The Quarterly

Fall 2013

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

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FOCUS
on
BRAIN
PLASTICITY

Scientific Council

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- ➡ **4** Former Directors of the National Institute of Mental Health
- ➡ **13** Members of the National Academy of Sciences
- ➡ **20** Chairs of Psychiatry and Neuroscience Departments

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Dear Members of Our Foundation Community,

Fall is a very special season for the Foundation, the time when we award our annual prizes for outstanding research achievements. The prizewinners are selected through committees of our Scientific Council; the prizes are among the most prestigious honors possible in neuroscience and psychiatric research. We will be celebrating the researchers and the important advances they have made to improve the lives of those with mental illness on October 25th at the Pierre Hotel in New York City. Earlier that day, they will honor us by presenting their latest work at our Mental Health Research Symposium at the Kaufman Music Center in New York City.

This year at the Dinner we will also be recognizing two remarkable individuals with Productive Lives Awards. Both have supported strong initiatives within their respective professions to help those living with mental illness. Rodolpho Cardenuto, President of SAP Americas, will represent and accept the award in honor of the progressive program at SAP to hire people with autism spectrum disorder. Academy Award-winning producer Bruce Cohen will accept an award in recognition of his recent film "Silver Linings Playbook," which addresses mental illness in a sensitive, powerful and open manner. I am hoping to see many of you at both the Symposium and Dinner to share in the excitement of continuing progress on many fronts to help our loved ones live more productive and fulfilling lives.

Many of the scientists receiving Outstanding Achievement Prizes began their careers with the support of NARSAD Young Investigator Grants, now considered the most coveted and competitive grants for those entering the field of neuroscience. You will find this year's new class of 200 Young Investigator Grantees on pages 8-24 in this issue. These investigators, with innovative project ideas, present great hope for breakthroughs in understanding, treating and ultimately preventing and curing mental illness.

You will also find highlights of important work of former NARSAD Grantees in the area of brain "plasticity." As work in the field continues to evolve, significant progress has already been made and supported by our research grants, including the finding that the human brain renews neurons throughout adult life ("neurogenesis")—a finding that overturned the common theory I was taught in medical school that adult brains don't grow new cells—and the discovery of the brain's amazing capacity to adapt to "stress" and remodel.

As I said, it is an exciting season for us at the Foundation, and one final piece of news I am delighted to share with you is that we have moved our office to midtown Manhattan, at 90 Park Avenue, between 39th and 40th Streets. We look forward to greeting Foundation friends and supporters at this new, convenient location in the heart of New York City.

I look forward to seeing you soon!

With thanks and warmest regards,

Jeffrey Borenstein, M.D.
President & CEO

Research Discoveries
in the News

Kirsty L. Spalding, Ph.D.
Assistant Professor
Department of Cell and Molecular Biology
Karolinska Institutet
2007 NARSAD Young Investigator Grantee

Fallout from Atom Bomb Tests Offers Evidence of Brain Plasticity

Researchers used a very innovative methodology to quantify, for the first time, the number of new neurons formed in the human brain throughout life (a process called "neurogenesis"). The work supports the view that the brain's capacity for change over time—its "plasticity"—persists throughout life, supporting cognitive functions and offering the potential for targeted treatments to recover healthy brain function in patients with a broad range of psychiatric disorders.

The current study was published in the June 6th issue of the journal *Cell* by 2007 NARSAD Young Investigator Grantee Kirsty L. Spalding, Ph.D., of Sweden's Karolinska Institutet, and colleagues. Dr. Spalding and team found physical evidence in the postmortem brains of people aged 19 to 92 by identifying the "birth date" of neurons in the brain samples. They discovered that new neurons are born in the brain's hippocampal region over the lifespan and estimate that the average adult generates 1,400 new hippocampal neurons every day

in the prime of life, a rate that does not vary greatly over time and corresponds with a turnover of almost two percent every year. This turnover does not occur across the brain. Neurogenesis was confirmed in a single brain region, the hippocampus, and only in one subregion within it called the dentate gyrus. Reduced neurogenesis in this region is believed to be associated with depression, bipolar disorder, schizophrenia and some anxiety disorders.

A particularly novel method was used to obtain this important result. Beginning in 1945 with the birth of the atomic age, and lasting until 1963, nuclear weapons were tested openly at above-ground sites. This resulted in increased atmospheric levels of Carbon-14 (14C). The Karolinska team reasoned they could "carbon-date" neurons in preserved postmortem brains since the DNA of these and all cells are essentially "stamped" with 14C (and other elements in the atmosphere) at the time of their birth. 14C levels spiked in 1963 and have fallen steadily ever since at a known

rate, making it possible to determine the birth date of neurons based on 14C levels in a cell's DNA. The team has used this methodology over the past decade to test a variety of cells, including fat cells, and was able to refine it to a point that it became sensitive enough to measure tiny amounts of 14C in small hippocampus samples.

Because the hippocampus is a region heavily implicated in many brain and behavior disorders, the new findings offer exciting proof of the brain's potential to recover from dysfunction throughout life. For researchers working on new treatment approaches to promote neuroplasticity and neurogenesis, this new work offers crucial evidence necessary for their further development. ❖

The Takeaway

Scientists quantify the number of brain cells renewed throughout human life, furthering evidence of the brain's capacity for recovery.

Researchers Find Way to Increase Neuroplasticity and Treat "Negative" Symptoms of Schizophrenia

Joseph T. Coyle, M.D.
Eben S. Draper Professor of Psychiatry and Neuroscience
Harvard Medical School
1995 and 2004 NARSAD Distinguished Investigator Grantee
Foundation Scientific Council Member

Recent research at McLean Hospital and Harvard University Medical School shows a very promising possibility for the future treatment of the "negative" symptoms of schizophrenia by improving neuroplasticity—the ability of the nerve cell networks in the brain to physically adapt to changing conditions. Negative symptoms in schizophrenia include decrease in motivation, lack of attention, emotional flatness, memory loss and social withdrawal.

The research team was led by Joseph T. Coyle, M.D., a NARSAD Distinguished Investigator Grantee and Foundation Scientific Council Member. Dr. Coyle's team at Harvard Medical School included Vadim Y. Bolshakov, Ph.D., a two-time NARSAD Grantee and Professor of Psychiatry. The researchers worked with mice to determine if they could find a cluster of abnormalities known to affect the brain's hippocampus in people with schizophrenia. The mice were genetically engineered to have very low N-methyl-D-aspartate (NMDA) receptor activity in the brain, a condition suspected to be linked to

impaired synaptic plasticity, memory formation and the negative symptoms of schizophrenia. The researchers investigated associated abnormalities including overall shrinkage of the hippocampus; decreased density of tiny nodules called dendritic spines, which serve as spots where synapses, or communications junctions, can form between neighboring neurons; and altered signaling pathways that help regulate neuroplasticity.

In a paper published in the May 31st issue of *Proceedings of the National Academy of Sciences,* Drs. Coyle, Bolshakov and colleagues reported that the mice with low NMDA receptor activity "displayed impaired hippocampal plasticity, as well as the morphological [shape], neurochemical and cognitive abnormalities consistent with what is observed in schizophrenia." This was an exciting finding, but then they went further. The mice used in the experiments had only about 10 percent of normal NMDA receptor activity because they had been engineered to lack D-serine, one of two molecules needed to activate
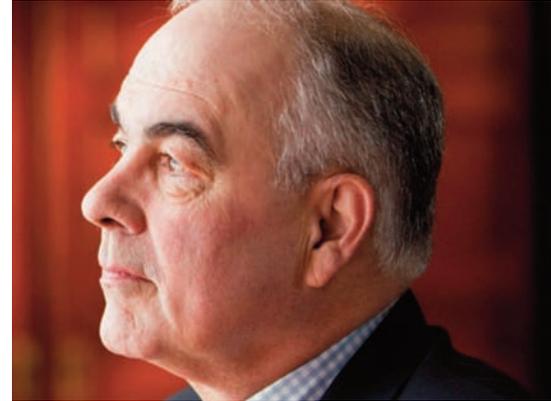
the receptors. When the researchers treated the mice with D-serine, NMDA receptor function in the hippocampus was restored. Over time, all of the observed hippocampal symptoms proved reversible.

This new work lends important support to the theory that low activity ("hypoactivity") in NMDA receptors in the brain can cause pathologies seen in people with schizophrenia and importantly, that the condition may be treatable and the symptoms reversed. While not the sole cause of schizophrenia, the ability to reverse this hypoactive condition in mice suggests it may be possible to develop D-serine-based treatments for use in people—what could prove to be a breakthrough in the treatment of schizophrenia. ❖

The Takeaway

New treatment approach shows potential to reverse symptoms of schizophrenia and restore healthy brain function.

Helen S. Mayberg, M.D.
Professor of Psychiatry, Neurology and Radiology
Emory University School of Medicine
1991, 1995 and 2002 NARSAD Young, Independent and
Distinguished Investigator Grantee
Foundation Scientific Council Member

Historic Study Finds Brain Scans Can Guide Depression Treatment Decisions

Using positron emission tomography (PET) scan images, researchers have identified specific brain activity that can potentially predict whether people with major depressive disorder (MDD) will best respond to an antidepressant medication or psychotherapy. This important new work offers a first step toward an evidence-based algorithm for treatment selection for depression, particularly significant since less than half of patients currently experience remission with an initial treatment.

Helen S. Mayberg, M.D., Professor of Psychiatry, Neurology and Radiology at Emory University School of Medicine, three-time NARSAD Grantee and Foundation Scientific Council member, led the study. Dr. Mayberg pioneered work using PET scans to better understand depression with her first NARSAD Young Investigator Grant in 1991, and went on to demonstrate that the subcallosal cingulate (or "Brodmann Area 25") region of the brain is a key locus of pathology in depression. Dr. Mayberg is now well known for her innovative work in piloting deep brain stimulation

(DBS) to target Area 25 to treat patients with resistant depression.

In the current study, funded by the National Institute of Mental Health and published in the June 12th issue of *JAMA Psychiatry,* Dr. Mayberg and her colleagues in the department of Psychiatry at Emory University including NARSAD Young Investigator Grantees Paul Holtzheimer III, M.D., and R. Cameron Craddock, Ph.D., sought to identify a biomarker (biological predictor) that could identify which type of treatment a patient would benefit from based on the individual's brain activity. After having an initial baseline PET scan, 33 patients completed 12 weeks on escitalopram (a common antidepressant medication) and 34 patients completed 12 weeks of cognitive behavioral therapy (or CBT, a specific type of "talk therapy"). Using the pre-treatment PET scans, they compared the scan patterns in those patients as a function of their treatment type and response. They found that in the 38 patients who had clear outcomes, there was lower-than-normal activity in a brain region called the right

anterior insula linked with remission after CBT and poor response to the antidepressant drug. Overactivity of the same region was linked with remission after drug treatment and poor response to CBT.

The results of this new work are of historic importance. The data clearly suggest that treatment decisions might be based on a patient's brain state—offering a first potential biomarker for treatment selection—rather than evaluation of behavioral symptoms or patient and doctor preferences. More study is needed to confirm how this approach may be used and if it is relevant for other treatment options and other types of depression (beyond MDD). ❖

The Takeaway

Groundbreaking new research shows brain activity may determine best treatment option in depression.

Interview

with

Bruce S. McEwen, Ph.D.

Alfred E. Mirsky Professor
Head, Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology
The Rockefeller University
1998 NARSAD Distinguished Investigator Grantee
2005 Goldman-Rakic Prize for Outstanding Achievement
in Cognitive Neuroscience
Foundation Scientific Council Member

Creative Scientist Explores the Brain and Discovers its "Plasticity"

Breakthrough Research Demonstrates the Brain's Capacity to Bounce Back from Stress and Depression

"The adult brain is considerably more malleable and resilient than previously believed," says Bruce S. McEwen, Ph.D., whose groundbreaking research on the brain began in the 1960s. This is an important message —not only for people who are depressed, have an anxiety disorder or have suffered some other kind of trauma to the brain—but for all those concerned about the impact of a high-stress life on their mental sharpness as they age.

Dr. McEwen's work has spawned more than a thousand scientific papers. In 1998 he received NARSAD Grant funding to support his quest to understand what happens when stress impacts and seems to "damage" the brain. While his research confirmed that stress does impact the brain and can cause shrinkage in the hippocampus region, for example, he also found that the impact is not necessarily permanent "damage." He discovered the brain's inherent capacity to adapt and remodel its architecture. His groundbreaking work effectively established what is now known as "neuroplasticity" in the field.

Dr. McEwen didn't begin his research expecting to discover these astonishing capacities of the brain. His initial focus was the endocrine system and the hormones it generates, which help regulate bodily functions. For example, the adrenal glands, just above the kidneys, release hormones called glucocorticoids when a person experiences stress. But in 1968, Dr. McEwen discovered that cells in the brain's hippocampus—a region important in memory and learning— had an abundance of receptors for such stress hormones.

Back then, research on hormonal action in the brain centered on the hypothalamus and the pituitary gland —places where signals from the nervous system and the endocrine system come together. "The idea that you could have stress hormone receptors beyond the hypothalamus changed our thinking about what was going on," Dr. McEwen says. The impact of this finding has proven to be enormous, completely changing understanding about how people respond to stress and how to treat stress-related conditions.

Cortisol, the main stress hormone, is often thought to be a "bad actor" in the human system, including in the brain. Elevated levels have now long been linked to anxiety disorders and depression. However, Dr. McEwen's work and that of his many scientific progeny over 45 years makes plain

Dendrites

A – control
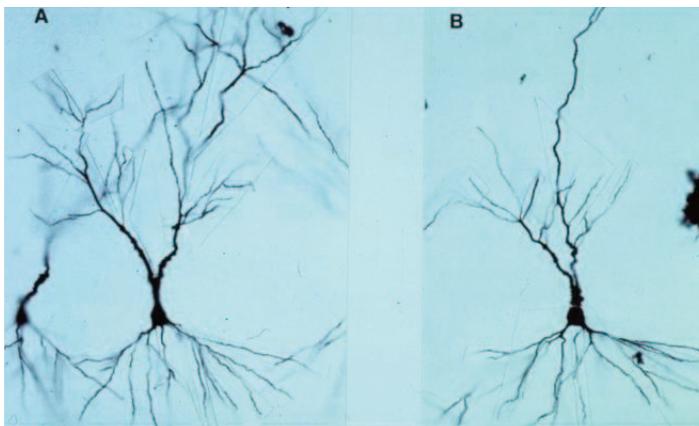
B- shrinkage after 21 days of chronic stress—this type of shrinkage has been shown to be reversible / does not represent permanent brain "damage"

Images courtesy of Bruce S. McEwen, Ph.D.

Dr. McEwen is heartened by research that shows the brain's plasticity is boosted when even a sedentary elderly person begins to exercise five days a week.

that feeling stressed is a valuable adaptive response to adverse experiences. Stress hormones play essential roles in the body's equilibrium by fine-tuning immune responses and the systems through which cells manufacture and adjust their energy levels. They also initiate important processes in the brain.

When cortisol and other hormones "dock" at nerve cells and along their branching projections called dendrites, which connect them in a grand network, Dr. McEwen and others have seen that under conditions of chronic stress the hippocampus can shrink. Dendritic spines—knoblike projections that provide contact points for other nerve cells—can disappear, and the "branches" of dendritic trees can shorten. Recent work in the lab has extended these observations to the amygdala, which expands under stress, and the prefrontal cortex, where stress causes dendrites and their spines to contract.

Dr. McEwen is careful to distinguish what he calls "tolerable" stress, where "the healthy person has the capacity to weather the storm," from "toxic" stress. "It's the difference between whether a person can bounce back or falls into a state where some kind of external help is needed" to counter the damage.

The shrinking and expansion of the hippocampus in stressed people is partly explained by a process called neurogenesis—the birth of new neurons (see Feature pp. 25-27). When people recover from depression or anxiety with the help of selective serotonin reuptake in-

hibitor (SSRI) antidepressants and other treatments, their recovery coincides with the formation of new neurons in a portion of the hippocampus called the dentate gyrus, which in turn promotes neuroplasticity.

Dr. McEwen acknowledges that as the human brain ages it has less natural resilience when under stress, but says he is heartened by research that shows the brain's plasticity is boosted when even a sedentary elderly person begins to exercise five days a week. Studies now suggest that even normal cognitive decline can, in many cases, be slowed through exercise and regular socializing. (This has been found to spur neurogenesis, and not only in the elderly). Similarly, when a depressed or anxious person is placed in an environment that is more interesting and supportive, plasticity seems to be enhanced, and with it, resilience.

It is hoped that such targeted medications will promote brain plasticity to more effectively restore healthy brain function across many psychiatric disorders.

Treatments for depression and anxiety succeed most often when a patient takes a neurogenesis-promoting antidepressant medication and receives individually tailored cognitive behavioral therapy (CBT, a specific type of "talk therapy"). But antidepressants don't always work, and one current objective of the McEwen lab is to develop faster-acting antidepressants and medications that enhance naturally occurring "neuroprotective factors." Such factors include proteins called neurotrophins that promote the brain's natural plasticity and resilience (see Feature pp. 25-27). It is hoped that such targeted medications will promote brain plasticity to more effectively restore healthy brain function across many psychiatric disorders.❖

Answers to *Ask the Researcher*

from

Karl Deisseroth, M.D., Ph.D.

Professor of Bioengineering and of Psychiatry and Behavioral Sciences
Stanford University
2005 NARSAD Young Investigator Grantee
Foundation Scientific Council Member

Can individuals volunteer to be part of the BRAIN Initiative? I'd be interested in having my brain scanned and mapped.

Though the programs that will be funded by the BRAIN initiative have not yet been determined, the best way to contribute along those lines would be to explore nearby academic neuroscience research centers, like those at universities, where there are (and will be) many carefully designed and exciting research studies involving human brain scanning and mapping and where volunteer subjects are very much appreciated.

I know you treat people like my young adult son, who has schizophrenia. None of the experts we consulted ever asked about his childhood behavior patterns, which we knew were not completely right. Is it possible to intervene early to curb severe mental illness later in life?

Indeed, we are now beginning to understand that people with neuropsychiatric diseases like schizophrenia that are diagnosed at a particular point in life actually can show behavioral signs much earlier. Though we have a long way to go, many studies are now seeking to define such signs, including in schizophrenia, which could serve as "biomarkers" to help us identify and intervene early in the course of these disorders. Of course it is important to carefully validate such possible markers in large populations; it would not be a good idea to intervene in people with a low probability of developing the disease, since any intervention would bring with it new risks and side effects. But even without knowledge of a safe and effective early intervention, simply understanding early biomarkers would also help us understand these mysterious diseases better, which would certainly help in creating better cures for people even diagnosed later in life.

Can you envision ways in which the optogenetics technology that you invented might eventually improve the design or use of psychiatric medications?

The major challenge we face in psychiatry is understanding. Psychiatric disease represents the leading cause of disability worldwide, but major pharmaceutical companies are withdrawing from developing new treatments, and many are shutting down psychiatry programs, a situation with major medical, social and economic implications. Reasons cited include the lack of neural circuit-level understanding of symptom states, which impairs identification of new treatments and development of predictive animal models. Part of the solution to this challenge may include technologies such as optogenetics, which has primary value as a research tool well-suited to probing circuit-level causality in complex behaviors. Identifying which patterns of circuit activity are actually causally involved in eliciting normal or pathological behaviors may provide a new kind of target, around which investigators can screen and build therapies (whether pharmacological, surgical, or electromagnetic).

Have any of the labs that are using your invention CLARITY to more precisely observe the brain after death found things that were particularly surprising in your view?

Though CLARITY technology is so new that these kinds of studies have not yet been published, indeed there are early reports of unusual and surprising three-dimensional structures in some patient-derived brain tissue. A great many laboratories around the world now have CLARITY operational, and it will be interesting and exciting to see what emerges in the decades to come.

Ask the Researcher

HAVE A QUESTION?
E-mail **asktheresearcher@bbrfoundation.org** with questions for **Dr. Bruce McEwen.** Select questions and answers will be published in the next issue of *The Quarterly.*

Please note that the researcher cannot give specific recommendations or advice about treatment; diagnosis and treatment are complex and highly individualized processes that require comprehensive face-to-face assessment.

NARSAD Young Investigator Grants in 2013

1,199 Applications

200 Grants

$11.8M Funded

Marking our 27th year of bestowing transformative research grants on young scientists in brain and behavior science, we are very proud to announce $11.8 million in 200 new two-year grant awards. NARSAD Young Investigator Grants enable early career scientists to garner pilot data for innovative ideas before they have "proof of concept" for their work. This year, a record-breaking 1,199 applications were received. Applications are reviewed by members of the Foundation's Scientific Council, comprised of 147 brain and behavior research experts who volunteer their time to select the most promising research ideas to fund.

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
- **Next Generation Therapies**—to reduce symptoms of mental illness and retrain the brain

BASIC RESEARCH

ANXIETY (See also Anxiety and Depression)

Natalina Salmaso, Ph.D., Yale University, is intrigued by the theory that fibroblast growth factor 2 (fgf2), a potent cellular growth factor involved in brain development and the birth of new brain cells (neurogenesis), may be involved in the manifestation of anxiety behavior both in rodents and in humans. Using rodent models, she will try to determine the role of fgf2 in the development of anxiety behavior and explore its therapeutic potential for anxiety symptoms.

ANXIETY AND DEPRESSION (See also Anxiety; See also Depression)

Kate D. Fitzgerald, M.D., University of Michigan, will conduct a study of children aged five to seven in an effort to elucidate biological and behavioral processes that mark susceptibility to anxiety and depressive symptoms before the onset of full blown illness. This should help identify those at risk and support interventions to promote resilience.

Katharina Kircanski, Ph.D., Stanford University, will compare the functioning of pre- and post-pubertal youths with a history of early life stress to a low-risk group to examine neuroendocrine, autonomic and affective responses to a laboratory stress-induction task. This work will assess brain reactivity and recovery and examine the relation of these measures to diagnoses and symptoms of depression and anxiety disorders.

Heide Klumpp, Ph.D., University of Illinois at Chicago, plans to identify neural predictors of response to cognitive behavioral therapy (CBT) in people with depression and anxiety. Though CBT can be effective for these disorders, many patients remain symptomatic. The evaluation of neural markers linked to effectiveness of CBT is a critical step towards developing a reliable predictor of CBT success.

Jodi Lukkes, Ph.D., McLean Hospital, Harvard University, will study gender-dependent increased vulnerability in adolescent girls to depressive and

anxiety-like disorders. New evidence shows that social stress during childhood delays the onset of menstruation. Delayed exposure to estrogen may alter development of emotional brain regions. The project will investigate a link between estrogen, social stress and alterations in stress-related brain regions during adolescent development.

Katie A. McLaughlin, Ph.D., Children's Hospital, Boston, aims to examine how exposure to maltreatment in childhood influences the architecture of the developing brain in ways that increase risk for anxiety and depression. The work will focus on neural networks involved in emotion regulation, particularly on areas of the brain involved in emotional reactivity and the ability to modulate emotional experiences.

Alina Patke, Ph.D., The Rockefeller University, will explore the genetic basis of the association between a strong preference for evening hours and sleeping late in the day. She has identified a genetic origin for this so-called late chronotype in a patient with a history of clinical depression and plans to investigate the mechanism by which this mutation affects circadian-clock behavior and its connection to mood.

YoneJung Yoon, Ph.D., Weill Cornell Medical College, Cornell University, studies a novel mechanism regulating expression of the serotonin transporter, the molecular target of selective serotonin reuptake inhibitor (SSRI)-class antidepressants. Dr. Yoon seeks to understand the pharmacology and signaling pathways that activate or repress the mechanism, in hope of enhancing early detection of individuals at risk for mood and anxiety disorders and likelihood of response to SSRI treatment.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Nicola M. Grissom, Ph.D., University of Pennsylvania, will explore the interaction of pre- and post-natal diet in a mouse model of ADHD. ADHD prevalence is elevated in children born too large for gestational age (LGA) or too small (SGA). The study will examine how attention is affected by feeding a high-fat diet to mice born SGA, LGA or typical development.

Julie S. Haas, Ph.D., Lehigh University, is interested in how the brain focuses attention. Attention deficits occur in ADHD and schizophrenia. The brain center of attention is found within the thalamic reticular nucleus (TRN), a subsection of the thalamus and this study will explore the plasticity of synapses in the TRN in the context of typical and atypical brain activity.

Maria Kharitonova, Ph.D., Children's Hospital, Boston, will investigate the cognitive and neural dysfunction in early childhood that constitute the central deficits in ADHD. The proposed functional magnetic resonance imaging (MRI) study will examine the role of working memory maintenance and interference control, two cognitive constructs that have been inconsistently postulated to be critically impaired in ADHD.

Hagai Maoz, M.D., Tel Aviv University, Israel, will explore the hypotheses that children with ADHD have deficits in empathy and "theory of mind," which is the ability to ascribe mental states, beliefs and intentions to oneself and others. Dr. Maoz will also investigate whether low levels of oxytocin, which enhances social bonds, are associated with theory of mind and empathy deficits in ADHD.

AUTISM SPECTRUM DISORDER (ASD)

Jyothi Arikkath, Ph.D., University of Nebraska Medical Center, will investigate how mutation in the gene CDKL5 leads to Rett syndrome, a neurodevelopmental disorder associated with ASD, epilepsy and intellectual disabilities. Alterations in synapses, the communication juncture between neurons, have been linked to the syndromes; the CDKL5 gene in cells called astrocytes is important for controlling the structure and function of synapses.

Christelle Golzio, Ph.D., Duke University, will use zebrafish as a model for developing tools to identify genes from copy number variations (CNVs) associated with ASD. CNVs are genetic alterations resulting in abnormal numbers of copies of sections of the DNA. The data generated should identify a number of genes responsible for ASD and provide a platform for the systematic study of CNVs discovered in patients.

Guy Horev, Ph.D., Cold Spring Harbor Laboratory, will assess brain development in mouse embryos with a genetic deletion on the chromosomal 16p11.2 region, a deletion that occurs in people with ASD. This study aims to pinpoint the genes that lead to autism-like impairment and establish a cellular assay for impairment and, ultimately, to see if reversing the developmental impairment will correct the behavioral impairments.

Alaine C. Keebaugh, Ph.D., Emory University, will explore the protective effect of oxytocin signaling and early-life immune activation on the development of social cognition. Dr. Keebaugh will develop an animal model to test the hypothesis that decreased expression of the oxytocin receptor gene will interact with early-life immune activation, resulting in the development of impaired social cognition such as that seen in ASD.

Ji-Ann Lee, Ph.D., University of California, Los Angeles, hopes to elucidate mechanisms that underlie neural circuit dysfunction in ASD and identify targets for treatment. Abnormalities in RNA processing in neurons contribute to ASD and Dr. Lee has identified the RNA-binding protein Rbfox1/A2BP1 as a candidate gene. He will explore the hypothesis that loss of Rbfox1 activity contributes to RNA dysregulation and development of the illness.

Lucas Matt, Ph.D., University of California, Davis, is studying a major ASD gene, PSD-95, the central structural element of post-synaptic excitatory synapses. His focus is a factor called α-Actinin, that he thinks is responsible for PSD-95 localization. Defining how PSD-95 is anchored will fill a crucial gap in information about synaptic structure and could aid in the development of new ASD therapies.

Tabrez J. Siddiqui, Ph.D., University of British Columbia, Canada, studies synapses, and specifically, alterations in proteins that organize and maintain them, which have been implicated in ASD, schizophrenia, ADHD and intellectual disability. This project, using mice, will test the theory that disruption of a protein complex called LRRTM4-HSPG impairs cognitive function and underlies certain forms of ASD by altering brain connections.

Courtney L. Thaxton, Ph.D., University of North Carolina, Chapel Hill, studies Pitt-Hopkins Syndrome (PTHS), on the spectrum of autism disorder, that is caused by de novo mutation(s) or partial deletion(s) in a single copy of a gene called TCF4. She seeks to develop a new mouse model of TCF4 that better mimics human PTHS so she can study symptom onset function of TCF4 in the nervous system.

BIPOLAR DISORDER (BP)

June Gruber, Ph.D., Yale University, will examine the behavioral and neural mechanisms that underlie the regulation of reward in BP. This work is based on her theory that reward dysregulation is a core marker of dysfunction in BP and is characterized by increased reward reactivity on the one hand, and decreased regulation for such responses on the other.

Shizhong Han, Ph.D., University of Iowa, hopes to speed gene discovery for BP, for which few genes have been found, by identifying rare or low-frequency gene variants that may contribute to susceptibility for developing the illness. The research will utilize newly available genetic and genomic data and will follow up with sequencing of candidate genes.

Hyung W. Nam, Ph.D., Mayo Clinic, will investigate whether acamprosate, a medication used to counter alcohol abuse, is beneficial for people with co-existing alcohol dependency and BP. Both disorders are regulated by glutamate neurotransmission. Therefore, inhibition of glutamate signaling by acamprosate treatment may be effective not only for avoiding alcohol, but also for alleviating the manic symptoms of BP.

Maria De Las Mercedes Perez Rodriguez, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, will follow-up research showing that people with BP and their unaffected siblings show some specific cognitive impairments. She will conduct brain imaging studies to learn whether the abnormalities found in the patients' brains also occur in the unaffected siblings, and whether the patients' brain abnormalities are associated with specific cognitive symptoms.

DEPRESSION (See also Anxiety and Depression)

Nicole L. Baganz, Ph.D., Vanderbilt University, will explore the possible relationship between depression and an inappropriate expression of immune response triggered by infectious agents. Patients with depression often display higher plasma levels of immune chemicals called cytokines. Peripheral administration of

bacterial extracts or of pro-inflammatory cytokines has been shown to produce depressive-like effects in rodent and human studies.

Adrienne J. Betz, Ph.D., Quinnipiac University, will explore cells and structures of the hippocampus to identify potential mechanisms underlying the effects of chronic stress in stress-related psychiatric illnesses such as depression. The main objective is to determine the role of a specific transcription factor that controls genes involved in stress-induced immune and inflammatory responses, which can play a role in depression.

Paul R. Burghardt, Ph.D., University of Michigan, will investigate the link between mood disorders and abnormal insulin sensitivity, which is the largest contributor to mortality among people with depression. To shed light on how these diseases can lead to and worsen one another, the research will utilize biomarker screening, psychobehavioral testing and neuroimaging to investigate common biological systems underlying depression and metabolic dysfunction.

Erin C. Dunn, Sc.D., M.P.H., Massachusetts General Hospital, Harvard University, will examine the interplay of genes and environment in depression, using data from the Avon Longitudinal Study of Parents and Children to examine the relationship between genes, exposure to adversity and functioning. The results may help identify when exposure to adversity is most harmful.

Jian Feng, Ph.D., Icahn School of Medicine at Mount Sinai, will use a mouse model of depression to explore the hypothesis that a gene called TET1 and a novel "epigenetic" regulation of DNA play a crucial role in mediating major mood disorders such as depression. (Epigenetic changes are changes in gene expression that do not alter DNA sequence.) This research may provide new targets for depression treatment.

Ellen K. Grishman, M.D., University of Texas Southwestern Medical Center at Dallas, will correlate severity of symptoms in depressed obese adolescents at risk for diabetes with levels of ceramides (fat molecules involved in insulin resistance) and adiponectin (a fat-tissue secretion that decreases risk of diabetes and inflammation by decreasing ceramide levels). Adiponectin levels are lower and ceramide levels higher in people with insulin resistance.

Tamar Lea Gur, M.D., Ph.D., University of Pennsylvania, will study the effect of stress and antidepressants on "epigenetic" regulation in reproduction. Epigenetics refers to environmental impacts that alter gene expression without altering DNA sequence. This research will examine epigenetic changes in eggs and sperm of mice exposed to stress and to antidepressants to determine whether epigenetic changes are passed on to offspring.

Avram Holmes, Ph.D., Harvard University Medical School, plans to establish common and unique patterns of dysfunction in people with unipolar and bipolar depression. This work is based on his recent identification of a biological "marker" of preferential disruption of the frontoparietal control network in individuals with

bipolar disorder relative to the general population. Patients with major depressive disorder will be recruited and the data will be coupled with an ongoing study of bipolar disorder.

Jianxiong Jiang, Ph.D., Emory University School of Medicine, will study inflammation in epilepsy-related depression (ERD). Current antidepressants are helpful for patients with this disorder, but can exacerbate seizures, especially when high doses are required. Dr. Jiang will test a hypothesis on the role of prostaglandin receptor signaling in inflammation and ERD, which could lead to novel treatment developments for the disorder.

Ilia N. Karatsoreos, Ph.D., Washington State University, Vancouver, will explore the question of whether disrupting the circadian clock can lead to changes in affect regulation. The research will use a combination of environmental disruptions with mice to probe how the circadian clock and environmental disruption of the clock can modulate behavior and may be not only a symptom of depression but perhaps also a contributing cause.

Stephanie H. Parade, Ph.D., Brown University, will conduct a clinical trial with 150 mothers and their infants to explore whether and how the infant hypothalamic-pituitary-adrenal (HPA)-axis, the body's stress response system, is involved in the intergenerational transmission of major depressive disorder. The aim is to determine whether interparental violence and maternal depression in pregnancy are associated with infant HPA-axis functioning and emotion regulation.

Christophe Proulx, Ph.D., University of California, San Diego, studies the lateral habenula (LHb) area of the brain, implicated in depression pathology. He will manipulate activity of LHb neurons projecting to a dopamine center, and measure impact on depressive behaviors in rats. His hypothesis is that increased activity of neurons projecting to the dopaminergic center will promote—and inhibition will alleviate—depressive behaviors in rats.

Crystal E. Schiller, Ph.D., University of North Carolina, Chapel Hill, will manipulate reproductive hormones in non-pregnant, healthy women to mimic the changes that occur during pregnancy and the postpartum period. This endocrine manipulation paradigm will be used to probe brain activity associated with the regulation of mood and reward processing under different conditions. Using MRI scans, she will examine whether those with a past episode of postpartum depression show differences in emotional arousal and reward processing relative to healthy controls.

Anne L. S. Teissier, Ph.D., Research Foundation for Mental Hygiene, Inc., Columbia University, studies the role of serotonin in the development of mood disorders. This study will focus on a sensitive period of postnatal development during which increased serotonin signaling leads to permanent alterations in adult mood and cognitive behaviors. She will test if a causal relationship exists between serotonin receptor-driven neuronal activity and emotional as well as cognitive behaviors, under normal and pathological conditions.

Brent J. Thompson, Ph.D., University of Texas Health Science Center, San Antonio, will study rodents given early-life exposure to selective serotonin reuptake inhibitor (SSRI) antidepressant medications, at a time corresponding to the third trimester of human development. He will examine biological causes of the anxiety-like symptoms observed in such animals. The results will indicate potential risks of prenatal SSRI exposure to developing fetuses.

Anne Venner, Ph.D., Beth Israel Deaconess Medical Center, Harvard University, seeks to provide insight into the role of serotonin in the regulation of rapid eye movement (REM) sleep and establish a clear link between selective REM sleep manipulation and the development and improvement of major depression. In order to do so she will create and work with a mouse model of depression in which she will identify downstream brain regions involved in REM sleep.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Martin Levesque, Ph.D., Laval University, Canada, will examine the role of a transcription factor, Lmx1a/b, in OCD. Transcription factors regulate gene activity and Lmx1a/b regulates the expression of a gene family involved in the dopamine neurotransmitter system and in OCD-like disorders, including Tourette's syndrome. Studies will be conducted with mice to better understand the function of Lmx1a/b.

Demetrio Sierra, Ph.D., Massachusetts General Hospital, Harvard University, will use non-human primates to find whether there is an anatomical segregation of prefrontal cortex subregions in aversive and rewarded behaviors. He will assess the contribution of neuronal activity in the primate dorsal anterior cingulate cortex to help understand the balance between avoidance and reward. The results will shed light on causes underlying addiction and OCD.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Jonathan D. Morrow, M.D., Ph.D., University of Michigan, will conduct studies in animal models of the neurocircuitry of conditioned fear and reward-seeking behavior to gain deeper understanding of the neurobiology underlying individual differences in vulnerability to co-existing PTSD and addiction. The research will pave the way for future studies aimed at prevention and treatment.

Xiaojing Ye, Ph.D., New York University, will study two brain regions in rats important for emotional memory formation: the dorsal hippocampus and the basolateral amygdala. He will examine whether insulin-like growth factor-II (IGF-II), a memory enhancer, is engaged in this process by regulating synaptic connections within and between these regions. Findings will advance knowledge of memory reconsolidation and strengthening, and may suggest novel strategies for cognitive improvement and means of disrupting maladaptive memory strengthening in PTSD and addiction.

SCHIZOPHRENIA

Sandra Ahrens, Ph.D., Cold Spring Harbor Laboratory, will study the role of a brain circuit called the thalamic reticular nucleus circuit and its dysfunction in a genetically-engineered mouse model of schizophrenia. The thalamic reticular nucleus is thought to play a critical role in sensory processing and in cognitive functions such as attention. Attention-deficit is a core feature of schizophrenia.

Hannah E. Brown, M.D., Massachusetts General Hospital, Harvard University, will focus on a gene variant associated with schizophrenia's "negative" symptoms (decrease in motivation, lack of attention and affect, memory loss, social withdrawal), cognitive impairment and brain dysfunction. This gene, MTHFR, is important in how the body processes folate, and influences DNA expression. The study will compare the way genes are expressed in people with schizophrenia who have different variants of the gene.

Solange P. Brown, M.D., Ph.D., The Johns Hopkins University, will investigate the poorly understood role of particular neurons located below the cerebral cortex, known to be abnormally distributed in patients with schizophrenia. Using mouse models, Dr. Brown's goal is to determine the impact of these neurons in generating the cognitive and behavioral symptoms of the illness.

Sarah E. Canetta, Ph.D., Columbia University, will use mouse models of maternal immune activation, a prenatal risk factor for development of schizophrenia in offspring. She will study effects on neuronal circuits related to cognition and working (short-term) memory, seeking to identify a relationship between maternal immune activation and development of prefrontal cortex neurons in the offspring.

Ioana Carcea, M.D., Ph.D., New York University School of Medicine, will examine the hypothesis that the rate of release of the neurotransmitter dopamine in the prefrontal cortex dictates adaptive behaviors. Dysfunction in the regulation of dopamine release could account for the incapacity to adapt to sudden changes in external conditions, which severely affects the quality of life in people with schizophrenia.

Anne L. Collins, Ph.D., University of North Carolina, Chapel Hill, will seek to learn whether and how the genetic pathways and processes regulated by microRNA-137 (miR-137) are involved in schizophrenia. (MicroRNAs are molecules that play a role in gene expression.) MiR-137 is also implicated in Alzheimer's disease and may have broad relevance to neuronal development and neurological disease.

Jennifer M. Coughlin, M.D., The Johns Hopkins University, will examine the hypothesis that oxidative stress (excess of free radicals) and associated inflammatory response in the brain may play a role in schizophrenia in high-risk people. She will test cerebrospinal fluid and serum from a large number of patients with recent-onset schizophrenia for predictive markers of increased oxidative stress and neuroinflammation. Results may aid in early treatment intervention.

Juan A. Gallego, M.D., Feinstein Institute for Medical Research, will compare MicroRNA expression profiles in patients with first-episode schizophrenia and healthy volunteers. MicroRNAs are small molecules involved in gene regulation. Recent studies have linked alterations in MicroRNA expression to schizophrenia, and the hope is that they can be useful biological markers of brain abnormalities and/or responsiveness to antipsychotic treatment.

Kazue Hashimoto-Torii, Ph.D., Children's National Medical Center, will investigate how genetic and prenatal environmental factors contribute to the pathogenesis of schizophrenia, a disorder in which the first episode is usually delayed until young adulthood. The study will explore the interaction of oxidative stress induced in neural progenitor cells by a variety of prenatal environmental factors.

Xiao-Hong Lu, Ph.D., University of California, Los Angeles, will take advantage of the recent discovery of a major risk factor for schizophrenia by generating a mouse model of over-expression of a gene called VIPR2 with a genetic switch that can be turned off in selective brain regions and at different periods of brain development. This research aims to identify how this particular mutation leads to schizophrenia.

Heline Mirzakhanian, Ph.D., University of California, San Diego, will investigate whether there is a relationship between the neurotransmitter glutamate and cortical thickness in people with first-episode psychosis. Abnormalities in the glutamatergic system may account for some abnormalities in schizophrenia; Dr. Mirzakhanian will study whether an increase in cortical glutamatergic activity leads to structural brain changes, including reduced cortical thickness, that in turn leads to neurocognitive impairments.

Amanda C. Mitchell, Ph.D., Icahn School of Medicine at Mount Sinai, will examine the association of epigenetic gene dysregulation with schizophrenia. Epigenetic activity, such as the addition of methyl chemicals to DNA, can alter a gene's expression without changing the underlying DNA sequence. The cause of schizophrenia is unknown, and few susceptibility genes have been found, but numerous gene-regulation alterations have been reported.

Lauren V. Moran, M.D., Massachusetts General Hospital, Harvard University, is looking for biological "markers" to account for the increased craving for and higher rate of smoking among people with schizophrenia. The research will follow up findings that the connection between two regions of the brain is decreased in nicotine addiction, and that smokers with schizophrenia have even greater impairment in this connection.

Semanti Mukherjee, Ph.D., Feinstein Institute for Medical Research, will examine as a risk factor for schizophrenia what are called runs of homozygosity, which are extended genomic regions in which the genetic material is inherited identically from both parents. This will be studied in an Ashkenazi Jewish population in which the overall occurrence of this phenomenon is higher than average.

Jess Nithiananantharajah, Ph.D., University of Edinburgh, United Kingdom, will investigate how key scaffold genes that are integral for organizing synapses (connections between brain cells) control different complex behaviors and mental processes and are involved in cognitive dysfunction in psychiatric disorders such as schizophrenia. Assessing mice with mutations in two scaffold genes will initiate identification of clusters of complex cognitive behaviors according to their distinct genetic underpinnings.

Katie L. Nugent, Ph.D., Maryland Psychiatric Research Center, University of Maryland, will conduct tests to learn why female schizophrenia patients fare better after illness onset than males, a response that may occur because more females than males employ adaptive strategies for coping with social stress, leading to differing biological stress responses. Results of the study may suggest specific targeted interventions for coping with social stress.

Melissa L. Perreault, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, will focus on how a specific protein, brain-derived neurotrophic factor, may contribute to the cognitive deficiencies of schizophrenia by inducing increased activation of the protein GSK-3 and altered activity of neurons that regulate cognitive function. Reduced GSK-3 activation has been associated with marked improvement in cognitive function in a number of other neurlogoical disorders.

Todd F. Roberts, Ph.D., University of Texas Southwestern Medical Center at Dallas, is interested in disordered speech and thought patterns, as well as auditory hallucinations and delusions in psychosis. He will test the theory that these "positive" core symptoms of schizophrenia arise from a disruption in structures called corollary discharge pathways in the brain. He will test whether the genetic lesions of this pathway in rodents cause disordered sequencing of learned vocalizations that may be akin to disordered speech in schizophrenia.

Juan Song, Ph.D., The Johns Hopkins University School of Medicine, seeks to discover the cause of disturbances in gamma-frequency oscillation—rhythms that emerge during performance of cognitive tasks—which are thought to be a source of brain dysfunction in schizophrenia. Focusing on a specific type of neuron called PV+, he hopes to get to the bottom of defects in neuronal synchrony to guide development of new schizophrenia medications.

Theodorus Tsetsenis, Ph.D., Stanford University, will create a mouse model of schizophrenia based on "truncating" mutations in the gene encoding the neurexin 1 protein. He will use this model to identify the specific circuits involved in disease pathophysiology to shed light on the molecular and cellular underpinnings of schizophrenia. He hopes to uncover new information about the dysfunction of specific brain circuits to guide therapeutic interventions.

MULTIPLE DISORDERS

Mulugeta S. Abebe, Ph.D., Columbia University, will use a primate animal model of human neural processing to develop a more comprehensive understanding of memory formation, specifically with environmental memory—or memory of objects in a particular location—which may, if needed, be turned into working, or short-term memory. Memory impairment is a significant factor in psychiatric disorders such as schizophrenia and depression.

Frederic Ambroggi, Ph.D., University of California, San Francisco, wants to explain the dysfunction in motivation common to many mental illnesses, including drug addiction, depression and eating disorders, by determining how internal information in the brain is communicated to the nucleus accumbens, where information is translated into actions in pursuit of rewards.

Beth E. Cohn, M.D., University of California, San Francisco, will examine the role of inflammation in PTSD and depression, using data from a large, ongoing study to determine whether patients with lower inflammation levels are more likely to recover and people with higher levels more likely to develop these disorders. The study will compare inflammation changes in patients whose symptoms improve, worsen or remain stable over time.

Laura M. Fiori, Ph.D., University of Ottawa, Canada, will investigate the relationship between gene expression and specific DNA methylation marks (a field known as "epigenetics") associated with early childhood adversity and the development of psychopathology later in life. Methylation is a process that adds methyl chemicals to DNA to change gene expression but not DNA sequence. Ultimately, these processes represent novel targets for early diagnosis and treatment of brain and behavior disorders.

Christina Gross, Ph.D., Emory University, will examine an enzyme of the PI3K/mTOR pathway, a molecular complex that is often defective in both autism spectrum disorder (ASD) and schizophrenia. This pathway is essential for neurons to respond to external signals, and thus might serve as a therapeutic target. The study will analyze molecular mechanisms in cells from patients with ASD and schizophrenia that carry defects in the enzyme.

Benjamin Y. Hayden, Ph.D., University of Rochester, is interested in the brain changes that underlie the decreases in cognitive flexibility that characterize schizophrenia and addiction and are thought to derive from changes to the striatum brain region. Neural activity in the striatum of healthy rhesus monkeys performing a cognitive flexibility task will first be recorded to establish typical activity.

Jia Sheng Hu, Ph.D., University of California, San Francisco, will explore the disruption in the balance between excitation and inhibition in brain activity by dysfunctional inhibitory neurons, a condition tied to epilepsy, schizophrenia and ASD. Building on work on the Coup-TF2 gene, identified as important in maintaining

a distribution of inhibitory neurons across the brain, this study will explore its pre-natal development.

Soo Young Kim, Ph.D., University of California, Berkeley, will examine mechanisms that underlie early-life stress-induced anxiety disorders and schizophrenia. Specifically, the study will look at the effects of stress on the development of the extracellular matrix (the space outside of cells in the brain) and on the maturation of GABAergic neurons, nerve cells involved in the activity of GABA, the brain's major inhibitory neurotransmitter.

Torsten Klengel, M.D., Max Planck Institute for Psychiatry, Germany, seeks to identify the impact of early-life stress on epigenetic changes, which affect gene expression but do not alter DNA sequence, in a research model with primates. By assessing epigenetic, endocrine and behavioral changes over time, it may be possible to determine when the organism is most vulnerable to stress and when lasting epigenetic modifications are established.

Pan Li, Ph.D., The Johns Hopkins University, will explore a possible regulatory mechanism affecting a protein called DISC (Disrupted-In-Schizophrenia) which is involved in development of the disease. This research will follow up on findings that led Dr. Li to hypothesize that DISC2 regulates DISC1, with implications for schizophrenia and bipolar disorder, and will advance the little explored area of RNA-mediated pathogenesis in psychiatric diseases.

Judy Liu, Ph.D., Children's National Medical Center, hopes to improve understanding of the cell biology behind the development of axons, the projections on nerve cells that carry the cell's signals. Disorders such as schizophrenia, autism spectrum disorder and epilepsy may result from problems in axonal development. The study will explore the role of doublecortin, a gene crucial to axon guidance.

Machteld C. Marcelis, M.D., Ph.D., Maastricht University, The Netherlands, plans to study the relationship between a novel intervention for early psychopathology and brain changes in young people at high risk for developing depression and/or psychosis. Patients will receive a self-management intervention training that targets stress in daily life and provides feedback of patterns of reactivity with the aim of helping participants identify and remedy dysfunctional emotional patterns.

Nadine M. Melhem, Ph.D., University of Pittsburgh, will conduct a study to look for biological "markers" (or predictors) of depression and PTSD in the stress-associated hypothalamic-pituitary-adrenal (HPA)-axis. The goal is to create a biological model of stress response with pre- and post-stress measures of HPA-axis activity to identify biological markers that signal risk for depression and PTSD.

Frederick C. Nucifora, Ph.D., D.O., M.H.S., The Johns Hopkins University School of Medicine, will focus on NPAS3, a protein associated with schizophrenia, bipolar disorder and antipsychotic treatment efficacy. NPAS3 belongs to a family of transcription factors involved in important neurobiological processes, including re-

sponse to cell signaling and regulation of the birth of new nerve cells (neurogenesis). The proposed experiments will determine whether mutant NPAS3 leads to abnormal neuronal structure and function.

Fereshteh S. Nugent, Ph.D., Uniformed Services University of the Health Sciences, will explore the role of dysfunction in the lateral habenula brain region in stress-related disorders, including depression, anxiety, psychosis and drug addiction. Specifically, the effect of a key mediator of stress response in the brain, corticotropin releasing factor (CRF), on neurons in the lateral habenula will be studied.

Edwin C. Oh, Ph.D., Duke University, will probe the role(s) of a single gene, Kctd13, located in a region of the genome called 16p11.2, which has most often been found to be deleted or multiplied abnormally in autism spectrum disorder (ASD) and schizophrenia. The aim is to resolve uncertainty about which gene in an abnormal genome region containing many genes is specifically responsible for pathology, a model that might be applicable in similar instances across the genome.

Angela R. Ozburn, Ph.D., University of Pittsburgh, will follow up strong evidence that circadian genes are important in the expression of mood-related symptoms in psychiatric disorders. Circadian gene expression is altered by stress, depression and drug abuse. The research will focus on the circadian transcription factor NPAS2.

Dirk J.A. Smit, Ph.D., Vrije Universiteit Amsterdam, The Netherlands, is interested in how the brain can switch from a state of attentiveness to one of inattentiveness. While generally a normal brain activity, inattentiveness is excessive in some psychiatric disorders. This project will test whether "brain switching" also explains differences in attentiveness in pairs of twins and could help clarify attention deficits in various psychiatric disorders.

Joyce So, M.D., Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, wants to determine the prevalence of common genetic conditions in psychiatric patients who have other medical or developmental issues. She is recruiting patients with birth defects, neurological conditions, unusual facial features, developmental delay, autism spectrum disorder (ASD) or a family history of these. The hope is to identify "red flags" that may aid in achieving a genetic diagnosis in the future for patients with similar histories.

Eli A. Stahl, Ph.D., Icahn School of Medicine at Mount Sinai, will use genomic data for schizophrenia and bipolar disorder that are part of ongoing genetic studies to build risk prediction models for schizophrenia or bipolar disorder (BP), and schizophrenia versus BP. Resulting models will be used to predict conversion to psychosis in clinically high-risk patients, in a longitudinally followed sample of early-onset patients.

Bin Xu, Ph.D., Columbia University, will clarify the functional impact of three genes involved in epigenetic regulation that are mutated in both schizophrenia and autism spectrum disorder. "Epigenetics" refers to environmental factors that affect gene expression without altering the underlying DNA sequence. Using

mouse models, Dr. Xu will study their temporal and spatial expression pattern, identify target genes and evaluate the functional impact of altered activity of these genes on brain development.

OTHER

Addiction

Jia-Hua Hu, Ph.D., The Johns Hopkins University, seeks to identify how the mechanisms of a protein he identified as regulating D1 dopamine receptor signaling are linked to cocaine addiction. Using knockout and transgenic mouse models that he generated, he will examine dysfunctions of dopaminergic systems also known to be associated with schizophrenia, Parkinson's disease, bipolar disorder and ADHD.

Shahrdad Lotfipour, Ph.D., University of California, Los Angeles, will use data from a study of 1,024 adolescents, half of whom have been exposed to maternal cigarette smoking. This research aims to determine the relationship between a particular genetic variation in a nicotinic receptor subunit, maternal smoking during pregnancy and susceptibility for increased substance use in offspring. He will look specifically at structural changes in reward-related brain regions.

Eating Disorders

Patricia Bonnavion, Ph.D., Stanford University, seeks to establish a model of chronic stress disturbances in anorexia to provide better understanding of its pathogenesis and to guide new treatment strategies. Dr. Bonnavian will explore what triggers the self-induced starvation and anxiety in anorexia nervosa by investigating the role of leptin, a hormone that modulates stress response.

Ida A.K. Nilsson, Ph.D., Karolinska Institutet, Sweden, will study the neurobiology of anorexia to understand how the normal

drive to eat becomes suppressed. The project will focus on the hypothalamus, the brain area where hunger and food intake is regulated, following up studies with animal models that show a breakdown of neuronal functioning in the hypothalamus and dysfunction in the mitochondria, the cellular energy factory.

Psychosis

Hanan D. Trotman, Ph.D., Emory University, will do a first-time study of longitudinal changes in gonadal hormones and subsequent effects on symptom progression and risk for psychosis in high-risk individuals. Using samples from patients with psychosis collected in the North American Longitudinal Study, Dr. Trotman will delineate the relation of gonadal hormones with symptom progression and with cortisol.

Suicide

Molly Adrian, Ph.D., University of Washington, will explore four types of genetic variations called single nucleotide polymorphisms (SNPs). These SNPs are associated with dysregulation of the HPA-axis, the body's stress system, and an increased risk for suicidal behaviors during adolescence. The project is based on the hypothesis that SNPs affect emotion regulation, causing hopelessness and impulsive-aggression traits, leading to suicide attempts.

Rashelle J. Musci, Ph.D., The Johns Hopkins University School of Medicine, will explore the relationship between aggressive and impulsive suicidal behavior and genes associated with serotonin neurotransmission, using a dataset from the Center for Prevention Research begun in 1993 with African American first-graders in Baltimore, and continued yearly since. This research could facilitate prevention programs by individualizing identification of people at risk of suicide.

NEW TECHNOLOGIES

ANXIETY (See also Anxiety and Depression)

Mark Aizenberg, Ph.D., University of Pennsylvania, will examine how abnormalities in fear responses can lead to anxiety disorders and PTSD. A central feature of anxiety disorders is an inability to distinguish between dangerous and safe situations. Using newly developed optogenetic tools, the research will test a neuronal circuit in the auditory cortex as a candidate for regulation of generalized fear responses in mouse models.

Anthony N. Burgos-Robles, Ph.D., Massachusetts Institute of Technology, will combine the use of animal models, optogenetics and neuronal recording to examine the mechanisms that regulate competing fear and reward memories in anxiety disorders and as related to the symptom of anhedonia (the inability to experience pleasure). The research will focus on two brain regions—the baso-

lateral amygdala and the medial prefrontal cortex—to learn how they interact and coordinate these conflicting behaviors.

Gerard Clarke, Ph.D., University College Cork, Ireland, will investigate the role of bacteria in the gut in anxiety disorders. MicroRNAs are molecules involved in controlling gene expression (activation) and in the development of anxiety disorders. Gene expression in the brain also can be controlled by gut bacteria. This research will seek to determine whether MicroRNAs important for anxiety can be influenced by gut bacteria.

Eli R. Lebowitz, Ph.D., Yale University, will study avoidance behavior in anxiety disorders. Youths aged eight to 16 diagnosed with clinical anxiety will take part in a clinical trial using an innovative motion-tracking technology, the Yale Interactive Kinect Environment Software, to quantifiably measure avoidance, to relate it to

self-report of anxiety and explore other questions such as to what extent anxiety is specific to a given trigger.

Kay M. Tye, Ph.D., Massachusetts Institute of Technology, will use optogenetics technology to manipulate neurons in specific pathways implicated in anxiety disorders. She will observe the effect on neural activity as well as corresponding behaviors. She ultimately seeks to "crack the neural code of anxiety" and gain new insight towards effectively treating these disorders.

ANXIETY AND DEPRESSION
(See also Anxiety; See also Depression)

Philip Trovote, Ph.D., Friedrich Miescher Institute, Switzerland, is interested in defensive avoidance and related coping strategies which are maladapted in human anxiety and mood disorders. Through careful dissection and analysis of defensive circuits in the midbrain periaqueductal grey area using optogenetics and other advanced techniques in freely moving animals, he hopes to find potential targets for future therapeutic interventions.

ATTENTION-DEFICIT HYPERACTIVITY DISORDER (ADHD)

Seung-Hee Lee, Ph.D., University of California, Berkeley, will combine molecular, physiological, anatomical and behavioral techniques to probe the neuromodulatory circuit in the basal forebrain, a brain structure important in attention. The focus will be on unraveling specific circuit mechanisms by which the basal forebrain adjusts the level of attention. Insights gained should be applicable to the treatment of Alzheimer's disease and attention-deficit disorder.

AUTISM SPECTRUM DISORDER (ASD)

Ronald M. Carter, Ph.D., Duke University, will use game play to probe the neural basis of social and motivational differences in ASD. Failures in social function thought to be due to deficits in social processing could be linked to deficits in motivation toward social stimuli. Analysis will focus on the temporal parietal junction, which the lab has shown to be uniquely involved in this differentiation.

Gianafilippo Coppola, Ph.D., Yale University, will develop an integrative and comprehensive analysis of the gene regulatory networks underlying the pathophysiology of ASD using the resources of a unique database. Reducing the problem from thousands of genes to a few modules could shed light on the cause and genetic architecture of the illness and identify network hubs as potential targets for medications and/or diagnostic tests.

Holly N. Cukier, Ph.D., University of Miami, will study the role played by the gene RBFOX1 in neuronal development and identify potential pathogenic mechanism(s) that could underlie the development of ASD. The research will utilize advanced stem cell technology and RNA sequencing to identify key pathways, functions and regulatory networks associated with either RBFOX1 silencing or over-expression.

Yongsoo Kim, Ph.D., Cold Spring Harbor Laboratory, will explore aspects of a finding that intranasal oxytocin can improve social behavior in ASD. The study seeks to determine the associated physiological mechanisms in an animal model and to identify what brain regions respond to the treatment and how brain activity is altered to lead to improvement in social behavior.

Keerthi Krishnan, Ph.D., Cold Spring Harbor Laboratory, will seek to unravel the pathogenesis of Rett syndrome, which falls on the spectrum of autism disorder. Rett syndrome is hypothesized to result from inappropriate neuronal maturation, function and plasticity. The study will advance methods of genomic analysis to characterize the altered gene expression of MeCP2 in relevant brain regions and examine the functionally relevant cells.

Hyungbae Kwon, Ph.D., Max Planck Florida Institute for Neuroscience, will examine proteins called neuroligins, mutations found in familial forms of ASD. The study will explore how they contribute to synapse formation to help answer open questions about neural circuit development and structural plasticity relating to the pathogenesis of ASD.

Setsuko Sahara, Ph.D., Institute of Psychiatry, King's College London, studies autistic macrocephaly, an enlargement of the brain seen in 20 percent of ASD patients. This project seeks to identify candidate genes and investigate their role in cortical development, in both mouse brains and induced-pluripotent stem cell-derived cortical progenitor cells gathered from patients with mutations of the candidate genes. The goal is to aid development of treatments tailored to specific subtypes of the disorder.

Jason W. Triplett, Ph.D., Children's National Medical Center, studies deficits in sensory processing and integration that can occur in neurodevelopmental disorders including ASD. He seeks to determine molecular mechanisms by which converging sensory inputs are organized during development, using genetic techniques to silence activity in specific neurons. He hopes to lay a foundation for future studies of the functional and behavioral consequences of misalignment of spatial "maps" generated by the brain.

Lasani S. Wijetunge, Ph.D., University of Edinburgh, Scotland, will use a powerful new kind of microscopy and an animal model of Fragile X syndrome to examine the state of synapses in the brain. The extremely high resolution microscope allows visualization of synapses and suggests their ability to transmit information in living brain tissue. It is hoped that this work will improve understanding of how the brain develops differently in people with ASD.

Akira Yoshii, M.D., Ph.D., Massachusetts Institute of Technology, will study a genetic syndrome called Tuberous Sclerosis Complex (TSC) that sometimes accompanies ASD. Using two-photon microscopy and molecular imaging, he will seek to determine if serotonin synapses are dysregulated in TSC, providing information on the causal relationship between dysregulated serotonin function during early brain development and ASD.

BIPOLAR DISORDER (BP)

Liping Hou, Ph.D., National Institute of Mental Health, will identify gene(s) on the X-chromosome that may affect the risk for developing BP by conducting a comprehensive study of X-chromosome markers derived from all of the genome-wide association studies of BP that have been published in five different trials.

Casey P. Johnson, Ph.D., University of Iowa, aims to identify new "biomarkers" (biological predictors) of BP and provide insight into the disease mechanisms. He will use advanced fast, high resolution quantitative methods of magnetic resonance imaging (MRI) that can produce exceptionally detailed and diverse images and will generate three-dimensional "maps" of a number of measures related to specific biophysical properties of the brain.

Nathan Kolla, M.D., Centre for Addiction and Mental Health, University of Toronto, Canada, will compare levels of a brain chemical called monoamine oxidase A (MAO-A) in people with BP depression and healthy volunteers. Patients with BP may have too much oxidative stress in their body causing damage to brain cells, and this could be caused in part by MAO-A.

Minjie Wu, Ph.D., University of Illinois at Chicago, will use innovative neuroimaging methods to delineate mood-specific biomarkers in pediatric BP in spontaneous activity at a resting state, in affect regulation and emotional memory domains during a task and in interactions of rest and task. Dr. Wu aims to enhance understanding of functional differences between multiple mood states and permit detailed delineation of mood-specific treatment targets.

DEPRESSION (See also Anxiety and Depression)

Jerome Brunelin, Ph.D., Lyon University, France, will use a new, non-invasive brain stimulation technique called transcranial direct current stimulation to investigate the relationship between frontal cortex activity, decision-making abilities and activity during acute stress. This relationship will be investigated first in healthy controls to determine the specific role of right and left frontal activity and then in people with major depression.

Xiaofu He, Ph.D., Columbia University, will use magnetic resonance imaging (MRI) data from a three-generational study of familial patterns of psychiatric and behavioral issues from childhood through adulthood in offspring at high and low risk for depression. Functional and structural interrelationships among the brain regions will be analyzed in search of a common cortical architecture in children and adolescents with depression.

Paraskevi V. Rekkas, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, believes early detection is a promising strategy for preventing major depression in perimenopause. This project will examine a protein in the brain and in the blood called monoamine oxidase A (MAO-A). New brain imaging and blood analysis technologies to measure MAO-A levels hold promise

for the development of MAO-A biomarkers in perimenopause, the ultimate objective of this work.

Elaine Setiawan, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, will conduct a first-of-its-kind study to explore whether unrecognized and untreated inflammation in the brain is one reason for the high rate of non-response to depression treatments. She will scan people with clinical depression using a new kind of brain imaging method that can detect inflammation to determine if treatment-resistant clinical depression is associated with brain inflammation.

Michael Treadway, Ph.D., McLean Hospital, Harvard University, will use simultaneously acquired positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) scan measures of inflammation in the brain to test the theory that this is an underlying cause of major depressive disorder. The results could help establish the role of corticostriatal neuroinflammation as a biological "marker" for impaired motivation, a common symptom of depression.

POST-TRAUMATIC STRESS DISORDER (PTSD)

Michael V. Baratta, Ph.D., University of Colorado, Denver, aims to elucidate the neural mechanisms that promote resilience to stress, information that could lead to the development of better therapies for PTSD. Previous work identified the medial prefrontal cortex (mPFC) as being involved in this process. The research will employ optogenetic strategies for determining the critical features of mPFC function that produce the enduring effects of resilience.

Meeryo C. Choe, M.D., University of California, Los Angeles, will study sports-related concussions in middle school athletes to identify possible resulting psychiatric diagnoses. Animal models of mild traumatic brain injury point to specific brain regions that may correlate with the development of PTSD. Advanced imaging shows promise of correlating brain structural abnormalities with symptoms and may help determine treatment and prognosis.

Sue-Hyun Lee, Ph.D., National Institute of Mental Health, aims to develop an effective strategy to disrupt fear memory in PTSD. To test the hypothesis that different components of the recalled memory are maintained in distinct cortical areas, Dr. Lee will use functional magnetic resonance imaging to identify target areas and transcranial magnetic stimulation as a treatment immediately after memory recall to see if the memory is disrupted.

Clarissa C. Parker, Ph.D., University of Chicago, will use mouse models to study conditioned fear as a way of identifying genes important in human PTSD. She proposes to map sites on the chromosome affecting naturally occurring variability in conditioned fear, hypothesizing that some of the genes identified in the mice will also be involved in human PTSD, and therefore candidates for further study.

Erel Shvil, Ph.D., New York State Psychiatric Institute, Columbia University, is studying irregularities in the hippocampus, a brain area central to memory and learning, as they correlate with PTSD. The volume of the hippocampus declines in people with the illness. This will be the first MRI-based study that will determine shrinkage (if any) in various sub-regions of the hippocampal formation, comparing brains of affected people with "controls."

SCHIZOPHRENIA

Mera S. Barr, Ph.D., University of Toronto, Canada, will examine cannabis use as a risk factor for developing schizophrenia. Chronic cannabis use results in the down regulation of GABA, a neurotransmitter that inhibits activity in the cortex of the brain. Patients with schizophrenia show deficits in cortical inhibition; cannabis abuse may further exacerbate it.

Chad Bousman, Ph.D., University of Melbourne, Australia, plans to identify a panel of genetic variants, such as single nucleotide polymorphisms, associated with schizophrenia. The research will be based on data from thousands of schizophrenia patients and healthy controls, so as to create a method that could be used to expedite and standardize schizophrenia diagnosis.

Kathleen Cho, Ph.D., University of California, San Francisco, will study parvalbumin interneurons, an inhibitory type of nerve cell in the prefrontal cortex of the brain. She seeks to determine how the properties of excitatory and inhibitory neurons or their interactions might be altered in ways that produce neural imbalance and give rise to abnormal brain-wave oscillations such as those observed in people with schizophrenia.

Vanessa L. Cropley, Ph.D., University of Melbourne, Australia, will use brain imaging in people with a first episode of psychosis to investigate whether increased dopamine function in the striatum, a region of the brain's cortex, is related to abnormalities in psychosis seen in an associated brain circuitry called the frontostriatal network. Schizophrenia, and particularly symptoms of psychosis, are thought to involve dysregulation of dopamine.

Inbal Goshen, Ph.D., Hebrew University, Israel, will investigate how astrocytes in the prefrontal cortex modulate behavior and neuronal activity in a mouse model of schizophrenia. Astrocytes are cells of the type called glia, which surround and support neurons. The ability to study astrocytic activity in real time is now possible with optogenetics, which combines optics and genetics to control cell activity in living animals.

Christopher Harvey, Ph.D., Harvard University Medical School, will apply advanced microscopy methods to measure the flow of information between two brain areas—the prefrontal cortex and the posterior parietal cortex—thought to be central to cognitive processing which is impaired in schizophrenia. The study will use mice trained to perform navigation tasks that require decision-making, memory and planning.

David J. Margolis, Ph.D., Rutgers University, will investigate cortical neurons called parvalbumin positive (PV) cells, which have been implicated in the cognitive deficits in schizophrenia. The study will aim to define the impact of PV cells on local neural signaling and long-range propagation of neural activity to enhance understanding of the neural circuit plasticity mechanisms underlying the onset and progression of schizophrenia.

Chiara Magri, Ph.D., Brescia University, will conduct genetic sequencing studies of people with schizophrenia who have high levels of autozygosity, a situation that occurs from inbreeding, when two chromosomal segments that are identical, coming from a common ancestor, are inherited from each parent. The identification of the mutations responsible should be useful in helping to clarify the biological mechanisms at the basis of schizophrenia.

Gemma Modinos, Ph.D., Institute of Psychiatry, King's College London, will use brain imaging technology to study people at high risk for schizophrenia, who are experiencing psychotic symptoms but do not meet the criteria for a clinical diagnosis. She will investigate whether they show abnormal brain activation while processing emotional information and whether the neurotransmitter glutamate modulates this activation, identifying how it may affect emotional and social functioning.

Krishnan Padmanabhan, Ph.D., Salk Institute for Biological Studies, hopes to develop insights into the still largely elusive biological basis of schizophrenia, using reprogrammed human stem cells in an animal system. Neurons derived from patients with schizophrenia will be studied by engrafting neuronal precursor cells into mice to observe the anatomical and physiological changes that occur.

Krystal L. Parker, Ph.D., University of Iowa, will investigate the relationship between the cerebellum and prefrontal cortex, brain areas essential for accurate timing control, which is impaired in schizophrenia. She will record neural activity in both areas in mice, analyze their interaction during a timing task and use optogenetics to stimulate the cerebellum in an attempt to normalize prefrontal activity and restore timing ability.

Panagiotis Roussos, M.D., Ph.D., Icahn School of Medicine at Mount Sinai, will identify and map non-protein coding sequences in the genome that are often irregular in people with schizophrenia. Many such regions are thought to have functions, but these are as yet unknown. Dr. Roussos will use postmortem human brain specimens, focusing study on cells in parts of the cortex and hippocampus that have consistently shown abnormalities in schizophrenia.

Karun K. Singh, Ph.D., McMaster University, will examine the impact on brain development of a gene copy-number variation on chromosome 15. The region has been associated with schizophrenia, but it's not known which of the seven genes in the region are specifically involved. Dr. Singh will use an innovative, cost-effective method to determine this and his work could identify genes that might be targets for novel therapies.

Joshua Woolley, M.D., Ph.D., University of California, San Francisco, will investigate the neurophysiological mechanisms of the drug oxytocin and its prosocial effects in people with schizophrenia and controls using magnetoencepholagraphy (MEG). This is the first study to investigate the neurophysiological effects induced by oxytocin in schizophrenia using any imaging modality, and the first study to use MEG to examine the effects of oxytocin on neural processing.

MULTIPLE DISORDERS

Chi-Hua Chen, Ph.D., University of California, San Diego, aims to develop new approaches to gene discovery relevant to schizophrenia, bipolar disorder and Alzheimer's disease. The research will apply novel brain phenotypes (outward, observable characteristics) and statistical approaches in a large sample with brain imaging and data on genotype (genetic makeup of a cell). The goal is to establish a database that has information about the contribution of specific genetic types to variation of characteristics in specific parts of the brain.

Kristen Foster, Ph.D., Duke University, will apply a novel approach that simultaneously monitors activity in large populations of neurons to provide identification of each cell type and its spatial relationship to other cells. This approach will be applied to the striatum, a brain region thought to have a critical role in obsessive-compulsive disorder, Parkinson's disease, Huntington's disease, Tourette's syndrome, eating disorders, ADHD and addiction.

Yongjun Gao, Ph.D., The Johns Hopkins University, aims to develop more effective radioligands—radioactive molecules that bind to receptor molecules—for use in PET imaging to examine the distribution of the seven nicotinic acetylcholine receptors. These receptors are implicated in neuropsychiatric disorders including schizophrenia, Alzheimer's disease, anxiety, depression and drug addiction. They may be useful for diagnosis and assessing treatment response.

Aryn H. Gittis, Ph.D., Carnegie Mellon University, will study neural circuits in the basal ganglia region of the brain involved in motor suppression and compulsive behavior. Compulsive behavior is a symptom of disorders such as OCD, ADHD, Tourette's syndrome, Huntington's disease and Parkinson's disease. The inability to control or suppress unwanted movements can arise from dysfunction of motor-suppressing circuits.

Conor Liston, M.D., Ph.D., Stanford University, will investigate how chronic stress during adolescence affects the development of neural circuits and assess whether it has a lasting impact on circuit function in adulthood. Using imaging and optogenetic tools for interrogating neural circuits, the research will focus on stress-sensitive brain regions of the medial prefrontal cortex and striatum, known to be central to the regulation of attention and other cognitive processes.

Gyorgy Lur, Ph.D., Yale University, will explore the association between alterations of the brain chemical norepinephrine with depression and PTSD. He seeks to determine how norepinephrine levels control function in the prefrontal region of the brain both at the network and cellular level, and how its dysregulation leads to the emotional and behavioral impairments seen in these disorders.

João Peca, Ph.D., University of Coimbra, Portugal, aims to discern the biological mechanisms that disrupt social behavior in schizophrenia and autism spectrum disorder. The research will identify synaptic proteins that vary with changing social environments and map the neuronal pathways in the brain that regulate social behaviors, applying optogenetics in animal models to directly manipulate the predisposition to seek or avoid social interactions.

OTHER

Addiction

Uma Vaidyanathan, Ph.D., University of Minnesota, seeks to determine whether brain structure and function anomalies (e.g., loss of frontal cortex neurons and disruptions in hippocampal plasticity) that are associated with alcohol misuse are a cause or consequence of the misuse. She will use functional and structural magnetic resonance imaging (MRI) to longitudinally compare the brains of identical twins who differ on alcohol use and/or abuse.

Eating Disorders

Zachary A. Knight, Ph.D., University of California, San Francisco, is seeking to better understand binge eating, the most common eating disorder in the U.S., using a technology he developed to map neurons that are activated when mice engage in voracious eating. These neurons express dynorphin; Dr. Knight will test the function of dynorphin neurons in regulating feeding behavior.

Sunila Nair, Ph.D., University of Washington, will conduct obesity studies to examine the role of the lateral habenula region of the brain in cue-induced relapse to seeking high-fat food. The research will utilize state-of-the-art genetic and chemical technology to selectively manipulate lateral habenula neurons in mouse models of obesity to elucidate the neuronal circuits that underlie cue-induced relapse.

Epilepsy

Ramin Pashaie, Ph.D, University of Wisconsin-Milwaukee, will study electrical activity in the cerebral cortex area of the brain, known to be associated with epilepsy. He will apply a combination of advanced technologies to record from large areas of neural networks in the cortex and will also use optogenetics to stimulate cortical activity.

NEXT GENERATION THERAPIES

ANXIETY

Paul Siegel, Ph.D., New York State Psychiatric Institute, Columbia University, studies the impact of non-conscious behaviors on anxiety disorders. Here he seeks to connect brain and behavior in the "very brief exposure (VBE) effect:" the reduction of phobic fear by presentation of a continuous series of non-conscious phobic images. Can phobic avoidance be reduced without conscious cognition? An MRI imaging experiment will test the hypothesis that VBE will reduce fear responses of phobic individuals.

Lisa E. Williams, Ph.D., University of Wisconsin-Madison, wants to know how cognitive behavioral therapy (CBT) for childhood anxiety changes brain function. She will test the theory that stronger amygdala-frontal connectivity predicts better response to CBT by taking a brain scan before and after treatment in children with anxiety. She argues a deeper understanding of the relationship between functional brain networks, anxiety symptoms and treatment outcome is needed to inform and improve treatment for childhood anxiety.

AUTISM SPECTRUM DISORDER (ASD)

Michael L. Gonzales, Ph.D., University of California, Davis Medical Center, will explore the modes of action of Methyl CpG Binding Protein 2 (MeCP2), an important regulator of neuronal development, to help inform selection of therapeutic targets for MeCP2-derived disorders, including a number of neurodevelopmental disorders, including Rett Syndrome, Fragile X-linked intellectual disability and ASD.

Hye Young Lee, Ph.D., University of California, San Francisco, is seeking new targets for treating Fragile X Syndrome, a disease associated with a high risk for developing ASD. Dr. Lee will test a potential target of Fragile X—Kv4.2 potassium channels—in mouse models. This work is based on evidence that a 50 percent reduction of Kv4.2 improved some autistic-like behaviors in mice.

Yoshitake Sano, Ph.D., University of California, Los Angeles, has discovered that decreasing levels of the DISC1 protein in the dentate gyrus—a part of the hippocampus region of the brain linked to the ongoing birth of new neurons (neurogenesis)—causes cognitive and affective disorders in rodents. This project will investigate whether an FDA-approved drug (sirolmus or Rapamune®) can reverse such behavioral abnormalities in a mouse model of ASD, which could open a new path for treatment of millions of adults with ASD.

BIPOLAR DISORDER (BP)

Andre R. Brunoni, M.D., Ph.D., Universidade de São Paolo, Brazil, will conduct a clinical trial to determine whether transcranial direct current stimulation, which has been shown to be effective in treating unipolar depression, can also be effective for treating BP depression. This technique uses a weak, direct electric current to modify brain activity in the area where the current is applied.

Paul E. Croarkin, D.O., M.S.C.S., Mayo Clinic, wants to optimize treatment for adolescent mood disorders. The neurotransmitter glutamate is believed to play a key role in BP; Dr. Croarkin will measure glutamate levels and functioning in depressed adolescents who are at risk for later developing BP. Half will receive escitalopram, half lamotrigine, to examine if and how depressive symptoms and glutamate measures change.

Ryan W. Logan, Ph.D., University of Pittsburgh, will investigate the role of "epigenetics" (environmental factors affecting gene expression without altering the DNA sequence) on circadian rhythms, known to be disrupted in BP. The specific focus will be on histone deacetylases (HDACs), based on indications that they could be developed as novel mood stabilizing agents. HDACs are epigenetic enzymes that repress gene transcription and are involved in regulating circadian rhythms.

Dorothy K.Y. Sit, M.D., University of Pittsburgh School of Medicine, investigates the effects of bright light therapy to treat bipolar depression. Improvement in symptoms with exposure to light is evidence of involvement of the circadian system in mood disorders. Some patients experience improved mood, sleep and energy by using morning light therapy but midday light therapy also can restore stable mood in people with rapid cycling bipolar illness. The study goal is to understand how light therapy works to improve bipolar symptoms.

DEPRESSION

Roee Admon, Ph.D., McLean Hospital, Harvard University, will investigate neural networks linked to depressive mood symptoms in patients with depression. Stabilizing positive mood is an important end point of antidepressant treatments, and the hope is that insights derived from this study can help guide the selection of treatments that will prolong positive mood and help identify individuals at risk for depressive disorders.

Eléonore Beurel, Ph.D., University of Miami, hopes to clarify mechanisms underlying the rapid antidepressant effect of the drug ketamine as well as its usefulness in treating otherwise treatment-resistant patients. To provide a means for countering the transient antidepressant response to ketamine, the research will test to find out whether its effect can be sustained by prolonging inhibition of GSK3, an enzyme involved in mood disorders.

Ashley M. Blouin, Ph.D., The Johns Hopkins University, will explore whether a gene called Narp (neuronal activity-regulated pentraxin) is acting in the brain to mediate the antidepressant effect of electroconvulsive therapy (ECT), and which signaling pathway plays a critical role. This information will aid in developing new treatment approaches for resistant depression with fewer side effects than ECT.

Anett Gyurak, Ph.D., Stanford University, will conduct a nation-wide clinical trial of a cognitive-effective remediation training intervention for depression with 150 people. The trial consists of Internet-based computer exercises that translate emerging knowledge about the disorder into a novel biologically-based intervention. Wide-scale use of the protocol has the potential to advance current understanding of treatment response and to dramatically change the delivery of care to patients.

Mei-Hua Hall, Ph.D., Harvard University Medical School, will evaluate the effects of a cognitive remediation training intervention for people with depression. The study will examine the underlying neurobiological mechanisms mediating the changes observed after the training, and the relationship between cognitive changes with changes in the cortex. The information acquired could guide further improvement of cognitive remediation intervention.

Shihoko Kojima, Ph.D., University of Texas Southwestern Medical Center at Dallas, aims to identify genes that play crucial roles in the fast antidepressant action of the drug ketamine. Better understanding of the mechanisms underlying ketamine's activity could guide the design of new antidepressants that are as rapid, long-lasting and reliable, with fewer of the adverse side effects that limit ketamine's use.

Li Li, M.D., Ph.D., University of Alabama at Birmingham, will study glucose metabolism and insulin sensitivity in 60 depressed patients with a history of early-life stress to determine how stress affects glucose levels, and whether a specific age range will put depressed patients at a greater risk for insulin resistance. Resolving this question will help clinicians identify people with depression at risk for developing diabetes.

Adriana Lori, Ph.D., Emory University, will explore evidence that variations in the ADRA1A gene influence response to antidepressant treatment. The variations, called single nucleotide polymorphisms (SNPs), showed a relationship to brain activity associated with remission. In the proposed study ADRA1A will be sequenced in samples from patients with depression to identify unique SNPs that affect the function of the gene.

Keri Martinowich, Ph.D., The Johns Hopkins University, will explore the role of brain-derived neurotrophic factor (BDNF), a nerve growth factor protein, in mediating the behavioral response to electroconvulsive therapy (ECT) in the treatment of depression. The gene encoding BDNF is highly complex, producing multiple variants. The study will investigate the consequence of the most highly expressed variants on the response to ECT.

Yong-Seok Oh, Ph.D., The Rockefeller University, will investigate ways to improve antidepressant therapy. Selective serotonin reuptake inhibitors, the most widely used antidepressants, take weeks to work, signifying complicated downstream molecular mechanisms. A novel chromatin remodeling factor involved in genetic regulation may be a possible mediator of antidepressant effects and this research aims to identify target genes in various neuronal subtypes.

Mariana Pereira, Ph.D., Rutgers University, will investigate recent evidence that postpartum depression (PPD) differs clinically from non-postpartum depression. Using rat models, she will examine whether alterations in dopamine function underlie the cognitive and motivational impairments in PPD that lead to deficits in parenting. Dr. Pereira will also evaluate use of the neuromodulator adenosine as a treatment for PPD.

Abigail M. Poulter, Ph.D., Brown University, studies the relation of stress to depression. Focusing on dopamine neurons of the ventral tegmental area (VTA), a crucial part of the brain's reward processing system and affected by acute and chronic stress, she will examine inhibitory synapses in animals susceptible and resilient to depression. She will then test whether enhancing inhibitory signaling in the VTA can protect susceptible animals from the negative effects of chronic stress.

Alan R. Prossin, M.D., University of Michigan, will study activation of pathways in the central immune system as they pertain to major depressive disorder. It is hoped that more robust measures of immune functioning will facilitate development of novel immune-derived personalized treatment strategies, particularly for those whose depression resists treatment. In this study 10 patients and 10 controls will receive PET scans; central immune activation will be compared, and in the patient group, correlated with history of treatment resistance.

Denise M. Ramirez, Ph.D., University of Texas Southwestern Medical Center at Dallas, is studying the action of the drug ketamine on symptoms of refractory depression. She recently determined that ketamine blocks spontaneous transmission of the neurotransmitter glutamate; this project seeks to characterize the mechanism(s) behind

this effect. A protein called presynaptic vesicle protein 7 that is involved in spontaneous neurotransmission is among the targets of this work.

Eric F. Schmidt, Ph.D., The Rockefeller University, will tease apart and target neural circuits in the cerebral cortex that control mood and malfunction in mood disorders such as major depression. Two strains of genetically-engineered mice will be used to expose different populations of cells in the medial prefrontal cortex. The goal is to identify distinct cell populations within these circuits that may serve as novel candidates for better antidepressant therapies with fewer side effects.

Charles T. Taylor, Ph.D., University of California, San Diego, will use functional brain imaging and applied cognitive neuroscience to develop new ways of understanding and modifying the brain to improve treatment outcomes in depression. He will determine the ability of a computerized "cognitive bias modification" approach/avoidance training procedure to enhance activity in brain regions that regulate responses to rewards and thereby reduce vulnerability to depression. He asks: "Can we train the depressed brain to obtain rewards?"

Stuart Watson, MBBS, M.D., MRCPsych, University of Newcastle, Australia, will test the theory that treatment response to antidepressants can be predicted by the regulation of the stress response system. He is conducting a trial involving more than 200 individuals taking metyrapone, which blocks the synthesis of the stress hormone cortisol, in treatment-resistant depression. This will shed light on prognosis in depression and will show how metyrapone exerts its therapeutic response.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

Michael H. Bloch, M.D., Yale University Child Study Center, will test N-Acetylcysteine (NAC), an over-the-counter supplement, as a treatment for OCD in children who do not respond to standard treatment with cognitive behavioral therapy or selective serotonin reuptake inhibitor antidepressants. People with OCD show elevated brain levels of the chemical glutamate and NAC has been shown to be a glutamate-modulating agent.

POST-TRAUMATIC STRESS DISORDER

Chaya G. Bhuvaneswaran, M.D., M.P.H., University of Massachusetts Medical School, will conduct a trial of the blood pressure medication mecamylamine as a treatment for PTSD. Mecamylamine has been shown to have some effect in alleviating anxiety and depression. In animal models it disrupts long-term potentiation, a process involved in learning and memory and the hope is that mecamylamine can disrupt the recurring bad memories that characterize PTSD.

Roger L. Clem, Ph.D., Icahn School of Medicine at Mount Sinai, will examine how emotional memory alters synaptic trans-

mission in the amygdala in mice exposed to fear conditioning. The amygdala is a brain area critical for anxiety-related disorders such as PTSD. Dr. Clem will investigate the role of the molecule mGlu1 in regulating fear memory by reducing amygdala synaptic strength, and whether fear attenuation can be augmented with mGlu1-activating medications.

Jennifer S. Mascaro, Ph.D., Emory University, will look for hormonal and immunological biological "markers" (predictors) related to emotional numbing in 30 male military veterans diagnosed with PTSD, and test the effectiveness of an intervention called cognitively-based compassion training to increase empathy and social connectedness. The study will assess the patients' levels of oxytocin, inflammation and self-reported emotional and social status before and after the training.

Gihyun Yoon, M.D., University of Minnesota, seeks to use intranasal insulin for PTSD. Emerging evidence indicates that it may reduce anxiety or stress-related behaviors. Dr. Moon's research will compare intranasal insulin and placebo in a randomized, double-blind, placebo-controlled crossover trial. Brain activity will be examined using functional magnetic resonance (fMRI) imaging.

SCHIZOPHRENIA

Marco Armando, M.D., Ph.D., Bambino Gesu Children's Hospital, Italy, will administer long chain omega-3 polyunsaturated fatty acids (PUFAs) to adolescents at high risk for schizophrenia due to a chromosomal abnormality associated with reduced PUFA. The goals are to identify the best neural targets for new treatments and to gain the ability to predict and prevent transition from the pre-psychotic to psychotic stage of illness.

Savita G. Bhakta, M.D., University of California, San Diego, aims to identify measures that counter the cognitive deficits common in schizophrenia. A variation in the gene for the enzyme catechol-O-methyltransferase (COMT) can affect cognition. The research will investigate the cognitive enhancing effects of tolcapone, a medication that blocks COMT activity.

Chi-Ming Chen, Ph.D, University of Connecticut, Hartford Hospital, will explore the hypothesis that the auditory verbal hallucinations that occur in schizophrenia are caused by abnormal connectivity between regions of the brain involved in language processing. Dr. Chen will test transcranial magnetic stimulation to brain regions believed to be involved in verbal hallucinations as a potential treatment in patients who are not relieved by standard medications.

Derin J. Cobia, Ph.D., Northwestern University, will conduct a study on people with schizophrenia given amphetamines. The research will examine the relationship between different modes of brain activation and try to determine whether certain brain patterns can predict a positive response to amphetamine as a treatment for

the negative symptoms of schizophrenia (social, emotional and motivational disturbances). Current treatments affect primarily the positive symptoms (hallucinations and delusions).

Paul Gorczynski, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, aims to identify the key individuals and best approaches for delivering information on physical activity to people with schizophrenia, who tend to be less active than the general population. These patients experience high rates of obesity and diabetes, predisposing them to cardiovascular disease and a considerably shortened lifespan.

Laura M. Harrison, Ph.D., Louisiana State University, will use a mouse, deficient in a protein that regulates signaling by dopamine receptors, to learn which intracellular signaling pathways are affected by antipsychotic schizophrenia medications that act on the neurotransmitter dopamine. Targeting specific signaling, rather than all signaling, should help define which pathways are involved in therapeutic effect and which in unwanted side effects.

Charles Albert Hoeffer, Ph.D., New York University School of Medicine, will study a molecule called regulator of calcineurin1 (RCAN1) as a potential target for the development of more effective schizophrenia medications. Both RCAN1 and the enzyme calcineurin are important in cognition. The aim of the research is to identify RCAN1 signaling as a central pathway involved in the expression of calcineurin-mediated behavioral abnormalities of schizophrenia.

Margaret McNamara McClure, Ph.D., Icahn School of Medicine at Mount Sinai, will conduct a clinical trial of guanfacine, a blood pressure medication, to enhance working memory in people with schizophrenia. It will be administered in conjunction with a program of cognitive remediation. The project follows a pilot study in which participants who received guanfacine showed significant improvement in working memory, a process compromised in schizophrenia.

Eric B. Oleson, Ph.D., University of Maryland School of Medicine, will examine the interaction of the endocannabinoid and dopamine systems in the brain in an effort to improve the efficacy of antipsychotic treatment. Antipsychotic medications work by affecting dopamine release. The endocannabinoid system is altered in schizophrenia but necessary for regulation of dopamine release. Fine-tuning endocannabinoid control of dopamine release could offer more effective therapy for schizophrenia.

Bart Peters, M.D., Ph.D., Zucker Hillside Hospital, Feinstein Institute for Medical Research, notes deficiencies of omega-3 fatty acids have been found in people with schizophrenia. He will study whether omega-3 supplementation increases white matter integrity in patients with first-episode schizophrenia, as seen with diffusion tensor imaging, and whether changes in white matter integrity are associated with improvement in clinical status. This may provide a basis for future, larger clinical trials.

Jingchun Sun, Ph.D., Vanderbilt University, seeks to distinguish the method of action of "typical" vs. "atypical" antipsychotic medications. Using extensive database information regarding the action of these medications on genes and signaling pathway networks in the brain, he seeks to better understand their underlying mechanisms of action and identify genes involved in order to develop better diagnostic tests and more effective medication strategies for schizophrenia.

Pierre Trifilieff, Ph.D., Université Bourdeaux II, France, studies the impact of n-3 PUFAs (polyunsaturated fats from the diet), which affect dopamine D2 receptors (D2Rs). D2R overexpression in development leads to dysfunction of the reward system, including behaviors that model the negative symptoms of schizophrenia. It may be that high-fat diets contribute to negative symptoms of schizophrenia. By identifying periods of vulnerability and reversibility of an imbalanced PUFA diet, this project could open new routes toward prevention and treatment.

Anne L. Wheeler, Ph.D., Centre for Addiction and Mental Health, University of Toronto, Canada, will use neuroimaging to determine the effects of transcranial magnetic stimulation (TMS) treatment on brain structure in people with schizophrenia who are given the treatment to address working memory deficits. This double-blind clinical trial will further understanding of how this treatment affects brain structures important for working memory performance.

MULTIPLE DISORDERS

Joshua W. Buckholtz, Ph.D., Harvard University, aims to aid development of new treatments for the impulsive behavior that is a hallmark of bipolar disorder, addiction, ADHD and personality disorders. The research will first explore the little understood biology of impulsivity and then test the therapeutic effects of direct current stimulation, a brain stimulation technique that can enhance the function of the frontal cortex.

Andrew C. Emery, Ph.D., National Institutes of Health, will look for specific molecules to act as potential therapeutic agents for stress-related psychiatric disorders such as depression and PTSD. The blockers would act by inhibiting the effects of a chemical, PACAP, which mediates the physiological response to stress and release of stress hormones, including cortisol.

Greg Perlman, Ph.D., Stony Brook University School of Medicine, will study people with schizophrenia and people with psychotic mood disorders and their unaffected siblings to find neural markers that distinguish between the two disorders. Establishing this distinction will facilitate use of event-related potential (ERP) technology to guide treatment decisions and identify risk. ERP is noninvasive and more cost-effective than other strategies to measure brain function.

OTHER

Addiction

Swapnil Gupta, M.D., Yale University, will test a treatment for cannabis-induced cognitive deficits, which are related to widespread release of and increase in the brain chemical glutamate. N-acetylcysteine reduces glutamate and should, in theory, attenuate the spatial working memory and verbal memory deficit effects of tetrahydrocannabinol, the main psychoactive compound in cannabis.

Borderline Personality Disorder (BPD)

Kate E. A. Saunders, BM, University of Oxford, uses a standard psychiatric test of "reciprocal altruism" called the Prisoner's Dilemma to gauge how well treatment works for people with BPD. She theorizes that successful completion of treatment for the disorder will be associated with an improvement in the acquisition and maintenance of cooperative behavior in a repeat test. She will compare 20 individuals with BPD who have completed long-term psychotherapy, 20 untreated individuals and 20 controls.

Psychosis

Michael M. Francis, M.D., Indiana State University, aims to demonstrate the efficacy of high frequency repetitive transcranial magnetic stimulation (rTMS) for treating cognitive dysfunction in psychotic disorders and to detect increased cortical activation. It is expected that rTMS will result in greater increases in cerebral blood flow during performance of cognitive tasks. The study will help define optimal rTMS treatment parameters for cognitive dysfunction.

Jenifer L. Vohs, Ph.D., Indiana School of Medicine, notes that no current treatment adequately addresses poor insight—that is, a realistic sense of one's situation—during the first few years of psychotic illness. She seeks to develop and test a stage I novel Integrated Metacognitive Therapy manual to improve insight in early psychosis. It will allow for close examination and determination of specific manual session tasks and content while also providing preliminary evidence to support efficacy of the intervention.

Suicide

James M. Bolton, M.D., University of Manitoba, Canada, hopes to improve suicide prediction. Using a state-of-the-art database, he will follow a large group of people who attended emergency departments so as to clarify which characteristics increase suicidality (suicidal thinking or behavior). The study will test the effectiveness of a scale designed to predict suicide risk, which is widely used but has never been evaluated.

New Treatments

Future Post-Traumatic Stress Disorder (PTSD) Preventative Treatment

Injecting mice with a new medication immediately after a traumatic event prevents the animals from developing behavioral symptoms of PTSD. This model of "mice fear" appears to be comparable to human fear, says Kerry Ressler, M.D., Ph.D., "and we have confidence that we're looking at the same thing." Dr. Ressler, a Brain & Behavior Research Foundation Scientific Council Member and NARSAD Grantee, led a team of scientists that included NARSAD Grantees Tanja Jovanovic, Ph.D., and Elisabeth B. Binder, M.D., Ph.D., at Emory University. The researchers have homed in on a brain receptor found in mice and humans that is a target for this new therapy.
Source: *Science Translational Medicine*, June 5, 2013

Study of Metabolism Offers New Approach to Treating Depression

A team of researchers at Duke University studied the metabolic profiles of people with major depression. They identified specific biochemical changes in a neurotransmitter pathway connected to the pineal gland, which controls the sleep/wake cycle, in those who got better after taking an antidepressant medication. The research was led by NARSAD Independent Investigator Grantee Rima Kaddurah-Daouk, Ph.D., whose team included NARSAD Grantees Ranga R. Krishnan, M.B., Ch.B., and John A. Rush, M.D. "This study revealed that the pineal gland is involved in mechanisms of recovery from a depressed state," said Dr. Kaddurah-Daouk, "and could help us to better target the right therapies for patients."
Source: *PLOS ONE,* July 17, 2013

What Parents Eat May Affect Children's Mental Health

Researchers at the University of Pittsburgh found that second-generation deficiencies of omega-3 fatty acids caused elevated states of anxiety and hyperactivity and affected memory and cognition in adolescents. The research team, led by Foundation Scientific Council Member Bita Moghaddam, Ph.D., worked with animal models. Dr. Moghaddam described their findings: "We found that this dietary deficiency can compromise the behavioral health of adolescents, not only because their diet is deficient but because their parents' diet was deficient as well. This is of particular concern because adolescence is a very vulnerable time for developing psychiatric disorders including schizophrenia and addiction."
Source: *Biological Psychiatry,* July 29, 2013

NARSAD Grantees at the Leading Edge:
A Quarter-Century of Groundbreaking Discoveries about the Brain's Plasticity

NARSAD Grantees and members of the Scientific Council of the Brain & Behavior Research Foundation have played a central role in a 25-year effort to prove the adult brain is highly "plastic"—that is, flexible in responding to life's experiences, both positive and negative.

The revolutionary discovery that the adult brain can add cells and change its circuit patterns has positive implications for the treatment of depression, post-traumatic stress disorder and other anxiety and mood disorders, and potentially all psychiatric disorders. It traces back, in part, to research performed in the 1980s in The Rockefeller University laboratory of Bruce McEwen, Ph.D., now a Foundation Scientific Council member. (See 'Interview with a Researcher' on pp. 5, 6).

Discovering "Neurogenesis" – the Birth of New Neurons in the Brain

Elizabeth Gould, Ph.D.
Professor of Psychology
Princeton University
1994 and 2006 NARSAD Grants
Foundation Scientific Council Member

Dr. McEwen's discovery in the late 1960s that stress hormones are active in a part of the brain called the hippocampus, important in learning and memory, led him and others toward the discovery of the adult brain's plasticity. Among his scientific "progeny" is Elizabeth Gould, Ph.D., who at age 26 started as a postdoctoral researcher in his lab.

Dr. Gould made a breakthrough in the late 1980s. In rodents, she removed the adrenal gland, which produces hormones in response to stress, and observed the impact on the animals' hippocampi (mammals have one hippocampus on each side of the brain). She saw evidence of cell death, which was expected. Yet when she counted cells in the small structures, the total didn't change even after the adrenal gland was removed. Later, as she explained, "I realized the brain *was making new neurons* to compensate for the ones that died."

In 1994, Dr. Gould used a NARSAD Young Investigator Grant to study the effects of stress hormones on cell birth in the adult hippocampus. She had another breakthrough in 1999, when she demonstrated that new cells in adult monkeys were being born in various cortical areas. Just a few months earlier, Fred H. Gage, Ph.D., a neuroscientist at The Salk Institute in California and a Foundation Scientific Council Member, had shown for the first time in the human brain that newly born neurons were present in the hippocampus throughout the full range of adulthood, from ages 19 to 92. Now known as a pioneer in stem-cell technologies that can generate new brain cells "on demand," Dr. Gage made history with that 1998 discovery.

> Later, as she explained, "I realized the brain *was making new neurons* to compensate for the ones that died."

Dr. Gould, meantime, has continued on her path of discovery. Her 2006 NARSAD Distinguished Investigator Grant has led to discoveries about how brain plasticity is affected by parenting. She is examining the impact of sex hormones on the brain in the postpartum period and the continuing impact of hormones on plasticity as parents are called upon to nurture their children. This work promises to improve the chances that children will receive the nurturing they need during the critical early years of life when the brain is more plastic and more vulnerable than at any other time in life.

Stress causes neurons to shrink or grow
...but not necessarily to die

Control
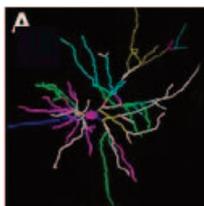
Chronic Stress
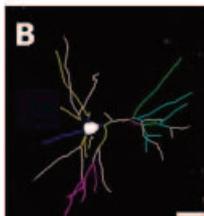
Medial prefrontal cortex and hippocampus

Amygdala, Orbitofrontal cortex

Images courtesy of Bruce S. McEwen, Ph.D.

Promoting the Brain's Natural Plasticity to Treat Psychiatric Illness

One major question about the plasticity of the brain concerns what the newly born cells of the adult brain actually do. Might they help the brain recover functions lost when stress or other adverse stimuli "damage" the brain?

This question has been addressed by two other NARSAD Grant-funded brain researchers: Ronald S. Duman, Ph.D., of Yale University, and René Hen, Ph.D., of Columbia University. Dr. Duman was curious about the six- to eight-week period that usually elapses before a person taking an antidepressant like Prozac® begins to feel better.

Dr. Duman realized that stress and depression might not just kill neurons; they might also prevent neurogenesis from taking place. Perhaps Prozac® stimulated neurogenesis and this explained the drug's therapeutic impact. And the lag? Those new neurons needed time to mature and become integrated into the circuits of the brain affected in depression.

Ronald S. Duman, Ph.D.
Professor of Psychiatry and Professor of Neurobiology and of Pharmacology
Director, Abraham Ribicoff Research Facilities
Yale School of Medicine
1989, 1997 and 2005 NARSAD Grants
Foundation Scientific Council Member

By 2000, Dr. Duman, who had received NARSAD Young Investigator and Independent Investigator Grants to support his research, and Dr. Hen, awarded a NARSAD Independent Investigator Grant in 1998, were separately on paths that would converge on the link between antidepressant treatments and neurogenesis.

When effective, Drs. Duman and Hen have found antidepressants do indeed spur neurogenesis in a part of the hippocampus called the dentate gyrus. Dr. Hen, backed in part by NARSAD Distinguished

René Hen, Ph.D.
Professor of Neuroscience
New York State Psychiatric Institute
Columbia University
1998, 2003, 2009 NARSAD Grants
Foundation Scientific Council Member

Dr. Hen, backed in part by NARSAD Distinguished Investigator Grants in 2003 and 2009, has recently published groundbreaking papers clarifying that antidepressants won't work unless new nerve cells are being generated in the hippocampus.

Remodeling of Neural Architecture or "Neuroplasticity"

Images courtesy of Elizabeth Gould, Ph.D.
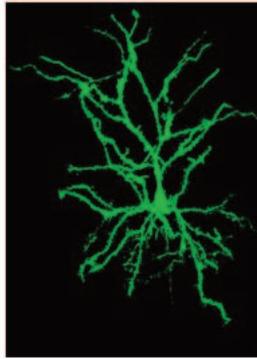
Dendrites
shrink and expand

Synapses
disappear and are replaced
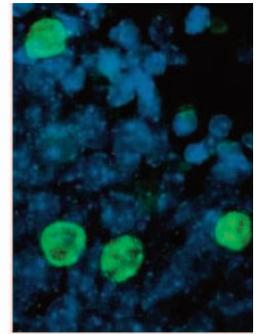
Neurogenesis
in the hippocampus

Investigator Grants in 2003 and 2009, has recently published groundbreaking papers clarifying that antidepressants won't work unless new nerve cells are being generated in the hippocampus. He and colleagues have also shown that antidepressants recruit new neurons to improve the response to stress, an indication of how the new cells enhance brain function.

Researchers funded by NARSAD Grants have also discovered other ways of enhancing the brain's plasticity. Regular exercise has been found to boost neurogenesis, including in older people in whom the natural birthrate of neurons is believed to be lower. It has also been demonstrated that new nerve cells come into being when a depressed or stressed person is placed in a supportive and enriching environment. Because of plasticity, regular socializing is a real boon for healthy brain function, and lowers the risk for depression.

A NARSAD Grant-funded scientist who has helped explain these beneficial effects in fine biological detail and tried to find new ways of exploiting them is Francis S. Lee, M.D., Ph.D., of Weill Cornell Medical College. Dr. Lee's two NARSAD Young Investigator Grants, in 2002 and 2005, followed by an Independent Investigator Grant in 2010, have supported research on a growth factor called BDNF (brain-derived neurotrophic factor), which supports the birth and growth of new brain cells.

Dr. Lee's work establishes that a common human genetic variant (called Val66Met) in the gene encoding BDNF produces a biological malfunction in the brain by generating genetically modified rodents with the human mutation. These mice tend to behave anxiously,

and they resist antidepressant therapy. In recent years, Dr. Lee has figured out that the mutation impairs a form of plasticity controlled by signal transmission at NMDA-type receptors on brain cells. These receptors are critical in modulating messages sent among neurons.

Dr. Lee's recent work on plasticity may explain changes in developmental and gender-based susceptibility to stress. BDNF and other nerve cell growth factors play very specific roles during early development, and later on, in response to sex hormone activity. Disturbances in their function may help explain differences in individual responses to stress. In 2012, he led a team that showed how the brain's plasticity is reduced during adolescence in parts of the prefrontal cortex that act to extinguish "fear" memories. This helps explain the risk-taking so common in young people. But Dr. Lee's new understanding of the underlying mechanisms of fear extinction also promises to help doctors improve the timing of therapies designed to help people who abnormally retain fear memories and suffer severe anxiety—for instance, those who suffer from post-traumatic stress disorder.

Francis S. Lee, M.D., Ph.D.
Vice Chair for Research
Department of Psychiatry
Weill Cornell Medical College
2002, 2005, 2010 NARSAD Grants
Foundation Scientific Council Member

Frequently Asked **Questions** on Brain Plasticity

Q What is neurogenesis and brain plasticity?

A The formation of new nerve cells is a process called neurogenesis—the birth of neurons. Brain plasticity (also called neuroplasticity) is the ability of the brain to respond to stimuli and stresses by remodeling its structure, function and connections. In the past, scientists believed that once a person reached adulthood, the brain remained static. But we now know that the brain has an extraordinary ability to adapt to new challenges. Research shows that the brain's plasticity can be increased, even in sedentary older people, if they exercise five days a week. Regular socializing also slows down normal cognitive decline.

Researchers have also found that when people recover from depression or anxiety with the help of selective serotonin reuptake inhibitor antidepressants and other treatments, new neurons form in the hippocampus (an area of the brain important to memory, learning and mood). This in turn promotes neuroplasticity.[1]

Q Can brain cells be regenerated?

A Scientists have believed that primate brains, including humans, do not restore or add new neurons after maturity. But in recent years scientists have made exciting new discoveries about the ongoing ability of the adult human brain to regenerate neurons and

to restore healthy function following so-called "damage" to the brain from various kinds of stresses. In 1998, Brain & Behavior Research Foundation NARSAD Grantee Bruce S. McEwen, Ph.D., demonstrated that the brain has a great deal of "plasticity"—that is, it can remodel its architecture and adapt to experience in an ongoing manner. Scientific Council Member Fred H. Gage, Ph.D., and colleagues also showed in 1998 that neurogenesis occurs in the human hippocampus—a brain area that is key to memory and learning and one that can play a role in the development of depression.[2]

In very exciting research just published this summer, NARSAD Grantee Kirsty Spalding, Ph.D., and team demonstrated that new neurons are formed in the adult human brain throughout life. They used an innovative methodology to quantify, for the first time, the number of neurons produced in adult humans. By carbon-dating neurons in postmortem brain samples, they discovered that more than one-third of neurons are regularly renewed through-out life—about 1,400 are added each day during adulthood. This rate declines only modestly with age. Hippocampus neurons also die each day, so the overall number remains more or less in balance.[3]

Q Can brain plasticity help relieve psychiatric or degenerative brain disorders?

A It has been established that stress can "damage" the brain, cause shrinkage in the hippocampus region and lead to the development of stress-related disorders, including depression. NARSAD Grant-funded researcher Ronald S. Duman, Ph.D., of Yale University has also demonstrated that in order for antidepressant treatment to be effective, the treatment must spur neurogenesis. In addition to antidepressant medication, regular exercise and social engagement have been found to promote the birth of new neurons.[4]

Another NARSAD Grant-funded researcher at Columbia University, René Hen, Ph.D., demon-strated that antidepressant medications recruit new neurons to improve "resilience" (the re-sponse to stress), an indication of how the new cells enhance brain function. Other NARSAD Grant-funded researchers are exploring the development of new treatments that can promote neuronal cell survival and synaptic plasticity for a broad range of psychiatric illnesses.[4]

Recent research at McLean Hospital and Harvard University Medical School show a very promising possibility for the future treatment of the "negative" symptoms and cognitive impairment of schizophrenia by improving neuroplasticity. Negative symptoms in schizophrenia include decrease in motivation, lack of attention and affect, memory loss and social withdrawal.[5]

Sources:
1   See "Interview with a Researcher," pages 5-6
2   Brain & Behavior Research Foundation 2012 Annual Report
3   See "Research Discoveries in the News," page 2
4   See Neuroplasticity Feature, pages 25-27
5   See "Research Discoveries in the News," page 3

With Persistence, Recovering from Depression

Staying the course to get the right treatments, and having lots of support, lets this man enjoy his family again

Twenty years ago, Steven Addlestone, then a recent graduate of Vanderbilt University Law School, had just begun his practice with a major Atlanta law firm and was newly engaged to his law school sweetheart. It was a time that should have been one of the happiest of his life. But seemingly out of the blue, he spiraled into a major depression that lasted four months. As his moods yo-yoed beyond his control, Steven went from one treatment to another without much success. It would be 12 years before his doctor was able to stabilize his symptoms.

What sustained him during those years and made it possible for him to function, if with difficulty, was the support he received from his family and colleagues who, he says, "understood what was going on and were willing to work with me." Now, at 44, having had no major relapses for the past seven years and feeling "really well," Steven holds a post as senior counsel at a Fortune 500 company in Tennessee, where he lives with his wife, Claire, and their teenage son and daughter. "Most importantly," he says, "I'm able to enjoy being with the family who supported me so much during the hard times."

Recently, hoping to help others who may not have adequate support, Steven signed on as a peer counselor in a program for members of his profession who are experiencing mental or emotional distress. "There's still a lot of stigma attached to mental illness," he says, "and often people don't seek treatment because they're embarrassed at having a 'weakness' they don't want to admit."

Steven was particularly fortunate that while still in Atlanta, when his worst crisis hit and his thoughts turned suicidal, he was treated at Emory University Hospital. There his journey to recovery finally began, jump-started by electroconvulsive therapy (ECT). "I responded well, and I have no doubt it saved my life," he says.

Steven and Claire, with their son Ethan and daughter Emily in Charleston, SC

Ethan, Steven and Emily in the Smokey Mountains

"There's still a lot of stigma attached to mental illness," he says, "and often people don't seek treatment because they're embarrassed at having a 'weakness' they don't want to admit."

In ECT, electrical currents are passed through the brain to trigger a brief seizure, which often works to ease the symptoms of depression when antidepressant medications fail. Unlike the "shock treatments" of years ago, today's ECT is painless and relatively free of side effects, but there can be some memory loss. In Steven's case, the treatment was effective, if short-lived. He had to return for additional ECT every couple of weeks. By the time he reached 100 sessions, his doctors became a bit concerned. "Every time we tried to stretch out the time between treatments," he says, "my depression recurred."

The doctor who finally came up with a mix of medications that allowed him to stop ECT was a young psychiatrist named Paul Holtzheimer, M.D., M.S., Associate Professor of Psychiatry at the Geisel School of Medicine at Dartmouth. Dr. Holtzheimer is a former trainee of Helen S. Mayberg, M.D., Professor of Psychiatry, Neurology and Radiology at Emory University School of Medicine, three-time NARSAD Grantee and Foundation Scientific Council member. Dr. Mayberg is widely regarded for her innovative work with brain imaging to identify depression pathology in the brain and develop new treatments to more effectively treat resistant depression. Dr. Holtzheimer received a NARSAD Young Investigator Grant in 2007 while working with Dr. Mayberg at Emory to further studies on an area of the brain called the subcallosal cingulate (or "Brodmann Area 25") that she identified as being involved in depression.

In addition to a combination of medications—the antidepressants fluoxetine (Prozac®) and buproprion (Wellbutrin®), the antipsychotic medication risperidone (Risperdal®), the anti-anxiety medication buspirone (BuSpar®) and the mood stabilizer valproic acid (Depacote®)—used to treat his depression, fluoxetine helps control Steven's symptoms of obsessive-compulsive disorder (OCD), which he is also addressing through

cognitive behavioral therapy, conducted via Skype with a therapist in Knoxville. The co-occurrence of more than one mental illness is not uncommon.

Steven now recognizes that he has had OCD symptoms since childhood, but, as he recounts with wry amusement, "I didn't know then that setting my alarm clock 100 times before I went to bed was anything unusual."

"We think the research is all so promising," Steven says. "We marvel how far research and treatment have come just since I started having my problems. It's really uplifting."

No one who has had experience with mental illness needs to be told that it's a family affair. Claire Addlestone was an up-and-coming corporate attorney when she put her career on hold to take care of her husband during his darkest days and to shoulder the lion's share of their children's early rearing. Today, she practices a very different kind of law, as a guardian *ad litem*, a court-appointed legal representative for neglected and abused children. In that role, she sees daily the ravages that parental stress and mental illness can inflict on families who lack the knowledge or resources to obtain appropriate diagnoses and help.

The Addlestones' support of the Brain & Behavior Research Foundation began for them with a very personal appreciation of the work of the NARSAD Grant-supported scientists at Emory.

"We think it [the research] is all so promising," Steven says. "We marvel how far research and treatment have come just since I started having my problems. It's really uplifting."

October 25, 2013
26th Annual National Awards Dinner
at The Pierre Hotel in New York City

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

The Brain & Behavior Research Foundation Honors
Those Dedicated to Improving the Lives of People with Mental Illness

Seven Outstanding Achievement Prizewinners
and Two Productive Lives Awardees to be Recognized

Each year, the Foundation recognizes outstanding leadership and contributions to mental health research with five annual prizes. Together these prizes are known as the **Outstanding Achievement Prizes** and are recognized by scientists as among the most prestigious honors possible in the field. The prizes are selected through a peer-review process of committees within the Brain & Behavior Research Foundation **Scientific Council**, a volunteer group of 147 pre-eminent mental health researchers.

The Lieber Prize for Outstanding Achievement
in Schizophrenia Research

The Lieber Prize was established in 1987 by Constance Lieber, Foundation President Emerita and Stephen Lieber, currently Chairman of the Foundation's Board of Directors.

The 2013 Lieber Prize recipient is **Marc G. Caron, Ph.D.,** the James B. Duke Professor of Cell Biology and Professor of Medicine and of Neurobiology at Duke University Medical Center. Selection Committee Chair William E. Bunney, Jr., M.D., describes Dr. Caron as "a remarkable scientist, who has published over 700 papers, including landmark studies relevant to schizophrenia, and is one of the most highly cited researchers in neuroscience and neuropsychopharmacology." Dr. Caron was drawn to the study of schizophrenia through a long-standing interest in the mechanisms controlling neurotransmission, the transmission of nerve impulses from a nerve cell to a target cell. Of particular interest with regard to schizophrenia is the system controlling the neurotransmitter dopamine, which he has studied in mouse models developed in his lab.

Among the landmark studies noted by Dr. Bunney, Dr. Caron and his colleagues identified a novel mode of signaling for the brain's dopamine D2 receptors, which are principal targets of antipsychotic medications. The team is now exploring whether the functional selectivity of the D2 receptor can be leveraged to develop more selectively targeted and effective antipsychotics.

A graduate of Laval University in his native Quebec City, Dr. Caron earned his Ph.D. in biochemistry at the University of Miami. After a postdoctoral fellowship at Duke he returned to Laval as an Assistant Professor in the Department of Physiology and then to the Duke University Medical Center faculty, where for a number of years he was a Howard Hughes Medical Institute Senior Associate and Investigator. A member of the Brain & Behavior Research Foundation Scientific Council since 2000, Dr. Caron received a NARSAD Distinguished Investigator Grant in 2005.

"Receiving the Lieber Prize for Schizophrenia Research is a tremendous honor not only for me but also for the many colleagues who contributed to the work we have accomplished over the years. This award celebrates the leadership of Constance (Foundation President Emerita) and Stephen (Chair, Foundation Board of Directors) Lieber, who have inspired a whole family of generous donors to support the Brain & Behavior Research Foundation to support mental disorder research for more than 25 years. This recognition is particularly humbling to me when I consider the immeasurable impact of the hundreds of millions of dollars that have been distributed in research support to several thousands of young and not-so-young neuroscience investigators worldwide in NARSAD Grants.

<div align="right">Marc G. Caron, Ph.D.</div>

The Colvin Prize for Outstanding Achievement in Mood Disorders Research
Established in 1993 and formerly known under the successive titles the Selo Prize, the Falcone Prize and the Bipolar Mood Disorder Prize, the Colvin Prize was renamed in 2012 in honor of the late Oliver D. Colvin, Jr., a longtime supporter who bequeathed the largest single contribution in the Foundation's history.

The Colvin Prize will be awarded this year to two recipients: **Boris Birmaher, M.D.**, of the University of Pittsburgh, and **Andrew A. Nierenberg, M.D.,** of Harvard University.

Dr. Birmaher has been treating and studying pediatric mood and anxiety disorders for more than 30 years and is currently involved in several National Institute of Mental Health (NIMH) investigations: a study of the course and outcome for adolescents with bipolar illness; a high-risk follow-up study of children of bipolar parents; and a longitudinal assessment of mania, aimed at evaluating the predictive value of early-onset manic symptoms in a large sample of children from six to 12 years old.

Dr. Birmaher is Professor of Psychiatry and holds the Endowed Chair in Early Onset Bipolar Disease at the University of Pittsburgh School of Medicine. He is Director of the Child and Adolescent Bipolar Services program at the Western Psychiatric Institute

Marc G. Caron, Ph.D.

2013 Lieber Prize for Outstanding Achievement in Schizophrenia Research

2005 NARSAD Distinguished Investigator Grantee

Boris Birmaher, M.D.

2013 Colvin Prize for Outstanding Achievement in Mood Disorders Research

and Clinic and is Co-Director of the Psychiatry Research Pathway for the training of residents in research. He is also a Visiting Professor at the University of Tel Aviv.

After receiving his medical degree from Valle University, in Cali, Colombia, Dr. Birmaher completed training in general psychiatry at Hebrew University Hadassah Medical Center, in biological psychiatry at Albert Einstein College of Medicine and in child psychiatry at Columbia University, New York Psychiatric Institute. He joined the University of Pittsburgh faculty in 1988.

In naming Dr. Birmaher, the Colvin Prize Selection Committee, chaired by Robert Post, M.D., cited his pioneering work in the description of the course and treatment of childhood onset bipolar disorder. "He has helped clarify many of the controversies surrounding the earliest presentations of the illness," said Dr. Post, and "he has played a leading role in major studies of psychosocial and psychopharmacological interventions for these children."

Dr. Nierenberg is Professor of Psychiatry at Harvard Medical School and Director of the Bipolar Clinic and Research Program and Associate Director of the Depression Clinical and Research Program at Massachusetts General Hospital, where he also co-directs the Education Unit of the Clinical Research Program. Recently, he was appointed Vice President for Research of the International Society for Bipolar Disorders.

Of Dr. Nierenberg's achievements, Dr. Post notes particularly his focus on new approaches to patients with difficult-to-treat depression, which affects up to half of people with depression, and about which Dr. Nierenberg has published more than 250 refereed articles and 60 review articles. Dr. Nierenberg helped establish treatment-resistant depression as a legitimate field for inquiry. In recent years, he has become particularly interested in children at risk for bipolar disorder and in the co-morbidity, or co-occurrence, of bipolar disorder with attention-deficit hyperactivity disorder, studies he has pursued with the support of two NARSAD Independent Investigator Grants.

Dr. Post also pointed to Dr. Nierenberg's leadership role in large-scale NIMH clinical trials, including the Systematic Treatment Enhancement Program for Bipolar Disorder and the Sequential Treatment Alternatives to Relieve Depression, both of which involved thousands of patients. Since 2005, Dr. Nierenberg has directed the NIMH Bipolar Trials Network and is principal investigator for the multi-site Lithium Moderate Dose Study on the comparative effectiveness of lithium with other medications. He is also principal investigator for a comparative study (Bipolar CHOICE) of lithium and a second-generation antipsychotic mood stabilizer, funded by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services.

Andrew A. Nierenberg, M.D.

2013 Colvin Prize for Outstanding Achievement in Mood Disorders Research

2000 and 2003 NARSAD Independent Investigator Grantee

> "The Brain and Behavior Research Foundation Colvin Prize for Bipolar Mood Disorder Research is an extraordinarily meaningful acknowledgement and recognition of the work my colleagues and I have done at the Bipolar Clinic and Research Program. The Colvin Prize affirms our focus on clinical trials of pharmacologic and psychosocial interventions to improve the lives of people with bipolar disorder. It is a great honor and will inspire me to continue to search for better treatments. — Andrew A. Nierenberg, M.D.

A graduate of the State University of New York at Buffalo, Dr. Nierenberg received his medical degree from the Albert Einstein College of Medicine of Yeshiva University in New York. He completed his internship and residency in psychiatry at New York University / Bellevue Hospital and studied clinical epidemiology at Yale University as a Robert Wood Johnson Clinical Scholar.

The Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research

The Ruane Prize was initiated in 2000 by philanthropists Joy and William Ruane to recognize important advances in understanding and treatment of early-onset brain and behavior disorders.

Jay N. Giedd, M.D., is the 2013 Ruane Prize recipient. Chief of the Brain Imaging Section at the NIMH Child Psychiatry Branch and Adjunct Professor of Family and Reproductive Medicine at The Johns Hopkins Bloomberg School of Public Health, Dr. Giedd is renowned for seminal studies in brain development that have helped explain why so many neuropsychiatric disorders emerge during adolescence.

For the past 22 years, Dr. Giedd has led a large-scale study with more than 3,500 participants to explore neurodevelopment in health and illness. His work combines brain imaging, genetics and psychological and behavioral assessments; data from his imaging study of twin children are helping explain the interactions of age, genetics and environment. His studies of people with atypical numbers of sex chromosomes are shedding light on why neuropsychiatric disorders of childhood differ between males and females in ages of onset, prevalence and behavioral symptoms.

Dr. Giedd's findings have spurred investigations around the world. His characterization of the neurobiology of the teen brain has influenced thinking in education, the judicial system and public policy. The Ruane Prize Selection Committee extolled not only his "groundbreaking" science but also a "national reputation for his unique ability to communicate these and other scientific advances to the general public."

Following undergraduate studies at the University of North Dakota, Grand Forks, where he graduated summa cum laude, Dr. Giedd earned his medical degree at the University of North Dakota School of Medicine in 1986. He completed his internship and residency in psychiatry at the Menninger School of Psychiatry, a residency at the Barrow Neurological Institute in Arizona and a fellowship in adolescent psychiatry at Duke University Medical Center.

> "After the initial shock and joy of being honored with this year's Brain & Behavior Research Foundation Ruane Prize, I have come to realize a deeper and more sustained fulfillment of feeling part of the Foundation family. It is incredibly gratifying and motivating to share the passion of alleviating the devastating impact of mental illness with such dedicated, competent, generous and caring people.
>
> Jay N. Giedd, M.D.

Jay N. Giedd, M.D.

2013 Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research

The Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience

The Goldman-Rakic Prize was created by Constance and Stephen Lieber in memory of Patricia Goldman-Rakic, Ph.D., a neuroscientist renowned for discoveries about the brain's frontal lobe, after her tragic death in an automobile accident in 2003.

Karl Deisseroth, M.D., Ph.D., is the 2013 Goldman-Rakic Prizewinner. He is the D.H. Chen Professor of Bioengineering and of Psychiatry and Behavioral Sciences at Stanford University and a Howard Hughes Medical Institute Investigator. In 2005, supported by a NARSAD Young Investigator Grant, Dr. Deisseroth developed a new technology called optogenetics that uses light to make neurons fire one at a time, giving researchers extraordinary control over specific brain circuits in living animals and enabling them to observe the impact on behavior. The technology offers a new level of precision necessary to identify the biology of brain and behavior disorders and is now in use at thousands of labs around the world. He and his team went on to develop another sophisticated new technology named CLARITY, announced in early 2013, that involves replacing the brain's fatty molecules with a clear hydrogel (such as that found in contact lenses) to render the brain transparent and enable 3-D imaging of the brain's internal cells, structures and connections.

In explaining the "groundbreaking contributions" of Dr. Deisseroth's achievements, Jack D. Barchas, M.D., Chair of the Goldman-Rakic Selection Committee stated that "a major goal of neuroscience has been to selectively control distinct groups of neurons in the brain in order to uncover brain 'circuits' that underlie animal and human behaviors. The development of these optogenetic techniques and the subsequent development of the CLARITY technique are sparking a revolution in neuroscience. Optogenetic technique application has already led to major breakthroughs in learning and memory research and increased our understanding of several neurological and psychiatric disorders."

A summa cum laude graduate of Harvard University with highest honors in biochemistry and molecular biology, Dr. Deisseroth earned a Ph.D. in neuroscience and an M.D. at Stanford, where he completed a residency in psychiatry in 2004 and joined the Stanford faculty.

> "I am tremendously honored to receive the Patricia Goldman-Rakic Prize from the Brain & Behavior Research Foundation. This recognition from my closest colleagues, and from the Foundation that supported my lab in the earliest stages, is personally meaningful and deeply moving—all the more so because we have taken very high-risk/high-payoff approaches in our work, including the development and application of the technologies of optogenetics and CLARITY. As both a psychiatrist and basic scientist, I continue to be pleasantly amazed by the long-term vision and dedication of the Foundation in supporting work of this type that is not directly applied, but instead may help lay the groundwork for fundamental insights into mental illness-related behavior.
>
> Karl Deisseroth, M.D., Ph.D.

Karl Deisseroth, M.D., Ph.D.

2013 Goldman-Rakic Prize for Outstanding Achievement in Cognitive Neuroscience

2005 NARSAD Young Investigator Grantee

The Sidney R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research

The Sidney R. Baer, Jr., Prize has been awarded since 2005 and is funded by the Sidney R. Baer, Jr., Foundation. This prize honors an exceptional young scientist or scientists selected by the current year's Lieber Prizewinner.

Dr. Caron, the 2013 Lieber Prizewinner, has selected **Kafui Dzirasa, M.D., Ph.D.,** and **Nikhil M. Urs, Ph.D.,** two gifted emerging scholars he has helped train.

Dr. Dzirasa is an Assistant Research Professor in the Department of Neurobiology and Assistant Professor in the Department of Biomedical Engineering at Duke University and Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center. He is also a Visiting Professor of Neuroscience at the Edmond and Lily Safra International Institute of Neurosciences of Natal, in Brazil.

In his research, said Dr. Caron, "Kafui uses the very exciting and innovative approach of ensemble of electrophysiological recording from multiple brain areas to functionally map brain circuits to determine how various genetic mutations that confer risk for neuropsychiatric illnesses in humans alter neuronal circuits that underlie cognitive and affective phenotypes when expressed in mice."

Dr. Dzirasa was a 2001 magna cum laude graduate in chemical engineering from the University of Maryland Baltimore County, where he studied under a prestigious Meyerhoff Scholarship. (He was featured on the CBS program "60 Minutes" in a segment about the Meyerhoff program.) Dr. Dzirasa received his M.D. and Ph.D. degrees at Duke, the first African-American to earn a doctorate in the Department of Neurobiology. He received the Somjen Award for Most Outstanding Dissertation Thesis, the Ruth K. Broad Biomedical Research Fellowship, the UNCF–Merck Graduate Science Research Fellowship and the Wakeman Fellowship.

In upcoming research, Dr. Dzirasa will be collaborating with Dr. Caron's laboratory to identify the functional circuits affected in mouse models currently being developed by Dr. Urs, a senior postdoctoral fellow in Dr. Caron's lab, and co-recipient of the Baer Prize.

Dr. Urs earned undergraduate and master's degrees at the University of Mumbai, in India, and a Ph.D. in molecular and cell biology at the Georgia Institute of Technology, in Atlanta. He joined the Caron lab in 2007, where he has been involved in developing genetically-engineered mice toward the goal of validating and developing the concept of functional selectivity at the dopamine D2 receptor. This receptor type is a prime target for antipsychotic medications. Dr. Urs's goal is to develop the basis for new, more selective and efficacious antipsychotics.

"Nikhil has now generated a whole new series of neuron-specific mouse knockouts of the beta-arrestin2 gene, which will be instrumental in our ability to test the function of the novel, functionally selective antipsychotics we are developing," Dr. Caron said. "Nikhil is also the individual in the group who is spearheading the *in vivo* characterization of novel functionally selective engineered dopamine D2 receptors, developed in our lab, by virally re-expressing these receptors in mice that have their own D2 receptors deleted. These animal models will provide unprecedented tools to understand the biochemical, cellular and circuit changes underpinning schizophrenia-like disorders."

Kafui Dzirasa, M.D., Ph.D.

2013 Sidney R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research

Nikhil M. Urs, Ph.D.

2013 Sidney R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research

PRODUCTIVE LIVES AWARDS

The Productive Lives Award, which began in 2009, has honored diverse individuals who have in common the resolve and resources to help people with mental illness live productive and meaningful lives.

Rodolpho Cardenuto is President of SAP Americas, the largest sales region of the world's leading enterprise applications software company that employs more than 64,000 people worldwide. SAP has established a forward-thinking program to hire people with autism spectrum disorder (ASD) who can "think differently and spark innovation." SAP recognizes the abilities of some people with ASD who possess extraordinary powers of observation, concentration, attention to detail and picture perfect memory. These traits enable the autistic employees to do tasks like identifying mistakes in software functionality quite efficiently. The program, already successfully piloted in India where people with ASD are employed as software testers, will expand to all of SAP's labs worldwide. Data show that one percent of the world population is autistic and SAP's goal is to reflect this diversity in its workforce by the year 2020.

Rodolpho Cardenuto

2013 Brain & Behavior Research Foundation Productive Lives Awardee

Bruce Cohen is the Academy Award-winning producer of SILVER LININGS PLAYBOOK, a new film directly addressing the challenges of living with mental illness. The film opens with Pat (Bradley Cooper), a young man with bipolar disorder, being released after many months in a mental institution to go live at his parents' home. He meets Tiffany (Jennifer Lawrence), a young woman living with depression and the other central character of the film, and a poignant and heartwarming story unfolds. Mr. Cohen is a film, television, and theater producer whose career has been distinguished by commercially successful productions addressing serious social issues, including "American Beauty," winner of the Best Picture Oscar in 1999 and "Milk," the 2008 film that told the story of Harvey Milk, the first openly gay person to serve in public office, who was assassinated in 1978.

Bruce Cohen

2013 Brain & Behavior Research Foundation Productive Lives Awardee
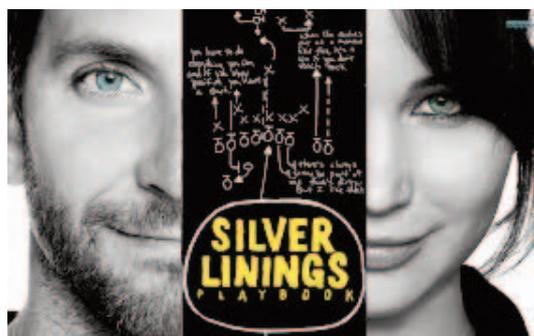
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Keynote Address: Living a Productive Life

Elyn R. Saks, J.D., Ph.D.
University of Southern California
Gould School of Law
University of California, San Diego
School of Medicine

Moderator

Robert M.A. Hirschfeld, M.D.
University of Texas Medical Branch

Commentator

Frederick K. Goodwin, M.D.
George Washington University Medical Center

MORNING SESSION:
OUTSTANDING ACHIEVEMENT PRIZEWINNERS

Integrated Approaches to Develop Improved Schizophrenia Therapies
Marc Caron, Ph.D., Duke University

Next Generation Neuropsychiatric Diagnostics and Therapeutics
Kafui Dzirasa, M.D., Ph.D., Duke University

Novel Approaches to Identify Functionally Selective Pathways in Schizophrenia and Antipsychotic Action
Nikhil Urs, Ph.D., Duke University

Groundbreaking New Technologies to Understand the Brain—in Illness and in Health
Karl Deisseroth, M.D., Ph.D., Stanford University

KEYNOTE ADDRESS:
Elyn R. Saks, J.D., Ph.D.

AFTERNOON SESSION:
OUTSTANDING ACHIEVEMENT PRIZEWINNERS

What Happens Over Time With Youth Who Have Been Diagnosed with Bipolar Spectrum Disorders?
Boris Birmaher, M.D., University of Pittsburgh

Gloria Neidorf Memorial Lecture

Making the Impossible Possible: The Challenges of Practicing Evidence-Based Psychiatry with a Focus on Bipolar Depression
Andrew A. Nierenberg, M.D., Harvard University

The Teen Brain: Insights from Neuroimaging
Jay N. Giedd, M.D., National Institute of Mental Health

YOUNG INVESTIGATORS

Specific Modification of DISC1 Protein as a Biological Predictor of Schizophrenia
Koko Ishizuka, M.D., Ph.D., The Johns Hopkins University

Therapies for Major Depressive Disorder – Enhancing the Brain's Metabolism
Paolo Cassano, M.D., Ph.D., Massachusetts General Hospital

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Glossary

amygdala (p. 6): An almond-shaped brain structure critical for processing memory and emotions, including fear.

brain-derived neurotrophic factor (BDNF) (p. 27): A growth factor that supports birth and growth of new brain cells.

buproprion (Welbutrin® and others) (p. 31): An antidepressant that works mainly by affecting the neurotransmitter dopamine.

CLARITY (p. 7): A sophisticated new technology that involves replacing the brain's fatty molecules with a clear hydrogel (such as that found in contact lenses) to render the brain transparent and enable 3-D imaging of the brain's internal cells, structures and connections. (Developed at the lab of Foundation Scientific Council member Karl Deisseroth, M.D., Ph.D.)

cognitive behavioral therapy (CBT) (pp. 4, 6, 31): A form of psychotherapy that helps patients correct maladaptive thoughts, emotions and behaviors. CBT was originally developed by Aaron Beck, M.D., to treat depression and has since been shown to be effective as a treatment for anxiety disorders, the negative symptoms of schizophrenia and other psychiatric illnesses.

cortisol (p. 5, 6): A hormone produced by the adrenal gland and released in response to stress.

deep brain stimulation (DBS) (p. 4): A "next generation therapy" for intractable depression in which an electrode inserted into the brain stimulates an area called the subcallosal cingulate or "Brodmann Area 25." (Developed with the support of NARSAD Grant funding by Helen S. Mayberg, M.D.)

dendrites (p. 6): Short extensions from neurons on which spine-like protrusions receive impulses from other nerve cells across the synapse. Dendrites can be destroyed by glucose overproduction, leading to a reduction in brain tissue volume; some studies have shown dendrite development can be restored with lithium treatment.

dentate gyrus (pp. 2, 6, 26): A subunit of the hippocampus. Reduced neurogenesis in this brain region is believed to be associated with depression, bipolar disorder, schizophrenia and some anxiety disorders.

electroconvulsive therapy (ECT) (p. 30): A procedure in which electric currents passed through the brain trigger a brief seizure that can ease the symptoms of depression when antidepressant medications are ineffective.

negative symptoms of schizophrenia (p. 3, 29): Decrease in motivation, lack of attention and affect, memory loss and social withdrawal are a few examples. Positive symptoms of schizophrenia are the hallucinations and delusions typical of a psychotic episode.

neuroplasticity (pp. 2, 3, 5, 6, 25, 28, 29): The ability of nerve-cell networks in the brain to physically adapt to changing conditions.

N-methyl-D-aspartate (NMDA) receptors (pp. 3, 27): Nerve cell receptors for excitatory neurotransmitters, mainly glutamate. NMDA receptor dysfunction may be linked to impaired brain plasticity, memory formation and the negative symptoms of schizophrenia.

optogenetics (p. 7, 35, 36): A new technology that uses light to make neurons fire one at a time, giving researchers extraordinary control over specific brain circuits in living animals and enabling them to observe the impact on behavior. Optogenetics offers a new level of precision necessary to identify the biology of brain and behavior disorders. (Developed with the support of NARSAD Grant funding at the lab of Foundation Scientific Council member Karl Deisseroth, M.D., Ph.D.)

positron emission tomography (PET) (p. 4): A brain-scanning technology that produces a three-dimensional image of brain processes.

prefrontal cortex (p. 6, 27): A brain region important in regulating complex thoughts, emotions and actions.

selective serotonin reuptake inhibitors (SSRIs) (p. 6, 9, 28): The most widely prescribed class of antidepressant medications, SSRIs exert their effect on the neurotransmitter serotonin.

serotonin (p. 6): A neurotransmitter, or chemical messenger of the nervous system, which, when improperly produced or regulated, is thought to be involved in a range of mental illnesses, including depression.

valproic acid (Depacote® and others) (p. 31): An anticonvulsant medication that is also used as a mood stabilizer in mental illness.

Women
Breaking the Silence
About Mental Illness

Decades ago no one would discuss breast cancer in polite company. Then women like First Lady Betty Ford broke the silence by speaking in public about her own diagnosis and treatment. In a conversation with journalist Ellen Levine, Ambassador Swanee Hunt will push back about the silence blanketing "mental illness." The Ambassador, Harvard University's Eleanor Roosevelt Lecturer in Public Policy, will share what she has learned by helping her daughter Lillian through years of struggle with brain illness. Ms. Hunt has taken her personal beliefs public to convince society to embrace change, discard shame and guilt, and shape policy.

Wednesday, November 13, 2013

Metropolitan Club
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Reception: 11:30 a.m.
Program / Luncheon:
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Ticket Price:
$250
per person

Join us for an intimate conversation with:

Ellen Levine
Editorial Director, Hearst Magazines

Ellen Levine made publishing history in October 1994 as the first woman to be named editor-in-chief of *Good Housekeeping* since the magazine was founded in 1885. During her tenure, she was instrumental in launching new titles at Hearst Magazines, including *O, The Oprah Magazine,* the most successful magazine launch ever. In May 2006, Ms. Levine was appointed editorial director at Hearst Magazines. Throughout her career in publishing, she has been recognized many times for outstanding achievements. Among her awards is the first annual Media Award by the American College of Neuropsychopharmacology for the numerous articles on mental illness she published in *Good Housekeeping.*

Ambassador Swanee Hunt
Advocate, Author and Philanthropist

Swanee Hunt has had a wide-ranging career in the arts, politics, journalism and mental health advocacy. Appointed by President Clinton as Ambassador to Austria from 1993-1997, a period that spanned the Balkan conflicts, Ms. Hunt has worked in 60 countries and is known internationally for her diplomatic leadership and efforts to achieve gender parity. In Colorado, she headed a successful reform of the mental health system, and served as co-director of Karis Community, a residential facility for adults challenged by mental illness. Currently, Ms. Hunt serves as Chair of The Institute for Inclusive Security and is the Eleanor Roosevelt Lecturer in Public Policy at Harvard's Kennedy School of Government.

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To bring the joy of living to those affected by mental illness—those who are ill and their loved ones.

HOW WE DO IT:
100% of all donor contributions for research are invested in NARSAD Grants leading to discoveries in understanding causes and improving treatments of disorders in children and adults, such as depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, and anxiety disorders like obsessive-compulsive and post-traumatic stress disorders.

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