

NARSAD Young Investigator Grantees

in 2012



This year, the Brain & Behavior Research Foundation Scientific Council reviewed applications from 1,030 researchers seeking NARSAD Young Investigator Grants—a grant program that has been the driving force behind thousands of scientific achievements. NARSAD Grants are among the most competitive in biomedical research because of the great ability and career success of the applicants. The grants are helpful in funding innovative research, research that would otherwise not get funded.

NARSAD Grants fund:

- **Basic Research**—to understand what happens in the brain to cause mental illness
- **New Technologies**—to advance or create new ways of studying and understanding the brain
- **Diagnostic Tools / Early Intervention**—to recognize early signs of mental illness and treat it as early as possible
- **Next Generation Therapies**—to reduce symptoms and retrain the brain

Although all of the applicants were worthy of funding, 202 were chosen to be 2012 NARSAD Young Investigator Grantees. We are proud to introduce them to you.

BASIC RESEARCH

ANXIETY DISORDERS

Obsessive-Compulsive Disorder (OCD)

Deqiang Jing, M.D., Ph.D., Cornell University

Findings suggest that deficiency of a gene called *Slitrk5* leads to OCD-like behaviors as a result of altered formation of the synapse, the site where brain-cell communication takes place. To test this hypothesis, Dr. Jing will include detailed analyses of the role of *Slitrk5* in synapse formation in vitro and in further animal studies.

Michael L. Lutter, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas

Dr. Lutter will perform tests to determine if pharmacologic inhibition of the melanocortin 4 receptor alters OCD-like behavior in a mouse model of OCD. This research intends to elucidate signaling pathways in mice in order to identify novel therapeutic targets.

Anxiety - Other

Alex Dranovsky, M.D., Ph.D., Columbia University

Neurons born in adulthood in the hippocampus can affect the neuroendocrine response to stress and alter behavior. In this proposal, Dr. Dranovsky will generate genetically modified animals in which adult-born hippocampal neurons do not effectively integrate into pre-existing hippocampal circuits. Through behavioral tests to model anxiety and depressive behaviors, he will compare behavior at the baseline with behavior following exposure to stress.

Anna M. Lee, Ph.D., Ernest Gallo Clinic & Research Center, University of California, San Francisco

Dr. Lee hypothesizes that protein kinase C epsilon (PKC epsilon) regulation of the high affinity nicotinic receptors promotes anxiety-like and depression-like behavior in mice. She will test this hypothesis by investigating these behaviors in PKC epsilon knockout and normal mice.

Carrie J. McAdams, M.D., Ph.D., University of Texas Southwestern Medical Center at Dallas

Using two fMRI tasks, in healthy women and recovering adult anorexia nervosa (RAN) subjects, Dr. McAdams compared the activity of several cortical regions that are related to understanding both one's self and other people and undergo neurodevelopmental changes in activation during adolescence. She found the RAN subjects had less activation. She and her team will follow up to examine adolescents recovering from anorexia nervosa with these fMRI tasks.

Kodeeswaran Parameshwaran, Ph.D., Auburn University

Using a mouse model of a Complex I (CI) subunit (a critical initiator of the cellular energy production process), Dr. Parameshwaran plans to investigate the effect of CI inhibition in mice—in combination with stress—on mood disorders. This could yield novel insights into the complex dynamics of stress and mood disorders involving mitochondria and a variety of signaling molecules in the brain.

AUTISM & AUTISM SPECTRUM DISORDERS (ASD)

Shu-Ling Chiu, Ph.D., Johns Hopkins University

Autistic-like behavior was observed in mice in which the GRIP1 gene, important for regulating synaptic transmission, was 'knocked out,' or deleted, and mutations similar to GRIP1 were found in autistic patients. GRIP1 is allied with another gene called GRASP1 and Dr. Chiu's research will explore how GRASP1 works in the GRIP complex to affect synaptic transmission and the molecular and cellular mechanisms underlying autism spectrum disorders.

Zhanyan Fu, Ph.D., Duke University

Shank3 mutant mice are mouse models of ASD. Dr. Fu will test the hypothesis that Shank3 disruption has differential effects on certain glutamatergic synapses*. The goal is to generate a novel mouse model of ASD harboring the deleterious Shank3 mutations from human patients with ASD, in order to yield clinically relevant insights into the underlying mechanism of human ASD and related disorders.

Daniel P. Kennedy, Ph.D., California Institute of Technology

In an initial exploration of anatomical features that underlie altered brain activity in autism, Dr. Kennedy will investigate, from a whole-brain perspective, whether communication across the cerebral hemispheres is disrupted as compared to communication within a hemisphere, and also whether those brain regions with altered connectivity are the ones that do not function properly in autism.

Isabelle Soulières, Ph.D., Hospital Rivière-des-Prairies, University of Montreal, Canada

Dr. Soulières intends to examine the neural network involved in visuo-spatial expertise in autistic individuals, assess the coordination of neural activity among the regions included in this neural network and investigate the integrity of white matter connections between regions involved in visuo-spatial processes in autistic and non-autistic individuals.

BIPOLAR DISORDER (BP)

Sofya Abazyan, Ph.D., Johns Hopkins University

Dr. Abazyan will evaluate the neuronal and behavioral effects of molecules called anti-NMDA receptor* antibodies in serum collected

from BP patients and from experimental mice infected with *Toxoplasma gondii*, a parasite that has been associated with BP. This research should advance knowledge of the pathophysiology of mania and the search for better treatments for mood disorders triggered by immune-system malfunction.

Ney Alliey-Rodriguez, M.D., University of Chicago

In addition to some genetic markers being associated with BP, rare structural variants, such as microdeletions, where part of the genome is missing, and microduplications, where there are abnormal numbers of DNA sections, may also contribute to risk for BP. These abnormalities, called copy number variants (CNVs), can induce large effects. Dr. Alliey-Rodriguez will explore the role of CNVs as a source of heterogeneous genetic risk for the disorder.

Ana Cristina Andreazza, Ph.D., University of Toronto

Dr. Andreazza will look at rat cortical neuron cultures and then patient postmortem brain tissue to determine how DNA oxidative damage affects DNA methylation* and impacts gene expression in people with BP.

Irina Esterlis, Ph.D., Yale University

Dr. Esterlis will give MRI brain scans to BP patients and healthy controls to determine differences in magnitude and distribution of metabotropic glutamate* receptors 5 (mGluR5)—a site in the brain where glutamate binds—and how these differences relate to mood and cognitive symptoms.

Nadja Freund, Ph.D., Harvard University

Dr. Freund's lab created a virus system that they injected into the brains of lab animals, allowing manipulation of the expression of the D1 dopamine receptor (D1R) gene. This induced elevated expression of D1R and behaviors comparable to mania in humans. Virus reduction reduced mania-like behavior and D1R levels fell below control levels, suggestive of a depressive-like state. This cycling will serve as a model for testing novel therapeutic agents for treating BP.

Sharmin Ghaznavi, M.D., Ph.D., Harvard University

Using functional magnetic resonance imaging (fMRI), Dr. Ghaznavi will investigate rumination (repetitive focus on the symptoms of distress) in individuals with BP who are in a normal-appearing state versus healthy controls by having them perform negative and positive rumination tasks. He believes the BP patients will show greater activation in default network regions of the brain than healthy controls while at rest and during both rumination tasks, consistent with the tendency to ruminate in BP.

DEPRESSION

Ruben P. Alvarez, Ed.D., Laureate Institute for Brain Research

Using functional magnetic resonance imaging (fMRI), Dr. Alvarez will investigate the effects of predictable and unpredictable pain stimuli on emotion and pain reactivity in depressed individuals as compared to healthy controls. Finding a common impairment of depression with anxiety and pain disorders could promote new ways of treating and classifying these conditions.

* See Glossary

Jean-Claude Beique, Ph.D., University of Ottawa

Dr. Beique is conducting a comprehensive analysis of the changes in synapse function and plasticity induced by selective serotonin reuptake inhibitors. Understanding how they are modulated by antidepressants is essential to understanding the biological basis of the antidepressant effect and developing more effective medications.

Chihye Chung, Ph.D., Konkuk University (Korea)

In animal models of depression, one brain region that appears to undergo synaptic plasticity is the lateral habenula* (LHb). Dr. Chung's lab revealed it was possible to alter LHb activity with pharmacological and other neuromodulators. She will investigate synaptic modulation as it affects behavior to better understand the pathophysiology of depression in order to identify new targets for treatment.

Huxing Cui, Ph.D., University of Texas Southwestern Medical Center at Dallas

Using the lab's unique mouse models, which enable brain-region-specific manipulation of the expression of a gene thought to play a key role in regulating both energy balance and emotional processing, Dr. Cui will study neurobiological mechanisms that underlie heightened risk for obesity, cardiovascular disease and diabetes among people with major depressive disorder.

Stephanie Dulawa, Ph.D., University of Chicago

Dr. Dulawa will examine a possible causal relationship between prenatal stress and later depression-related behavior in people with epigenetic* alterations in a gene called CALCA. She and colleagues will explore their finding that genetically identical mice gestated by different mouse strains with different stress-responsiveness showed differential CALCA methylation*, gene expression and depression-related behavior as adults.

Deveroux Ferguson, Ph.D., Mount Sinai School of Medicine

Dr. Ferguson's lab shows that chronic social-defeat stress, an animal model of depression, modulates the levels of a gene called SIRT1 in the nucleus accumbens to increase stress sensitivity. By first inhibiting SIRT1 activity and then overexpressing it, the study will test whether modulation of SIRT1, and identification of the molecules SIRT1 acts on, will uncover new candidate targets for antidepressant therapy.

Chaitali Ghosh, Ph.D., Cleveland Clinic Foundation

Dr. Ghosh will investigate how the blood-brain barrier affects drug efficacy in patients resistant to antidepressants. The study will use tissue samples obtained in brain resections of patients affected by epilepsy and depression with a focus on the metabolism of selective serotonin reuptake inhibitors.

Catherine E. Hagan, D.V.M., Ph.D., University of Washington

To learn how interactions among the various cell types in the brain lead from inflammation to depression, Dr. Hagan will work with animal models examining the behavioral effects of signaling by an immune cell protein called toll-like receptor 4 (TLR4). She hypothesizes that TLR4 receptors on microglia, structural support cells in the nervous system, are key mediators of stress-induced depression.

Georgia E. Hodes, Ph.D., Mount Sinai School of Medicine

To better understand how the immune system and brain interact in depression, and whether the source of dysregulation of the immune system in depression occurs within the brain or within the body, Dr. Hodes will investigate the influence of Interleukin 6 (IL-6). IL-6 is a pro-inflammatory chemical of the immune system that is up-regulated in the blood of patients with depression. This study has the potential to help direct the development of novel antidepressant compounds that would target IL-6.

Linnea Karlsson, M.D, Ph.D., University of Turku (Finland)

Part of a larger birth cohort study, this project will focus on a sub-population of families where at least one parent experiences prenatal stress, depression or anxiety. Dr. Karlsson will examine the effect of prenatal stress on infant emotion regulation and depression by investigating the effects on the child's brain structure and balance of pro-inflammatory and anti-inflammatory proteins. She hopes to identify a genetic fingerprint for children vulnerable to the effects of stress.

Jing Liu, Ph.D., University of Texas Health Science Center at San Antonio

Dr. Liu and his team want to validate their hypothesis that adiponectin plays a role in dendritic remodeling in the chronic social defeat (CSD) mouse model of depression. They found that retraction of dendrites in the medial prefrontal cortex of CSD mice was accompanied by reductions in circulating adiponectin levels, and that these, in turn, led to increased susceptibility to stress-induced depression-like behavior.

Poornima A. Kumar, Ph.D., Harvard University

Anhedonia* is a core symptom of depression that may be attributed to a dysfunctional reward system in the brain caused by disrupted dopamine neurotransmitter function. Dr. Kumar will investigate neural correlates of reinforcement learning using socially relevant feedback stimuli in order to determine whether or not brain regions rich in dopamine activity are involved in both reward and aversive learning.

Sarah Ann Osborne, M.D., Institute of Psychiatry/ King's College London, England

Dr. Osborne will examine the epigenetic* mechanisms (specifically methylation*) that influence programming of the hypothalamic-pituitary-adrenal (HPA) axis in offspring with HPA axis dysregulation. Altered function of the HPA axis—the child's hormonal stress response system—is an adverse consequence to a child's development and health resulting from exposure to maternal depression in pregnancy.

Benjamin A. Samuels, Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI/Columbia University

Dr. Samuels seeks to determine the mechanisms underlying the neurogenesis-dependence of the antidepressant response. He will use a genetic mouse model of tissue-specific serotonin 1A heteroreceptor deficiency to test for potential alterations in the response to fluoxetine (Prozac).

* See Glossary

Jennifer L. Schmidt, Ph.D., The Rockefeller University

Having identified and begun to molecularly characterize a type of cell called the cholinergic interneuron (CIs) in a small brain area that can control depression-like behavior in rodents, Dr. Schmidt's team can now induce or reverse depression-like behaviors by manipulating the levels of a single protein called p11 just in these neurons. The knowledge gained from these experiments will fuel future studies to determine which input(s) control depression-like states.

Suzanne Vrshek-Schallhorn, Ph.D., Northwestern University

Dr. Vrshek-Schallhorn will compare methylation* patterns of individuals with high-stress histories who have had major depressive disorder (MDD), to those with low-stress histories who have never had MDD. She will look for signatures of transcription factors—proteins that help regulate gene expression—that methylated genes have in common in order to identify chemical pathways in the brain by which life-stress confers its effects on MDD.

Joanna L. Workman, Ph.D., University of British Columbia

Dr. Workman's studies are designed to investigate the behavioral, endocrine and neurobiological consequences of disrupted lactation in a rat model of postpartum depression (PPD) in order to determine if the cessation of breast feeding contributes to risk of developing PPD.

Lira K. Yoon, Ph.D., University of Maine

Dr. Yoon proposes to examine and integrate reward learning, HPA axis functioning (i.e., cortisol) and HPG axis functioning (i.e., estradiol) at different phases of the menstrual cycle for maximal sex hormone contrast in two groups of women: one with a history of major depressive disorder and one without any prior history of psychiatric disorder. The goal is to more precisely determine the mechanisms responsible for sex differences in depression.

SCHIZOPHRENIA

Sergey Akimov, Ph.D., Johns Hopkins University

Dr. Akimov is pursuing the study of a novel mutation in the Disrupted-in-Schizophrenia 1 (DISC-1) gene that was identified in his laboratory. The study aims to expand understanding of DISC1 biology in patient-specific neurons and to develop an assay for screening specifically targeted agents for the treatment of schizophrenia.

Alan Anticevic, Ph.D., Yale University

To gain a multi-level mechanistic understanding of the cellular mechanisms involved in cognitive dysfunction of working memory in schizophrenia, Dr. Anticevic will combine brain scanning with a mathematical model of working memory, and will align its predictions with cognitive tests, an approach that may provide a more focused framework for developing treatments for cognitive dysfunction.

Segev Barak, Ph.D., University of California, San Francisco

Dopamine hyperfunction is believed to be associated with schizophrenia, but the precise role of the GDNF* gene in the process has not been demonstrated. Dr. Barak will test the hypothesis that epigenetic* processes alter the gene's activity in a way that increases

release of GDNF, leading to hyperfunction of dopamine.

Stephanie L. Barrow, Ph.D., University of California, Davis

Dr. Barrow is exploring the convergence of immune and genetic signaling pathways in ASD and schizophrenia. The identification of a common pathway affected in both disorders as a result of genetic mutations and environmental exposures could have significant implications for the treatment of both disorders.

Melissa D. Bauman, Ph.D., University of California, Davis

Dr. Bauman is examining prenatal risk factors for schizophrenia, particularly exposure to certain environmental factors. She will use rhesus monkeys, which are very similar to humans in brain and behavior complexity, comparing the neuropathology of the monkeys to that of humans with schizophrenia, as a potential pathway to identifying preventive or therapeutic strategies.

Sarah E. Bergen, Ph.D., Harvard University

Dr. Bergen aims to examine genetic influences affecting age at onset of illness and severity by sex, and whether different genetic risk factors exist in people with and without a family history of schizophrenia. A further objective is to investigate whether the genetic variants identified in these associations cluster in known biological pathways.

Simon J. B. Butt, Ph.D., University of Oxford

Dr. Butt will take advantage of new genetic strategies that allow researchers to follow brain cells, understand their contribution to early brain function and learn how and when they are directed to assume a particular role. Using genetically modified animal models of schizophrenia, he will investigate what events in the embryonic brain affecting nerve cells called interneurons lay a foundation for the onset of schizophrenia later in life.

Jiwon Choi, Ph.D., Salk Institute for Biological Studies

The prefrontal cortex receives inputs from different brain regions, each regulating different brain functions. Dr. Choi will compare alterations in neuronal connectivity in the prefrontal cortex of schizophrenia-model mice and untreated mice. Analysis in multiple regions may help elucidate neural correlates of specific schizophrenic symptoms.

Javier Contreras, M.D., University of Costa Rica

microRNA are smaller, noncoding RNAs that have been implicated in the post-transcriptional regulation of mRNA. Mutations in these microRNA genes and their target mRNAs may be linked to schizophrenia. Based on the hypothesis that errors in this mechanism may be implicated in mental illness, Dr. Contreras will analyze genes collected from subjects to localize those that increase susceptibility to schizophrenia.

Natalia V. de Marco Garcia, Ph.D., New York University

Recent research strongly implicates abnormal glutamate* function in schizophrenia. Using a mouse model, Dr. de Marco Garcia will look into the role of a particular receptor called NMDA, which is associated with the system that regulates the glutamate neurotransmitter system. The project will also assess how a blockade in signaling through the NMDA receptor* may give rise to schizophrenia-like symptoms.

Emma L. Dempster, Ph.D., Institute of Psychiatry/ King's College London, England

Dr. Dempster and colleagues performed the first systematic genome-wide screen of DNA methylation* in identical twins discordant for schizophrenia and bipolar disorder, and identified numerous disease-associated DNA methylation differences. By applying epigenomics technology along with postmortem brain studies of identical twins, she will build upon and expand these preliminary findings.

Sarah A. Eisenstein, Ph.D., Washington University

The dopamine hypothesis of schizophrenia posits that symptoms may be attributed to excessive dopamine release and upregulation of dopamine receptors (D2Rs). Dr. Eisenstein seeks to determine how levels of D2R are related to altered reward-related behaviors in people with schizophrenia and those at risk for the disease.

Eric A. Epping, M.D., Ph.D., University of Iowa

Many genetic alterations, in conjunction with environmental factors, cause the cellular and brain abnormalities that give rise to schizophrenia. Dr. Epping plans to identify novel genetic risk factors and genetic changes in patients with copy number variants, small deletions or duplications of DNA segments, and link the genetic changes to clinical and molecular features of the disorder.

Melanie Foecking, Ph.D., Royal College of Surgeons in Ireland

Multiple candidate genes for psychosis and mood disorders converge in the postsynaptic density (PSD), found in the anterior cingulate cortex, a brain region known to be affected in schizophrenia. Dr. Foecking will attempt to characterize protein expression changes in the PSD in schizophrenia based on advanced tissue enrichment techniques and mass spectrometry methods recently made available.

Corinna Haenschel, Ph.D., City University London

Impaired working memory in patients with schizophrenia is the root cause of many of the cognitive problems associated with the disorder. Dr. Haenschel has shown that deficits in processing the initial visual perception of objects are of particular importance when committing them to memory, and aims to gain a more comprehensive understanding of the contribution of visual problems to working memory deficits in schizophrenia.

Adam L. Halberstadt, Ph.D., University of California, San Diego

In order to identify the mechanisms that cause disturbed time perception in schizophrenia, Dr. Halberstadt will investigate whether serotonin acts specifically in the prefrontal cortex (PFC) to modulate interval timing, whether increasing serotonin release in the PFC disrupts interval timing and whether the ability of serotonin release to disrupt interval timing is dependent on a particular receptor.

Christian Hammer, Dr. Rer. Nat., Max-Planck-Institute for Experimental Medicine

Increasing evidence suggests that infectious agents may be risk factors for schizophrenia in predisposed individuals. To expand on this theory, Dr. Hammer will unite two lines of evidence: the genetic association of major histocompatibility complex molecules (essential to immune

response as well as neuronal development) with the incidence of schizophrenia and the patients' status and history of infections.

Xue Han, Ph.D., Boston University

Cognitive impairments in schizophrenia, such as deficits in working memory and attention, have been associated with dysfunctions of the prefrontal cortex (PFC). As the thalamus is a structure important in relaying sensory signals, Dr. Han plans to examine the causal role of thalamic integration in modulating PFC functions and its pathology in schizophrenia.

Joshua Hunsberger, Ph.D., National Institute of Mental Health

Dr. Hunsberger seeks to determine the relevance of mutated microRNA (miRNA) binding sites and miRNA dysregulation in the modulation of candidate genes involved in schizophrenia and BP. To do this, he will combine a candidate-gene approach with an investigation of miRNA. This research could help to identify new susceptibility genes for these disorders.

Koko Ishizuka, M.D., Ph.D., Johns Hopkins University

The protein product of the Disrupted-in-Schizophrenia 1 (DISC1) gene is a major susceptibility factor for schizophrenia. Dr. Ishizuka will investigate whether DISC1 reduction induces deficits in microtubules (part of the skeletal scaffolding within cells) during neurodevelopment in schizophrenia patients, possibly underlying the pathophysiology of the disorder.

Joshua Jacobs, Ph.D., Drexel University

Dr. Jacobs hypothesizes that working memory relies on precise patterns of activity across widespread regions of the brain, and that working-memory problems that occur in patients with schizophrenia, may be caused by disorganized brain activity across these networks. To test this hypothesis he will conduct a study with epilepsy patients whose brain activity is being recorded for surgical resection. They will perform a computerized working-memory task while Dr. Jacobs tracks the neural 'signature' of each remembered stimulus item.

Euseok J. Kim, Ph.D., Salk Institute for Biological Studies

The hypothesis of this research is that abnormal long distance fine-scale connectivity of fast-spiking inhibitory interneurons contributes to compromised gamma oscillation activity in the cortex, which underlies the cognitive deficits in schizophrenia. Using mouse models, Dr. Kim seeks to increase understanding of the neuronal connectivity basis of gamma oscillation in the healthy brain and the brain affected by schizophrenia.

Ulf Knoblich, Ph.D., Yale University

Converging evidence suggests that inhibitory interneurons underlie the ability to function under continuously varying conditions. Dr. Knoblich seeks to understand the specific roles of interneurons in fast and slow perceptual processes, and thus provide a direct link between the physiological and cognitive symptoms of schizophrenia.

Shupeng Li, M.D., Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada

This project will test the possibility that clozapine exerts its therapeutic

* See Glossary

effects via the GABA-B receptor (GBR)-mediated inhibitory neurotransmission. Dr. Li will investigate the molecular mechanisms underlying clozapine's effects on GBR through testing its functional modulation in vitro in schizophrenia animal models. He will also explore the longitudinal correlation of clozapine through transcranial magnetic stimulation.

Claudia Lodovichi, M.D., Ph.D., Venetian Institute of Molecular Medicine, Italy

Dr. Lodovichi and her team will investigate neuronal morphology and circuit formation and function in a mouse carrying the candidate gene Disrupted-in-Schizophrenia 1 (DISC1). The analysis will be focused on the olfactory system which is severely affected in patients with schizophrenia and highly expresses DISC1.

Attila Losonczy, M.D., Ph.D., Columbia University

The hippocampus has been widely implicated in the pathogenesis of schizophrenia, with morphological evidence that hippocampal inhibitory (GABAergic) circuits are particularly impaired. Dr. Losonczy aims to determine the activity patterns of distinct classes of hippocampal inhibitory interneuron and pyramidal cell populations in vivo during spatial behaviors and their potential alterations in animal models of schizophrenia.

Jiangteng Lu, Ph.D., Cold Spring Harbor Laboratory

Using techniques developed in his lab that will allow his team to visualize and manipulate a large number of chandelier cells (CHCs), which are thought to be the most powerful cortical neurons that exert control over excitatory cell firing, Dr. Lu plans to examine several fundamental questions about CHC function in the prefrontal cortex, adding to our knowledge of the pathology that gives rise to schizophrenia.

Hirofumi Morishita, M.D., Ph.D., Mount Sinai School of Medicine

Dr. Morishita has formed a hypothesis that links the onset of schizophrenia to two major developmental events: maturation of GABAergic inhibitory circuits and myelination. He and his team seek to identify the molecular and cellular mechanisms mediating this novel GABA-myelin link during development and determine if it is disrupted in animal models and postmortem brains of people with schizophrenia.

Nandakumar Narayanan, M.D., Ph.D., Yale University

The prefrontal cortex receives dopamine signals mainly from the ventral tegmental area. By recording, disrupting and stimulating neurons in the ventral tegmental area and in the prefrontal cortex, Dr. Narayanan will explore how dopamine affects prefrontal networks in great detail with several cutting-edge techniques. This could lead to new approaches to treating schizophrenia.

Saleem M. Nicola, Ph.D., Albert Einstein College of Medicine of Yeshiva University

Dr. Nicola will test the possibility that cognitive deficits in schizophrenia are due to dysfunctional value representation in neurons of the cingulate cortex. To determine dopamine's role in this, his team will use a novel technique to locally treat cingulate neurons with dopamine receptor antagonists while recording their firing in rats performing a risky decision-making task.

Ruth M. Paredes, Ph.D., University of Texas Health Science Center at San Antonio

Dr. Paredes will investigate molecular mechanisms that cause alterations in cell signaling cascades and transcriptional events. This research would contribute to the characterization of the function of neuregulin-1 (a strong candidate gene for schizophrenia and psychosis) in regulation of the immune response. Dr. Paredes' work may shed light on the role of neuregulin-1 in schizophrenia pathology.

Sebastien Parnaudeau, Ph.D., Columbia University

Using virally mediated gene expression, Dr. Parnaudeau will silence mediodorsal thalamus (a source of excitatory input to the prefrontal cortex) neurons in adolescent mice and assess for the morphology and the activity of prefrontal interneurons in adult mice. Analysis of behavioral deficit will also be performed. This work should lead to a better understanding of the circuits involved in cognitive deficits in schizophrenia and help to find new treatments.

Michael J. Parsons, Ph.D., Medical Research Council (MRC) Harwell, England

In this project, Dr. Parsons plans to develop mouse models of numerous candidate genes for schizophrenia identified via genome-wide association studies. These new mouse models will be made freely available to the scientific community.

Anirban Paul, Ph.D., Cold Spring Harbor Laboratory

Utilizing four genetic and pharmacological models of schizophrenia to determine the set of common altered transcripts, which would then serve as biomarkers, Dr. Paul seeks to shed light on the molecular underpinnings of schizophrenia. He will target specific neuronal cell types for analysis, focusing on transcriptome changes in GABAergic basket and chandelier cells which are altered in the prefrontal cortex of schizophrenia patients as well as in various pharmacological and genetic mouse models. This research will be useful for diagnostic, prognostic and therapeutic purposes.

Heather E. Ross, Ph.D., Emory University

22q11DS, also known as DiGeorge syndrome, is the second most common childhood genetic disorder after Down syndrome. Dr. Ross seeks to determine several fundamental characteristics of 22q11DS including fully characterizing the immune dysfunction outcomes and examining how immune changes contribute to structural and functional brain abnormalities as well as atypical behavioral development.

Leah H. Rubin, Ph.D., University of Illinois at Chicago

This study seeks to determine whether endogenous oxytocin (OT) and OT DNA methylation* levels are altered in schizophrenia patients and their relatives as compared to controls. It also seeks to determine whether OT levels and OT DNA methylation are associated with clinical symptom severity and social cognition in patients with schizophrenia, their relatives and controls. This work can help identify potential therapeutic targets for the disease.

William B. Ruzicka, M.D., Ph.D., McLean Hospital and Harvard University

Epigenetic* changes in brain cells that use the neurotransmitter GABA to communicate with each other are key in generating cognitive symptoms in schizophrenia. These changes in GABAergic cells include decreased activity of the GAD1 gene, which produces the enzyme responsible for synthesizing GABA in the brain. Dr. Ruzicka will study the hypothesis that methylation* contributes to the dysfunction of genes in a network that regulates the gene GAD1 and hopes to shed light on the role of epigenetics in disease etiology.

Peggy Series, Ph.D., University of Edinburgh, Scotland

Dr. Series will use behavioral data from patients studied at the Royal Edinburgh Hospital in order to develop mathematical and computational models of decision-making and psychosis in schizophrenia. These models will be used to: i) quantify decision-making deficits more precisely; ii) study how poor decision-making as well as psychotic symptoms are related to learning deficits and problems in knowledge representation; iii) test the hypothesis that decision-making deficits and psychosis could be related to impairments in prediction error signals in the brain, thought to be mediated by dopamine.

Douglas J. Sheffler, Ph.D., Vanderbilt University

Group II metabotropic glutamate* receptors (mGlu2 and mGlu3) are expressed in many brain regions implicated in schizophrenia and anxiety disorders, and numerous clinical and animal studies have suggested that activation of these receptors provides a viable therapeutic approach for novel antipsychotics and anxiolytics. Dr. Sheffler has recently developed highly selective allosteric ligands for these receptors and has gained access to mGlu2 and mGlu3 'knockout' mice. Together, this provides an unprecedented opportunity to establish the roles of mGlu2 and mGlu3 in regulating hippocampal function. The results of these experiments will provide a clearer understanding of the mechanisms involved in the efficacy of mGlu2/3 activators in behavioral models of schizophrenia and anxiety disorders.

Kyriaki Sidiropoulou, Ph.D., Foundation for Research and Technology-Hellas and Institute of Molecular Biology and Biotechnology, Greece

Using animal models, Dr. Sidiropoulou and his team will employ a computational approach to determine whether cell-type specific microcircuits exhibit differential characteristics of persistent activity, the cellular phenomenon underlying working memory. The results will give rise to predictions as to which microcircuits might be more vulnerable in schizophrenia, and provide important insights to how specific cortical circuits are affected by schizophrenia and how these could be targeted for treatment.

Melissa A. Snyder, Ph.D., Drexel University

Using a combination of techniques, Dr. Snyder will examine the time course of NMDA receptor* (NMDAR) mis-expression and dysfunction in the prefrontal cortex in rats to determine when and how NMDAR transmission is changed during cortical development. She hypothesizes this change is involved in the early cognitive symptoms, disease initiation and progression of schizophrenia. These experiments will elucidate the

progression of NMDA hypofunction, provide mechanistic insight into its cause, and generate possible new avenues for therapeutic intervention.

Alexander E. Urban, Ph.D., Stanford University

Dr. Urban will try to gain a better understanding of the genetic basis of schizophrenia in velocardiofacial syndrome (VCFS). VCFS is caused by the loss of a large segment of the genome on chromosome 22, and patients with this syndrome are 30 times more likely to develop schizophrenia. By detecting all genetic differences between VCFS patients with and without schizophrenia, and observing differences in gene expression as stem cells are converted to neurons, he and his team hope, in follow-up projects, to determine if those same genes and genetic variants are also relevant to the development of schizophrenia in patients without the VCFS deletion on chromosome 22.

Jing Wu, M.D., Johns Hopkins University

Noting that antipsychotic medications suppress dopamine and that impaired function of a signaling enzyme, PI3 kinase, is implicated in schizophrenia pathogenesis, Dr. Wu wants to flesh out the molecular link, if any, between the two. The current research will determine if genetically engineered mice in which the molecular interaction between a synaptic plasticity protein called Arc and the PI3K domain are respectively 'knocked out.' If so, the mice would be novel mouse models of schizophrenia.

Dongmin Yin, Ph.D., Georgia Health Sciences University

Dr. Yin has shown that NRG1, a candidate gene for schizophrenia, was expressed at abnormally high levels in the forebrain of mutant mice displaying schizophrenia-like behavioral deficits. Using doxycycline to switch off NRG1 overexpression, he now seeks to learn if synaptic dysfunction and abnormal behaviors in his mice model require continuous overexpression of NRG1 in the adult brain. He will also evaluate whether overexpression only during adulthood can lead to schizophrenia-related deficits or whether damage done in development by elevated NRG1 can be reversed in adulthood.

OTHER

Addiction and Related Disorders

Ami Citri, Ph.D., Stanford University

Dr. Citri will build upon his lab's previous studies of EGR2, a protein that may be an important factor directing the production of other proteins involved in the initiation of addictive behaviors. He will apply a novel approach to identifying neuronal ensembles believed to mediate the initiation of drug addiction in order to find new avenues for therapeutic intervention.

Jie V. Deng, Ph.D., Duke University

Preliminary findings point to a potential molecular basis for the persistence of drug addiction. Dr. Deng will examine the regulation of cocaine reward induced by methyl CpG-binding Protein 2 (MeCP2), an epigenetic* regulatory protein that is required for normal neurological function. The research will characterize the impact of cocaine reward in neural networks of mice genetically altered to have a mutated MeCP2 gene.

* See Glossary

Susana Mingote, Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI, Columbia University

Stimulants increase dopamine release to abnormally high levels in the brain which can lead to addiction. It is also known that dopamine neurons co-release glutamate*. Dr. Mingote seeks to elucidate the role of glutamate* co-transmission in the development of amphetamine-induced behaviors, thereby revealing processes involved in the transition to addiction.

Xiangmin Xu, Ph.D., University of California, Irvine

Dr. Xu hypothesizes that disruption of dopamine D2 receptor signaling alters local inhibitory circuit connections to cause reversal learning deficits, which he believes may be an underlying susceptibility in drug abusers. The proposed research should elucidate the essential link between dopamine receptor mutations, the affected neuronal circuits and the corresponding learning deficits.

Mental Illness - General

Lior Appelbaum, Ph.D., Bar-Ilan University

Evidence shows that sleep/wake behavior affects synaptic plasticity, learning and performance. Dr. Appelbaum will use long-term, time-lapse imaging of the zebrafish as an experimental model to examine structural synaptic variations in narcolepsy and video-tracking monitoring systems to link synaptic changes to activity and sleep patterns. He hopes to uncover and characterize novel mechanisms of the role of synaptic plasticity in regulating sleep and mental behavior.

Andres E. Chavez Navarrete, Ph.D., Yeshiva University

Serotonin activity is determined by distinct receptor subtypes, but their individual contributions are not fully understood. Dr. Navarrete seeks to pinpoint the contributions of key receptors. In so doing, he hopes to uncover the means by which certain cellular and molecular mechanisms interact to affect synaptic function and neuropsychiatric illness. He also hopes to better identify the therapeutic action of selective serotonin reuptake inhibitors.

Brian E. Chen, Ph.D., McGill University

Wanting to know how the brain's neural circuitry controls synaptic connections—the all-important conversations between nerve cells—Dr. Chen will focus on two neuronal receptor molecules associated with schizophrenia and anxiety disorders, PlexinA and PlexinB. Molecular genetics and imaging in a fruit fly model will be used to examine how mutations in these receptors affect neural circuit formation and function.

Ali G. Crawford, Ph.D., University of California, San Diego

Dr. Crawford and colleagues have identified a mutation in a gene whose normal function is to regulate the DNA damage repair pathway. The mutation was identified in a family with developmental delay who display severe cerebellar atrophy (wasting of tissues of the cerebellum) and microcephaly (a genetic abnormality causing an abnormally small head). The research will test the hypothesis that mutations in this gene perturb DNA damage repair.

Ryan M. Drenan, Ph.D., Purdue University

Disorders such as depression, anxiety, schizophrenia and attention-

deficit hyperactivity disorder may result from imbalances in dopamine transmission. Dr. Drenan plans to study a group of brain neurons called the medial habenula* to help elucidate how dopamine transmission is regulated. This will open the way to new therapies to modulate dopamine transmission.

David P. Gavin, M.D., University of Illinois at Chicago

Emerging data suggest that in psychosis there is a dynamic equilibrium between DNA methylation* and demethylation activity. Dr. Gavin's focus is on a family of proteins called GADD45. GADD45b involvement is implicated in schizophrenia. In Dr. Gavin's research, he will use genetically engineered mice to try to determine the role of DNA demethylation and GADD45b in psychosis.

Milena Girotti, Ph.D., University of Texas Health Science Center at San Antonio

Levels of Interleukin 6 (IL-6) are elevated in patients with major depression, but it is not known whether IL-6 is involved in induction or aggravation of depressive symptoms. Using rat models, Dr. Girotti seeks to unveil a causal link between the IL-6 pathway and symptoms of mood disorders in order to help understand the disorder and in the search for more effective interventions.

Sebastian Haesler, Ph.D., Harvard University

Dr. Haesler will investigate mechanisms in the brain for reward prediction that are disturbed in schizophrenia and depression. He will combine the tools of optogenetics* and electrophysiology to measure the activity of dopamine neurons in mice performing a learning task, and then observe the effects of dopamine manipulation on subsequent behavior related to prediction ability.

William J. Joiner, Ph.D., University of California, San Diego

Dr. Joiner will test whether neurofibromatosis-1 (Nf1) mutations lead to problems with learning and memory because of their effects on the sleep/wake cycle. He aims to identify brain cells responsible for the effects of Nf1 on activity and sleep, and then by manipulating Nf1 levels and electrical properties of the cells determine if restoring circadian rhythms or sleep leads to changes in learning and memory.

Quan Lin, Ph.D., University of California, Los Angeles

Using mouse model systems, developed by Dr. Lin's team, that permit microRNA knockdown and overexpression, they will explore microRNA expression changes in the prefrontal cortex of prenatal mouse brains. This research aims to advance our understanding of the molecular and cellular mechanisms underlying prenatal stress that influence cognitive functions such as learning and memory, in the context of neurodevelopmental disorders.

Devanand S. Manoli, M.D., Ph.D., University of California, San Francisco

Pioneering work in the prairie vole has identified Oxytocin (OT), a neuropeptide and hormone, as a critical mediator of pair bonding. Strikingly, OT and OXTR, the human OT receptor, have also been implicated in social-attachment-type behaviors in humans. Disruptions in the OT axis have been correlated with numerous psychiatric disorders. Dr. Manoli plans to test the genetic requirement of OTR

(a target gene) in pair bonding in voles.

Julie A. Markham, Ph.D., University of Maryland, Baltimore

Dr. Markham notes that early-life trauma (ELT), both physical and sexual, is associated with increased risk for schizophrenia. She is examining, in rodents, the consequences of stress during the pre-adolescent, juvenile period, which closely corresponds to the post-infancy/pre-adolescent childhood in humans. She seeks to establish an animal model with clinical relevance to psychiatric illness that is associated with ELT.

Amaya Miquelajauregui-Graf, Ph.D., University of California, Los Angeles

Dr. Miquelajauregui-Graf will use a mouse model in which the expression of the Disrupted-in-Schizophrenia 1 (DISC1) candidate gene is transiently disrupted in small subsets of cortical pyramidal neurons during embryonic development. She aims to utilize time-lapse in vivo 2-photon imaging of dendritic structure as a reliable read-out of early genetic disruptions. This work will shed light on the time-course of the disease and help identify possible molecular targets for future treatments.

Ardesheer Talati, Ph.D., New York State Psychiatric Institute and Columbia University

Using functional MRI, Dr. Talati will examine the effects of smoking during pregnancy on offspring's brain function. He will examine whether exposed offspring have different brain responses than those not exposed to smoking and if these differences explain why those exposed to smoking go on to have behavioral problems.

Masaaki Torii, Ph.D., Children's Research Institute at Children's National Medical Center

In prior work, Dr. Torii showed the cerebral cortex consists of a columnar mosaic of neuronal subtypes, and specific disruptions in this mosaic may underlie distinct psychiatric disorders. Dr. Torii will use an immunohistochemical approach to label various neuronal subtypes and quantitatively evaluate their columnar clustering and distribution in the cortex by a statistically-based density map method, setting the stage for further research in this area.

Ipek Yalcin Christmann, Ph.D., Pharm.D., Centre National de la Recherche Scientifique (CNRS), France

Dr. Christmann will test, in mice, the potential implication of the anterior cingulate cortex (ACC) in chronic pain-induced mood disorder phenotypes. She will assess time-dependent changes in gene expression and in protein expression profiles in the ACC with neuropathic pain. This analysis has future diagnostic and treatment implications.

Psychosis

Ricardo E. Carrion, Ph.D., The Feinstein Institute for Medical Research

Dr. Carrion will investigate neural mechanisms of social functioning in adolescents at high risk for psychotic illness. The hypothesis of the study is that early sensory processing deficits lead to an inability to

read relevant social cues. In the study, 40 high-risk adolescents and 40 healthy controls will be compared to assess the impact of early auditory sensory processing deficits on higher-order social cognition and its relationship to social functioning.

Martin Debbané, Ph.D., University of Geneva

Atypical social cognition, a trademark feature of the earliest phases of psychosis, represents the most important challenge to remission in adults with schizophrenia. Oxytocin, a neuromodulating hormone, has been shown to increase accuracy in facial emotion recognition and facial memory. To understand this process, Dr. Debbané will use functional magnetic resonance imaging to examine neural modulation after intranasal administration of oxytocin to adolescents with risk symptoms for psychosis.

Elaine K. Green, Ph.D., Cardiff University

Dr. Green's lab suggests a causative role for a gene called FLT1—whose functions include involvement in placental growth—in postpartum psychosis. The proposed study will investigate genetic differences in the FLT1 gene in a large sample of women with postpartum psychosis and healthy controls in an effort to further explain the biological contribution of FLT1 to postpartum psychosis.

Laurie M. McCormick M.D., University of Iowa

Research suggests that mirror neuron activity underlies many aspects of social cognition, and that the disruption of this system may be a core problem in schizophrenia. Dr. McCormick will attempt to replicate recent findings that 'mirror neuron activity'—using electroencephalography—in response to observing live hand movement, was significantly greater in schizophrenia patients than in age- and sex-matched healthy controls.

Mahesh Menon, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada

Using a series of experimental tasks designed to capture delusion while patients experiencing them undergo a brain scan, Dr. Menon found abnormal activity in a number of brain regions, including a part of the brain rich in dopamine receptors known as the striatum. This work should help to determine whether first-episode patients show the same abnormal activity in the striatum, whether this abnormal activity 'recovers' as delusions respond to antipsychotic medication and whether brain activity helps predict who will recover completely.

Yang Yang, Ph.D., Yale University

The proposed research will help reveal how dopamine D1 receptors influence prefrontal cortex (PFC) neurons through actions at ion channels that reduce PFC cell firing. Dr. Yang's thesis is that ion channels contribute to D1 gating actions, and that these ion channels may provide a novel therapeutic target for cognitive disorders.

NEW TECHNOLOGIES

ANXIETY DISORDERS

Obsessive-Compulsive Disorder (OCD)

Brian P. Brennan, M.D., Harvard University

Dr. Brennan's laboratory has developed an application of a brain imaging technique called magnetic resonance spectroscopy that allows a more accurate assessment of the glutamate* system than ever before possible. Identifying glutamate-system dysfunction in OCD patients could promote development of novel glutamate-modulating treatments.

Post-traumatic Stress Disorder (PTSD)

John P. Christianson, Ph.D., University of Colorado, Denver

The mechanism by which the brain perceives safety and danger is impaired in patients with PTSD. In this study, Dr. Christianson will apply optogenetics* in the insular cortex* so as to bolster or strengthen safety learning. This represents critical first steps towards advancing therapy to improve safety learning in PTSD patients.

AUTISM & AUTISM SPECTRUM DISORDERS (ASD)

Mark Christian Eldaief, M.D., Harvard University

Dr. Eldaief and team will compare repetitive transcranial magnetic stimulation (rTMS)-induced effects in people with ASD and healthy controls. They have shown that rTMS can change the strength of connections in neural networks that shape learning and memory. This research could advance understanding of ASD mechanisms, which could help diagnose disease and possibly pave the way for rTMS use to correct ASD network abnormalities.

Avniel S. Ghuman, Ph.D., University of Pittsburgh

Reduced long-distance brain connectivity in ASD is believed to contribute to cognitive pathologies. Dr. Ghuman will use magnetoencephalography* to examine the dynamics of connectivity between critical regions of networks involved in sensory and auditory processing, and assess how this may relate to social and cognitive impairments in ASD.

Yun Li, Ph.D., Whitehead Institute for Biomedical Research

Using the newly-developed TALEN technology, Dr. Yi has generated novel stem cell models of Rett and Fragile X syndromes (FXS) in human cells. Neural and glial cell types will be subjected to extensive phenotypic characterization with respect to structure, electrophysiology, transcription, translation and intracellular signaling. Findings may provide critical insights into the pathogenic mechanism of Rett and FXS in human cells, and could serve as a platform for future therapeutic identification efforts that could lead to treatments.

Michael E. Talkowski, Ph.D., Massachusetts General Hospital and Harvard University

A striking number of genes associated with a spectrum of neuropsychiatric disorders (NPD) were found to be disrupted in subjects with ASD and related neurodevelopmental disorders (NDD). Employing

innovations in sequencing and bioinformatics developed during his postdoctoral research, Dr. Talkowski seeks to prove that careful genomic approaches can elucidate locations at which some genetic changes confer risk for NPD and NDD.

DEPRESSION

Paolo Cassano, M.D., Harvard University

Based on a recently discovered association between depression and decreased metabolism in specific brain regions, Dr. Cassano will conduct a clinical trial to test the efficacy of a brain stimulation technique called transcranial laser therapy (TLT) as a treatment for patients with major depressive disorder. TLT safely and noninvasively administers infrared light that is absorbed by mitochondria, the energy-generating structures in cells. Thus activated, the mitochondria jump-start cerebral metabolism to restore bioenergetic balance.

David T. Plante, M.D., University of Wisconsin-Madison

Dr. Plante will utilize high density electroencephalography to characterize patterns of brain function during sleep and wakefulness in major depressive disorder (MDD) patients with hypersomnolence (excessive sleepiness), as compared to MDD patients without hypersomnolence and healthy controls. He seeks to better understand the causes of depression and hypersomnolence in order to develop better ways of diagnosing and treating these problems.

Bechara J. Saab, Ph.D., University of Zurich, Switzerland

Using optogenetics*, Dr. Saab plans to selectively excite serotonergic neurons of the dorsal raphe nuclei in living mice during fMRI to elucidate the serotonergic connectivity of the mammalian brain in order to determine the brainwide serotonergic impact of the antidepressant fluoxetine (Prozac). This research promises to shed light on the underlying physiological principles of the development of depression, as well as the mode of action for a treatment strategy undertaken by millions of patients.

Yunjie Tong, Ph.D., McLean Hospital/Harvard University

Dr. Tong will use multimodal brain imaging to study the response of patients with major depressive disorder to repetitive transcranial magnetic stimulation (rTMS). To establish a biomarker that may predict outcome, the real time hemodynamic reaction of the brain to rTMS during each treatment session will be measured by functional near infrared spectroscopy. The research will contribute to the establishment of novel biomarkers in treatment evaluations, as well as individualization of treatment plans.

SCHIZOPHRENIA

Kristen J. Brennand, Ph.D., Salk Institute for Biological Studies

Dr. Brennand will create models of schizophrenia by reprogramming skin-cell samples from schizophrenia patients and healthy controls into stem cells that will then be induced to differentiate into defined sub-populations of neurons. Cellular and molecular differences between

the neurons derived from patients and from controls can then be identified, addressing the unanswered question of which types of neurons are most affected in schizophrenia. The tools developed in this research could serve as the basis for screening new drug treatments.

Kimberly M. Christian, Ph.D., Johns Hopkins University

Dr. Christian will use stem cells from patients with a specific Disrupted-in-Schizophrenia 1 (DISC1) gene mutation to generate human neurons to investigate the role of this gene on neuronal development. It will also aid in identifying abnormalities at the single cell level associated with disease causation and thereby facilitate diagnostic evaluations of at-risk populations.

Marina Frantseva, M.D., Ph.D., University of Toronto

Dr. Frantseva will conduct transcranial magnetic stimulation and electroencephalography recordings in psychotic and healthy subjects to elucidate normal and abnormal mechanisms of cortical conductivity and how that might translate into specific symptoms of schizophrenia. She believes it is possible that interventions to normalize cortical conductivity might be effective in treating schizophrenia.

Michael M. Halassa, M.D., Ph.D., Harvard University

Schizophrenia is characterized by difficulties in filtering sensory information and disrupted sleep, and the brains of people with schizophrenia show decreased spindles, or brain waves. Using optogenetics* in experimental mice, Dr. Halassa will look at how brain regions behave across the sleep/wake cycle and whether the decrease in spindles predicts a decrease in the ability to filter out sensory information.

Michael J. Higley, M.D., Ph.D., Yale University

Using optogenetics*, Dr. Higley will measure the actions of interneurons on their synaptic targets to find out how synaptic inhibition is modulated by dopamine and how its dysregulation may be an important factor in schizophrenia. He will also examine dopamine and inhibition in synaptic plasticity—a disruption of which likely represents a key pathology associated with schizophrenia.

Toshikazu Ikuta, Ph.D., Feinstein Institute for Medical Research

To study the pathways implicated in auditory hallucinations, Dr. Ikuta will apply multimodal brain imaging technologies, including functional magnetic resonance imaging and diffusion tensor imaging, to compare measures of white matter integrity in schizophrenia patients experiencing auditory hallucinations, schizophrenia patients who have not had auditory hallucinations and healthy volunteers.

Brady J. Maher, Ph.D., Lieber Institute for Brain Development, Johns Hopkins University

Velocardiofacial syndrome (VCFS) results from a large DNA deletion on chromosome 22. Dr. Maher will compare cellular and electrical properties of neurons from patients diagnosed with VCFS and schizophrenia to properties of neurons derived from unaffected siblings. The physiological differences observed will represent potential phenotypes associated with schizophrenia in part due to the deletion of genes on chromosome 22. He will also try to identify which genes are responsi-

ble for the observed phenotypes by performing ‘rescue’ experiments—reintroducing individual genes that are absent due to the chromosomal deletion—to see if they correct the abnormal phenotype.

Sergiu P. Pasca, M.D., Stanford University

Dr. Pasca and his team have generated pluripotent stem cells (iPSCs) from a cohort of patients with chromosome 22 (22q11.2) deletion syndrome (22q11DS), with a diagnosis of schizophrenia or autism, and with no psychiatric diagnosis. In prior work they have generated neurons from some of these cells and identified defects in dopamine signaling. They will now extend this initial characterization by studying other aspects of neuronal development and signaling in 22q11DS neurons and by characterizing dopamine signaling in neurons from additional 22q11DS patients. The goal of this project is to develop in vitro models of psychiatric disease and to identify new therapeutic targets.

Xin Wang, Ph.D., Salk Institute for Biological Studies

Developing and using a novel multi-channel mouse electroencephalography platform coupled with sensory stimulation and behavioral monitoring, Dr. Wang will study the similarity and differences in brain dynamics among three mouse models of schizophrenia, each of which uses different mechanisms to induce glutamate* hypofunction in diverse neuron types and brain regions. The aim is to find unifying denominators in schizophrenic brain dynamics which could translate into reliable diagnostic tools.

Xiaoyan Xu, Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI and Columbia University

Dr. Yu seeks to develop a new imaging paradigm to assess cortical dopamine (DA) release, which would be useful in assessing the so-called dopamine hypothesis of schizophrenia. (The hypothesis relates striatal DA hyperactivity to positive symptoms, and cortical DA deficit to negative symptoms.) Dr. Yu will test human subjects as a part of this study. If verified, this will provide both a new imaging paradigm for cortical DA and proof of concept for a potential therapeutic strategy.

Haining Zhong, Ph.D., Vollum Institute, Oregon Health and Science University

Utilizing a suite of advanced technologies, Dr. Zhong seeks to determine how dopamine shapes the dynamics of the cAMP-dependent kinase (PKA) pathway, downstream of dopamine activity in individual neuronal microcompartments. He seeks to identify functionally significant changes in PKA localization and activity following endogenous dopamine release. This should further the understanding of schizophrenia at a molecular level.

OTHER - Mental Illness - General

Alexandre Saez, Ph.D., Columbia University

Dr. Saez will use optogenetics* in combination with neurophysiological and complex behavioral experiments to advance the study of prefrontal/amygdala interactions. He will elucidate how prefrontal input can regulate the responsivity of the amygdala, a key mechanism in maintaining normal adaptive emotional responses that likely becomes dysfunctional in many patients with psychiatric disorders.

* See Glossary

DIAGNOSTIC TOOLS / EARLY INTERVENTION

ANXIETY DISORDERS

Obsessive-Compulsive Disorder (OCD)

Cara Bohon, Ph.D., University of California, Los Angeles

An obsessive fear of weight gain leading to dangerous food restriction and compulsive rituals around food are common symptoms of OCD and anorexia. By applying functional magnetic resonance imaging to compare brain responses to selected stimuli among adolescents with anorexia, OCD and healthy controls, Dr. Bohon seeks to determine how abnormal brain activity relates to symptom formation, what accounts for shared characteristics among these disorders, and whether deficits in specific circuitry underlying their defining features could lead to targeted strategies for preventive interventions.

Post-traumatic Stress Disorder (PTSD)

Erin C. Berenz, Ph.D., Virginia Commonwealth University

In the proposed project, Dr. Berenz will initiate a clinical investigation of fear conditioning and PTSD experienced by returning combat veterans. This research will provide key insights into the pathophysiology of PTSD risk as well as identify key biomarkers of risk to optimize prevention and intervention approaches.

Dennis C. Choi, Ph.D., Emory University

Dr. Choi is concerned with the question of why some people are more vulnerable than others to developing PTSD. In an effort to answer this question, Dr. Choi will examine two vulnerability factors thought to increase risk for PTSD: prior trauma history and the role of hippocampal functioning and neuronal plasticity.

Ryan J. Herringa, M.D., Ph.D., University of Wisconsin-Madison

Studies have documented changes in brain structure in youths with PTSD, but few have examined changes in brain function. Brain imaging studies in adults with PTSD suggest increased activity in the amygdala, the brain's fear center, but less activity in the medial prefrontal cortex, a region responsible for calming amygdala responses and extinguishing fear memories. In this study, Dr. Herringa will ascertain whether adolescents with PTSD show abnormalities similar to adults, findings that could lead to better detection and treatment.

Alicia K. Smith, Ph.D., Emory University

In this study, Dr. Smith will examine DNA methylation* and messenger RNA (mRNA) expression of candidate genes, specifically looking at lymphocytes, prefrontal cortex, amygdala and hippocampal tissue in two different models of PTSD in mice. Correlation between blood and brain DNA methylation or mRNA expression in response to stress sensitization and fear acquisition will support further development of the genes as peripheral biomarkers of PTSD and will provide insight into the pathophysiology of PTSD and other stress-related disorders.

Moriah E. Thomason, Ph.D., Wayne State University

Dr. Thomason will examine ways in which trauma reprograms genetic and neural machinery to alter neurogenetic development in children.

She will identify DNA methylation* patterns in blood and neural development related specifically to trauma exposure in a unique cohort of at-risk urban children, and will evaluate interactions between these measures. Her aim is to discover reliable risk factors to serve as targets for future intervention in pediatric post-traumatic stress disorder.

Anxiety - Other

Elizabeth A. Lawson, M.D., Massachusetts General Hospital/Harvard University

Secretion of the hormone oxytocin, a peptide involved in the regulation of food intake that has anti-anxiety and antidepressive properties, is abnormal in patients with anorexia nervosa (AN) and is associated with severity of disordered eating psychopathology, anxiety and depression. Since testosterone promotes oxytocin signaling in the brain, Dr. Lawson hypothesizes that the therapeutic effects of testosterone in AN are partially mediated by a normalization of oxytocin secretion. She will test this hypothesis in a group of 40 women suffering from AN, over the course of a study period that spans 6 months.

Siobhan S. Pattwell, Ph.D., Weill Cornell Medical College/Cornell University

Dr. Pattwell seeks to identify windows of maximal opportunity for therapeutic interventions that are tailored to appropriate individuals at the most appropriate time. She hopes to do this by delineating age-specific variation in the regulation of fear responses that are at the very core of therapeutics for anxiety disorders. She will perform parallel mouse and human studies to investigate the developmental role of reconsolidation update on the erasure of conditioned cued and contextual memories.

AUTISM / AUTISM SPECTRUM DISORDERS (ASD)

Kelly Anne Barnes, Ph.D., National Institute of Mental Health

Functional connectivity MRI is a technique that examines the coupling between neural activity in different brain regions. Such coupling is atypical in ASD, and measures of functional connectivity correlate with differences in symptom expression. Dr. Barnes will use functional connectivity MRI data to predict subsequent measures of symptom expression and adaptive behaviors, and to establish guidelines to provide a detailed understanding of the relationship between neural circuitry and long-term outcomes in ASD. She hopes to identify those patients who might benefit from interventions.

Mikail Rubinov, Ph.D., University of Cambridge, England

Dr. Rubinov will use cutting-edge neuroimaging and data analysis methods to accurately reconstruct complex brain networks, or connectomes, and to detect abnormalities of these networks in adolescent patients with autism and in their siblings. The detection of such abnormalities could result in objective diagnostic markers of autism. Objective markers should play an important role in providing individuals with more accurate information about their disease outcomes and may inform the choice of autism treatments in the future.

BIPOLAR DISORDER (BP)

Cynthia V. Calkin, M.D., Dalhousie University

A third of patients with BP have abnormal glucose metabolism, and those with diabetes appear to have a more severe form of BP. Dr. Calkin's trial, involving 500 patients, is intended to establish rates of insulin resistance to determine whether a specific BP sub-population is at greater risk. Dr. Calkin will also examine the impact of insulin resistance on the course of BP and treatment response.

Fei Du, Ph.D., Harvard University

Using advanced functional magnetic resonance spectroscopy, Dr. Du plans to identify and quantify alterations in the function of mitochondria (the energy-producing structures in cells) in patients with BP as they undergo a cognitive challenge. The research hypothesis is that they will show decreased ability to meet the energy demands of intensive cognitive activity. The method, once established, would have potential for risk diagnosis and treatment monitoring for BP and related disorders, including depression and schizophrenia.

Steven M. Miller, Ph.D., Monash University, Australia

Dr. Miller will examine genetic and clinical aspects of a visual test called binocular rivalry rate (BRR) that he pioneered and which appears to satisfy several criteria for being a risk-indicator biomarker for BP. Being able to identify individuals with BP, or individuals at genetic risk for developing BP, would be of great benefit to both clinical and biological psychiatry.

Fei Wang, Ph.D., Yale University

Dr. Wang will compare the white matter integrity and functional connectivity of medication-naïve adolescents and young adults experiencing their first episode of BP versus those experiencing their first episode of schizophrenia (SZ). This will provide unique opportunities for understanding the development of both illnesses, their neuro-pathophysiological differences and potentially the identification of markers that differentiate them. This information will be key in the development of early identification, treatment and prevention strategies.

DEPRESSION

Lara C. Foland-Ross, Ph.D., Stanford University

This study will examine abnormalities in brain structure and function in girls with mothers with depression compared with girls of never-depressed mothers. Dr. Foland-Ross will observe how such deficits in the girls at risk relate to a form of the serotonin transporter gene in the serotonin neurotransmitter system, which has been implicated in depression risk. The girls at risk will then be followed long-term to see whether abnormalities in brain structure and function predict subsequent depression symptoms.

David E. Kemp, M.D., Case Western Reserve University

People with major depressive disorder experience a shortened lifespan from type-2 diabetes and cardiovascular disease. Dr. Kemp will test indications that treatment with the diabetes drug pioglitazone (Actos™) can reduce the severity of depression and co-occurring insulin resistance and look into whether it can mitigate aspects of cardiovascular risk.

Snezana M. Milanovic, M.D., Massachusetts General Hospital/Harvard University

Using novel brain imaging technology to generate estimates of human neural stem and progenitor cells, key to neurogenesis, Dr. Milanovic will apply algorithms in order to identify metabolic networks that are impaired in certain brain conditions and connect them to genomics networks. Dr. Milanovic will use this analysis to identify biomarkers that are diagnostic and predictive of the course of major depressive disorder and its response to therapy.

Lisa A. Pan, M.D., University of Pittsburgh

Dr. Pan will examine the role of central nervous system-specific in-born errors of metabolism in disease pathophysiology in young adults with history of severe, treatment-resistant depression. She will recruit participants with refractory depression who have been referred for electroconvulsive therapy, and healthy-matched controls to see how novel metabolites in blood and cerebrospinal fluid differ. Metabolic signatures for disease could provide valuable biomarkers and insights about disease mechanisms.

Pia Pechtel, Ph.D., McLean Hospital/Harvard University

By investigating whether deficits in reward processing are associated with high-risk behavior, specifically in adolescents who develop major depressive disorder following sexual abuse, Dr. Pechtel hopes to identify functional mechanisms that motivate maladaptive development in order to identify individuals at risk for psychopathology and to develop more targeted interventions to prevent high-risk behavior.

Karina Quevedo, Ph.D., University of Pittsburgh

Child abuse is a risk factor of adolescent-onset depression that follows a chronic and severe course. Dr. Quevedo will study the brain activity of depressed adolescents (with or without a history of abuse) and healthy adolescents, using functional magnetic resonance imaging while they perform various tasks, and sample and record cortisol levels at various times of wake up. She expects that abused depressed adolescents will show lower cortisol awakening response and lower neural activity in brain areas that process emotional self-other information. The study may inform personalized treatment for early depression and will help to identify neurodevelopmental markers of chronic depression.

Ramiro Salas, Ph.D., Baylor College of Medicine

Using functional magnetic resonance imaging in a group of patients with major depression before and after antidepressant treatment, Dr. Salas will study the involvement of the habenula* in depression. He predicts that before medication, the habenula will be hyperactive, and that this will abate in patients in which the treatment is effective. If correct, this could set the basis for future use of fMRI to predict treatment outcome as well as the best treatment option for each patient.

Natalie J. Shook, Ph.D., West Virginia University

Dr. Shook proposes that performance-based measures rather than self-report measures, may provide more objective, accurate assessments of negative cognitive style and treatment efficacy in depression. She will utilize an attitude formation paradigm referred to as

* See Glossary

'BeanFest,' a computer simulation requiring people to learn novel stimuli that must become differentially associated with positive and negative outcomes in order to succeed at the task. Dr. Shook will record participants' behavior and judgments and examine the use of 'BeanFest' as a potential performance-based diagnostic tool.

Melissa R. Warden, Ph.D., Stanford University

In an effort to understand how communication between the medial prefrontal cortex and the dorsal raphe nucleus mediates depression-related behavior, Dr. Warden will investigate how changes in functional connectivity between these two areas are reflected by changes in depression-related behavior. This research will point toward new diagnostic methods, while a detailed understanding of the underlying functional anatomy will suggest precise therapeutic targets.

Sara L. Weisenbach, Ph.D., University of Michigan

Dr. Weisenbach aims to first identify and then combine biomarkers, in individuals with first-onset, unmedicated, late-life depression (LLD), with neuropsychological and behavioral measures. This will allow for the mechanistic definition of simplified, relatively inexpensive, non-imaging measures, anchored on a background of neurobiological correlates that may predict the course of cognition and functioning in individuals suffering LLD. This could lead to more accurate assessments and better targeting of preventive and treatment strategies.

Sarah L. Whittle, Ph.D., University of Melbourne, Australia

Dr. Whittle's study will have 30 healthy adolescents (aged 15-17) participate in a one-hour MRI assessment. This will include an assessment of brain function as they complete a novel social rejection task, as well as a self-report assessment of rejection sensitivity. The study could provide the first clues as to the neural underpinnings of the types of real-life feelings associated with social rejection that might contribute to the development of depression in adolescence.

SCHIZOPHRENIA

Julia B. Deakin, Ph.D., University of Cambridge

Using a brain imaging method called T2 MRI which measures changes in brain volume to detect early pathology in schizophrenia patients, Dr. Deakin will examine images in newly diagnosed, untreated patients to distinguish them from treated patients, since schizophrenia treatment itself can cause brain changes. Untreated patients and healthy controls will be compared to assess which parts of the patients' brain the disease changes. The ability to detect brain tissue loss might provide a method of detecting the risk of psychotic brain disease before its onset.

Alice Egerton, Ph.D., Institute of Psychiatry/ King's College London, England

Aided by an MRI scanner, Dr. Egerton will attempt to determine whether initial levels of glutamate* predict subsequent treatment response for schizophrenia and whether improvements in symptoms following treatment are associated with reductions in glutamate. This research can ultimately lead to tests for predicting the types of medication most likely to benefit individual patients.

Hesheng Liu, Ph.D., Massachusetts General Hospital/ Harvard University

Multiple lines of investigation point toward altered lateralization in schizophrenia, and preliminary experiments demonstrated that aberrant functional lateralization in schizophrenia is closely associated with altered cross-hemisphere communication in specific brain regions. Dr. Liu proposes using a data-driven approach to identify the hemispheric interaction pattern unique to schizophrenia and explore the genetic underpinnings in a large cohort of healthy subjects.

Tara A. Niendam, Ph.D., University of California, Davis

Utilizing fMRI and AXCT, an established measure of cognitive control in schizophrenia, Dr. Niendam will examine the impact of age at onset on prefrontal cognitive dysfunction present at ascertainment, as well as the pattern of individual differences that occur in prefrontal functioning as a result of development over follow-up. By identifying the age-related pattern of impairment in prefrontal cognitive functioning after the first episode of illness, the investigation will lend new insights on potential developmental mechanisms that contribute to the cognitive impairment associated with age at onset.

Ofer Pasternak, Ph.D., Brigham and Women's Hospital/ Harvard University

Noting recent suggestions that neuroinflammation is involved in the early stages of schizophrenia, Dr. Pasternak will address the difficulty in distinguishing between inflammation and degeneration in vivo. He will explore the hypothesis that neuroinflammation may precede and even result in white-matter degeneration. Evidence of inflammation could be used as an early diagnostic biomarker and could support the use of anti-inflammatory drugs as preventive treatment.

Fiza Singh, M.D., University of California, San Diego

Dr. Singh is interested in the potential biomarker presented by the naturally occurring neural hormone oxytocin (OT) for application in the treatment of schizophrenia. OT, known for its role in bonding between mother and newborn infant, can act to increase levels of trust, generosity and reduce activation of brain areas related to fear—properties that might be harnessed for improving social cognition.

OTHER

Addiction and Related Disorders

Barbara J. Weiland, Ph.D., University of Michigan

Dr. Weiland will longitudinally examine the role of dopamine in neural reward circuitry during the key transitional period of ages 18-23, during which substance use trajectories are expected to diverge in vulnerable versus resilient individuals. The mechanistic knowledge gained may help in the development of targeted interventions for high-risk populations as well as potential treatment strategies for youth with substance use disorders.

Borderline Personality Disorder

Edward A. Selby, Ph.D., Rutgers University

People who suffer from borderline personality disorder (an emotional disorder) and bulimia nervosa (an eating disorder) have been known to ruminate intensely, rehearsing over and over their feelings about an upsetting situation. Dr. Selby speculates self-damaging behaviors may serve as numbing substitutes for intense self-examination of this sort. In the current research project, he seeks to examine people affected by each disorder separately, as a means of distinguishing one from the other for the ultimate purpose of refining diagnosis and tailoring treatments more precisely and effectively for individual patients.

Mental Illness- General

Linda Booij, Ph.D., University of Montreal

Low levels of the nerve-cell chemical serotonin combined with early life stressors can increase the risk for depression and anxiety. Recent findings in Dr. Booij's lab suggest it may be possible to use DNA methylation*, assessed in blood or saliva, as a noninvasive biomarker for low serotonin in the human brain, prompting further exploration for its use determining associated risk of mental illness. Dr. Booij's proposed trial will explore DNA methylation as a diagnostic measure for low serotonin levels and associated risk of mental illness.

Richard W. Morris, Ph.D., University of New South Wales, Australia

Neuroimaging data will be collected from schizophrenia patients and healthy adults to test whether activity in the ventral striatum, critical for reward learning, is directly related to the amount of motivated behavior in people with schizophrenia. The results will help to explain why some people suffer from a lack (or an excess) of motivation and provide clues as to why disorders of motivation are so difficult to treat. Dr. Morris seeks to establish a novel test for treatment of motivation deficits, and to help identify new treatment targets in schizophrenia and other disorders affecting motivation.

Psychosis

David Luck, Ph.D., University of Montreal

Approximately 30% of people with bipolar disorder (BP) may receive an erroneous diagnosis of schizophrenia (SZ). Dr. Luck seeks to identify objective markers of vulnerability that would distinguish with greater certainty the two diseases by looking in the hippocampal region and the dorsolateral prefrontal cortex—brain areas essential for memorizing association between multiple stimuli (commonly named binding). He intends to investigate cognitive and neural perturbations of binding in patients with psychosis using functional magnetic resonance imaging and then systematically compare SZ and BP patients, in order to clearly identify the similarities and the differences in binding impairments.

Kanchna Ramchandran, Ph.D., University of Iowa

Dr. Ramchandran is adopting a cutting edge framework in examining stages of brain reward processing that are disturbed across tradi-

tional categories of psychotic conditions. She will create a reward processing nomenclature for psychotic populations. Schizophrenia and bipolar patients would have different patterns, which could lead to a new dimensional approach for characterizing psychosis type based on underlying neurobiological processing difference.

Tiago Reis Marques, M.D., Institute of Psychiatry/ King's College London, England

Several modes of neuroimaging were utilized in order to predict clinical outcome in first-episode psychotic patients as well as healthy controls from the same geographical area. Dr. Marques anticipates that the integration of different available data will provide a better understanding of what structurally and functionally changes in the brain.

Sarah I. Tarbox, Ph.D., Yale University School of Medicine

In an effort to develop more effective means of identifying risk for psychosis early in life and develop interventions, Dr. Tarbox will study high-risk individuals and normal-risk siblings. Her goals are to determine whether social functioning deficits across development as well as the association between social functioning deficits and psychosis-risk symptoms are more strongly influenced by within-family effects compared to unique environmental effects.

Suicide

Zainab Samaan, M.D., McMaster University, Canada

Dr. Samaan will test the association between suicide attempts and obesity to see if it holds up when one controls for the presence of variables such as psychiatric diagnosis, medical illness and lifestyle factors. She also plans to test the association between cholesterol blood level and suicide attempts, as well as the effect of cholesterol on the relation between obesity and suicide. Studies show that low cholesterol, one of the lipids in the brain essential for normal brain function, might be associated with suicide and low serotonin levels.

Clement C. Zai, Ph.D., Centre for Addiction and Mental Health at the University of Toronto

By sequencing of regions around significant DNA variants, Dr. Zai and his team seek to identify novel DNA variants across the human genome in archival samples of chronic schizophrenia/bipolar disorder patients. They will compare the frequency distributions of the genotypes and alleles of these polymorphisms between patients with and patients without lifetime history of suicidal attempts. The ultimate aim of the research is to generate information that would permit screening of people at risk for suicide.

NARSAD Young Investigator Grants help researchers launch careers in neuroscience and psychiatry and gather pilot data to apply for larger federal and university grants.

* See Glossary

NEXT GENERATION THERAPIES

ANXIETY

Obsessive-Compulsive Disorder (OCD)

Susanne E. Ahmari, M.D., Ph.D., Columbia University

Deep brain stimulation (DBS) shows promise for treating OCD, but optimal targets for stimulation have not been determined. Working with mice, Dr. Ahmari will apply optogenetics* to effect direct, precise stimulation of specific neuronal populations in the mouse brain. The goal is to optimize target selection for DBS use in humans so as to maximize symptom reduction and minimize side effects.

Post-traumatic Stress Disorder (PTSD)

Matthew A. Cooper, Ph.D., University of Tennessee, Knoxville

Dr. Cooper will test a new approach for disrupting the stress-related memories that persist in patients with PTSD. The activation of a brain protein called brain-derived neurotrophic factor (BDNF) is a critical step in the formation of stress-related memories. The signaling pathway that regulates the synthesis of BDNF has been identified, providing a means for manipulating the BDNF system. This study will use a mouse model of social defeat to investigate whether treatments that target BDNF signaling, including alcohol consumption (which inhibits BDNF signaling), will interfere with the consolidation of trauma-induced memories in PTSD and other stress-related mental illnesses.

Richard A. Sewell, M.D., Yale University School of Medicine

In all types of animals tested so far, activating cannabinoid receptors enhances fear extinction, but this has never before been attempted in humans. Dr. Sewell aims to increase our understanding of the neurobiology of fear and anxiety by testing whether enhancing cannabinoid function can enhance extinction learning in healthy human subjects, providing a first step towards development of new treatments for PTSD.

Anxiety - Other

Amit Etkin, M.D., Ph.D., Stanford University

Deficits in emotion regulation are central to generalized anxiety disorder (GAD) which typically starts in late adolescence. Dr. Etkin will examine the efficacy of a novel intervention for emotion regulation. Delivered as Internet-based computer games, forty adolescents with GAD will receive either the intervention or control games while functional magnetic resonance imaging (fMRI) examines brain effects, comparing pre- and post-training neuroimaging and symptom data.

Ovsanna Leyfer, Ph.D., Boston University

While the role of D-cycloserine (DCS) has been investigated in cognitive-behavioral treatment (CBT) of adults with panic disorder, its effects have not been examined in youth. Dr. Leyfer aims to assess the efficacy of DCS-enhanced intensive therapy as an intervention for panic disorder, with or without agoraphobia, in adolescents through a randomized control pilot trial. Dr. Leyfer will evaluate the effects of DCS-enhanced intensive therapy at a 3-month follow-up.

Sara E. Trace, Ph.D., University of North Carolina at Chapel Hill

Oxytocin (OT), a neuropeptide related to anxiety reduction and social bonding, improves social cognitive functioning and treatment outcomes in several psychiatric disorders, including autism spectrum disorders, bipolar disorders and schizophrenia. Dr. Trace's goal is to evaluate the effects of OT in the treatment of anorexia nervosa (AN) in a three-week double-blind placebo cross-over design in 20 individuals who are currently undergoing partial hospitalization for AN.

AUTISM & AUTISM SPECTRUM DISORDERS (ASD)

Peter G. Enticott, Ph.D., Monash University (Australia)

In this project, Dr. Enticott will work with a sample group of adults with ASD who will receive repetitive transcranial magnetic stimulation (rTMS), either active or placebo, directed at a brain region involved in understanding others' thoughts and feelings. They will be assessed over various time intervals to determine whether rTMS has improved their social relating ability, and whether improvements can be maintained over time.

Irina Voineagu, M.D., Ph.D., Riken Omics Science Center, Japan

In a recent study, Dr. Voineagu demonstrated there are shared abnormalities in a large subset of ASD cases, at the level of gene expression. Using a next-generation RNA sequencing approach to analyze postmortem brain tissue from ASD cases and matched controls, she hopes to identify specific gene expression dysregulation in the ASD brain. This finding would contribute significantly to the design of targeted therapeutic approaches for ASD.

BIPOLAR DISORDER (BP)

Jieun E. Kim, M.D., Seoul University

It has been suggested that hyperbaric oxygen therapy (HBOT), used to treat various medical and neurological conditions, restores mitochondrial energy production and metabolism. Dr. Kim will examine the efficacy and safety of HBOT in a small number of patients based on the concept that mitochondrial dysfunction might be one of the key pathologies of BP, and that improvement in mitochondrial function would bring about abatement of depressive symptoms.

Wendy K. Marsh, M.D., University of Massachusetts Medical School

Dr. Marsh, in a search for a well tolerated and safe option that would reduce depression symptoms in BP, believes vitamin D supplementation might be that treatment. Vitamin D acts in parts of the brain known to be involved in mood and also affects several of the key neurotransmitters targeted by antidepressants and mood stabilizers. In a randomized double-blind placebo-controlled pilot trial of vitamin D supplementation, participants will have BP depression and low vitamin D levels in their blood. Their mood and vitamin D levels will then be followed to see if an increase in vitamin D blood levels is associated with improved mood, and in particular less depression.

DEPRESSION

Chadi Abdallah, M.D., Yale University

Dr. Abdallah will use a brain imaging method called magnetic resonance spectroscopy on a small group of patients with severe treatment-resistant depression to examine the effect of ketamine. Ketamine is an anesthetic medication that provides rapid antidepressant effects on glutamate*. This work may facilitate the development of medications similar to ketamine, but with reduced adverse side effects.

Olivia May Dean, Ph.D., University of Melbourne

Based on evidence that inflammation and oxidative stress may play a causative role in major depressive disorder, Dr. Dean will test a new approach to treatment. Raised levels of inflammatory chemicals called cytokines have been seen extensively in people with depression and are an increased risk factor. Her study will compare the efficacy of the antibiotic minocycline with a placebo treatment on a trial group of 100 patients with moderate to severe depression.

Marcelo T. Berlim, M.D., M.Sc., McGill University

Sixty patients, age 18 to 60, with a current major depressive episode of at least moderate intensity and a lifetime history of at least one serious suicide attempt, will be enrolled in the study. Dr. Berlim will use repetitive transcranial magnetic stimulation in an effort to relieve symptoms in depressed patients at high risk for suicide.

Elif Engin, Ph.D., Harvard University

Several findings implicate GABAergic neurotransmission in both the development of depression and the therapeutic effects of antidepressants, but only after long delay. Findings from animal studies in Dr. Engin's laboratory point to a specific GABA receptor type as a possible mediator of depression symptoms and drug effects. Enhancing GABAergic effects by enhancing this receptor's activity may make the receptor a viable target for faster-acting, more effective antidepressants with fewer side effects.

Shannon Leigh Gourley, Ph.D., Emory University

During adolescence, brain cells grow markedly and then undergo pruning and reorganization, which optimize connectivity, but may also increase vulnerability to insults like stress: that has been linked to depression. Concerned with the vulnerability of the adolescent brain to depression, Dr. Gourley will test whether compounds that target molecules that control cellular shape, as opposed to the usual approach of targeting neurotransmitters, may serve as effective antidepressants.

Benjamin J. Hall, Ph.D., Tulane University

The antidepressant ketamine, in a single low dose, produces relief in otherwise treatment-resistant patients and the effects are almost immediate. Ketamine, an NMDA receptor* antagonist, likely causes a rapid increase in activity in neurons in the cortex of the brain. Through genetic manipulation of mice models of depression, Dr. Hall seeks to find out how that cortical activity occurs in order to move toward development of a ketamine-like antidepressant without negative side effects.

Brian M. Lacoviello, Ph.D., Mount Sinai School of Medicine

In order to investigate the effectiveness of a computerized training program to modify the negative bias in working memory in depressed participants, Dr. Lacoviello will have two groups of participants experiencing depression undergo a computerized training program lasting the same amount of time. One group's training program will be designed to reduce the negative working memory bias in depression, while the other group's will not. Dr. Lacoviello will look for effects on cognition such as negative cognitive styles, biases in working memory and rumination, as well as improvements in depression symptoms.

Gretchen N. Neigh, Ph.D., Emory University

Multiple small strokes have been found in the brains of over 94% of patients who have their first episode of depression after age 65. Dr. Neigh will test the ability of Triflusal, a well tolerated anti-inflammatory, to reverse depressive-like behavior in rodents with small cerebral infarcts. After two weeks of daily administration, depressive-like behavior will be tested to determine to what extent Triflusal reverses depressive-like behavior following small strokes either on its own or in combination with fluoxetine, a selective serotonin reuptake inhibitor.

Steven T. Szabo, Ph.D., Duke University

Using optogenetics*, Dr. Szabo seeks to characterize the effect of seizures on the strength and focality of neural activation. Optogenetics provides the ability to model seizures and concomitantly record cortical and deep brain structures in mice. This will lend to elucidating the mechanism of action of seizure-producing therapeutics with increased therapeutic responsiveness and decreased side-effects.

Katja Wingenfied, Ph.D., Charite-University Medicine Berlin and Freie Universitat Berlin, Germany

To study the phenomenon of overgeneralized memory in major depressive disorder (MDD), Dr. Wingenfied will extend her investigations of the association between HPA* axis functioning and memory in MDD focusing on the mineralocorticoid receptors (MR), to which the stress hormone cortisol binds. In two independent double-blind placebo-controlled studies, which include MDD patients and controls, she will examine whether MR stimulation via fludrocortisone leads to improved memory retrieval in MDD patients and whether MR blockade impairs memory retrieval in MDD. The long-term goal is to improve treatment strategies for MDD patients by modulating the MR.

SCHIZOPHRENIA

Christina Andreou, M.D., Ph.D., University of Hamburg

Metacognitive training (MCT) is an intervention that targets cognitive errors and biases in schizophrenia symptoms, such as impairments in learning and memory. Recently, an individualized program was developed that tailors MCT to patients' individual needs. In a study involving 154 schizophrenia patients, Dr. Andreou will compare the long-term effects of MCT with other therapeutic methods currently in use.

Caline S. Karam, Ph.D., Columbia University

Many studies support that altered presynaptic dopamine levels play a central role in schizophrenia. In an effort to uncover the signaling

* See Glossary

pathways that modulate presynaptic dopamine stores, Dr. Karam will use a genetic screen to identify novel regulators of presynaptic dopamine accumulation and release. This research can guide the development of pharmacological interventions for schizophrenia.

Junghye Lee, Ph.D., University of California, Los Angeles

Psychosocial intervention programs focused on the improvement of social cognition in schizophrenia patients have shown encouraging results, including one from Dr. Lee's group. They will now begin a large-scale randomized, controlled 12-week clinical trial to examine the efficacy of social cognitive training on social cognitive performance measures and community functioning. The initial efficacy of the social cognitive training on behavioral measures suggests that potential biomarkers might capture, at a more basic level, the benefits of social cognitive training. As an add-on project, Dr. Lee plans to identify biomarkers of social cognitive training in individuals with psychoses.

Maya Libben, Ph.D., McLean Hospital/Harvard University

Language-based disruptions associated with schizophrenia can significantly impair a patient's social and occupational functioning. Dr. Libben seeks to determine where in the brain abnormal language activation stems from and at what stage of processing it occurs. She will use a variant of a semantic priming paradigm called masked priming, the defining feature of which is the subliminal presentation of the initial cue. Patients are not consciously aware of the information that is being presented to them, and any processing abnormalities can be attributed to the 'initial activation stage' associated with the temporal areas of the brain. Dr. Libben will measure the electrical activity produced by the brain while patients are performing these tasks to give exact measures of language activation in real-time.

Yingwei Mao, Ph.D., Pennsylvania State University

Dr. Mao proposes that RBM8a, a protein-coding gene which he found binds directly to the Disrupted-in-Schizophrenia 1 (DISC1) gene mRNA, participates in DISC1-mediated signaling during neurodevelopment and modulates the Wnt* signaling pathway which in turn contributes to onset of schizophrenia pathology. This research may potentially elucidate the functional gene network underlying schizophrenia and provide new targets for drug screening and therapeutic treatment of schizophrenia and related disorders.

Naren P. Rao, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada

Dr. Rao believes that low levels of brain dopamine in the brains of people with schizophrenia could be the cause of their cognitive deficits and negative symptoms. She aims to measure brain activity changes in schizophrenia patients with predominantly negative symptoms before and after treatment with L-dopa, a drug that increases brain dopamine levels. If the dopamine hypothesis is true, cognitive deficits and negative symptoms of schizophrenia could potentially be treatable in a new way, with implications for improved functioning and quality of life.

David L. Roberts, Ph.D., University of Texas Health Science Center at San Antonio

Dr. Roberts has developed a treatment in which schizophrenia patients are taught a strategy that he says is easy to understand, can be rehearsed to the point that it is very easy to remember and use, and can be applied flexibly in real-world circumstances. He predicts that by practicing this strategy daily on tablet computers, patients will show improvements in their speed, accuracy and general ability to interpret others' thoughts and feelings. He also believes this daily training will lead to patients' brain circuits becoming more efficient at social cognition, which will be measured with brain imaging methods.

Sivan Subburaju, Ph.D., McLean Hospital and Harvard University

It is known that schizophrenia is associated with pathological dysfunction of the GABA system in the hippocampus. Several genes have been identified whose expression is changed in schizophrenia, specifically factors which control other genes like the GABA-producing enzyme GAD67. Dr. Subburaju will test these genes to find out which is capable of changing GAD67 expression and consequently the GABA cell type. Identifying these factors and understanding the mechanisms by which they control GABA cell fate can be exploited to develop new therapeutic approaches for treatment.

Akio Sumioka, Ph.D., Yale University

Dr. Sumioka has established a new type of genome-wide screening for regulatory genes of the NMDA-type* glutamate* receptor (NMDAR) activity, and has identified several genes as NMDAR modulators. This research will examine roles of these genes and identify auxiliary subunits of the NMDAR protein, providing a fundamental understanding of NMDAR regulation which may contribute to the development of new therapeutic approaches for schizophrenia.

Toral S. Surti, M.D., Ph.D., Yale University

Dr. Surti seeks to develop a cognitive training exercise for improving visual processing in schizophrenia. He chose a model visual processing task called visual backward masking, success at which demands better social and cognitive abilities and greater functioning. Dr. Surti will compare how healthy people and those with schizophrenia learn to improve on this task, and he will examine whether, at the end of the training, people with schizophrenia are better able to learn visual information and identify facial expressions.

Jared W. Young, Ph.D., University of California, San Diego

Dr. Young believes that reduced reward-related learning among many schizophrenia patients limits the potential benefits of cognitive-reward (CR) therapy. His research seeks to test whether varying expression of the nicotinic acetylcholine receptor (nAChR)—linked to cognitive dysfunction in schizophrenia—makes it possible to alter memory capacity in mice, and further, to examine whether nAChR expression is required for nicotine- or varenicline-induced cognitive improvements. The hope is that varenicline, an FDA-approved smoking cessation aid with a reduced side-effect profile compared to nicotine, could augment CR therapy to enhance functional outcome in schizophrenia patients.

OTHER

Borderline Personality Disorder

D. Bradford Reich, M.D., McLean Hospital and Harvard University

Dr. Reich, seeking a neurobiological distinction between borderline personality disorder (BPD) and bipolar disorder (BP), will lead an fMRI study of BPD and BPII patients examining how they react to various affective stimuli. Among other things, this research could prevent medications for BP patients from being incorrectly prescribed for those suffering from BPD. These medications are often prescribed in lieu of evidence-based psychotherapies known to be effective for BPD patients.

Mental Illness—General

Kelly Anne Aschbrenner, Ph.D., Dartmouth College

People with mental illness have impaired concentration, memory and motivation, making it difficult for them to follow diet and exercise plans. Their life expectancy is 25 to 30 years shorter than average, mainly due to a high rate of cardiovascular disease. The course of mental illness has been shown to improve when family members are involved in the process of psycho-education. Dr. Aschbrenner plans to develop and test a program in which the patient and a support person form a dyad to facilitate healthier behavior in the patient.

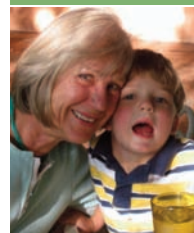
Renana Eitan, M.D., Hebrew University

In this project, deep brain stimulation (DBS), which targets dysfunctional brain regions through electrodes implanted in the skull, will be used in the target region of the subthalamic nucleus (STN). Dr. Eitan will explore neural patterns in response to emotional stimuli in a primate model of emotional dysregulation and in human patients undergoing treatment with deep brain stimulation (DBS). She wants to understand how emotions are processed in the STN and to determine the most suitable area within its subdivisions for electrode implantation since neural response is different in the various STN sub-regions.

Psychosis

Caitlin E. McOmish, Ph.D., Research Foundation for Mental Hygiene, Inc./NYSPI/Columbia University

This research aims to elucidate the manner by which hallucinations, a core symptom of schizophrenia, are produced. Dr. McOmish and team have established that a heterodimeric receptor complex, comprising the 5-HT_{2A} receptor and the metabotropic glutamate* receptor 2, is critical to the unique properties of hallucinogenic 5-HT_{2A} receptor agonists. Knowing how these heterodimers produce behavioral consequences is important for future drug discovery efforts.



With a Will There's a Way to Help

Did you know that many people affected by mental illness—friends, partners and families—have a rich history of remembering the Brain & Behavior Research Foundation in their estate plans? This support has helped fund research that is improving lives.

A gift in your Will can fund research that one day funds a possible cure for the many forms of mental illness. You can direct your attorney to name the Brain & Behavior Research Foundation as the beneficiary of a percentage of your estate, of a set dollar amount, or of a particular asset (your home, jewelry artwork, etc.). Your estate is entitled to an estate tax deduction for the full value of your bequest and you will receive the full satisfaction of knowing that your investment in our scientists will improve life for those affected by mental illness.

Suggested legal wording:

I give and bequeath, absolutely and forever, the sum of \$_____ (or, __% of the rest, residue and remainder of my estate) unto the Brain & Behavior Research Foundation, 60 Cutter Mill Road, Great Neck, New York 11021, for its general purposes.

If you have already remembered the Brain & Behavior Research Foundation in your Will, then please let us know. Doing so activates your membership in the NARSAD Legacy Society!

To learn more, please call the Office of Planned Giving at 516.829.0091.