeld, M.D., University of Toronto/Centre for Addiction and Mental Health, Canada, will examine the relationship between brain imaging biomarkers and the therapeutic effects, or cognitive side effects, of magnetic seizure therapy (MST) for patients with treatment-resistant schizophrenia (TRS.). Patients who have developed TRS and are taking clozapine or non-clozapine medications are eligible to participate in the trial. The proposed pilot study follows patients enrolled in a parent "MAST-Neuro" trial and collects brain scans before, during, and after their course of brain stimulation. Brain imaging biomarkers that emerge from this study can be particularly impactful given that they originate from the largest clinical trial examining MST and ECT for the most severely impacted patients with schizophrenia.

Next-Generation Therapies

Diagnostic Tools/Early Intervention

Azahara Oliva, Ph.D., Columbia University, aims to understand the underlying cellular mechanisms of disrupted hippocampal circuit activity and social memory deficits in genetic mouse models of schizophrenia. Dr. Oliva will implement a novel closed-loop optogenetic approach to manipulate hippocampal activity in a cell-type specific manner during social memory consolidation. Replacing abnormal hippocampal activity patterns in the animals with normal physiological ones could in theory reverse cognitive deficits in these animals. These experiments could open the door to more selective interventions in schizophrenia and other neuropsychiatric disorders with accompanying memory deficits.

Basic Research

Tiago Oliveira, M.D., Ph.D., University of Minho, Portugal, observes that chronic stress can lead to neuronal dendritic atrophy in the hippocampus and to hippocampus-dependent behavioral alterations. At least some of these stress-induced effects have been shown to be reversible. Knowing that hippocampal functions are differentially regulated along its longitudinal axis, from dorsal to ventral poles in rodents, and posterior to anterior in humans, Dr. Oliveira aims in this project to understand how hippocampal subregions are differ-

entially affected by chronic stress exposure. The longitudinal hippocampal axis will be analyzed using magnetic resonance imaging (MRI) in a rat model of chronic unpredictable stress.
Basic Research

Lindsay Oliver, Ph.D., University of Toronto/Centre for Addiction and Mental Health, Canada, wants to determine if individualized rTMS stimulation to the dorsomedial prefrontal cortex (DMPFC), a key social brain region, can alter social brain connectivity, and ultimately social deficits, in individuals with schizophrenia spectrum disorders (SSDs). Sixty people with SSDs will be randomly allocated to three treatment groups, each receiving 5 sessions/week for 2 weeks: 20 to a conventional form of rTMS; 20 to a newer, more rapid form known as intermittent theta burst stimulation; and 20 to a placebo group. The goal is to determine if individualized active versus placebo DMPFC brain stimulation changes connectivity within and between social brain networks during the emotional understanding task.
Next-Generation Therapies

David Omer, Ph.D., The Hebrew University of Jerusalem, Israel, notes that a core symptom of autism spectrum disorder (as well as social anxiety disorder, another prevalent social neuropathology) is atypical behavioral response to eye contact. The marmoset monkey, a social primate, will be used as an animal model to study the neural basis of eye contact and social gaze behaviors. This study is expected to shed light on the neuronal mechanisms underlying human neuropathologies that affect perception and understanding of others.
Basic Research

Maya Opendak, Ph.D., Nathan S. Kline Institute for Psychiatric Research, is trying to develop environmental enrichment interventions in psychosocial disorders arising from exposure to adversity as a therapeutic approach for recovery, particularly when these target offspring and parents. Preliminary data suggest that during enrichment, developing amygdala circuits are buffered from altered activation patterns resulting from trauma. This project will record and manipulate connectivity between two parts of the amygdala, the BLA and CeA, over the course of enrichment in rodent pups. The aim is to determine if exposure to an enriched mother reduces pups' atypical amygdala activity induced by early adversity to restore typical social behavior in the nest.
Next-Generation Therapies

Massimiliano Orri, Ph.D., McGill University, Canada, is focusing on an irritable subtype of depression that is often more severe than non-irritable forms. Dr. Orri will lead a genome-wide association study to identify specific genetic variants associated with irritable and non-irritable depression, using data from large genotyped samples from the UK Biobank and 23andMe, with data on almost 2 million individuals reporting on their depression as well as on irritability traits. The results may enable characterization of how genetic liability for each subtype relates to genetic liability for a range of other traits, such as cognitive skills, social outcomes, and other mental and physical disorders, and establish a score of genetic liability for irritable and non-irritable depression, among other endpoints.
Diagnostic Tools/Early Intervention

Alexandre Paim Diaz, M.D., Ph.D., University of Texas Health Science Center at Houston, calls attention to a critical period for suicide-related behavior that occurs just after psychiatric hospitalization, especially within 30 days of discharge. Neuroimaging studies demonstrate an association between suicidal ideation and alterations in neural circuits, including increases in functional connectivity within the brain's default mode network. Dr. Diaz will lead a pilot randomized placebo-controlled trial to examine the feasibility and acceptability of a home-based transcranial direct-current stimulation (tDCS) to reduce the risk of suicidal ideation relapse in adult patients after discharge from a psychiatric hospitalization for suicidal behavior.
Next-Generation Therapies

Alan Park, Ph.D., Columbia University, is trying to establishing biomarkers linked to cognitive deficits which can be a first step toward treating and one day curing cognitive symptoms of schizophrenia. To determine biomarkers, Dr. Park will use a mouse model and study patients carrying 22q11.2 genomic deletions who exhibit impaired cortical processing of auditory stimuli and cognitive functions. Based on these well-established deficits, he will first investigate the impact of deviant auditory stimuli on cortical circuits that govern cognitive functions. Then, he will test whether the auditory stimuli-evoked cortical dynamics can serve as biomarkers that predict performance in separate auditory-based cognitive tasks.
Diagnostic Tools/Early Intervention

Linden Parkes, Ph.D., University of Pennsylvania, is interested in deviations from normative development that are thought, in may cases, to precede the emergence of schizophrenia symptoms by several years. Dr. Parkes will use a large longitudinal cohort of developing youths (N = 580, 8-22 years old, assessed at 2-3 timepoints) to characterize within-person trajectories of neurodevelopmental abnormalities. The data include rich longitudinal neuroimaging and clinical phenotyping, which will enable the team to investigate whether individuals' neurodevelopmental trajectories predict change in schizophrenia symptomatology over time. To achieve this

goal, they will use a novel machine learning technique called normative modeling.

Diagnostic Tools/Early Intervention

Mario Penzo, Ph.D., National Institute of Mental Health (NIH), is studying mechanisms behind a dominant feature of anxiety disorders—the presence of irrational or exaggerated defensive reactions, such as excessive avoidance or hypervigilance. This project focuses on the contribution of the paraventricular nucleus of the thalamus (PVT) to this process. The PVT sends divergent anatomical projections to the amygdala and the ventral striatum, areas of the brain known to, respectively, drive the expression of passive and active defensive behaviors. Dr. Penzo will test whether bias in the expression of passive vs. active defensive behaviors is associated with experience-dependent modifications of the afferent inputs and intrinsic properties of PVT neurons selectively innervating the amygdala or the ventral striatum.

Basic Research

Kiryl Piatkevich, Ph.D., Westlake University, People's Republic of China, builds upon research showing that driving neuronal activity in the visual cortex at gamma frequency by flickering lights at 40Hz induces blood vessel dilation and recruits microglia, which in turn results in amelioration of Alzheimer's-associated pathology and improves cognition. This project seeks to determine molecular mechanisms of neural-immune interactions in Alzheimer's disease, using multicolor imaging to visualize at single-cell resolution VIP and chemokine release *in vivo* during and after non-invasive gamma stimulation in healthy mice and mouse models of Alzheimer's disease.

Basic Research

Santosh Pothula, Ph.D., Yale University, is studying the mechanism behind the rapid-acting antidepressant effects of ketamine. Recent studies demonstrate that ketamine enhances synaptic plasticity mediated by a portion of the NMDA receptor called the GluN2B subunit. Yet it remains unclear how ketamine, an NMDA antagonist, enhances GluN2B function. Dr. Pothula hypothesizes that ketamine regulates the signaling cascades involved in GluN2B trafficking and enhances the synaptic localization of GluN2B, which is crucial for enhancing synaptic plasticity. He aims to test this theory using multidisciplinary approaches, and also plans to evaluate the potential rapid antidepressant effects of a molecule called a STEP61 inhibitor.

Next-Generation Therapies

Abha Rajbhandari, Ph.D., Icahn School of Medicine at Mount Sinai, aims to delineate how the neuropeptide PACAP (pituitary adenylate cyclase activating peptide) and its receptor PAC1 regulate traumatic fear in post-traumatic stress disorder (PTSD) via the so-called brain-vagus-body axis. The rationale is that numerous drugs used or researched for PTSD are designed to regulate neurotransmitter availability/action, while very few are designed to target the vagus nerve despite the fact that vagus nerve stimulation is an FDA-approved therapy for depression and PTSD. This project will explore the role of the brain-vagus-body axis in the regulation of fear behaviors via neuropeptidergic modulation integrating genetics, molecular biology, novel mouse lines, novel viruses, and a well-validated behavioral model of PTSD.

Basic Research

Rachel Reetzke, Ph.D., Moser Research Institute/Johns Hopkins University, seeks to examine the extent to which familial risk for autism spectrum disorder (ASD) affects neural speech processing at different stages of the auditory pathway, in the brainstem and cortex. ASD has been linked with aberrant speech processing early in life. While it is known that infant siblings of children with ASD (at high-risk for ASD) exhibit aberrant speech processing in cortical brain regions, the extent to which this cortical pathophysiology interacts with aberrant brainstem speech processing has not been established. This project will study brainstem and cortical speech-evoked potentials in high- and low-risk infants to characterize the early developmental trajectories of brainstem and cortical speech-evoked potentials between ages 6 and 12 months, among other objectives.

Basic Research

Andrea Reiter, Ph.D., Max Planck UCL Centre for Computational Psychiatry and Ageing Research, Germany, notes that cognitive therapies are assumed to bring about change by changing maladaptive cognition in mood disorder patients, while behavioral therapies are assumed to become effective by changing maladaptive behaviors. She aims to provide empirical evidence for this assumption by using state-of-the art neurocognitive assessment tools and computational analysis methods to delineate mechanisms of cognitive and behavioral change in psychotherapy. She will test patients with major depression (n=50) before, during and after undergoing evidence-based psychotherapy and will compare them to a control group. Treatment will be accompanied by module-specific computer games designed to specifically test neurocognitive processes that are hypothesized to be modified by different treatment modules of CBT.

Next-Generation Therapies

Jing Ren, Ph.D., The Medical Research Council Laboratory of Molecular Biology, UK, will lead research seeking to bridge the gap between the molecular mechanisms of developmental wiring and the behavioral functions of serotonin neurons. The goal is to determine how developmental defects of sero-

tonin sub-systems lead to different aspects of abnormal mental states. Dr. Ren will examine the roles of candidate genes in serotonin neuron development in an *in vitro* culture system; then, investigate how the candidate genes affect the wiring properties in a mouse model; finally, characterize how mis-wired serotonin circuitry influences different aspects of anxiety and depression-like behaviors, by employing sophisticated behavior paradigms in translational psychopathology.
Basic Research

Anna-Sophie Rommel, Ph.D., Icahn School of Medicine at Mount Sinai, studies phthalate plasticizers, which are pervasive in consumer products. Able to cross the placental and blood–brain barriers, they are thought to potentially affect fetal brain development and later functioning. Prenatal exposure to phthalates has been associated with adverse cognition and behaviors central to ADHD, including inattention and externalizing behaviors, and with increased risk for ADHD diagnosis. This project seeks to understand the biological basis through which phthalates act on the brain and affect behavioral functioning to increase risk for ADHD at 2 years of age. She will use a pregnancy cohort of mother-child pairs, whose consent was obtained in the first trimester of pregnancy and followed up until birth.
Basic Research

Luis Rosas-Vidal, M.D., Ph.D., Vanderbilt University Medical Center, studies the endocannabinoid (eCB) system, a neurotransmitter system that has been implicated in regulating fear and anxiety. This research focuses on 2-arachidonoylglycerol (2-AG), one of the major fatty lipids in the eCB system which is thought to mediate resiliency to traumatic experiences as well as aspects of fear learning including expression and extinction. Dr. Rosas-Vidal will test the hypothesis that 2-AG is involved in regulating fear generalization. Specifically he will address whether 2-AG signaling in prelimbic prefrontal cortex is required for the specificity of fear memories and how prelimbic neurons encode fear memory specificity and how this process is disrupted when 2-AG signaling is impaired.
Basic Research

Diego Rovaris, Ph.D., University of São Paulo, Brazil, is studying reasons for the gap between the genetic contribution to ADHD in any given individual (about 80%) and the much lower proportion of variability in symptoms among ADHD patients (about 20%) which are accounted for by genetic differences. He is looking to epigenetics, a mechanism by which the environment can interact with the genetic context and contribute to phenotypic variance related to mental conditions. Epigenetics involves gene regulation via factors (e.g., DNA methylation) other than differences in the individual DNA sequence. He will lead an epigenome-wide association study (EWAS) to examine epigenomic modulation involved in the biology and clinical course of ADHD in adulthood. He will draw from a set of GWAS data, with matched neuroimaging, with DNA samples collected 13 years apart.
Basic Research

Matthew Sacchet, Ph.D., Harvard University/McLean Hospital, seeks to contribute to patient-tailored healthcare in psychiatry ("precision psychiatry") by advancing the brain-based conceptualization and treatment of major depressive disorder (MDD). He will use a recently developed fMRI-based brain mapping method to characterize the rich organizational structure of large-scale functional brain systems at the level of individuals (yielding "individualized brain systems"). He will access over 530 existing clinical MRI datasets acquired through data sharing, in addition to new data collected from 60 individuals, using computational methods, in part, to compare depressed and healthy brains in an effort to characterize relations between individualized brain systems and core MDD symptoms and behavioral deficits.
Basic Research

Sara Sanchez-Alonso, Ph.D., Haskins Laboratories, notes that deficits in social communication skills are often cross-diagnostic and appear in both social communication disorder (SCD) and autism spectrum disorder (ASD). This project will probe whether shared neural mechanisms map onto these overlapping symptoms. She will use a predictive modeling approach called Prediction of Multi-Level Neural Effects (Prime-Net) to map via neuroimaging shared variance in functional connectivity (FC) patterns that predict cross-diagnostic social communication-skills deficits across individuals diagnosed with either SCD or ASD. Aiming to utilize non-invasive neuroimaging paradigms during early development, when most social communication deficits emerge, she will also employ, in addition to fMRI, fNIRS, a non-invasive neuroimaging technique more suitable for pediatric research.
Basic Research

Takashi Sato, Ph.D., Medical University of South Carolina, is probing the circuit mechanisms underlying impulsive actions, which are commonly observed in various disorders including ADHD, schizophrenia, substance-use disorder, and borderline personality disorder. The team will use an improvement upon past mouse models to study this, having developed a novel behavioral task that recapitulates the Stanford Marshmallow Test, a classic experiment for impulsive actions. Analysis will focus on the prelimbic cortex (PL), based on preliminary data in which this area, when deactivated, was specifically linked with impulsive actions. This project seeks to identify downstream areas, including

the nucleus accumbens core (NAc), thalamus, and entorhinal cortex, which help translate signals into behavior.
Basic Research

Benjamin Scott, Ph.D., Boston University, studies stress-related memory impairment, which is caused by an alteration in information processing in the hippocampus. This project focuses on how stress alters information processing in hippocampal circuits during behavior. Dr. Scott will record neural dynamics throughout the hippocampus during memory formation and retrieval and will compare this activity in chronically stressed and otherwise healthy subjects. Of particular importance is the dentate gyrus (DG), the input region of the hippocampus, which is believed to be critical for the discrimination of similar experiences. This key function, combined with its highly conserved cell types and connectivity across mammalian species, positions the DG as a promising site for future interventions to rescue memory deficits associated with anxiety disorders.
Basic Research

Katlin Silm, Ph.D., Gladstone Institutes/University of California, San Francisco, notes that dopamine neurons regulate various physiological processes like reward and motor control by switching between low frequency firing and high frequency bursts, with resulting changes in extracellular dopamine concentration. Conversely, synaptically acting neurotransmitters like glutamate and GABA convey precise information about the timing of neural activity. Dr. Silm studies two modes of signaling thought to reflect the location and properties of different receptors, exploring in the context of dopamine the idea that storage in vesicles with different release properties allows different neurotransmitters to extract different information from neural activity and to transmit the output as distinct signals.
Basic Research

Gijsje Snijders, M.D., Utrecht University, the Netherlands, is interested in changes in microglia, the brain's immune cells, in patients with psychiatric disorders such as bipolar disorder, major depressive disorder, and schizophrenia. To better understand whether these changes are related to underlying disease mechanisms, the team will test the hypothesis that genetic risk factors for these disorders affect microglial cells. They will generate genome and transcriptome profiles from microglia cells isolated from 113 brain donors.
Basic Research

Hansem Sohn, Ph.D., Massachusetts Institute of Technology, notes that laminar organization of the neocortex—its distinctive layered configuration—is a key feature of cortical microcircuitry, providing a structured scaffold for neural computation. Recent technical developments have opened the possibility of simultaneous recording from multiple cortical layers, allowing investigators to dissect the underlying circuitry. But little is known about the role of laminar information processing in the frontal cortex, which is critically involved in flexible cognitive control. In this project Dr. Sohn will address this using cutting-edge neural recording technology and carefully designed cognitive tasks in non-human primates. The work is prelude to using newly developed high-density Neuropixels probes to identify the exact laminar location of individual neurons.
Basic Research

Isabelle St-Amour, Ph.D., CERVO Brain Research Center, Canada, notes the finding that maternal infection and/or immune activation during pregnancy will increase the risk of psychosis or autism spectrum disorder in the offspring. She will explore the hypothesis that maternal immune activation directly impairs neuronal maturation and that the increased risk of psychiatric disorders is partly due to modifications of GABA inhibitory activity in the brain. The specific objective of this project is to study how immune challenges can affect the neural network and inhibitory activity. Digital holographic microscopy and iPSC stem cell-based technology will help provide a new perspective on the role of impaired immunity in neurodevelopmental disorders. It will also allow the development of innovative tools to conceive, test and guide patient-oriented treatments and personalized medicine.
Basic Research
New Technologies

Trevor Steward, Ph.D., University of Melbourne, Australia, seeks to discover mechanistic links in eating disorders between neurobiology and complex human behaviors (e.g., the interaction between affect and food intake). He contends that developing brain-based profiles that can be directly related to real-world eating behaviors is a necessary step in moving beyond a one-size-fits-all approach to treating binge eating. Using ultra-high yield MRI he will examine the role of the habenula—a forebrain structure that acts as a major point of convergence for dopaminergic and serotonergic regions—when subjects are engaging in repetitive negative thinking, a common trigger for binge eating episodes. He will compare habenula connectivity parameters in binge eating participants to those of healthy controls, taking advantage of a large, ongoing clinical project.
Basic Research

Joel Stoddard, M.D., University of Colorado, Denver, notes that a major dimension of child and adolescent mental health difficulties is irritability, which in youth is associated with anxiety, depression, and suicidality later in life. Treating irritability early may prevent negative outcomes, and a promising way to do so, says Dr. Stoddard, is to address negative

biases. This work will study biased social judgments, in terms of behavior and neural activity, by understanding how clinically irritable youth make these interpretations, a prerequisite for diagnostic tests and better treatments. Experiments will include measurement of neural activation as participants are thinking about ambiguous information during functional magnetic resonance imaging, enabling determination of what is common in how people react to ambiguity and to what degree these reactions are related to clinical irritability.
Basic Research

Lu Sun, Ph.D., University of Texas Southwestern Medical Center at Dallas, notes evidence suggesting that abnormalities of glial cells, including those in myelinating glia called oligodendrocytes, contribute to the occurrence and progression of autism spectrum disorder (ASD) and other social behavioral disorders. This project seeks to characterize oligodendrocytes and myelination in a battery of ASD animal models and to address their roles in social behaviors. To achieve this goal, Dr. Sun will take advantage of several ASD animal models to determine myelination location and timing with a focus on the prefrontal cortex. The team will combine genetic and pharmacological approaches to manipulate PFC myelination to rescue social behavioral deficits in ASD animal models.
Basic Research

Werner Surbeck, M.D., Ph.D., University of Zurich/Zurich University Hospital of Psychiatry, Switzerland, builds upon clinical evidence in brain surgery on awake patients showing that direct electrical stimulation of the left inferior fronto-occipital fasciculus (IFOF) causes semantic processing anomalies similar to those observed in psychosis patients and in people with schizophrenia and schizotypal disorders. To gain insight into the anatomical correlates of semantic processing alterations, Dr. Surbeck, in a sample of schizophrenia patients and controls, will look for a correlation between verbal semantic processing performance, delusional symptoms, and rightward deviations in line-bisection tasks with selected diffusion tensor imaging-related measures. He aims to shed light on a possible correlation of the integrity of the ventral language stream, in particular the IFOF, with semantic processing deficits as well as in visuo-spatial attention deviation in schizotypy and schizophrenia.
Basic Research

Jacob Taylor, M.D., Harvard University/Brigham and Women's Hospital, says that in order to maximize the impact of health systems-based biobanks on psychiatric genetic research, tools are needed to structure the extraction of disorder-relevant clinical data (beyond diagnosis) from patient records. The Schizophrenia Phenotype Inventory (SPI) is a recently developed instrument designed for use by clinicians in large-scale genetic studies of psychosis. It contains 30 items chosen to measure variation that is specifically relevant for advancing genetic research in patients with schizophrenia and schizoaffective disorders. This project seeks to adapt the SPI for use with patients diagnosed with schizophrenia and schizoaffective disorder in the Partners Biobank and to develop a similar instrument (the Bipolar Phenotype Inventory – BPI) to extract relevant clinical data on patients with bipolar disorder.
Diagnostic Tools/Early Intervention

Hugo Tejeda, Ph.D., National Institute of Mental Health (NIH), notes that dynorphin, which interacts with the kappa-opioid receptor (KOR), is implicated in mediating stress-induced behaviors, including fear. Compounds that block activity of the KOR are being tested in clinical trials for the treatment of mood and substance-use disorders. This project will study how different populations of dynorphin-containing neurons regulate affective behavior through the peptides they release, which will help explain how dynorphin/KOR system architecture within medial prefrontal cortex circuitry regulates emotional behavior. Collectively, this research could determine the role of endogenous opioid systems in regulating affective behavior and provide novel therapeutic targets for the treatment of psychiatric disorders.
Basic Research

Summer Thyme, Ph.D., University of Alabama at Birmingham, notes that many neuropsychiatric disorders share symptoms and risk factors. Schizoaffective disorder patients exhibit symptoms of both schizophrenia and bipolar disorder, and both autism and schizophrenia present with an increased risk of epilepsy. Dr. Thyme's research goals are to understand overlapping and separable mechanisms of neuropsychiatric disorders by functionally characterizing genes linked to individual or multiple disorders. Ultimately, the aim is to help develop therapies by illuminating molecular underpinnings of these illnesses and also through unbiased drug screening. This project, conducted in zebrafish, focuses on the relationship of schizophrenia and autism, and includes characterizing genetic mutants and conducting drug screens.
Basic Research

Eric Trautmann, Ph.D., Columbia University, notes that cognitive functions like decision-making are closely related to higher-order aspects of planning and controlling movements and that cognitive and motor deficits are seen in various disorders. He will use a novel movement sequence generation task in rhesus monkeys to study how multiple brain regions coordinate to form decisions in the context of controlling movements. Specifically, he plans to record from the supplemental motor area (SMA), premotor and primary motor cortex (PMd, M1), and dorsal and ventral striatum (VS,

DS) to understand the circuit-scale computations during decision-making and action selection.

Basic Research

Justin Trotter, Ph.D., Stanford University, notes that the gene encoding Neurexin-1 (Nrxn1), a synaptic cell adhesion molecule, has often been implicated in the etiology of schizophrenia, yet little is known about its function and regulation at synapses. Challenging the conventional view that Nrxn1 is exclusively presynaptic, Dr. Trotter has found that it is highly expressed by astrocytes. This project uses various molecular biology tools to explore the hypothesis that astrocytic Nrxn1 mediates an important form of communication between astrocytes and synapses required for excitatory synapse development and which may be compromised in patients carrying Nrxn1 gene variants.

Basic Research

Caroline Trumpff, Ph.D., Columbia University, is studying the possibility that mitochondrial and immune adaptations are involved in the physiological embedding of psychosocial stress and the development of depressive symptoms. Recent evidence suggests that mitochondria, in their signaling role, can actively release pro-inflammatory DNA into the circulation as cell-free mitochondrial DNA (ccf-mtDNA). This study seeks to determine the extent to which mitochondrial and immune adaptations to psychosocial stress mediate the risk for late-life depressive symptoms. It will include longitudinal assessment of psychosocial exposures and depressive symptoms, postmortem brain proteomic data, and stored biospecimens from the Religious Order Study (ROS) and Memory and Aging Project (MAP).

Basic Research

Gergely Turi, Ph.D., Research Foundation for Mental Hygiene, Inc., is interested in fear generalization, reflected in the fact that those with anxiety disorders and PTSD not only fear stimuli and situations that are dangerous or closely resemble those in which the original trauma occurred but also fear stimuli and situations that are objectively safe or just faintly resemble the original trauma context. The ability to distinguish between similar contexts, a process called pattern separation, was thought to rely on granule cells, but new evidence suggests that mossy cells (MCs), also found in the dentate gyrus of the hippocampus, may also participate in this process. This project tests the hypothesis that fear generalization in a mouse model of PTSD may be reflected by impaired contextual discrimination function of MCs. This will be tested by recording the calcium activity of MCs *in vivo* in stressed mice during a head-fixed pattern separation paradigm.

Basic Research

Jennifer Tuscher, Ph.D., University of Alabama at Birmingham, wants to better understand which molecular adaptations initiated by drug use are necessary for the transition to the addicted state. Harnessing the therapeutic potential of genetic and epigenetic manipulations in addiction has been limited by the lack of detailed insight into which specific gene signatures are initiated during persistent drug taking, and the inability to selectively target gene programs in real time to interrogate their role in molecular and behavioral function. To overcome these hurdles, this project will utilize single-nuclei RNA-sequencing (snRNA-seq) to define cell type-specific gene signatures of drug use in the nucleus accumbens of male and female rats. Dr. Tuscher will selectively modify expression of multiple gene targets simultaneously, making it possible to test the requirements of complex gene programs in a model of volitional drug use. Together, the proposed experiments will be the first to define the exact nature and scope of cell-type specific gene signatures following sustained drug experience.

Basic Research

Celia van der Merwe, Ph.D., The Broad Institute of MIT and Harvard, has aggregated all available autism spectrum disorder (ASD) datasets that include exome sequencing, genotype, and phenotype data. This unprecedented resource now includes over 15,000 cases, and will continue to grow. Using it, she will expand on previous, successful studies that used genetic data to clarify ASD heterogeneity. The aim of this research project is two-fold, (1) to more deeply characterize heterogeneity across ASD cohorts so that we can identify similar subgroups of ASD cases, and (2) to identify genetic influences on ASD risk that are most consistently observed between cohorts and proband groups.

Diagnostic Tools/Early Intervention

Basic Research

Marco Venniro, Ph.D., University of Maryland School of Medicine, seeks to overcome limitations in the construction and predictive validity of animal models of addiction, which rarely incorporate social factors. Social interaction with peers is highly rewarding to both rodents and monkeys, but surprisingly, there is a paucity of research testing whether operant access to social interaction can "compete" with drug self-administration. To address this question, Dr. Venniro developed an operant rat model of choice between drugs and social interaction and showed the profound protective effects of the latter on addiction. This project will investigate the neural encoding mechanisms of positive social interaction vs. opioid choice using *in vivo* electrophysiology, focusing on the orbitofrontal cortex (OFC) because of its critical role in associative learning, decision-making, and reward valuation.

Basic Research

Gisella Vetere, Ph.D., ESPCI (Ecole Superieure de Physique et Chimie Industrielles), France, hopes to shed light on how traumatic events are stabilized in the brain to be recalled later and why only some aspects of them are retained over time. This is pertinent to post-traumatic stress disorder (PTSD), in which memory stabilization becomes pathological. Patients suffer from uncontrollable recall of the traumatic event even in minimally related contexts, suggesting an overgeneralization of the fear memory. This work will use optogenetic and other techniques to identify neuronal structures and populations that process spatial and aversive information in traumatic memory and how these circuits and cells change during traumatic memory stabilization.

Basic Research

Georgios Voloudakis, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, seeks to elucidate the genetic basis of suicidal behavior. He will perform a large genome-wide association study in the Million Veteran Program (MVP) and a transcriptome-wide association study to identify the contribution of common variants to increasing the likelihood of a suicide attempt and the severity of its outcome. The study will leverage expert-validated tracking data for suicidal behavior in the MVP and will adjust for known factors that epidemiologically affect suicide rates. Dr. Voloudakis says this will be the first large-scale study of its kind focusing on African Americans, a particularly vulnerable group.

Basic Research

Gordon Wang, Ph.D., Stanford University, observes that the complexity and distributed nature of the synaptic network have been a barrier that has kept scientists from identifying core deficits that contribute to autism behavioral characteristics. His lab has created methods that will allow for the quantification of all synapses within a single piece of brain tissue. This could enable the team to embrace the complexity of the synaptic network and understand the common molecular and synaptic substrate that drives the shared behavioral characteristics of autism. In doing so, they hope to reveal specific synaptic targets for study and treatment in autism.

Basic Research

Shuyu Wang, M.D., Ph.D., Gladstone Institutes/University of California, San Francisco, observes that social attachment, which is impaired in autism, has been difficult to study because traditional models like mice do not display long-term social attachment behaviors. Prairie voles are among the few mammals known to exhibit social monogamy; separation from a partner provokes anxiety behaviors and activates the stress response. Using novel techniques, Dr. Wang will investigate how social attachment behaviors vary across developmental stages and genetic backgrounds in voles, in the hope of finding behavior patterns that are specifically linked with mutations associated with ASD or schizophrenia. Having these behavioral signatures would significantly advance our ability to study and to understand social deficits in mental illness.

Basic Research

Donna Werling, Ph.D., University of Wisconsin-Madison, is exploring one way in which sex could influence risk of various disorders differentially: if the genes that contribute to a disorder are regulated differently in males and females. Patterns could also vary across organ systems, brain regions, cell types, and stages of development. Disruption of risk genes or the regulatory mechanisms that determine when, where, to what level, and with what variability these genes are expressed could then steer males and females to different outcomes. This project will combine information about DNA sequence with read-outs of gene expression in brain tissue from male and female human donors to identify genetic variants associated with the expression levels of nearby genes in one sex or the other. This information will be applied to genetic risk variants associated with autism, attention deficit hyperactivity disorder, schizophrenia, major depressive disorder, multiple sclerosis, anorexia nervosa, Parkinson's disease, and Alzheimer's disease.

Basic Research

Frank Wolters, M.D., Ph.D., Erasmus University Medical Center, the Netherlands, notes that antidepressants and anti-anxiety medications are among the most prescribed drugs in the U.S. and Europe. He will investigate whether antidepressants and benzodiazepines are associated with an increased risk of cognitive impairment and dementia, using a database that includes 20,000 individuals who since 1990 have formed part of a large, population-based cohort. The data the study will use comprises >15,000 MRI scans of ~7,000 individuals. In between center visits, participants are monitored for dementia through contact with general practitioners, nursing home physicians, and hospital discharge letters. These data will be used to examine the associations between 10-year total use of antidepressants and benzodiazepines and subsequent risk of dementia across the 30-year study period.

Basic Research

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