

## 2018 Young Investigator Grantees

### Addiction

**Hamed Ekhtiari, M.D., Ph.D.**, Laureate Institute for Brain Research, will test transcranial alternating-current stimulation as a possible treatment for opioid addiction. In previous research, Dr. Ekhtiari found that people with this addiction showed fewer connections between frontoparietal areas of the brain, which are involved in self-control and emotion regulation, and the amygdala, key for emotional processing. His team will try to regulate communication between these brain areas using transcranial stimulation, which applies low levels of electric current to the scalp to alter activity in the brain. They will measure how any resulting differences in brain activity correspond with behavioral changes among people with opioid addiction.

#### Next-Generation Therapies

**Mark Alexander Grainger Eldridge, Ph.D.**, National Institute of Mental Health, hopes to pinpoint the neurological basis of addiction relapse that is triggered by images of drugs. Some people start using drugs again following a period of sobriety after seeing visuals that remind them of the substance to which they were addicted. Using the technique of chemogenetics, which can halt activity in specific brain areas, Dr. Eldridge will study the brain's response to images of items, like drugs, that are linked to the feeling of reward. He aims to identify brain areas that can eventually be targeted to prevent visually stimulated relapse.

#### Basic Research

**Diana I. Escalona-Vargas, Ph.D.**, University of Arkansas for Medical Sciences, will test the effects of treatment for opioid addiction on babies in utero. Some pregnant women with dependency receive opioids from medical professionals to avoid relapsing, as relapse can harm fetuses and make them dependent on opioids in turn. Dr. Escalona-Vargas will look at how exposure to buprenorphine, an opioid administered in this type of treatment, alters a baby's neurodevelopment. Her team will use the imaging technique of fetal magnetoencephalography to compare spontaneous brain activity, as well as responses to visual and auditory stimuli, in babies exposed to buprenorphine, compared to babies whose mothers no longer take any opioids.

#### Basic Research

**Chiara Giuliano, Ph.D.**, University of Cambridge, UK, will probe the biological basis of alcohol addiction. Her team wants to pinpoint brain processes that make someone transition from controlled to compulsive consumption, a shift associated with addiction. One hypothesis is that addiction stems from failures in regions of cortex that tamp down our automatic responses. Building on her past studies with rats, Dr. Giuliano seeks to demonstrate that rats showing compulsive addiction are experiencing that kind of cortical failure—disruptions to the connection between the brain's prelimbic cortex and posterior dorsomedial striatum, a pathway that mediates goal-directed behavior.

#### Basic Research



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**Nicholas M. Graziane, Ph.D.**, Pennsylvania State University, hopes to uncover neural mechanisms behind opioid-context relapse. This kind of relapse occurs when recovering addicts start using again in response to features of their environment that remind them of the drug. Dr. Graziane's team predicts that such environmental exposure triggers activity in the nucleus accumbens and ventral pallidum, brain regions that preserve the knowledge of opioid-associated contexts. They seek to uncover evidence that would point toward activation of the nucleus accumbens—for example by electrical brain stimulation—as a way to disrupt opioid associations and so prevent relapse.

### **Basic Research**

**Rebecca Sue Hofford, Ph.D.**, Icahn School of Medicine at Mount Sinai, hopes to lay the groundwork for a drug to treat addiction to cocaine and other psychostimulants. She previously found a link between cocaine-induced behaviors and the activity of granulocyte-colony stimulating factor, or G-CSF, which is a cytokine—a signaling protein released by the immune system. Her team now hopes to identify which neurons are affected by G-CSF in the nucleus accumbens, a brain region that is associated with reward processing and involved in addiction. They will study how affected neurons change their activity in response to G-CSF.

### **Basic Research**

**Xuan (Anna) Li, Ph.D.**, University of Maryland, is studying methamphetamine relapse after a period of abstinence. Her earlier research suggests that relapse and drug-seeking behaviors are controlled in part by gene modifications within critical circuits such as the striatal output pathway. She will build on these studies by focusing on the role that HDAC5, an enzyme that modifies gene expression, has on neurons within the striatal output pathway during methamphetamine-seeking behavior after prolonged withdrawal from the drug.

### **Basic Research**

**Leah M. Mayo, Ph.D.**, Linköping University, Sweden, will be studying emotional and stress responses in people who have been exposed to childhood trauma, to learn more about how such trauma may impact their risk of developing alcohol use disorder. Dr. Mayo will look at the role that the brain's endocannabinoid system plays in stress response, and how trauma may dampen its protective effect in ways that support the transition from alcohol use to dependence. Data for the study will come from a large registry of Swedish patients who can be linked to child or adolescent trauma and alcohol dependency clinics in the country.

### **Basic Research**



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**Vijay Mohan K. Namboodiri, Ph.D.**, University of North Carolina at Chapel Hill, will explore neural mechanisms behind the dysfunctional reward-seeking behaviors that characterize addiction. Drug abuse weakens the appeal of natural, or non-drug, rewards and past research suggests this stems from activity in the orbitofrontal cortex, a brain region crucial for decision-making. Using imaging tools, Dr. Namboodiri will study how exposure to cocaine changes the activity of neurons in the orbitofrontal cortex that typically respond to natural rewards. He hopes to shed light on how cocaine in particular might disrupt natural reward-seeking via the orbitofrontal cortex in a way that facilitates addiction.

### **Basic Research**

**Alexander C. W. Smith, Ph.D.**, Icahn School of Medicine at Mount Sinai, notes that relapse to addictive drugs can be triggered by environmental cues repeatedly paired with the drug. These cues cause a massive release of glutamate at corticostriatal synapses in the nucleus accumbens, and lead to neuronal activation the intensity of which correlates with the intensity of drug-seeking behavior. This research seeks to identify shared neurobiological substrates of cue-induced relapse across classes of drugs, using mice in which cell populations activated by relapse can be tagged. These experiments will generate a large data set of genes and circuits involved in relapse across classes of drugs, a starting point for new therapeutic approaches to relapse.

### **Basic Research**

**Oliver Vranjkovic, Ph.D.**, Vanderbilt University, aims to contribute to the development of compounds that prevent withdrawal-induced anxiety in people trying to wean themselves off of alcohol dependence. He is interested, in the longer term, in the way alcoholism can exacerbate anxiety disorders, depression, schizophrenia, and PTSD, by changing key brain circuits. One of these circuits is the excitatory input into the Bed Nucleus of the Stria Terminalis (BNST). His team has shown that excitatory responses into the BNST are enhanced in rodents with a history of chronic alcohol use. The current research takes advantage of advances that enable the team to manipulate and measure in vivo and in real time circuits that are likely involved in promoting affective disturbances.

### **Basic Research**

**Yi-Zhi Wang, Ph.D.**, Northwestern University, is interested in the unusually strong learned associations about drug rewards and drug-related cues and contexts that are part of drug addiction. Neuronal ensembles within the ventral medial prefrontal cortex mediate self-administration of both food and drug reinforcers. Dr. Wang's current research seeks to shed light on potential differences in neuronal ensembles associated with food self-administration and drug self-administration. His team has developed the means to study both in a single animal, research which he hopes will lay the foundation to test whether unique neuroadaptations in neurons activated by cocaine seeking underlie the relative strength of those associations compared to natural rewards.

### **Basic Research**



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**Brandon Warren, Ph.D.**, National Institute on Drug Abuse/NIH, is interested in strong learned associations about drug rewards and drug-related cues and context -- associative learning thought to be mediated through sparsely distributed patterns of neurons, called neuronal ensembles, selected by drug-related stimuli and reinforcers. This project aims to distinguish neuronal ensembles activated by food self-administration and drug self-administration within the same animal model. It is hoped this will lay a foundation for experiments designed to test whether unique neuroadaptations in neurons activated by cocaine-seeking underlie the relative strength of those associations compared to natural (food) rewards.

### **Basic Research**

**Sylia Wilson, Ph.D.**, University of Minnesota, will examine functional connectivity deviations in key neural circuits associated with addiction in a sample of 1,152 adult twins. She will apply quantitative methods to get at issues of causality, including differentiation of pre-existing liability from effects related to substance abuse. She will assess the theory that deviations seen in addicted individuals are evident prior to substance initiation or misuse, which would suggest a way to predict prior susceptibility to substance use. She will also examine whether connectivity deviations identified in the adult sample that reflect genetic risk are also evident in a subsample of their young children (n = 180) prior to any substance exposure.

### **Basic Research**

**Sarah Winsland Yip, Ph.D., M.S.c.**, Yale University, will assess the relationship between two factors thought to contribute to the relapse of people being treated for addiction to opioids -- chronic pain and individual differences in patterns of brain connectivity. Dr. Yip's pilot data suggest that individual differences in patterns of brain function contribute to variability in opioid relapse, but that this relationship differs between patients with and without chronic pain. The team will assess the interaction between these two factors among patients entering medication-assisted treatment for opioid-use disorder, recruited from a local outpatient clinic and invited to participate in fMRI scanning. Neuroimaging data will be analyzed in a way that may reveal brain networks predictive of opioid relapse.

### **Diagnostic Tools/Early Intervention**

## **Attention-Deficit Hyperactivity Disorder (ADHD)**

**Atul Maheshwari, M.D.**, Baylor College of Medicine, will analyze electroencephalogram (EEG) readings in mice that capture the coupling between slow and fast EEG rhythms or waveforms, which are thought to be a mechanism in the brain that coordinates attention. Dr. Maheshwari will investigate how these rhythms work together in normal mice during attention tasks, and how medications known to enhance or impair attention affect these rhythms. The research will also look at the EEG patterns in mice with genetic mutations that model attention deficit hyperactivity disorder (ADHD), testing whether Ritalin, the first-line treatment for ADHD, affects both EEG rhythms and performance on attention tasks.

### **Basic Research**

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**Aki Nikolaidis, Ph.D.**, Child Mind Institute, will be analyzing data collected from more than 10,000 children to look for variations in how the brain's cortex, its region of thinking and perceiving, is connected to the striatum, a region involved in motor control and reward processing. Dysfunction in the corticostriatal connection is known to be linked to attention deficit hyperactivity disorder (ADHD), and Dr. Nikolaidis wants to find out whether different corticostriatal neurotypes may be linked to different types of ADHD.

### **Basic Research**

**Nikhil Urs, Ph.D.**, University of Florida, wants to know more about the paradoxical calming effect of psychostimulants like Aderall and Ritalin on patients with attention deficit hyperactivity disorder (ADHD). His team seeks to determine the action of psychostimulants in the prefrontal cortex (PFC) on locomotor activity and the release of dopamine (DA) in the striatum. They hope to identify the neuron subtypes involved in this psychostimulant action using knockout mice. They also aim to artificially activate PFC neurons and reduce locomotor activity and striatal DA release, which may shed light on the mechanism of psychostimulant action in ADHD therapy and facilitate development of new therapies.

### **Basic Research**

## Anxiety

**Nicholas I. Balderston, Ph.D.**, at the National Institute of Mental Health (NIMH/NIH), seeks to expand the therapeutic use of transcranial magnetic stimulation (TMS), applying it in anxiety disorders by using knowledge of brain circuitry as a guide. Building on preliminary findings that suggest that the brain's attention networks are involved in anxiety, Dr. Balderston will make people mildly anxious in a controlled laboratory setting and then study the effects of stimulating their attention networks with TMS. This approach will allow rapidly testing of new therapeutic applications of TMS before conducting lengthy trials in patients.

### **Next-Generation Therapies**

**Tali Manber Ball, Ph.D.**, at Stanford University, will investigate the role of avoidance behavior in adults with anxiety disorders. Reducing the unnecessary avoidance of safe situations is a key element of anxiety treatment strategies, and as a result, there is a need to be able to measure a patient's tendency to avoid. Dr. Ball aims to validate, in adults with an anxiety disorder, an approach that was recently developed through studies of healthy people and uses virtual reality to assess the tendency to avoid safe situations.

### **Basic Research**



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**Jeremy Stanford Biane, Ph.D.**, at The J. David Gladstone Institutes at the University of California, San Francisco, will examine an area of the brain that is crucial to generating and processing anxiety. Known as the ventral hippocampus (vHPC), this region becomes active when a person explores an anxiety-inducing environment. By tracking the activity of individual mouse brain cells in the vHPC in real time, Dr. Biane will elucidate how the vHPC reacts to anxiety-inducing cues from the environment and influences behavior.

### **Basic Research**

**Brendan E. Depue, Ph.D.**, at the University of Louisville, will explore the distinction between fear and anxiety. Dr. Depue believes that fear responses have often been studied at the expense of sufficient attention to true anxiety responses, and that this distinction is critical. To address this issue, Dr. Depue will examine a brain region called the bed nucleus of the stria terminalis, which responds when a potential—but unconfirmed—threat is detected.

### **Basic Research**

**Elliot Kale Edmiston, Ph.D.**, at the University of Pittsburgh, will test a new target in the brain for treating anxiety disorders with transcranial direct current stimulation (tDCS). People with anxiety disorders are more likely to perceive neutral facial expressions as threatening, and tend to display alterations in a threat detection network that includes the brain's visual cortex. Dr. Edmiston will test the effectiveness of targeting this and related brain areas with tDCS in individuals tasked with pressing a button as they watch a video of a face morphing from a neutral expression to an emotional one.

### **Next-Generation Therapies**

**Alexxai V. Kravitz, Ph.D.**, National Institute of Diabetes & Digestive & Kidney Diseases, NIH, will explore whether the modern diet contributes to long-standing rises in obesity and anxiety in the U.S. Dr. Kravitz believes the increasingly high-fat content of the foods we eat directly fuels anxiety as well as weight gain. To test this, he will expose rats to a high-fat diet and then measure their avoidance of objects in the environment as a reflection of anxiety. He will also record the response in neurons that release the neurotransmitter dopamine, crucial for reward processing, to see if they play a role in any anxiety that results from a high-fat diet.

### **Basic Research**

**Jayne Morriss, Ph.D.**, University of Reading, UK, is studying how individual differences in responding to uncertainty relate to anxiety and learning under different levels of uncertainty and threat. Previous research has shown a link between anxiety and intolerance of uncertainty, but there are few studies that explore why the two may be related. With a project that measures participants' response to computer-based tasks that emulate uncertain and threatening situations, Dr. Morriss hopes to learn more about whether intolerance of uncertainty disrupts an individual's learning of safety information. This will provide a foundation for further study of this connection in children and adolescents and its relevance to the development of anxiety-based disorders.

### **Basic Research**

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**Fernando M. C. V. Reis, Ph.D.**, University of São Paulo, Brazil, will be using a miniaturized microscope technique to study the hippocampus in mice to learn more about the neural mechanisms behind contextual fear, where certain locations or contexts are considered dangerous. Such fear can be useful, but the ability to unlearn fear sometimes goes awry in people with anxiety disorders. Dr. Reis is studying how cells in the hippocampus are activated during fear learning, fear extinction, and fear reinstatement, and how these neural pathways are controlled by stress-signaling molecules called glucocorticoids. The research could offer insights as to how contextual fear is altered in anxiety patients.

### **Basic Research**

**Michael Grady Wheaton, Ph.D.**, Barnard College, Columbia University, is seeking to enhance treatment efficacy and reduce relapse risk, testing the concept that “safety learning” is more robust when subjects learn to exercise behavioral control by actively avoiding threat cues rather than simple extinction. To explore this, he will test patients with anxiety disorders (n=40) and matched healthy controls (n=40), who will undergo Pavlovian threat conditioning before being randomized to one of two safety learning conditions: active avoidance (learning to perform an action to prevent shock) and yoked extinction (repeated exposure to presentation of the threat cue without shock). Comparative results could inform future treatments.

### **Basic Research**

## **Autism / Autism Spectrum Disorder (ASD)**

**Daniel Arthur Abrams, Ph.D.**, at Stanford University, aims to improve diagnosis and treatment of autism spectrum disorders (ASD) in females by focusing on the brain systems that process the sounds of human voices. Considering prior observations that suggest females with ASD are “protected” from more severe forms of the disorder, Dr. Abrams will search for brain circuits that are intact in girls with ASD, but not in boys. The research will also track how voice-processing circuitry in the brain may change as girls and boys with ASD mature into adolescence.

### **Basic Research**

**Claudio Acuna-Goycolea, Ph.D.**, at the University of Heidelberg, Germany, will investigate how mutations in parts of the genome known as human accelerated regions, or HARs, may contribute to autism spectrum disorders (ASD). HARs are regions of the genome that appear to have changed significantly during human evolution despite having stayed essentially the same throughout much of the rest of evolutionary history. Using a genome editing tool called CRISPR, Dr. Acuna-Goycolea will introduce ASD-linked mutations to HAR regions in stem cells primed to develop into human neurons, and study the effects.

### **New Technologies**



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**Benjamin D. Auerbach, Ph.D.**, at the Research Foundation for the State University of New York (SUNY) on behalf of the University at Buffalo, hopes to obtain new insights into brain abnormalities at the core of autism spectrum disorders (ASD) by studying aberrant sensory processing, a key diagnostic criterion. Intolerance to loud sounds is one such aberration, which Dr. Auerbach will examine in mice using behavioral tests and brain activity recordings. The team will also test several pharmacological therapies aimed at reversing these sensory disturbances.

### **Basic Research**

**Robert Paul Bonin, Ph.D.**, at the University of Toronto, Canada, will investigate how social touch may influence the difficulty that many individuals with autism spectrum disorders (ASD) have in forming social connections. Specialized nerves detect and transmit information about social touch, and abnormalities in the responses of these nerves may impair the ability of people with ASD to form social connections. Dr. Bonin will selectively create a sensation similar to social touch in mouse models of ASD and measure the degree of social bonding between them.

### **Basic Research**

**Simon Chen, Ph.D.**, at the University of Ottawa, Canada, wants to help develop therapeutic strategies to counteract brain circuit dysfunctions associated with motor skill-related deficits in autism spectrum disorders (ASDs). One strong genetic risk factor for developing an ASD is a specific mutation that researchers have been able to mimic in mice, which has the impact of delaying motor-skill learning. Dr. Chen will image the brains of these mice to elucidate the roles of the hormone and neurotransmitter noradrenaline in motor learning and examine whether stimulating the brain cells that produce noradrenaline can affect motor learning.

### **Basic Research**

**Crystal T. Engineer, Ph.D.**, University of Texas at Dallas, will explore a potential treatment for auditory symptoms of autism spectrum disorder. People with autism often struggle to process speech, and experience hearing deficits even after training to strengthen their auditory skills. Using an established rat model of autism, Dr. Engineer will test whether such training has stronger effects when paired with stimulation of the vagus nerve, which contributes to sensory processing. She hopes to point toward better treatment for auditory deficits among people with autism, and to identify brain networks involved in the improvement of sound processing.

### **Next-Generation Therapies**

**Aaron Gordon, Ph.D.**, University of California, Los Angeles, will study patterns of changes in gene expression that appear in a range of autism spectrum disorders. Using induced pluripotent stem cells, Dr. Gordon will create neuronal cultures that model the unique brain characteristics of different spectrum disorders. He will identify gene expression that uniquely marks cells grown from autism patient samples. His team will map these expression patterns onto cellular functions, seeking to understand how they give rise to symptoms of spectrum disorders.

### **Basic Research**



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**Junjie Guo, Ph.D.**, Yale University, will study the functions of a mutant protein that can cause the neurodevelopmental disorder fragile X syndrome as well as autism spectrum disorder. The fragile X mental retardation protein—or FMRP—regulates RNA messages in gene expression. To understand the protein’s precise role in neural development, Dr. Guo’s team will compare RNA movement in stem cell cultures from people with fragile X syndrome compared to those without the disorder. They will also test whether FMRP production can be restored by genetic intervention, or via drugs that stimulate receptors for the neurotransmitter glutamate, as two potential routes for treatment.

### **Basic Research**

**Xin Jin, Ph.D.**, Harvard University, will investigate the genetic origins of autism spectrum disorder, focusing on de novo genetic variants, “spontaneous” mutations that appear in a child but in neither parent. These variants have shown strong developmental effects in people with autism and intellectual disability. To better understand their role in autism, Dr. Jin’s team will conduct gene editing in rodent models to uncover the cellular changes that result from disruptions to autism-risk de novo genes.

### **Basic Research**

**Ruchi Malik, Ph.D.**, University of California, San Francisco/Gladstone Institutes, is studying the genes behind tuberous sclerosis (Tsc), a brain disorder that can cause autism spectrum disorder (ASD) in some patients. The goal of the research is to learn more about the role of Tsc genes in regulating the function of interneurons, cells that modulate signals between excitatory neurons in the brain. The study will help researchers learn more about how Tsc mutations might contribute to abnormal behavior and communication in people with tuberous sclerosis and ASD, and to find potential markers in the brain that would aid in the diagnosis and future treatment of these disorders.

### **Basic Research**

**David A. Matuskey, M.D.**, Yale University, will use positron emission tomography (PET) scanning of people with and without diagnosed autism spectrum disorder (ASD) to determine whether the density of synapses (connections between brain cells) can be used as an effective marker to diagnose people with ASD. Dr. Matuskey would also like to know whether differences in synaptic density are linked to specific behavioral and clinical symptoms of the disorder. The study, to be conducted over two years, will be the first to directly investigate synapse density in living ASD patients.

### **Diagnostic Tools/Early Intervention**



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**Galen Missig, Ph.D.**, McLean Hospital/ Harvard University, will study adult mice that were challenged with immune-activating drugs during their perinatal development. These mice developed symptoms similar to those associated with autism spectrum disorder (ASD), strengthening the findings that inflammation and immune system activation during pregnancy may increase the risk of a child developing ASD. Dr. Missig will use a newly developed drug in the adult mice to discover whether the treatment can rebuild the population of brain immune cells called microglia. This experiment may help determine whether ongoing immune dysfunction is responsible for symptoms in ASD.

### **Basic Research**

**Tomasz J. Nowakowski, Ph.D.**, University of California, San Francisco/ Gladstone Institutes, will continue examining the role that a class of regulatory RNA molecules, called microRNAs, may have on neuropsychiatric disorders in general and autism spectrum disorder (ASD) in particular. microRNAs act to fine-tune gene expression, and Dr. Nowakowski has learned that previously identified ASD genes may be a target of microRNAs. His goal is to learn more about what happens when groups of these microRNAs are depleted or increased, to confirm which are most closely linked to ASD genes, and to learn more about the role of these RNAs in human brain cell development.

### **Basic Research**

**Neville Espi Sanjana, Ph.D.**, New York Genome Center, will use human brain cells engineered with mutations associated with autism spectrum disorder (ASD) to examine alterations in gene expression that may reveal common mechanisms of disrupted neural function. To understand if such shared mechanisms could be viable therapeutic targets, Dr. Sanjana will design CRISPR-based gene therapy tools to activate or inhibit genes with altered expression in ASD-linked neurons. For a particular ASD mutation or group of ASD mutations, the research will seek to determine if the resulting gene expression changes can be reversed.

### **Basic Research**

**Simon Thomas Schafer, Ph.D.**, Salk Institute for Biological Studies, aims to foster the development of new biological pattern-recognition tools for studying changing disease trajectories as opposed to disease states in autism spectrum disorders (ASDs), and to establish machine-learning strategies for identifying causal interactions within and across different biomedical data sets. Based on prior results indicating that aberrant timing of gene regulatory networks may have far-reaching consequences for coordinating maturation and interconnection of neuronal circuits, he will test when and where during development the earliest disease-associated signatures appear and try to determine whether transiently vulnerable periods exist during ASD development.

### **Diagnostic Tools/Early Intervention**



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**Tingting Wang, Ph.D.**, Georgetown University, is studying the role of glial cells in the context of autism spectrum disorder. Given their importance in modulating synaptic transmission and plasticity, Dr. Wang notes, it is essential to understand how glia respond and adapt to genetic and environmental perturbations by epigenetic regulation of gene expression, and how failed glia-dependent regulation of synaptic activity may be linked to the cause of disease. In this project Dr. Wang will use both fruit flies and mouse systems to delineate the novel function of glia as a critical signaling unit for neurons to sense and maintain their own activities in the face of perturbations.

### **Basic Research**

**Kai Yu, Ph.D.**, Cold Spring Harbor Laboratory, will conduct research that addresses the roles of the brain's basal ganglia in distinct behavioral changes observed in a mouse model of autism in which mutations affect a genome region called 16p11.2. He hopes to establish a framework for research into the mechanisms underlying the core symptoms and comorbid symptoms of autism spectrum disorders (ASDs). Mice with 16p11.2 deletion syndrome have behavioral changes including increased locomotor activity and repetitive behaviors, cognitive deficit and enhanced anxiety, all of which point to functioning of the basal ganglia. Dr. Yu will test this hypothesis using a combination of state-of-the-art technologies including electrophysiology, imaging, optogenetics, chemogenetics, and novel behavioral techniques.

### **Basic Research**

## **Bipolar Disorder**

**Jaroslav Bendl, Ph.D.**, at the Icahn School of Medicine at Mount Sinai, will scan the genome for gene mutations and other regions that increase the risk of bipolar disorder. Prior research highlights the importance of stretches of the genome that do not themselves encode genes but may regulate the expression of genes. Dr. Bendl will search for differences in the way that genes are expressed in patients' brains compared with brains of unaffected individuals, including differences in their epigenomes—collections of molecular tags that attach to DNA and affect gene expression.

### **Basic Research**

**Arianna Di Florio, M.D., Ph.D.**, at Cardiff University, UK, will explore the genetic association between bipolar disorder and sleep disturbances. Bipolar disorder is often associated with sleep disturbances such as insomnia or excessive sleep, regardless of mood. By combining genome-wide information with clinical data for over 5,700 individuals with bipolar disorder, Dr. Di Florio aims to determine whether variations in the genetic risk for sleep disturbances can identify clinically useful sub-groups of bipolar disorder patients.

### **Diagnostic Tools/Early Intervention**

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### Borderline Personality Disorder

**Chui-De Chiu, Ph.D.**, at the Chinese University of Hong Kong, will evaluate a potential framework to explain how, in borderline personality disorder (BPD), people process social information about perception of the self in relation to others. BPD is a mental illness rooted fundamentally in a biased view of the self. Dr. Chiu hypothesizes that dual mechanisms may contribute synergistically to the misperception of social information in people with BPD, resulting in fluctuating mood state and impulsive behavior that disturbs social and occupational functions. In this project, patients with BPD, other mood or anxiety disorders, and healthy controls will be compared. By marking the continuous variation in the socio-cognitive propensities and early relational experiences in community residents with varying degrees of BPD traits, Dr. Chiu hopes to reveal a spectrum of phenotypes, which may heighten understanding of the interaction between traumatic stress and brain function in the development of BPD.

#### Basic Research

### Depression

**Petr Bednarik, M.D., Ph.D.**, at the University of Vienna, Austria, seeks to reveal how ketamine influences symptoms in patients with treatment-resistant depression. Ketamine interacts with a neurotransmitter called glutamate, which is vital for normal brain functioning, but the details of this interaction are not known. Dr. Bednarik will use new imaging technology known as magnetic resonance spectroscopy imaging (MRSI) to measure with unprecedented accuracy glutamine levels in living human brains before and after ketamine administration.

#### New Technologies

**Katie L. Burkhouse, Ph.D.**, at the University of Illinois at Chicago, will evaluate markers in the brain that may predict the effects of Family Group-Based Cognitive Behavioral Therapy (FGCB). This approach is designed to treat young people whose mothers were diagnosed with major depressive disorder, and therefore are at high risk of developing depression themselves. Using functional magnetic resonance imaging (fMRI), Dr. Burkhouse will assess the activity of and connectivity between brain networks involved in reward processing among a group of mothers with a history of depression, and their children, half of whom will undergo FGCB.

#### Next-Generation Therapies

**Michelle Lynn Byrne, Ph.D.**, at the University of Oregon, will focus on the role of social-evaluative stress—in other words, the consideration of how peers think of you—in depression among girls. Responses to social-evaluative stress can involve the immune and hormone systems of the body, in addition to the brain, but the way in which these systems may interact with one another in this context is unknown. In an effort to elucidate this, Dr. Byrne will image the brains of puberty-aged girls as they

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participate in a social-evaluative task; she will collect saliva samples for measuring hormone and immune response levels.

### **Basic Research**

**Erin S. Calipari, Ph.D.**, at Vanderbilt University, will work at the intersection of genetics, neuroscience, and behavior with the aim of better understanding how social stress may contribute to depression. A gene's instructions for making proteins must first be copied, or transcribed, into RNA molecules, in order to engage the cell's protein-making machinery. By analyzing levels of transcription in brain cells and combining this information with brain imaging data in mice, Dr. Calipari will learn about how transcription influences the activity of populations of brain cells known to guide complex social behaviors.

### **Basic Research**

**Frederic Christophe Casse, Ph.D.**, at the University of Lausanne, Switzerland, will test a potential antidepressant, which contains molecules naturally released by "support" cells called astrocytes. Earlier research from Dr. Casse's lab suggests that this astrocyte-conditioned medium (ACM), when injected into mice, increases the generation of new brain cells and improves memory performance. Dr. Casse will assess the ability of ACM to treat mice with depression-like symptoms, and evaluate whether the generation of new brain cells is necessary to achieve therapeutic outcomes.

### **Next-Generation Therapies**

**Meaghan Claire Creed, Ph.D.**, at the University of Maryland, aims to validate a potential therapeutic target for depression, brain cells known as ventral pallidum (VP) neurons. In mouse models of depression, Dr. Creed will test whether the activity of VP neurons drives behaviors of despair in specifically designed tasks. This project will also include work toward identifying molecules that may be able to affect the activity of VP neurons and point to new therapeutic strategies.

### **Basic Research**

**Nicole Ashley Crowley, Ph.D.**, at Pennsylvania State University, seeks to expand understanding of the alcohol use disorder (AUD) among people with major depressive disorder. In the forebrain, inhibitory brain cells that express the peptide somatostatin (SST-expressing neurons) have been implicated in MDD. Dr. Crowley will seek to show in mice that SST neurons in a brain area implicated in AUD and depression change after binge-like alcohol consumption, consequently altering another key signaling pathway in that area.

### **Basic Research**

**Alec Lindsay Ward Dick, Ph.D.**, at the Max-Planck Institute of Psychiatry, Germany, will employ a new technique for monitoring genetic messages sent among cells in freely moving mice to study how stress contributes to depression. Molecules known as microRNAs have been implicated in depression, and act as fine-tuners and on-off switches of gene expression in response to cues from the environment. Dr. Dick will investigate the effects of stress on the release of microRNAs within stress-related brain circuits.

### **Basic Research**



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**Riddhi Prakash Doshi, MBBS, MPH, Ph.D.**, at the University of Connecticut Health Center, will carry out the first-ever application of a treatment strategy known as “video directly observed therapy” (VDOT) among patients diagnosed with depression, designed to address the issues of patients missing doses of their medications. VDOT is a smartphone-based app that sends video of patients taking their medicine to a secure server accessible only by their healthcare providers. Measures of success will include patients’ acceptance of the technology and likelihood to miss a dose of prescribed medication.

### **Next-Generation Therapies**

**Ada Diane Eban-Rothschild, Ph.D.**, at the University of Michigan, seeks a better understanding of the link between sleep/wake disturbances and depression. These issues are thought to arise from a common source within the brain, such as the ventral tegmental area (VTA), which is central to regulating the sleep/wake cycle and displays altered activity in individuals with depression. In studies of mice, Dr. Eban-Rothschild will test whether chronic alterations in the activity of the VTA during sleep can induce sleep/wake disturbances and result in depression-related symptoms.

### **Basic Research**

**Katherine Babcock Ehrlich, Ph.D.**, at the University of Georgia, will investigate how difficult socioeconomic circumstances may have physiological consequences that result in mental illnesses such as depression. Considering that individuals from disadvantaged backgrounds who demonstrate the most resilience in terms of socioemotional functioning and educational attainment often show the poorest physical health, Dr. Ehrlich suspects these issues extend into mental health. To test this, Dr. Ehrlich will assess young people’s depressive symptoms and behavioral problems at school, and measure indicators of inflammatory immune responses, which are linked to depression.

### **Basic Research**

**Peter Grace, Ph.D.**, University of Texas, MD Anderson Cancer Center, will explore the biological basis of depression that arises from chronic pain. He will focus on microglia, immune cells in the central nervous system that activate in response to injury and have been shown to be implicated in depression-like symptoms, including lack of motivation. Dr. Grace’s team expects to show that microglia in the nucleus accumbens, a key brain region for goal-oriented behavior, are activated after injury to reduce transmission of the neurotransmitter dopamine. They will be testing the hypothesis that microglia activity leads to depression by inhibiting goal-seeking behavior.

### **Basic Research**



## 2018 Young Investigator Grantees

**Brendan Deegan Hare, Ph.D.**, Yale University School of Medicine, will study the neural mechanisms underlying fast-acting treatment for depression. Typical antidepressants do not improve symptoms in many people, and they require weeks to take effect even when they work. Past research has found that a faster antidepressant effect can arise from stimulating dopamine D1 receptors in the medial prefrontal cortex. Dr. Hare hopes to discover the circuits involved in this effect by identifying the brain regions that receive signals from the medial prefrontal cortex when depression symptoms are actively being reduced.

### **Next-Generation Therapies**

**Alexander Z. Harris, M.D., Ph.D.**, Research Foundation for Mental Hygiene/NYSPI, Columbia University, will measure neural circuits associated with anhedonia as a possible biomarker for depression. Anhedonia, or a lack of interest in pursuing pleasure, is a symptom of depression. In a mouse model of the illness, Dr. Harris will use electroencephalography to detect the brain circuits and groups of neurons that contribute to anhedonia. His team will focus on activity in the ventral tegmental area and nucleus accumbens, brain regions that regulate reward processing.

### **Diagnostic Tools/Early Intervention**

**Lisa Holper-Nellen, M.D.**, University of Zurich Brain Research Institute, Switzerland, will study two potential biomarkers for depression. Past research has linked depression to dysfunction in mitochondria, the major energy producers in cells, and to elevated inflammation levels in blood cells. Looking at patients with depression and bipolar disorder that includes depressive episodes, Dr. Holper-Nellen will compare mitochondrial function and neuro-inflammation to levels detected in non-depressed people. She predicts that depression involves reduced mitochondrial activity in the prefrontal cortex and peripheral nervous system, accompanied by increased neuro-inflammation in blood cells.

### **Diagnostic Tools/Early Intervention**

**David Mark Howard, Ph.D.**, University of Edinburgh, Scotland, looking at large-scale genetic data, will build computer models to identify risk-factor genes and predict whether someone will develop depression. He will incorporate into his models separate data on life history, including hospital records and personality measures, methylation, which indicates which genes are actively expressing proteins, and the overlap of depression with other illnesses. Ultimately, he wants his models to identify not only risk factors for depression, but also specific sub-groups of the condition, allowing physicians to tailor medication and treatment to the range of underlying pathologies.

### **Diagnostic Tools/Early Intervention**



## 2018 Young Investigator Grantees

**Jessica Jenness, Ph.D.**, University of Washington, Seattle, wants to identify behavioral and environmental factors that reflect and predict depression among adolescents. Comparing 30 adolescents with depression to 30 non-depressed adolescents, her team will track brain activity, physical activity, social behavior, stressful life events, and depression symptoms to develop a picture of how these factors interact to drive the illness. They will look at the relation between function and connectivity in the brain's frontostriatal region. They hope to create behavioral profiles of adolescent depression that map onto biomarkers of the illness.

### **Diagnostic Tools/Early Intervention**

**Makoto Kawai, M.D.**, Stanford University, will study the relationship between sleep disruptions and late-life depression, which is the experience of the illness for the first time roughly after the age of 60. Looking at older adults with this condition, the team will measure brain activity, oxygen levels in the blood, and other biological states during sleep. The project will focus especially on obstructed breathing during sleep, a common condition for elderly people. Dr. Kawai hopes to identify sleep-based biomarkers associated with late-life depression that may be used to predict onset of the illness.

### **Diagnostic Tools/Early Intervention**

**Kate Ryan Kuhlman, Ph.D.**, University of California, Irvine, hopes to develop more precise treatment for adolescents with sleep disorders that put them at risk for depression. Sleep disturbances are known to increase depression risk and have been linked with exaggerated immune system responses to stress. Dr. Kuhlman's team will explore the idea that adolescents with clinical sleep problems have elevated levels of immune system inflammation, as measured in their blood and saliva, and also respond differently to stressful situations. They will test these hypotheses in 45 adolescents, who they will monitor for symptoms of depression in the year after the study.

### **Basic Research**

**Autumn Joy Kujawa, Ph.D.**, Vanderbilt University, wants to identify traits that predict depression in adolescents. Her team will build off work suggesting that young people at risk show a blunted neural response to social rewards and an elevated response to social threats. Using electrophysiological measures of brain activity, they will test how young people with depression, or with mothers living with the illness, respond to rewards and threats. They will also study whether any unusual reward and threat processing increases adolescents' responses to social stress and, as a result, produces depression symptoms. Their last steps will be studying how these factors form patterns that predict depression, pointing toward treatment strategies.

### **Diagnostic Tools/Early Intervention**

**Salvatore Lecca, Ph.D.**, University of Lausanne, Switzerland, is looking into the role that a part of the brain called the lateral habenula may play in postpartum depression (PPD), a severe syndrome that affects 10% to 22% of mothers but is poorly understood. Dr. Lecca and colleagues will examine the lateral habenula in a mouse model of stress-driven PPD, imaging and mapping the circuitry of the lateral habenula to pinpoint how these circuits may be involved maternal behavior and how the normal functioning of these circuits goes awry in the disorder.

## 2018 Young Investigator Grantees

### Basic Research

**Yi Lu, Ph.D.**, Karolinska Institute, Sweden, will conduct a large genome-wide association study of major depressive disorder (MDD) using national health databases from Sweden, Denmark and Norway. Dr. Lu plans to develop an “optimal” definition of the clinical symptoms of major depressive disorder and to use this definition to comb through national biobanks and patient registers to find more than 100,000 cases of MDD to use in the study. The results will be used to learn more about the biological pathways, brain tissues, and cell types associated with MDD and to inform drug discovery for depression.

### Basic Research

**Alexander McGirr, M.D.**, University of Calgary, Canada, is studying ways to increase the benefits of repetitive transcranial magnetic stimulation (rTMS), a noninvasive treatment that uses an electromagnetic coil to send magnetic pulses to areas of the brain that affect mood. The treatment, used to improve depressive symptoms, is thought to work by altering the connections of specific neurons in the brain. Dr. McGirr will test whether patients undergoing rTMS and also taking a low dose of an antibiotic called d-cycloserine, a drug known to affect neural connections, will experience stronger changes in neural connectivity than patients treated with rTMS alone.

### Next-Generation Therapies

**Lisa M. McTeague, Ph.D.**, Medical University of South Carolina, is hoping to determine the optimal dose for repetitive transcranial magnetic stimulation (rTMS), a noninvasive brain stimulation using electromagnetic coils placed near the head. rTMS has been approved by the FDA for the treatment of major depression, but the relationship of the “dose” of rTMS to the response of remediating depression symptoms has not yet been quantified. Dr. McTeague will study how different rTMS doses correspond to the alleviation of depressive symptoms, to determine if and how it might be possible to shorten the typical therapeutic course of rTMS, from four to six weeks to three days to two weeks.

### Next-Generation Therapies

**Mark Ronald Mizee, Ph.D.**, Netherlands Institute for Neuroscience, The Netherlands, will be examining postmortem brains from the Netherlands Brain Bank to determine the relationship between changes in microglia, the immune cells of the brain, and major depression. In previous analyses, Dr. Mizee determined that in subjects diagnosed with depression, microglia in the visual cortex are much different than those in healthy brains. The goal is to expand this comparison of microglia in samples from the prefrontal cortex and hippocampus, brain areas known to be affected in depression. The findings could help guide future microglial-targeted therapies to treat the disorder.

### Basic Research



## 2018 Young Investigator Grantees

**Marco Pignatelli, M.D.**, National Institute on Drug Abuse, is examining why drugs such as ketamine and its metabolite “cousin” hydroxynorketamine (HNK) are such powerful, fast-acting antidepressants, by probing how they alter signaling in the brain. Using mouse models, Dr. Pignatelli will focus specifically on a part of the brain called the nucleus accumbens, a region critical for mood and pleasure seeking, and how the drugs may increase the strength of brain cell signaling through their impact on a class of receptor proteins called AMPARs. The findings could help guide the development of other promising antidepressant medications without ketamine’s side effects, and perhaps shed light on the neural alteration involved in drug addiction and schizophrenia as well.

### **Next-Generation Therapies**

**Arjun Ramakrishnan, Ph.D.**, University of Pennsylvania, is developing a tool to screen for depression-based on biomarkers such as EEG readings and physiological responses such as pupil dilation during a decision-making task. These objective measures may help improve screening for depression that is otherwise based on questionnaires and self-reports. The goal will be to create a tool that patients can take home with them to monitor their own mental states. Dr. Ramakrishnan also says the project’s data might be useful in mapping depression symptoms over the long term, to learn what factors elevate the risk of a patient converting to major depression over time.

### **Diagnostic Tools/Early Intervention**

**Robb Brooks Rutledge, Ph.D.**, University College London, UK, will test the hypothesis that antidepressants affecting the glutamate and serotonin neurotransmitter systems work differently, in ways that can be measured and used to inform which patients should receive which type of treatment. Using computational modeling and a study population of patients and unaffected controls who will interface via smartphone app, he will obtain data for behavior and mood dynamics that he hopes will provide clinicians and researchers with potential candidate computational biomarkers.

### **Diagnostic Tools/Early Intervention**

**Durga Roy, M.D.**, Johns Hopkins University School of Medicine, will be looking at functional magnetic resonance imaging (fMRI) data in people with mild traumatic brain injury to investigate the severity and persistence of decreased functional connectivity immediately and one month after the injury. The goal is to determine the relationship between these functional changes and the development of depressive symptoms. Dr. Roy hopes to clarify whether there are levels of severity and persistence of altered connectivity required to reach a threshold for developing post-injury depressive symptoms in the early post-injury period.

### **Basic Research**



## 2018 Young Investigator Grantees

**Katherine Scangos, M.D.,Ph.D.**, University of California, San Francisco/Gladstone Institutes, will use high-density intracranial electroencephalography (iEEG) in humans to study circuits thought to be involved in major depression (MDD). In this technique, electrode strips are placed directly on the cortical surface and thin electrodes are inserted through deep structures in patients undergoing pre-surgical monitoring for medication-refractive epilepsy. This provides a powerful tool to study the circuit dynamics involved in people with epilepsy who also suffer from major depression. She will specifically investigate neural activity patterns within corticolimbic structures that may underlie MDD, building on pilot data.

### **New Technologies**

**Marianne Louise Seney, Ph.D.**, University of Pittsburgh, studies the sex-specific molecular pathology of major depression using human postmortem brain analysis. She has shown that depression is not only distinct in men and women, but is characterized by differing molecular pathology: increased markers of synaptic function coupled with decreased markers of immune function and microglia in women, and the opposite in depressed men. The current research will employ rodent models to assess dendritic spines and activated microglia in men and women with MDD, and test for sex-specific mechanisms driving these opposite effects.

### **Basic Research**

**Kanzo Suzuki, Ph.D.**, University of Texas Southwestern Medical Center at Dallas, aims to learn more about how the experimental drug ketamine exerts rapid and powerful antidepressant effects. In previous work his team proposed that ketamine, by blocking inactive NMDA receptors, deactivates an enzyme called eEF2K. Now they will test the hypothesis that eEF2K inhibition augments the function of AMPA receptors, leading to synaptic maturation and AMPAR insertion into the postsynaptic membrane -- which may account for ketamine-mediated changes in synaptic plasticity responsible for the behavioral effects.

### **Next-Generation Therapies**

**Benjamin Seavey Cutler Wade, Ph.D.**, University of California, Los Angeles, seeks to characterize treatment-response biomarkers to inform the future development of personalized treatment strategies in treatment-resistant depression (TRD). The team will leverage data from a large NIH/NIMH-funded project investigating the connectome in 200 TRD patients receiving electroconvulsive therapy, serial ketamine infusion, and total sleep deprivation. They will use machine learning algorithms to identify patterns predictive of individual antidepressant response. This could reveal whether biomarkers predictive of response to one of these interventions generalizes to predict clinical outcome following treatment with the other interventions or whether response to each intervention is best predicted by unique sets of biomarkers.

### **Diagnostic Tools/Early Intervention**



## 2018 Young Investigator Grantees

**Christian Anthony Webb, Ph.D.**, McLean Hospital/Harvard University, aims to develop more efficient, data-driven methods to optimize treatment selection for individuals suffering from depression, using machine learning algorithm-guided treatment recommendations. The current project is a two-year, two-phase effort to validate an approach his team has recently devised. Phase I will involve the development of a machine learning algorithm in two psychiatric treatment settings across the continuum of care at McLean Hospital. Phase II will test the algorithm in a separate sample of 100 patients with major depression to evaluate the validity of the model.

### **Diagnostic Tools/Early Intervention**

**Nolan Ryan Williams, M.D.**, Stanford University, notes that during sadness in depressed patients, the subcallosal cingulate cortex becomes excessively activated, while the left dorsolateral prefrontal cortex become hypoactive. Dr. Williams will conduct a double-blind, placebo-controlled clinical trial designed to assess high-dose spaced theta-burst TMS (transcranial magnetic stimulation) as a rapid-acting and durable brain network modulation technique, enrolling 60 individuals with treatment-resistant depression, half of whom will receive sTBS treatment. He hopes sTBS results will lay the groundwork for elucidating the stimulation conditions necessary to produce long-lasting changes in the human brain, a targeted treatment approach that can be completed on the inpatient unit resulting in a durable anti-depressant effect that is sustained weeks after treatment.

### **Next-Generation Therapies**

## **Eating Disorders**

**Estefania Pereira Cardoso Azevedo, Ph.D.**, at The Rockefeller University, will test how specific circuits may influence how the brain processes sensory cues from food, an important factor in understanding eating disorders. In real-time, Dr. Azevedo will study how food-related sensory cues such as odor affect lab animals' perception of "fullness" and the creation of rewarding memories. Insights into these processes have the potential to improve understanding of how sensory cues used in food marketing may contribute to eating disorders, such as binge eating disorder.

### **Basic Research**

**Fabricio H. Do Monte, Ph.D.**, at the University of Texas Health Science Center at Houston, seeks a better understanding of the association between fear disorders and eating disorders such as anorexia, bulimia, and obesity. A brain region called the paraventricular nucleus of the thalamus (PVT) is known to be directly interconnected with areas of the brain implicated in the control of food-seeking and fear response. Focusing on the PVT, Dr. Do Monte will investigate the relationships among the brain regions that control fear and food-seeking by manipulating and measuring the brain activity of rats.

### **Basic Research**



## 2018 Young Investigator Grantees

**Cindy Cherise Hagan, Ph.D.**, California Institute of Technology, will investigate the role of the orbitofrontal cortex in anorexia nervosa. This brain region helps us assess the nutritional value of foods and choose from different options. People with anorexia have shown disrupted connectivity in the orbitofrontal cortex that corresponds with symptom severity. Connectivity deficits persist even after they have gained back weight. Dr. Hagan will use neuroimaging to compare brain activity in people who have had anorexia to people without the disorder, to determine whether anorexia involves abnormal nutritional evaluations centered in the orbitofrontal cortex.

### **Basic Research**

**Carol Kan, Ph.D.**, Institute of Psychiatry, King's College London, UK, seeks to develop personalized treatment and prevention strategies for anorexia nervosa. Many anorexia patients struggle to recover and avoid relapse, and treatment response varies hugely from person to person. To lay the groundwork for personalized treatment programs, Dr. Kan's team will combine data from seven clinical trials and a database of female patients to compare their responses to four psychological programs, inpatient treatment, and support tools for caretakers in their lives. The long-term goal is to sort patients into groups according to their unique course with the illness, perhaps enabling physicians to customize treatment.

### **Basic Research**

**Sung Il Park, Ph.D.**, Texas A&M University, is working on a way to study, record, and stimulate the nerve circuitry in the hindbrain that collects input on feeling full after eating and controlling the body's energy intake. The research will improve our understanding of some of the neural circuitry that may be involved in obesity and in eating disorders including anorexia. Dr. Park will use a variety of methods to explore how manipulating cells in the nucleus tractus solitarius (NTS) of the hindbrain can regulate food intake in mice. The experiments will also include engineering a unique device capable of long-term wireless recording and stimulation of nerve signals in the NTS.

### **Basic Research**

**Sarah A. Stern, Ph.D.**, The Rockefeller University, seeks to develop behavioral models of eating disorders in which mice are conditioned to increase or decrease food intake in a manner that does not reflect bodily needs. Such a model could enhance our understanding of the neural circuitry controlling complex feeding-related disorders. To this end she will employ methods of profiling cells in the insular cortex to explore cue-food associations with negative outcomes (e.g. nausea, stomachache), which can lead to long-lasting memories in which food intake is later restricted. She seeks to generate an understanding of how maladaptive food choice behavior arises in the brain, and to illuminate potential therapeutic targets for eating disorders such as anorexia nervosa and binge-eating disorder.

### **Basic Research**

## 2018 Young Investigator Grantees

### Biology of the Brain

#### Brain Stimulation

**Evangelos Antzoulatos, Ph.D.**, at the University of California Davis Medical Center, seeks a better understanding of how a new therapy known as transcranial direct-current stimulation (tDCS) affects brain activity. While tDCS is now used to treat a number of mental illnesses, including schizophrenia, little is known about how it achieves its therapeutic effects in the brain. Through studies on non-human primate brains, Dr. Antzoulatos will examine how tDCS regulates brain activity, focusing on a key area known as the frontostriatal network.

#### New Technologies

#### Early-life Stress

**Jessica Lynn Bolton, Ph.D.**, at the University of California, Irvine, will shed light on how adversity early in life can contribute to vulnerability or resilience to mental illness through changes in brain circuitry. In particular, stress-responsive circuits are known to change in response to early-life adversity. Dr. Bolton will image the brains of live mice, focusing on a type of brain cells called microglia, immune cells that are involved in the visual system.

#### Basic Research

#### Biomarkers

**Alexander William Charney, M.D.**, at the Icahn School of Medicine at Mount Sinai, envisions a future in which it is possible to assess mental illnesses via a routine blood draw, and will search for cues from immune system that may aid to make this concept feasible. These cues, Dr. Charney believes, may be found in genetic messages floating around patients' cells, presumably in transit to help accomplish immune-related tasks. To find them, Dr. Charney will draw genetic information from single cells in blood and brain samples in psychiatric patients, revealing additional insights into whether certain cell subtypes regulate interactions between the brain and the rest of the body.

#### Diagnostic Tools/Early Intervention

#### Stress and Sleep

**Shinjae Chung, Ph.D.**, at the University of Pennsylvania, will work to elucidate the brain circuitry involved in sleep, and how good quality sleep restores emotional balance. Stress has been shown to impair sleep, and may consequently lead to the development of psychiatric disorders. By studying the activity of specific brain circuits in mice, Dr. Chung will characterize the effects of stress on brain cells and test how sleep may help in coping with stress-induced sleep disturbances.

#### Basic Research

## 2018 Young Investigator Grantees

### Learning and Memory

**Giannina Descalzi, Ph.D.**, at New York University, aims to advance understanding of the way learning and memory occur in the brain. Recent research shows that brain cells known as astrocytes are critical for memory formation. Dr. Descalzi will test how astrocytes affect brain cells during learning, and whether they provide energy to brain cells during memory creation in the form of a molecule called lactate.

#### Basic Research

### Dopamine System

**Aliza T. Ehrlich, Ph.D.**, McGill University, Canada, will investigate a potential treatment for illnesses such as Parkinson's, depression, and schizophrenia that involve disrupted transmission of dopamine, a neurotransmitter central to movement, learning, memory, reward, and emotion. Working with mice, Dr. Ehrlich will test receptors for a chemical called neurotensin that inhibits dopamine neurons. It is hoped that triggering neurotensin will reduce excessive movement caused by dopamine transmission. The team aims to lay the groundwork for a treatment that stimulates neurotensin via arrestin proteins, an approach that has shown promise in lessening symptoms without producing side effects.

#### Next-Generation Therapies

### Brain Patterns in Sleep

**Maria Jose Galazo, Ph.D.**, Tulane University, will study the disruptions to brain oscillations associated with sleep and memory deficits. Brain oscillations are rhythmic patterns of electrical activity produced by neural tissue; oscillations that occur during sleep help to create new memories. In schizophrenia and other disorders, patients have shown abnormal sleep linked to unusual oscillations. They have also shown memory impairments. Using mouse studies, Dr. Galazo aims to uncover the basis of these oscillations and their role in memory formation. She hopes this work will lay the groundwork for manipulating brain oscillations as a new treatment for sleep and memory deficiencies in schizophrenia and other conditions.

#### Basic Research

### Substance Use and Epigenetics

**Suhas Ganesh, M.D.**, Yale University, will study whether cannabis use has epigenetic effects in adolescents that can lead to lasting changes in brain structure and resulting psychological issues. Use of other substances like alcohol and tobacco has been shown to affect methylation, a process in which specific groups of atoms attach to DNA and set up potential changes in gene expression. Expanding their research on children aged 13 to 16, Dr. Ganesh's team will study whether the DNA methylation process looks different in adolescents who use cannabis compared to those who do not, and whether any such changes are associated with long-term physiological and behavioral outcomes.

#### Basic Research

## 2018 Young Investigator Grantees

### Attention

**Adam John Granger, Ph.D.**, Harvard Medical School, will study the neurological mechanisms that underpin attention. Sustained attention improves with the release of the neurotransmitter acetylcholine, which promotes activity in the cortex. Yet neurons that release acetylcholine can also release GABA, a neurotransmitter that inhibits cortical activity and so might disrupt attention. Dr. Granger seeks to show that acetylcholine and GABA are released at different times or places, which may heighten cortical activity to promote attention. He hopes to provide insight into disorders like attention-deficit hyperactivity disorder and schizophrenia that are characterized by impaired attention.

### Basic Research

### Apathy and Motivation

**Tobias U. Hauser, Ph.D.**, University College London, University of London, UK, will study the neural basis of apathy, a common symptom in disorders including Parkinson's disease, depression, and schizophrenia. Apathy can occur when someone believes the costs of an action outweigh the potential benefits, meaning the action is not worth attempting. This mindset has been linked to disrupted function of the neurotransmitter dopamine. Dr. Hauser's team will use imaging to measure brain activity while suppressing dopamine activity in two neural pathways, one associated with assessments of reward and the other with assessments of effort. These pathways, Dr. Hauser predicts, hold new clues to the dysfunctional cost-benefit analyses that produce apathy.

### Basic Research

### Modeling Illness

**Yungil Kim, Ph.D.**, Icahn School of Medicine at Mount Sinai, wants to build models that combine genetic risk factors for neuropsychiatric disorders with brain measurements and clinical data to more precisely define those diseases. Large-scale studies have identified genetic risks for illnesses by examining gene variants in thousands of people with and without defined neurological conditions. Dr. Kim wants to extend that work by incorporating data not just on specific genes, but also on communication patterns in the brain, illness symptoms, chemicals outside of genes that can modify their activity, and messenger RNAs, which contain the blueprints for proteins. He hopes the project will help define illness pathology in enough detail to enable more personalized treatments.

### Diagnostic Tools/Early Intervention

### Decision-Making

**Shinichiro Kira, M.D., Ph.D.**, Harvard Medical School, will study the neural underpinnings of sensory-based decision-making, which is impaired in disorders including schizophrenia, autism, and obsessive-compulsive disorder. When evaluating options, our brains often combine sensory information with memories of past experiences to help us make effective decisions. Dr. Kira will investigate this behavior by disrupting activity in certain brain areas in mice while they perform sensory-based decision-making tasks. He predicts that specific brain areas crucial for making associations, like the posterior parietal cortex, are necessary for this kind of decision-making.

### Basic Research



## 2018 Young Investigator Grantees

### Decision-Making

**Aaron Christopher Koralek, Ph.D.**, Columbia University, will investigate the channels of communication in the brain that help us decide between safe and risky decisions. While safe decisions make sense in stable environments, bold decisions can have unexpected payoffs during environmental change. The ability to navigate these options is impaired in a range of illnesses including obsessive-compulsive disorder, schizophrenia, and addiction. Dr. Koralek will study the neural underpinnings of this skill by measuring activity in dopamine neurons, crucial for processing rewards, and their effect on communication in the dorsal striatum, a key decision-making region in the brain, during evaluations of both safe and risky options.

### Basic Research

### Dopamine System

**Polina Kosillo, Ph.D.**, University of California, Berkeley, will investigate dopamine dysfunction as a crucial source of pathology in mental disorders. Attention-deficit hyperactivity, autism spectrum, obsessive-compulsive, and anxiety disorders have all been linked to abnormal release of the neurotransmitter, which affects learning, motor control, emotion, and the brain's ability to manage itself. Dr. Kosillo will look at the mTORC1 tangle of proteins that, when overactive, is associated with increased risk of dopamine-related disorders. Using mice, her team will deactivate genes that regulate mTORC1 activity and measure the resulting dopamine production, which they predict will be abnormally low. They will also test whether this deficiency can be reversed.

### Basic Research

### Memory

**Kishore V. Kuchibhotla, Ph.D.**, Johns Hopkins University, will probe the brain cells and circuits that trigger memories in response to objects we encounter in the environment. These context-dependent memories and associations can have both positive and negative outcomes in relation to psychiatric illness. A familiar environment can comfort a child with autism and as a result improve her learning. Alternatively, loud noises can spark painful memories and cause trauma in someone with post-traumatic stress disorder. To understand the mechanisms underlying these memories, Dr. Kuchibhotla will investigate the release of neurochemicals that spur communication between neurons in response to environmental triggers, and how these chemicals act throughout different parts of the brain.

### Basic Research

### Genetic Damage

**John R. Lukens, Ph.D.**, University of Virginia, will be studying protein sensors that look for DNA damage in the nervous system. Previous research has shown that DNA damage sensors in immune cells can be found in the brain, but their exact function has been unclear. The findings could shed light on how the brain surveys itself for genetic damage and how possible inflammatory responses to that damage may play a role in a variety of neurodevelopmental and psychiatric disorders, including anxiety disorders.

### Basic Research



## 2018 Young Investigator Grantees

### Dopamine and Reward

**James W. Maas, M.D.**, University of California, San Francisco/Gladstone Institutes, is studying how dopamine signaling in the brain differs from signaling by other neurotransmitters. Dopamine signaling plays a critical role in normal brain functioning, but can go awry in a number of illnesses, including substance abuse. Dr. Maas wants to learn more about the mechanisms behind the unusual release of dopamine by neurons, and to manipulate these mechanisms to learn more about how dopamine acts in signaling the brain about unexpected rewards.

#### Basic Research

### Brain Development

**Simone Mayer, Ph.D.**, University of California, San Francisco/Gladstone Institutes, is examining how the brain's neurons assemble themselves into circuits and communicate with each other before birth. Her study will follow the communication of neurons in the lab using high-resolution microscopy techniques, and lay the groundwork for selectively interfering with these communication pathways to discover ways they may go awry in development or as the result of potential prenatal influences including stress or substance abuse by the mother. The findings could shed light on the development of a range of mental illnesses, including autism and schizophrenia, and to help devise treatments for prematurely born babies to improve their development of appropriate brain activity.

#### Basic Research

### Visualizing Neurons

**Arnab Mukherjee, Ph.D.**, University of California, Santa Barbara, is pursuing a new imaging strategy to visualize neuron activation in the mammalian brain, with hopes of learning more about how these activation patterns go awry in a range of disorders including schizophrenia, bipolar disorder, depression and addiction. Dr. Mukherjee and colleagues are developing a new type of magnetic resonance imaging (MRI) that relies on a class of proteins called aquaporins rather than the typical metal particles that send back signals from brain tissue to create images of neuronal activation. The team will use this technology to study the effects of two widely used antipsychotic drugs, haloperidol and clozapine, on patterns of neural activity in mice.

#### New Technologies

### Connectivity

**Michael Murphy, M.D., Ph.D.**, McLean Hospital/ Harvard University, is studying brain processing in psychotic disorders such as schizophrenia, to determine whether certain symptoms of these disorders may be caused by dysfunctional brain connectivity, where some connections between brain regions are inappropriately strong or weak. Dr. Murphy is testing the idea that thought disorder in people with schizophrenia may be related to dysfunctional connections in brain networks that maintain conscious awareness compared to networks that regulate attention, favoring attention by sensory stimuli over attention to goal-related stimuli.

#### Basic Research



## 2018 Young Investigator Grantees

### Early-life Abuse

**Maya Mikhailovna Opendak, Ph.D.**, Nathan S. Kline Institute for Psychiatric Research, is examining the impact that early-life abuse has on the amygdala. Amygdala dysfunction has been connected to social behavioral problems in social anxiety and a number of other psychiatric disorders. Dr. Opendak will look at how a mouse model of early-life caregiver abuse affects amygdala circuitry and function, and how the amygdala operates during tests of social behavior during weaning and adulthood. She will also examine the ways in which maternal enrichment following abuse could reverse some of the effects of early-life abuse in their offspring. The findings may guide future treatments for trauma and anxiety.

### Basic Research

### Gender Differences and Stress

**Abigail Marie Polter, Ph.D.**, George Washington University, is looking at the mechanisms behind the differences in susceptibility for depression and anxiety disorders between women and men—women are twice as likely to be diagnosed with these diseases. Specifically, Dr. Polter will be examining the role of neurons in the brain's ventral tegmental area, a group of cells that regulate reward, aversion and anxiety, in a mouse model in which male and female mice respond differently. The findings could help reveal circuit mechanisms that underlie female vulnerability to stress, and aid development of treatments that address the stress pathways that can lead to depression, anxiety disorders and post-traumatic stress disorder (PTSD) in women.

### Basic Research

### Expectation Bias/Inflexibility

**Erin Leigh Rich, M.D., Ph.D.**, Icahn School of Medicine at Mount Sinai, is interested in expectation bias, where expectations of an event can drive subsequent behavior and cognition in complex ways. People with depression, anxiety, substance abuse and other disorders often have difficulties modifying these biases when new information becomes available. Dr. Rich will be exploring how abnormally persistent activity in the brain circuits that underlie expectation bias may lead to this inflexibility, and how normal brains suppress this persistent activity. Her work will directly record the activity of neurons in the brains of monkeys as they engage in an expectation bias task, with the goal of analyzing expectation bias circuitry and testing how these circuits may be stimulated as a form of treatment.

### Basic Research

### Cognitive Reappraisal/Flexibility

**Maureen Elizabeth Ritchey, Ph.D.**, Boston College, is focusing on the basic mechanisms behind successful regulation of negative emotional memories. These memories have a powerful influence on current emotional states. Controlling the way we remember certain events could help treat depressive symptoms. Dr. Ritchey will look at cognitive reappraisal, a strategy that has been associated with improvements in mental health. She is interested in how cognitive reappraisal may reactivate the brain's hippocampus to modify memories in a lasting way, and will analyze functional magnetic resonance imaging (fMRI) data to measure this brain activity while study participants retrieve emotional and neutral memories.

### Basic Research



## 2018 Young Investigator Grantees

### **Imaging**

**Kerstin Ritter, Ph.D.**, Charité-University Medicine Berlin Freie Universität Berlin, Germany, will use a machine-learning technique called convolutional neural networks (CNNs) to find new ways to represent data contained in neuroimaging records from the UK Biobank, a massive open resource of health data. Dr. Ritter will then apply these new representations in the Research Domain Criteria, a research framework that uses multiple lines of information to explore the full range of human brain functioning, from normal to abnormal. The idea behind this project is to find ways to represent and characterize brain and behavioral illnesses that will provide new perspectives and insights that are not evident in the “disease”-centered labels that have long been used in the clinic.

### **Diagnostic Tools/Early Intervention**

### **Motivation**

**Mark A. Rossi, Ph.D.**, University of North Carolina at Chapel Hill, is taking a closer look at some of the neural circuitry behind motivated behavior in the brain, which can be dysfunctional in a number of mental illnesses including eating and mood disorders, addiction, and PTSD. Dr. Rossi will use two-photon imaging to study how the brain’s lateral hypothalamic area, a critical hub of motivated behavior, is connected to two other brain regions that are also involved in motivated behavior and are a treatment target for deep brain stimulation for treatment-resistant mood disorders. The imaging study will show how these connections respond during exposure to rewarding and aversive stimuli.

### **Basic Research**

### **Coping Behavior-Orexin System**

**Robert Sears, Ph.D.**, Nathan S. Kline Institute for Psychiatric Research, is interested in the neurobiological mechanisms underlying proactive coping behaviors. Basic research has shown that the orexin (or hypocretin) system, a brain neuromodulatory system, elicits proactive behavioral activation when survival is on the line. Thus, the orexin system may enforce proactive coping behavior, such as escape or avoidance during heightened levels of stress. He will conduct experiments designed to uncover the orexin system's role in adaptive coping behaviors, seeking to provide evidence-based support for novel treatments of maladaptive coping, including proactive coping therapy combined with drugs to target the orexin system.

### **Basic Research**



## 2018 Young Investigator Grantees

### **Modifying Neural Circuits**

**Jerzy Olgierd Szablowski, Ph.D.**, California Institute of Technology, aims to develop a means to noninvasively control neural circuits with cell-type, spatial, molecular, and temporal specificity. He will experiment with an approach called acoustically targeted chemogenetics, or ATAC, which uses ultrasound to transiently open the blood-brain barrier in millimeter-sized regions of the brain and allow for the manipulation of neurons in these regions with virally encoded engineered protein receptors. His team has used ATAC to noninvasively activate or inhibit neurons in the hippocampus of mice, showing they could pharmacologically control their ability to form memories. The current project seeks to scale-up ATAC for use in larger animals and improving its safety, tissue specificity, and transduction efficiency by developing a new viral vector optimized for gene delivery.

### **New Technologies**

### **Genetic Regulation**

**Hyejung Won, Ph.D.**, University of North Carolina at Chapel Hill, hypothesizes that portions of the genome that confer unusual risk impact psychiatric conditions through complex gene regulatory networks. This project aims to unravel the gene regulatory landscape of the human brain to discover biological mechanisms of how risk variants drive gene expression patterns underlying psychiatric disorders. Dr. Won will utilize brain enhancer maps and statistical algorithms to prioritize regulatory variants that may underlie or indicate psychiatric conditions, then leverage chromatin interaction maps and other methods to assign schizophrenia risk variants to potential target genes. The functional relationship between non-coding variants and target genes will be explored.

### **Basic Research**

### **Social Isolation**

**Ofer Yizhar, Ph.D.**, Weizmann Institute of Science, Israel, notes that social isolation alters the functional properties of neural circuits to yield adverse behavioral and cognitive symptoms. He seeks to better understand the molecular, synaptic and circuit-level changes resulting from social isolation in the hope of discovering new avenues for treatment. The project aims to achieve a multi-faceted understanding of social isolation and its impact on the structure, connectivity and function of the brain's prefrontal circuits. Dr. Yizhar expects to show how social isolation alters the prefrontal cortex to shape cognition and emotion, work that could yield new targets for prevention and treatment of mental disability induced or exacerbated by social isolation.

### **Basic Research**

## 2018 Young Investigator Grantees

### Multiple Disorders

#### Schizophrenia, Addiction

**Davide Amato, Ph.D.**, at the Medical University of South Carolina, will search for underpinnings of the high rate of substance abuse among people with schizophrenia. One possibility is that antipsychotic drugs prescribed to treat the disorder may sensitize parts of the brain in a way that promotes substance abuse. Dr. Amato will test this idea in mice by observing how haloperidol, a medication used to treat schizophrenia, may alter part of the brain's reward system and its sensitivity to cocaine.

#### Basic Research

#### Addiction, OCD, Depression

**Matthew Ryan Banghart, Ph.D.**, at the University of California, San Diego, will probe brain circuits that may contribute to opiate addiction, obsessive-compulsive disorder, and depression. The neurotransmitter dopamine is used to send signals about rewards in the brain, and compromised dopamine signaling is implicated in a range of neurological disorders. Working in mice, Dr. Banghart will investigate how molecular signals such as those prompted by opiates influence brain cells that release dopamine, and in turn, influence behavior.

#### Basic Research

#### PTSD, Anxiety

**Christian R. Burgess, Ph.D.**, at the University of Michigan, will investigate the processes in the brain that underlie learned associations between cues from our environment and predicted outcomes. For example, a candy wrapper is more likely to draw our attention when we are hungry than when we are full, and fundamentally similar associations can become detrimental in illnesses such as post-traumatic stress disorder (PTSD). By imaging the brains of mice over the course of learning tasks, Dr. Burgess will look for brain circuits and behaviors that are necessary for forming learned associations.

#### Basic Research

#### Depression, Anxiety

**Samuel William Centanni, Ph.D.**, at Vanderbilt University, seeks insights into how the endogenous cannabinoid (eCB) system may provide a treatment target for affective disorders including depression and anxiety. The eCB system can be stimulated by cannabis use, but it can also be stimulated naturally by molecules created within the body. Such stimulation affects the release of the neurotransmitter glutamate, which can in turn regulate behavioral responses to stress. Dr. Centanni's team is using a recently developed glutamate sensor to measure release of the neurotransmitter to reveal the effects of enhancing eCB signaling on glutamate activity during and after coping with stress.

#### New Technologies

## 2018 Young Investigator Grantees

### **Schizophrenia, Bipolar Disorder**

**Michael Ben Clark, Ph.D.**, at the University of Oxford, UK, will investigate risk genes for schizophrenia and bipolar disorder using groundbreaking “long-read” genetic sequencing technology. Obtaining the sequence of genes in one piece has been challenging because most genetic sequencing technologies can read out only short pieces of the genome at a time—a problem that the newest generation of sequencing technology addresses. Dr. Clark will use this technique on human brain tissue to decipher the instructions of the most important risk genes for schizophrenia and bipolar disorder.

### **New Technologies**

### **Anxiety, PTSD**

**Cyril Dejean, Ph.D.**, at INSERM, France, hopes to refine clinically relevant invasive and noninvasive treatments for fear- and anxiety-related disorders such as post-traumatic stress disorder. Newer treatments such as electrical deep brain stimulation, transcranial current stimulation, and repetitive transcranial magnetic stimulation have generated encouraging but mixed results in patients with fear- and anxiety-related disorders. Working in mice, Dr. Dejean will alter a brain area that underpins fear expression to help guide refinements.

### **Next-Generation Therapies**

### **OCD, Addiction, ADHD**

**Becket Ebitz, Ph.D.**, at the University of Minnesota, strives to identify brain areas that can serve as treatment targets for addiction, obsessive-compulsive disorder (OCD), and attention deficit hyperactivity disorder (ADHD). All of these disorders involve an inability to change behavior in response to changing reward possibilities, resulting in repeated negative outcomes. An interconnected network of subcortical and cortical regions is implicated in flexibility and inflexibility, including the dorsal anterior cingulate cortex (dACC), the dorsolateral prefrontal cortex (dlPFC), and the locus coeruleus (LC). Dr. Ebitz hopes to determine if targeted interventions in these areas can regulate flexibility in brain activity and behavior.

### **Basic Research**

### **ADHD, Autism, Schizophrenia**

**Evan Harriman Feinberg, Ph.D.**, University of California, San Francisco, Gladstone Institutes, will probe the attention deficits that often come with conditions like attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and schizophrenia. People with these illnesses sometimes struggle to focus, even on stimuli that naturally grab attention—like flashing lights and sirens—through what are called bottom-up processes. Dr. Feinberg’s team will study the neurological basis of these processes. His team will test mice to discover how subcortical brain structures communicate with the cortex to give rise to bottom-up processing. They hope this knowledge will lead to a better understanding of how this process is disrupted in mental illness.

### **Basic Research**

## 2018 Young Investigator Grantees

### **Tourette, OCD, Autism**

**Daniel John Foster, Ph.D.**, Vanderbilt University, will investigate a possible new treatment for the repetitive behaviors that are often a debilitating symptom of obsessive-compulsive disorder, Tourette syndrome, and autism spectrum disorder. Potential for more targeted treatment lies in evidence that abnormal repetitions result from activity in the striatum, a brain region crucial for habitual and goal-directed behaviors. Using mouse models, Dr. Foster will test the hypotheses that excessive repetition stems from high release of glutamate and dopamine in the striatum, and that it can be treated with a type of muscarinic acetylcholine receptor that reduces the transmission of both neurotransmitters.

### **Next-Generation Therapies**

### **Bipolar Disorder, Suicide**

**Dorian Ashley Lamis, Ph.D.**, Emory University School of Medicine, will examine the roles of childhood abuse and gene modifications in suicidal behaviors among low-income African-Americans with bipolar disorder (BP). BP has the highest associated risk of suicide among major mental illnesses. Dr. Lamis' study will collect data on childhood abuse and gene modifications (assessed through saliva samples) from 125 men and women to search for associations between abuse, gene modifications, and suicidal behavior.

### **Basic Research**

### **Anxiety, Panic Disorder**

**David MacLean, Ph.D.**, University of Rochester, will examine how acid-sensing ion channels (ASICs) are involved in the strengthening of brain circuits involved in the formation of fear memories, using studies in mice. Knowing more about ASICs, Dr. MacLean says, could lay the groundwork for studying their potential role in anxiety and panic disorder. Anxiety and panic disorder are associated with higher level of carbon dioxide inhalation, which acidifies the blood and extracellular fluid. ASICs sense this change and help to spur physiological and behavioral responses. Previous studies have also shown that genetic mutations in ASIC genes are associated with panic disorder in humans.

### **Basic Research**

### **Depression, Anxiety**

**Stefanie Malan-Muller, Ph.D.**, The University of Stellenbosch, South Africa, will conduct a large-scale, population-based study in South Africa to learn more about how different kinds of gut bacteria are associated with anxiety and depression in patients. Previous research strongly suggests that the gut microbiome plays a role in several neuropsychiatric disorders, but most studies have been small or conducted in animal models. The South African study will compare individuals with anxiety and depressive symptoms with healthy participants, using surveys and genetic analysis of gut bacteria extracted from stool samples. The study could guide clinical research of probiotic and similar gut treatments to impact mental illness.

### **Basic Research**

## 2018 Young Investigator Grantees

### **Anxiety, PTSD, Panic Disorder**

**Rachel Denise Moloney, Ph.D.**, University of Cincinnati, will examine the neurocircuitry that underlies fear- and anxiety-related disorders, including post-traumatic stress disorder (PTSD). Dr. Moloney will be tracing the role that a protein called glucocorticoid receptor (GR) modulator plays in a part of the brain called the anterior bed nucleus of the stria terminalis. Variants of the protein have been linked to PTSD. The region of the brain under study helps to perceive and evaluate environmental cues as either stressful or neutral, and guides behavior in response to these cues, including producing a fear response. Understanding the details of this circuitry can help pinpoint ways that it may malfunction in anxiety and fear-related disorders.

#### **Basic Research**

### **Autism, Schizophrenia**

**Anna Rachel Moore, Ph.D.**, Temple University, is exploring one aspect of how brain cells remain flexible in a changing environment, altering their signaling capabilities when necessary. One way a neuron can maintain this flexibility is through changes in its membrane that help to shape its output signal to other neurons. Autism spectrum disorder (ASD) and schizophrenia have been linked to disruptions in this type of neuronal flexibility. Dr. Moore will be using the protein Rem2 as a way to probe the types of signaling mechanisms needed to establish and maintain neuronal flexibility.

#### **Basic Research**

### **Depression, Alzheimer's Disease**

**Ines Moreno-Gonzalez, Ph.D.**, University of Texas Health Science Center at Houston, is exploring whether late-life depression may accelerate the progression of Alzheimer's disease (AD). There are some signs that people with a history of depression may have an earlier age of onset for AD, and that those with mild cognitive impairment and depression have larger amounts of the toxic proteins associated with AD. Dr. Moreno-Gonzalez will further explore this idea by analyzing the blood of patients with and without depression to compare their levels of AD-related toxic proteins. The findings could shed light on whether antidepressants may be a useful preventive therapy for AD in some patients.

#### **Basic Research**

### **Anxiety, ADHD**

**Sahana Murthy, Ph.D.**, Princeton University, will study some of the molecular mechanisms that may link anxiety disorders and attention deficit hyperactivity disorder (ADHD) with adverse experiences in early life. Childhood physical abuse has been shown to greatly increase susceptibility to both ADHD and anxiety, highlighting the need to understand how experiences like abuse may alter brain circuits. Building on earlier work, Dr. Murthy will focus on the activity and interactions between specific populations of interneurons, the extracellular matrix that surrounds them, and other protein factors to determine how they may be responsible for inducing anxiety and hyperactivity in mice with adverse early life experiences like premature weaning and maternal separation.

#### **Basic Research**

## 2018 Young Investigator Grantees

### **Depression, Anxiety, OCD**

**Benjamin Okaty, Ph.D.**, Harvard University, will identify and characterize specific subtypes of serotonin neurons in mice, to learn more about which serotonin cells are involved in depression and other illnesses such as anxiety and obsessive-compulsive disorder. Although many treatments for depression and affective disorders target the neurotransmitter serotonin, they can cause side effects and not all patients respond, making it essential to come up with new therapies. Dr. Okaty will be conducting a series of experiments in mice to learn whether two newly discovered serotonin neuron subtypes are related to neural circuitry and behaviors involved in depression.

#### **Basic Research**

### **Autism, OCD, Tourette**

**Scott Owen, Ph.D.**, The J. David Gladstone Institutes, will use a variety of methods to closely examine how local microcircuits in the brain running between the striatum and the basal ganglia may be involved in obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), Tourette syndrome and other similar disorders. The basal ganglia help to balance the automatic performance of everyday tasks and the learning of new behaviors, and an imbalance in these two factors has been associated with illnesses like OCD and ASD. Dr. Owen will examine this circuitry in mouse models of autism to learn more about how defects in local signaling contribute to specific symptoms and behavioral problems.

#### **Basic Research**

### **Autism, Schizophrenia**

**Mercedes F. Paredes, M.D., Ph.D.**, University of California, San Francisco/Gladstone Institutes, is studying the role that late-migrating neurons in the developing human brain may play in a broad spectrum of psychiatric diseases from autism spectrum disorder (ASD) to schizophrenia. Dr. Paredes will be looking for ways to identify and trace a subset of inhibitory neurons which continue to migrate within the human brain even several months after birth. These late-migrating neurons help to maintain the balance in the activation and quieting of nerve cells needed for normal brain function. Dr. Paredes would like to learn more about their function and to understand the clinical implications of disrupting the movement of these cells after birth, in experiments using the piglet brain as a model for the human infant brain.

#### **Basic Research**

### **Depression, Suicide**

**Stephane Richard-Devantoy, M.D., Ph.D.**, McGill University, Canada, will examine whether alterations in the brain's "pain network," particularly the region called the thalamus, are associated with suicidal behavior in elderly patients with depression. The aim is to learn whether these alterations lead to psychological pain, which is prominently associated with suicidal behavior. The study will look at whether there are differences in the pain network between those patients who attempt and those who think about suicide, and whether there is also an association between the cognitive impairment in depressed patients and psychological pain and any accompanying cerebral alterations.

#### **Basic Research**

## 2018 Young Investigator Grantees

### **Schizophrenia, Psychosis**

**Srivatsun Sadagopan, Ph.D.**, University of Pittsburgh, will use an animal model to study the effect of schizophrenia-like pathologies on sound processing in the auditory cortex, which past studies have linked with auditory and verbal hallucinations. The team will recreate two pathologies observed in auditory cortex neurons of schizophrenia patients -- functionally lower levels of inhibition and reduced density of dendritic spines. It is hoped these experiments will illuminate how schizophrenia-like circuit pathologies can lead to aberrant activity in sound-encoding neurons.

#### **Basic Research**

### **Addiction, ADHD, Borderline Personality Disorder**

**Sandra Sanchez-Roige, Ph.D.**, University of California, San Diego, will study impulsivity, a maladaptive trait associated with addiction and attention-deficit hyperactivity disorder (ADHD) and other disorders. Genome-wide association studies have identified robust associations between the gene *CADM2*, which encodes a mediator of synaptic signaling, and various measures of risky and impulsive behavior. Using mice in which the gene is knocked out, she seeks to discover the gene's role in modulating impulsive behavior and synapse morphology, hoping to apply this knowledge in the context of psychiatric conditions associated with high levels of impulsivity.

#### **Basic Research**

### **Depression, Anxiety, PTSD**

**Aparna Shah, Ph.D.**, Johns Hopkins University, is studying the link between microRNA molecules – which are involved in regulating gene activity – and the response to stress. It is uncertain how an observed change in expression of a handful of microRNAs occurs and if it is instrumental in inducing the behavioral effects of stress. The current research seeks to identify ways to mimic these changes in rodents in order to test their behavioral impact. Among the experiments: assessing the effects of stress alone and in combination with antidepressant treatment on enzyme activity of a microRNA complex called TN/TX, and on microRNA expression levels in the dentate gyrus.

#### **Basic Research**

### **Epilepsy, Schizophrenia, Autism**

**Lakshmi Subramanian, Ph.D.**, University of California, San Francisco/Gladstone Institutes, seeks to understand the molecular and cellular causes of Focal Cortical Dysplasia (FCD), a type of cortical malformation that gives rise to pediatric epilepsy. Using donated brain tissue from patients undergoing surgical treatment for intractable epilepsy, Dr. Subramanian will focus on errors in the maturation of a specific group of progenitor cells called the outer radial glial (oRG) cells. In order to understand how these errors translate into disease, Dr. Subramanian hopes to build a detailed cellular profile of the disease, using advanced genomic technologies on donated human patient tissue to generate large-scale transcriptomic datasets. This research also may be pertinent in other developmental illnesses including schizophrenia and autism.

#### **Basic Research**

## 2018 Young Investigator Grantees

### **ADHD, Addiction, Depression**

**Emily Lauren Sylwestrak, Ph.D.**, Stanford University, is interested in the flexibility in neural circuits generated partly by neuromodulatory cell types. She focuses on a dense and diverse cluster of neuromodulators in the habenula, a brain area implicated in ADHD, addiction and depression. She will monitor changes in habenula activity as animals perform a task in pursuit of a reward. To map how different neurons participate in motivated behavior, she will label each cell type according to the neuromodulators they release, then determine if these cell types are required for animals to flexibly adjust their behavior to changing reward environments. The aim is to map cellular diversity in the habenula, determine how that diversity is organized to drive motivated behavior, and identify groups of cells that are selectively compromised in neuropsychiatric disorders.

#### **Basic Research**

### **Depression, Anxiety**

**Christine Lucas Tardif, Ph.D.**, McGill University, Canada, will use in vivo quantitative magnetic resonance imaging (MRI) to enable non-invasive longitudinal investigations of myelination in mice. Myelin is a lipid-rich sheath wrapped around axons that facilitates the rapid transmission of information between neurons. Recent research has shown that myelin is dynamically adapted throughout life in response to experience, a form of brain plasticity. This project seeks to determine if it is the restoration of myelin that alleviates depressive and anxiety-like behaviors in mice after their reintegration from social isolation. This could lead to the design of psychosocial or pharmaceutical interventions to promote adaptive myelination and enhance resilience to adverse events such as social isolation.

#### **Basic Research**

### **Fragile X, Autism, Epilepsy**

**Nien-Pei Tsai, Ph.D.**, University of Illinois at Urbana-Champaign, will study synaptic plasticity, the changing strength of connections between neurons, and synaptic depression in particular, which is crucial to the proper refinement of experience-dependent synaptic connections during circuit development and throughout life. Dysregulation of group 1 (Gp1) metabotropic glutamate receptor (mGluR)-mediated synaptic plasticity has been shown to be related to many disorders including Fragile X syndrome, autism spectrum disorders (ASDs), and cognitive impairment following epilepsy. Characterizing the specific molecular mechanisms involved in Gp1 mGluR-mediated synaptic depression in mouse models could allow for a deeper understanding of synaptic plasticity and new insight into treatments of neurological disorders.

#### **Basic Research**



## 2018 Young Investigator Grantees

### **Autism, Depression**

**Silvana Valtcheva, Ph.D.**, New York University School of Medicine, New York University, notes that autism-spectrum disorders (ASDs) and depression are both characterized by insensitivity to social stimuli, which leads to social dysfunction. The inability to extract socially-relevant information may be due at least in part to abnormal perceptual processing of speech and language. This research focuses on the neuropeptide oxytocin. It has been shown to increase the salience of infant vocalizations at the level of the auditory cortex and promote maternal behavior. Therefore, oxytocin might enhance neural responses to social vocalizations and enable the recognition of the behavioral meaning of socially relevant cues. This project aims at directly connecting activity of oxytocin neurons triggered by natural stimuli to different aspects of social behavior (maternal and non-parental), providing a biological basis for specialized processing of social communication.

### **Basic Research**

### **Schizophrenia, Psychosis, Autism**

**Smita Yadav, Ph.D.**, University of Washington, Seattle, studies TAOK2, a gene associated with autism, schizophrenia and psychosis. It is expressed in the developing human brain in neurons and neural progenitor cells, is a target of FMRP regulation, and it resides in the 16p11.2 genomic region, a hotbed of copy number variations (CNV) in people with autism spectrum disorder and schizophrenia. Aberrant expression of the protein the gene encodes has been linked to neurodegeneration. By investigating how perturbations in TAOK2 signaling pathways caused by mutations or abnormal gene dosage result in neurodevelopmental defects, Dr. Yadav hopes to elucidate how they contribute to neuropathology in autism and schizophrenia.

### **Basic Research**

### **Depression, Addiction**

**Hang Zhou, Ph.D.**, Yale University, will build upon past work in which he and colleagues provided evidence for shared genetic risk between major depression (MDD) and alcohol dependence (AD). Specifically, they identified SEMA3A linked to comorbid MDD and AD. To extend understanding of genetic susceptibility for comorbid MDD and substance use disorders, Dr. Zhou will conduct analyses on a large-scale whole exome sequencing sample of 2,838 subjects. Using next-generation sequencing data, the team hopes to address the issue of missing heritability by considering rare variants. Additionally, they hope to address the possibility of predicting comorbid conditions using exome-wide coding of rare variants.

### **Basic Research**

## 2018 Young Investigator Grantees

### Obsessive-Compulsive Disorder (OCD)

**Zirong Gu, Ph.D.**, Columbia University, will study the neural mechanisms underlying a defining trait of obsessive-compulsive disorder. People with OCD often have difficulty controlling their actions with flexibility and attention to goals, instead defaulting to habitual and compulsive behaviors. Dr. Gu's team will use a mouse model to probe this deficit by searching for brain-wide patterns of activity that characterize goal-directed versus habitual action control. They will also compare neural activity during action control in OCD model mice compared to wild ones, with the aim of identifying neural circuits that may prove to be treatment targets for the disorder.

#### **Basic Research**

**José Oliveira, M.D., Ph.D.**, Fundação Champalimaud, Portugal, is studying the role of inflammation in obsessive-compulsive disorder (OCD), and in particular whether immune responses in the brain's basal ganglia, which have been implicated in some cases of child OCD, could help explain the severity of the disorder more broadly across patients. Dr. Oliveira and colleagues will also use brain imaging and non-invasive brain stimulation to determine whether molecular markers of autoimmunity and inflammation are associated with differences in brain processing during a decision-making task related to OCD.

#### **Basic Research**

**Reza Tadayon-Nejad, M.D., Ph.D.**, University of California, Los Angeles, seeks a new perspective of the brain mechanisms of impaired decision making in obsessive-compulsive disorder (OCD). The focus will be an arbitration mechanism that controls the balance between two strategies -- goal-directed and habitual. These strategies come into play when we are making decisions that involve rewarding or punishing outcomes. This project will study the neurobehavioral characteristics of the arbitration system and explore its potential role in the goal-directed/habitual decision-making imbalance in OCD, and will explore the behavioral consequences of causally manipulating the targeted arbitration system by using non-invasive brain stimulation method of transcranial magnetic stimulation (TMS) in participants with OCD and a healthy control group.

#### **Basic Research**

**Peter Johannes van Roessel, M.D., Ph.D.**, Stanford University, will explore the use of nitrous oxide in the treatment of obsessive-compulsive disorder (OCD). Recent studies have demonstrated that abnormalities in glutamate signaling may underlie OCD symptoms, and that intravenous infusion of ketamine, an experimental drug that inhibits the NMDA receptor, may be effective in the rapid treatment of OCD. Yet ketamine has risks and transient adverse effects that limit its broad therapeutic acceptance, hence this effort to test nitrous oxide, which also blocks the NMDA receptor but is safe and well-tolerated as an inhaled anesthetic. This randomized, placebo-controlled pilot study if successful could lead to larger-scale clinical trials.

#### **Next-Generation Therapies**

## 2018 Young Investigator Grantees

### Other Disorders

#### Parkinson's Disease

**Canan Dagdeviren, Ph.D.**, at the Massachusetts Institute of Technology, plans to develop a new interface that precisely targets areas of the brain known to be involved in Parkinson's disease. The device will monitor electrical activity and levels of brain chemicals in an area called the striatum. In doing so, Dr. Dagdeviren hopes to bridge the gap between cutting-edge neuroscience research and advanced engineering devices.

#### New Technologies

#### Fetal Alcohol Syndrome

**Yohaán Mikhail Fernandes, Ph.D.**, University of Texas at Austin, will investigate the biological basis of fetal alcohol spectrum disorder, which develops when babies are exposed to alcohol during pregnancy and can lead to social deficits. Dr. Fernandes has shown that alcohol exposure causes similar deficits in zebrafish. Using the zebrafish model, his team will test the hypothesis that the genetic basis of these symptoms traces to signaling from the mTOR protein pathway. They predict that signaling changes disrupt social behavior by acting on the brain's dopamine system. Their findings aim to uncover potential targets for treating the disorder.

#### Basic Research

#### Hoarding

**Katie Fracalanza, Ph.D.**, Stanford University, will test a potential new treatment for hoarding disorder. Although cognitive behavioral therapy often reduces hoarding, some people do not want to start, or cannot handle, that option. To help such individuals, Dr. Fracalanza will test the alternative therapy of imaginal exposure, in which hoarders imagine discarding possessions as a way of becoming acclimated to the idea. Her team predicts that imaginal exposure will improve hoarding symptoms as well as two psychological experiences linked to the condition: intolerance of uncertainty and emotional avoidance.

#### Next-Generation Therapies

#### Neonatal Abstinence Syndrome

**William Christopher Risher, Ph.D.**, Marshall University, will study the formation of synapses, the connections between brain cells, in a mouse model of neonatal abstinence syndrome (NAS)—the condition of withdrawal symptoms in infants born to mothers with an opioid addiction. Specifically, Dr. Risher will be testing whether synapse formation in the mice, controlled by special types of brain cell called astrocytes, is disrupted in NAS. He will also examine how astrocyte-controlled synapse formation might be affected by gabapentin, a pain management drug that results in a unique type of NAS when abused with opioids. The goal will be to learn more about the long-term effects of NAS on brain development and to guide the development of therapies to treat NAS.

#### Basic Research



## 2018 Young Investigator Grantees

### Panic Disorder

**Amanda Waters Baker, Ph.D.**, at Massachusetts General Hospital and Harvard University, aims to identify factors that can help predict how panic disorder patients will respond to cognitive behavioral therapy (CBT). Dr. Baker will monitor the symptoms of patients with panic disorder through clinical evaluations and data from a wearable device, before, during, and after undergoing CBT. With these results Dr. Baker aims to map out the patients' "panic network," which comprises thoughts, biomarkers, and behaviors, and may point to opportunities for personalizing treatments.

#### **Diagnostic Tools/Early Intervention**

**Weisheng Wang, Ph.D.**, University of California, Los Angeles, is studying panic disorder. We have natural responses to lethal danger, but in 4 in 100 people these can be invoked in inappropriate situations, provoking a catastrophic fear of death or an overwhelming urge to flee. Dr. Wang and colleagues believe panic circuits are understudied, particularly relative to reactions to less intense threat. Preliminary data revealed a novel site in the hypothalamus (the dorsal premammillary nucleus, or PMd), that can induce hallmark behavioral and physiological panic-related symptoms. They will target the PMd and its target downstream circuits and characterize how they control panic and escape and represent different threats; they will also examine how this region affects behavior, possibly revealing potential therapeutic targets.

#### **Basic Research**

### Psychosis

**Anastasia Bobilev, Ph.D.**, at the University of Texas Southwestern Medical Center at Dallas, seeks to identify the biological basis of illness in three sub-groups of psychosis patients. With induced pluripotent stem cell technology, it is possible to take a skin sample from patients and reprogram these skin cells into stem cells and then various brain cell types, all of which carry the patient's genetic information. This approach will allow Dr. Bobilev to noninvasively study the biological characteristics of brain cells derived from living patients.

#### **New Technologies**

**Hengyi Cao, Ph.D.**, at Yale University, aims to use maps of the connections between brain areas to predict psychotic disorders in individuals at high risk. Research suggests that the human functional connectome—a map of connections between brain areas, identified by imaging brain activity—possesses a unique "fingerprint" that may be useful for predicting behavior. Dr. Cao will test this idea in young adults at high risk of psychosis.

#### **Basic Research**



## 2018 Young Investigator Grantees

**Hanna Summer Gauvin, Ph.D.**, Queensland University of Technology, Australia, will test a treatment for auditory verbal hallucinations—the phenomenon commonly experienced in schizophrenia of hearing voices when no one is talking. A possible explanation is that some people incorrectly perceive someone else as talking when they quietly, or even inaudibly, talk to themselves. Dr. Gauvin wants to help such people by training them to interrupt themselves when they produce inaudible speech. Her team will train participants to visualize their muscle activity during inaudible speech, and to intervene to preempt hallucinations.

### Next-Generation Therapies

**Gregory P. Strauss, Ph.D.**, University of Georgia, is interested in the early identification and prevention of psychosis. He hopes to facilitate efforts to target the prodromal phase of illness, which occurs prior to the onset of psychotic disorder when functioning declines and clinical symptoms gradually emerge over late adolescence. He will conduct a trial in 50 youth at clinical high-risk for psychosis, and 50 demographically matched healthy controls, who will complete a series of reinforcement learning tasks and clinical interviews at baseline and after 12 months. Each participant's trial-by-trial reinforcement learning data will be fit to three computational models of reinforcement learning. Dr. Strauss hopes to identify patterns associated with increased symptomatic progression of psychosis symptoms.

### Diagnostic Tools/Early Intervention

**Eva Velthorst, Ph.D.**, Icahn School of Medicine at Mount Sinai, will explore how parental genes that are not passed on to the child may nevertheless help explain the link between childhood adversity and the development of psychosis. It is theorized that such non-inherited genes are able to affect the child through their parents' contribution to the child's environment. This phenomenon, called "genetic nurturing," has been largely ignored in genetic studies but may point to preventable exposures, Dr. Velthorst suggests. Leveraging the Avon Longitudinal Study of Parents and Children (ALSPAC) study, the team will integrate genetic and developmental data on 3,000+ individuals followed from birth up to age 24, and their parents. This will provide the opportunity to examine the effect of non-transmitted genes of the mother and father separately (accounting for the transmitted genes) in the childhood adversity-psychosis relationship.

### Basic Research

**Danhong Wang, M.D., Ph.D.**, Massachusetts General Hospital, Harvard University, seeks to establish functional connectivity signatures that reliably track global and dimension-specific symptoms in patients with psychotic illness (both affective and non-affective psychosis), using a longitudinal approach to focus on the early phase of psychotic symptoms. A cohort of 235 patients (111 bipolar, 64 schizophrenia, 60 schizoaffective) will be examined for cortical and subcortical connectivity, data which could serve as a proof of concept for subsequent application to other psychiatric disorders. Dr. Wang hopes this research will establish connectivity biomarkers that track changes in both global and dimension-specific symptom severity, enabling the identification of symptom-specific brain connectivity abnormalities in psychotic and bipolar disorders.

### Diagnostic Tools/Early Intervention



## 2018 Young Investigator Grantees

### Post-Traumatic Stress Disorder (PTSD)

**Michael Sean Breen, Ph.D.**, at the Icahn School of Medicine at Mount Sinai, will leverage an established cohort of mothers and infants to investigate the effects of maternal post-traumatic stress disorder (PTSD). Using samples of the newborns' umbilical cord blood, Dr. Breen will examine the patterns of gene expression in babies born to mothers with and without PTSD. The study will also include analysis of gene expression in samples from the babies at two years of age, providing measurements of the effects of maternal PTSD on children over time.

#### Basic Research

**Denise Cai, Ph.D.**, at the Icahn School of Medicine at Mount Sinai, will investigate how emotional context can alter the process of linking one memory with another, providing insight into how traumatic experiences can lead to post-traumatic stress disorder (PTSD). Experiences of intense fear can lead to PTSD by linking traumatic memories with harmless memories, thereby changing the way safe environments are perceived in the future. Dr. Cai aims to elucidate how particular groups of brain cells form connections that underlie memory-linking, specifically in the context of negative experiences.

#### Basic Research

**Nikolaos P. Daskalakis, M.D., Ph.D.**, at the McLean Hospital and Harvard University, will use the genome-editing tool known as CRISPR to study a gene associated with post-traumatic stress disorder (PTSD). Called SNRNP35, this gene is thought to contribute to stress-related disorders. Dr. Daskalakis will examine the expression of this gene and those in related gene networks in postmortem samples from people with PTSD as well as in healthy people, and aims to unravel the mechanism behind its role in disorders.

#### New Technologies

**Joseph Dunsmoor, Ph.D.**, at the University of Texas at Austin, aims find new ways to strengthen fear-extinction—the basis of exposure therapy—in patients with post-traumatic stress disorder (PTSD). Past studies on fear-extinction strategies have typically spanned treatment periods of less than one week, limiting insights into the underlying brain processes. Dr. Dunsmoor will test for the effects of fear-extinction-based therapy six months later, using functional magnetic resonance imaging.

#### Next-Generation Therapies

**Sam Adler Golden, Ph.D.**, National Institute on Drug Abuse, will investigate the biological basis of elevated aggression as a symptom of post-traumatic stress disorder. Dr. Golden plans to develop a preclinical model of PTSD-induced aggression using rodents that have experienced chronic social defeat, which causes PTSD-like stress and is a phenomenon for which Dr. Golden has identified underlying neural mechanisms. His team will then train rodents to receive both rewards and punishment for aggression and try to map the full set of connections in the brain activated during aggression, which may eventually provide new targets for treatment.

#### Basic Research



## 2018 Young Investigator Grantees

**Alfred P. Kaye, M.D., Ph.D.**, Yale University, will study the resting pupil of the eye to find clues to the pathology of post-traumatic stress disorder. Over-active mental states are a major symptom of PTSD and are thought to be driven by the neurotransmitter norepinephrine, which acts primarily on the locus coeruleus, the same brain region that controls the eye's pupil. Using a mouse model of PTSD, Dr. Kaye's team will test their hypothesis that stress prompts the release of a specific hormone that changes norepinephrine activity in the locus coeruleus. They expect to detect this shift in the resting pupil.

### **Basic Research**

**Gideon Rothschild, Ph.D.**, University of Michigan, is interested in learning more about how post-traumatic stress disorder (PTSD) can occur when strong fear memories are formed in the brain. Dr. Rothschild's previous research has found that the formation of long-lasting memories may occur in part as the brain's hippocampus and cortical regions communicate during sleep. In experiments with rats, he hopes to test the hypothesis that these same mechanisms are involved in the formation of long-term traumatic memories, and to discover whether this phenomenon can be weakened or prevented by interfering with this hippocampal-cortical communication.

### **Basic Research**

**Hein Johan Floris van Marle, M.D., Ph.D.**, VU Medisch Centrum Vrije Universiteit Amsterdam, The Netherlands, aims to open up sleep as a potential treatment window in post-traumatic stress disorder (PTSD). Recent advances show that memory consolidation can be significantly enhanced by presenting reminder cues during subsequent sleep (known as targeted memory reactivation). This project seeks to apply memory reactivation strategies during sleep in patients for the first time in an effort to increase therapy effectiveness. It will specifically test whether re-administering auditory cues that are already part of a treatment, again, during subsequent sleep, will strengthen the (re)consolidation of updated traumatic memory.

### **Next-Generation Therapies**

**Sanne J.H. van Rooij, Ph.D.**, Emory University, proceeds from research suggesting that surgical removal of the amygdala (amygdala ablation) could be a potential treatment for severe, chronic PTSD. Dr. van Rooij will investigate the effect of amygdala ablation on PTSD symptoms in epilepsy patients with PTSD who undergo amygdala ablation for their otherwise untreatable epilepsy. The team expects a decrease in PTSD symptoms after ablation surgery in epilepsy patients with PTSD. Furthermore, they expect neuroimaging and psychophysiological markers to improve after amygdala ablation only in the epilepsy patients with PTSD, and not in two control groups.

### **Next-Generation Therapies**

## 2018 Young Investigator Grantees

**Franz Weber, Ph.D.**, University of Pennsylvania, is studying how abnormalities in rapid-eye movement (REM) sleep likely play a role in the formation and progression of anxiety disorders such as posttraumatic stress disorder (PTSD). A core brain structure for fear learning and extinction is the infralimbic prefrontal cortex (IL), which is strongly activated during REM sleep. The current project seeks to demonstrate that REM sleep supports the successful extinction of fearful experiences by promoting the excitability of IL neurons. To test this hypothesis, the team will counteract the fragmentation of REM sleep following fear learning through optogenetic manipulation of the brainstem circuits controlling REM sleep. This will indicate whether potentiating REM sleep after a fearful experience supports its successful extinction.

### **Next-Generation Therapies**

**Xi Zhu, M.D., Ph.D.**, Research Foundation for Mental Hygiene, Inc./NYSPI Columbia University, seeks to capitalize on recent advances in computational power and machine learning methodology, which have shown promise in their ability to classify psychiatric disorders at the individual level. By using multimodal magnetic resonance imaging (MRI) features including structural MRI, resting state functional MRI (rs-fMRI) and diffusion tensor imaging (DTI), the team aims to differentiate post-traumatic stress disorder (PTSD) patients from trauma-exposed healthy controls by utilizing a large dataset of some 3,000 individuals. The findings may improve diagnosis and provide means of objective individualized classification of the neural deficits characterizing patients with PTSD as well as reveal new treatment targets.

### **Diagnostic Tools/Early Intervention**

## Schizophrenia

**Megan A. Boudewyn, Ph.D.**, at the University of California Davis Medical Center, will target the brain circuits that underlie disabling language comprehension deficits in schizophrenia, using a non-invasive method called transcranial direct current stimulation (tDCS). Diminished cognitive control—the ability to adapt behavior and information processing to achieve goals—in the context of everyday tasks significantly impairs schizophrenia patients. By examining how treatment with tDCS affects schizophrenia patients' levels of cognitive control, particularly in language comprehension tasks, Dr. Boudewyn hopes to open the door to new treatments.

### **Next-Generation Therapies**

**Alberto Cruz-Martín, Ph.D.**, at Boston University, will investigate how the loss of connections between brain cells, known as synapses, contributes to schizophrenia. Recent genetic studies show that schizophrenia risk is highly associated with increased amounts of a protein called complement component 4 (C4), which may be involved in the loss of synapses. In mice, Dr. Cruz-Martín will experimentally increase the amount of C4 in a brain region known to be particularly affected in schizophrenia, and observe how it affects connectivity between brain cells in that region.

### **Basic Research**



## 2018 Young Investigator Grantees

**Erin W. Dickie, Ph.D.**, at the Centre for Addiction and Mental Health at the University of Toronto, Canada, aims to improve outcomes for schizophrenia patients using repetitive Transcranial Magnetic Stimulation (rTMS). A brain region known as the dorsolateral prefrontal cortex (DLPFC) has been shown to be important for cognitive and working memory functions, which are impaired in schizophrenia patients. Dr. Dickie will use functional magnetic resonance imaging data to develop and validate an approach for determining patient-specific DLPFC targets for rTMS treatment.

### **Next-Generation Therapies**

**David Dodell-Feder, Ph.D.**, at the University of Rochester, will search for ways to treat the problem of social disconnection among people with schizophrenia. Recent research suggests that this difficulty in forming social connections may stem from impairment of the brain network that supports “theory of mind”—the ability to attribute and reason about the beliefs, emotions, desires, and intentions of others. Dr. Dodell-Feder aims to train schizophrenia patients to more effectively engage this network with feedback, using real-time functional magnetic resonance imaging to enable the patients to view their own brain activity as it occurs.

### **Basic Research**

**Tae-Yeon Eom, Ph.D.**, St. Jude Children’s Research Hospital, will study the genetic basis of a brain abnormality associated with schizophrenia. Patients with schizophrenia who also have a particular gene deletion syndrome show unusual brain structures, included enlarged lateral ventricles, which are spaces in the brain that contain fluid. Using a mouse model, Dr. Eom will test his hypothesis that the related genetic syndrome is caused by the Dgcr8 gene. His team will examine if Dgcr8 activity leads to ventricular enlargement, and if it does so specifically through the activity of microRNA molecules.

### **Basic Research**

**Jennifer Ann Erwin, Ph.D.**, Lieber Institute for Brain Development, Johns Hopkins University, will investigate how stressors in early life increase a child’s risk for developing schizophrenia. Past research suggests that complications during pregnancy, labor, and early life interact with a genetic predisposition to make infants twice as likely to develop the illness. Dr. Erwin wants to shed light on the ways environmental stressors in early life alter neural development via the mother’s placenta. She will identify schizophrenia-associated regions of the genome as well as broader physiological profiles in infants that respond to stress.

### **Basic Research**

**Jennifer Katherine Forsyth, Ph.D.**, University of California, Los Angeles, hopes to shed light on the genetic basis of schizophrenia by determining which symptoms are linked with different genetic risks. Using genome-wide data, Dr. Forsyth expects to find that rare genetic variants linked to schizophrenia are associated with more intense symptoms and earlier age of onset than are common variants. Her team expects that patients with genetic variants that affect early developmental processes function less well than patients with other kinds of variants.

### **Basic Research**



## 2018 Young Investigator Grantees

**Mary Elizabeth Gaine, Ph.D.**, University of Iowa, will conduct a family-wide study looking at the relationship between DNA methylation and schizophrenia. Methylation occurs when a methyl group—a kind of molecular tag—attaches to a particular piece of DNA. The process leads to changes in gene expression that can vary over time and as a result of environmental factors. Methylation has shown unique patterns in schizophrenia patients. Using genetic data from patients and their parents who do not have the illness, Dr. Gaine will examine the relationship between methylation patterns and schizophrenia, including whether those patterns shift with medication use and throughout disease progression. Her team hopes to identify methylation patterns as a biomarker for schizophrenia.

### **Diagnostic Tools/Early Intervention**

**Vanessa F. Gonçalves, Ph.D.**, Centre for Addiction and Mental Health, University of Toronto, Canada, will explore a potential genetic basis for schizophrenia. Mitochondria, structures that provide energy for cells, play a role in several neuronal processes that are compromised in schizophrenia. The team will use a massive genetic sample to examine whether variants in mitochondrial genes are linked to risk for, and clinical presentation of, the illness. They will also test whether any such genetic relationship arises from disrupted communication between mitochondria and chromosomes. They hope to identify mitochondrial genes as a biomarker for severe schizophrenia.

### **Basic Research**

**David Gosselin, Ph.D.**, Centre de Recherche du CHU de Quebec, Canada, will probe the genetic basis of microglial cells that help direct brain development. Microglia are immune cells that shape the connections between neurons by positioning them, refining their communication, and other activity. Research suggests these functions are regulated by the Mef2C gene, mutations in which are linked to schizophrenia. Dr. Gosselin's team will disable the Mef2C gene in mice, measure the impact in gene expression, study how microglia functions change in turn, and assess behavioral performance in the mice.

### **Basic Research**

**Synthia Guimond, Ph.D.**, Beth Israel Deaconess Medical Center, Harvard Medical School, seeks to develop a preventive treatment for schizophrenia. A low ability to function with schizophrenia often corresponds with poor emotional recognition, a trait that has been linked to the onset of psychosis as well as abnormalities in the amygdala, a crucial brain region for emotional processing. These findings point to emotional recognition training as an intervention to preempt or lessen the symptoms of schizophrenia. Dr. Guimons will train youth who are at-risk for developing schizophrenia on a computerized program to see if it improves their emotion recognition skills. She will also measure activity in the amygdala to understand the neural basis of any changes.

### **Next-Generation Therapies**



## 2018 Young Investigator Grantees

**Yash B. Joshi, M.D., Ph.D., M.B.E.**, University of California, San Diego, hopes to improve treatment options for the cognitive symptoms of schizophrenia. Commonly used medications to treat schizophrenia often address psychosis symptoms but do not address cognitive impairments. A treatment called targeted cognitive training has shown promise for improving cognition. Its effectiveness may be predicted by biomarkers that characterize early-stage processing of sounds in the brain. Dr. Joshi's team will test whether taking a drug known to improve early auditory processing, called memantine, can make targeted cognitive training more effective in schizophrenia patients.

### **Next-Generation Therapies**

**Catherine Anne Marcinkiewicz, Ph.D.**, University of Iowa, will take a closer look at the connection between two regions of the brain that contribute to social functioning to see if it is disrupted in schizophrenia. Using a technique that enables simultaneous recording of neuronal activity in two different brain regions at once, she will determine if mice that exhibit deficits in social interaction have reduced connectivity between these two regions. The results of these studies will reveal important insights regarding how these two regions of the brain interact during social interaction, potentially relevant in efforts to find new targets for treatment of social deficits in schizophrenia.

### **Basic Research**

**Anna Migdalska-Richards, Ph.D.**, University of Exeter, UK, is examining modifications in gene expression, sometimes called epigenetic changes, which impact the different nerve cell types in the brain in schizophrenia. She will be studying a cell type called oligodendrocytes, which provide support and insulation to the axons through which nerve cells signal. Dr. Migdalska-Richards will measure epigenetic changes in these cells in schizophrenia patients and healthy individuals, comparing them in the two groups and also comparing her findings to epigenetic changes in neurons. The findings could help determine whether drugs that reverse epigenetic changes could be used to treat schizophrenia.

### **Basic Research**

**Athanasia Papoutsis, Ph.D.**, Institute of Molecular Biology and Biotechnology (IMBB), Greece, is taking a closer look at the cells in the prefrontal cortex of the brain to determine whether modifications of the "spines" in single neurons (points from which signals are transmitted) contribute to inflexible behavior in some psychiatric disorders. In particular, people with schizophrenia exhibit an inability to adapt to a changing environment and dysfunctional decision-making. Dr. Papoutsis's research goal is to identify how such inflexible behavior is determined at the cellular level, with regard to the spatial and density properties of spines and processing in the prefrontal cortex. Identifying the mechanisms that allow for flexible decision making could help guide new therapies for schizophrenia.

### **Basic Research**



## 2018 Young Investigator Grantees

**Anirban Paul, Ph.D.**, Cold Spring Harbor Laboratory, is studying the role that chandelier cells (CHCs) play in impaired working memory and other cognitive deficits in schizophrenia. Dr. Paul has developed a procedure to genetically mark CHCs in the mouse brain, with the intention of learning more about CHC subtypes, the kinds of biomarkers that can be used to identify these subtypes, and how these cells behave when perturbed. The findings could help identify how CHCs are altered in schizophrenia, as well as pinpoint the exact circuits in the prefrontal cortex of the brain that become dysfunctional in the disease.

### **Basic Research**

**Nelson Rebola, Ph.D.**, Brain and Spine Institute, will evaluate the properties and function of a family of protein receptors called NMDARs that help to modulate the activity of inhibiting interneurons, which modulate signals between brain cells. Postmortem analysis of the brains of schizophrenia patients suggest that NMDAR activity levels are low in certain interneuron subtypes called PV+ interneurons, making it important to understand how they may affect other interneurons. The findings could help define how low NMDAR activity impacts cells that are thought to contribute to the development and progression of schizophrenia.

### **Basic Research**

**Ryan Matthew Smith, Ph.D.**, University of Iowa, seeks to better understand the impacts of risk genes in schizophrenia at the molecular level. The current research has two foci. One is genetic factors regulating two major targets for atypical antipsychotics--the dopamine D2 receptor and the serotonin 2A receptor, which will be explored via stem cell technology using patient samples. The other is to use the stem cell-derived neurons to identify the specific genetic variants underlying risk for schizophrenia, focusing on genes that encode readily druggable proteins. By identifying causative variants underlying risk for schizophrenia, molecular mechanisms affected by the risk variants may become visible and subject to therapeutic modulation.

### **Basic Research**

**Andre Steinecke, Ph.D.**, Max-Planck Florida Institute, is interested in cortical chandelier cells (ChCs), a type of inhibitory brain cell that is thought to be implicated in schizophrenia. Postmortem studies have revealed that biochemical markers in ChCs are reduced in patients. This symptom could explain defects in working memory that characterize the illness. The current research focuses on the role of tiny channels (VGCCs) that control the flow of calcium into and out of neurons. The context is the postnatal development of cortical ChCs, specifically their axon branch formation and subsequent synaptic integration. This has the potential to reveal new targets for the development of future therapies.

### **Basic Research**



## 2018 Young Investigator Grantees

**Ivy Fei Tso, Ph.D.**, University of Michigan, is studying social cognition--the ability to process and use social information accurately and efficiently. It is impaired in schizophrenia and strongly predicts patients' functional outcomes. Treating social cognitive deficits could improve functioning, and this research seeks a deeper understanding by focusing on eye-gaze perception, a basic building block of sophisticated social cognition. The team's work suggests abnormalities in eye-gaze perception are present in schizophrenia, possibly originating from basic visual processing deficits and dysfunction of the visual cortex. A non-invasive brain modulation technique called continuous theta burst transcranial magnetic stimulation (cTBS) will be used to elicit a temporary, virtual lesion in the visual cortex in healthy volunteers. This could lead to a clinical trial using transcranial magnetic stimulation (TMS) to engage the visual cortex to improve social cognition and broader functional outcomes in schizophrenia.

### **New Technologies**

**Jodi Jay Weinstein, M.D.**, State University of New York, Stony Brook, notes that molecular imaging studies in schizophrenia patients have revealed an excess of dopamine synthesis and release in the brain's striatum, associated with severity of psychotic symptoms and predicting both conversion from prodrome and treatment response. Recent observations from PET imaging studies of dopamine system function in schizophrenia suggest an intricate pattern of alterations that, if better characterized, might lead to more targeted treatments. Clinical PET imaging at Stony Brook now enables such investigation. Dr. Weinstein will analyze the relationship between cholinergic and dopaminergic function in schizophrenia using in vivo data about cholinergic system integrity in patients.

### **Basic Research**

**Jun Yamamoto, Ph.D.**, University of Texas Southwestern Medical Center at Dallas, wants to test the concept that reduced neural synchrony can account for the typical psychotic symptoms of schizophrenia, such as delusions and hallucinations, and thus whether it can be used as a diagnostic marker. Dr. Yamamoto will study abnormal neural oscillations and synchronies in schizophrenia model mice with the aim of elucidating a neural substrate of psychotic symptoms to enable earlier diagnosis and treatment of the illness. To do so the team will employ large-scale in vivo ensemble recordings and optogenetic intervention technologies they have already demonstrated.

### **Basic Research**

**Liuqing Yang, Ph.D.**, Johns Hopkins University, will examine novel molecular mechanisms that are hypothesized to link a gene called Arc with two fundamental phenomena observed in schizophrenia: enhanced D2 dopamine receptor signaling and reduced NMDA receptor function. Screens for de novo and rare disruptive mutations have recently revealed Arc (activity-regulated cytoskeleton-associated scaffold protein) as a signaling node of many schizophrenia risk genes. It is translated in response to neural activity. Arc depletion in mice results in abnormal synaptic plasticity and memory consolidation deficits, as well as schizophrenia-like symptoms including prepulse inhibition impairment and social indifference. This study will look at the link between multi-risk genes identified in human genetic studies and the complex networks of schizophrenia manifestations.

### **Basic Research**



## 2018 Young Investigator Grantees

### Suicide Prevention

**Tory Anne Eisenlohr-Moul, Ph.D.**, University of Illinois at Chicago, will study the impact of hormone levels on suicidal thoughts among women. Previous work has suggested that women are most likely to attempt suicide the week during and before their periods, when their levels of ovarian hormones drop. Dr. Eisenlohr-Moul has found that increasing these levels decrease the likelihood of attempting suicide. She will now examine how hormone stabilization might have that effect. She hopes this research will shed light on the neurobiology of suicidal thoughts in women to point toward new treatments.

#### **Basic Research**

**Charles P. Lewis, M.D.**, Mayo Clinic, is studying how the GABA and glutamate neurotransmitter systems can be disrupted in depressed youth over time, potentially affecting their risk of suicidal behavior. Previous studies have shown that some GABA measures are impaired in youth with histories of suicidal behavior, and Dr. Lewis would like to know more about whether these impairments indicate long-term risk or whether changes in these neurotransmitter systems indicate an acute risk for suicide. Over three months, the team will study 30 adolescents with depression and a hospitalization for suicidal behavior, using transcranial magnetic stimulation (TMS) and fMRI imaging.

#### **Basic Research**