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Dear Members of Our Foundation Community,

As I embark on my second year as Foundation President, I cannot help but feel a sense of awe and excitement as a witness to this truly unprecedented period in neuroscience. From learning how to enhance the brain's natural plasticity and capacity to adapt and repair throughout life, to a movement toward personalized medicine where an individual's genetic risk profile and potential to respond to treatments can be affordably identified, to exciting new neurostimulation therapies that correct malfunctioning in brain circuitry or metabolism, this is a time of unparalleled advancement in the knowledge of the brain and how to treat its illnesses.



In this issue of *The Quarterly*, we share some remarkable examples of next-generation therapies currently under development. These new approaches are shifting the paradigm toward a wholly new era in the treatment of mental illnesses. You will discover how Foundation-supported scientists are closing in on faster, more reliable antidepressants with fewer side effects, applying new knowledge about brain circuitry to improve treatments for schizophrenia and bipolar disorder, and working toward early intervention approaches that can stave off the development of illness. Across a broad range of psychiatric conditions, from autism spectrum disorder to post-traumatic stress disorder, new treatment approaches are being explored and advanced.

I am also very proud to present to you the newest class of NARSAD Distinguished Investigator Grantees. The funding of NARSAD Grants is only possible through the generous contributions of our donor community, and this year's selection is exceptional. Fifteen outstanding researchers were chosen from among two hundred applicants by a committee drawn from members of the Foundation's Scientific Council. Each grantee will receive an award of up to \$100,000 to pursue a new, unexplored area of inquiry.

In announcing the grants, Selection Committee Chair Jack Barchas, M.D., of Weill Cornell Medical College, said that the "importance of the Distinguished Investigator Grants of the Brain & Behavior Research Foundation cannot be overestimated. The Foundation can be very proud of its remarkable impact in so many ways, highlighted by this critical set of awards. It provides the equivalent of venture capital for extraordinary ideas and people."

Dr. Barchas' statement could be applied equally to all NARSAD Grants, and to the overarching mission of the Brain & Behavior Research Foundation—working toward a future in which mental illness is not only treatable and curable, but preventable.

Venture funding, by its nature, implies a calculated risk. We are confident—and our track record confirms—that our Scientific Council is extremely adept at choosing productive research proposals. Please continue to support the critical "capital" we offer to brilliant minds working to improve the lives of all those suffering from mental illness.

Thank you and my very best wishes for a happy and healthy 2014!

Jeffrey Borenstein, M.D.  
President & CEO

# Research Discoveries *in the News*



**Stephanie Dulawa, Ph.D.**

Associate Professor of Psychiatry and Behavioral Neuroscience  
University of Chicago  
2007, 2012 NARSAD Young Investigator Grants

## Potential New Class of Rapid-Acting Antidepressant

Depression is a major public health concern worldwide. According to the World Health Organization, it is the leading cause of disability worldwide. While there are current treatments available for depression, including psychotherapy, medications and brain stimulation techniques, many patients do not get relief from symptoms with the current options. The medications that are currently available can take weeks—sometimes months—to take effect, and only about half of patients respond to them.

“One of the biggest problems in the treatment of depression today is a delay in onset of therapeutic effects,” says Stephanie Dulawa, Ph.D. “There has been a great need to discover faster-acting drugs.”

In a paper published on October 29th in the journal *Molecular Psychiatry*, Dr. Dulawa and her team report on such a potential development. In a study supported by a 2012 NARSAD Young Investigator Grant, they found that when serotonin 2C receptors were selectively blocked in mouse models of depression, reduction in the animals’ depression-like behaviors

occurred within five days. While the most commonly used antidepressant medications affect signaling by serotonin, a neurotransmitter known to play a role in mood, the researchers here studied serotonin pathways previously shown to generate antidepressant effects but that had never been studied for how quickly symptoms were alleviated. Among the serotonin receptor subtypes the researchers studied, serotonin 2C receptors stood out in that regard.

In recent years, there have been intensive efforts to develop new medications that act with alternative mechanisms to those in the current antidepressant medications, and that act more quickly to alleviate symptoms. Among the pharmacological approaches developed to date, only ketamine and scopolamine have been shown to lift depression symptoms quickly. Ketamine is believed to work through the glutamate system in the brain and scopolamine interacts with cell receptors for the neurotransmitter acetylcholine. Both of these medications can have serious side effects and Dr. Dulawa believes that her team’s discovery may offer a safer alternative.

Serotonin 2C receptors normally inhibit the release of dopamine from certain neurons. Dopamine is another neurotransmitter commonly associated with mood. Dr. Dulawa thinks what is happening when 2C is blocked is that more dopamine is released into the medial prefrontal cortex of the brain. The researchers also observed that blocking serotonin 2C receptors induced classical markers of antidepressant action, none of which were induced by five days of treatment with the antidepressant citalopram (Celexa®), a selective serotonin reuptake inhibitor (SSRI). SSRIs are the most commonly prescribed class of antidepressants available.

Dr. Dulawa’s team is now investigating ways to block 2C receptors in clinical trials. The research team hopes this work will lead to the development of a new class of fast-acting antidepressant medications. ❖

### The Takeaway

NARSAD Young Investigator Grant supports research showing promise in the development of novel rapid-acting antidepressants.

## “Sleep to Forget:” A Potential New Way to Treat PTSD

It is well known that memories are consolidated and strengthened during sleep. 2010 NARSAD Young Investigator Grantee Asya Rolls, Ph.D., and colleagues at Stanford University, have shown that memories can also be weakened during sleep. They are using this finding as the basis for a potential new approach to alleviating symptoms of post-traumatic stress disorder (PTSD) and other psychiatric disorders involving painful memories. The team reported results of its experiments in a paper titled “Sleep To Forget: Interference of Fear Memories During Sleep,” published October 1, 2013 in the journal *Molecular Psychiatry*.

Many of the commonly used treatments for PTSD and other disorders triggered by traumatic or painful memories seek to modify the response to such memories, to render them harmless or less likely to cause pain, through a method called extinction therapy. To achieve memory extinction, the patient must first recall the traumatic event while in a safe environment such as a therapist’s office, and then learn to make new, safe associations with the memory, thus de-activating it as a fear trigger.

Because extinction therapy has the disadvantage of making the patient remember, and to varying extents, relive the original trauma, Dr. Rolls and team, working in the laboratory of Craig Heller, Ph.D. and Luis de Lecea, Ph.D., had the novel idea of manipulating the memories during sleep rather than during wakefulness. For their experiments, they used mice conditioned to feel fearful when exposed to a frightening cue—in this case a jasmine odor—to see whether the fear memory could be weakened while the animals were asleep.

The researchers succeeded in both strengthening the fear memory, and in an accompanying set of experiments, weakening it. They accomplished the latter by taking the mice already conditioned to experience fear when the odor was introduced in their cage and then treating them with protein synthesis inhibitor, or PSI, a substance that blocks natural processes that build new proteins. PSI was injected into a portion of the amygdala, a brain area known to be central in the processing of fear memories. The animals’ subsequent behavioral responses indicated that



**Asya Rolls, Ph.D.**  
Postdoctoral Fellow  
Stanford University  
2010 NARSAD Young Investigator Grant

the fear memory was weakened.

These findings demonstrate that specific fear memories can be selectively reactivated and either strengthened or attenuated during sleep, suggesting the potential for developing new, promising sleep therapies for human emotional disorders. Among the benefits that might result from therapies based on Dr. Rolls’ investigations is that patients would not have to re-experience fear in order to defuse it.

“We see this as proof of concept that memories can be manipulated during sleep and that such manipulation offers diverse therapeutic potential,” Dr. Rolls says, but, she cautions, “we must remember that there is still a long way to go until such therapy can be applied to humans. There are many challenges ahead.” ❖

### The Takeaway

NARSAD Grantee’s discovery offers potential to manipulate fear or traumatic memories during sleep to treat PTSD.



**Olivier Berton, Ph.D.**

Assistant Professor  
Department of Psychiatry  
University of Pennsylvania Perelman School of Medicine  
2001, 2005, 2008 NARSAD Young Investigator Grants

In research initiated with the support of a 2008 NARSAD Young Investigator Grant, Olivier Berton, Ph.D., led a team that has found what may be a new target for treating symptoms of depression: GABA neurons, nerve cells that produce GABA (gamma-aminobutyric acid), a neurotransmitter that inhibits the activity of other cells.

Dr. Berton and collaborator Sheryl Beck, Ph.D., of Children's Hospital of Philadelphia, published the results of their study August 28, 2013 in the *Journal of Neuroscience*.

At present, the most commonly prescribed antidepressant medications are SSRIs (selective serotonin reuptake inhibitors), which increase brain levels of serotonin, a neurotransmitter long known to play a key role in depression and other mood and anxiety disorders, including social phobia. Low levels of serotonin in the brain influence the way we perceive others and make us less prone to engage in social interaction. But SSRIs alleviate symptoms of depression in only about 50 percent of patients, for reasons that have not been understood.

## A Possible New Target for Treating Depression and Social Anxiety

In the reported study, Dr. Berton and his colleagues, including graduate student Collin Challis, exposed mice to short periods of aggression from "bully" mice. They then studied a subset of the mice that became excessively socially avoidant as a consequence of the bullying. Their behavior resembled behavior exhibited by people with affective disorders who withdraw when facing social pressures. In previous studies Dr. Berton has shown that these behavioral symptoms can be reversed by long-term treatment with antidepressants.

To understand what is happening in the brains of these mice as symptoms arise (or not), the researchers measured electrical and biochemical indices of neuronal activity. They found that in the extremely avoidant mice, a specific population of neurons located in the brainstem that release GABA, the main inhibitory neurotransmitter in the nervous system, entered an overly excitable state and began shutting down the activity of nearby serotonin neurons. In contrast, resilient mice that remained socially interactive did not exhibit this GABAergic sensitization (and sero-

tonin neurons were not shut down). The researchers then used the new technology optogenetics to temporarily silence the overactive GABA neurons and found that lifting the brake on the serotonin cells for periods that were precisely timed with the periods of bullying was sufficient to prevent development of avoidance symptoms.

"This is the first time that GABA neuron activity—found deep in the brainstem—has been shown to play a key role in the cognitive processes associated with social approach or avoidance behavior in mammals," Dr. Berton says. "The results point to a new direction to understand why current antidepressants, which are used to treat depression and social phobia, may not work for everyone and how to make them work better, by targeting GABA neurons that put the brake on serotonin cells." ❖

### The Takeaway

Studying the brain biology underlying social avoidance helps identify potential new target to increase effectiveness of antidepressants.

# Interview

with

## Carlos A. Zarate, M.D.

Chief, Section on the Neurobiology and Treatment of Mood Disorders,  
Chief of Experimental Therapeutics and Pathophysiology Branch,  
National Institute of Mental Health;  
Clinical Professor of Psychiatry and Behavioral Sciences,  
The George Washington University;  
1996 NARSAD Young Investigator Grant,  
2005 NARSAD Independent Investigator Grant,  
Winner of the Foundation's 2011 Bipolar Mood Disorder Outstanding  
Achievement Prize (renamed the Colvin Prize for Outstanding Achievement  
in Mood Disorders Research in 2012)

## Getting Patients Better, Quicker

### Dr. Carlos Zarate Carries the Torch Toward FDA Approval of Rapid-Acting Antidepressant

Why do we have to wait six to 12 weeks for an antidepressant medication to kick in, while patients may be contemplating suicide, losing their job and worrying everyone close to them, asks Dr. Carlos Zarate. Why can't everyone who suffers a major depressive episode get relief in an hour, or within a couple of hours or a few days, at most? If we can accomplish that, he says, "we can subtract from the cumulative time people spend in a depressed state, and thus limit depression's destructive impact on the brain and overall physical health."

Dr. Zarate, who studied to be a doctor in his native Argentina, received the first of his two NARSAD Grants in 1996. Foundation support enabled him to study ways of stabilizing patients with bipolar disorder. Then in 2001, he was

appointed to be an Investigator in the Mood and Anxiety Disorders program at the National Institute of Mental Health (NIMH).

In 2000, Foundation Scientific Council Members Dennis S. Charney, M.D., Dean of the Icahn School of Medicine at Mount Sinai, and John H. Krystal, M.D., Chair of Psychiatry at Yale School of Medicine (both of whom have had NARSAD Grant support) had described the astonishing effect of ketamine (Ketalar®) on seven depressed patients. Previously, ketamine had been used as an anesthetic. But when given to people with major depression, Drs. Charney, Krystal and colleagues found their symptoms were dramatically reduced within 72 hours. In some, the effect was virtually immediate. While there is not yet a clinically viable medication approved for this use by the U.S. Food and



Drug Administration (FDA), with Dr. Zarate's persistent and highly regarded clinical translational research, that milestone may well be met within a few years.

At first, he says, the report of ketamine's effectiveness seemed so unusual that "some people frankly didn't believe it." Ketamine could cause "dissociative" side effects—hallucinations and other psychotic-like symptoms—and it was a drug of abuse. How could it ever be used to treat depression? As a result, research on ketamine's antidepressant effect was largely abandoned.

Then, in 2006, Dr. Zarate, along with Dr. Charney and Hussein Manji, M.D., a Scientific Council Member and NARSAD Independent Investigator Grantee who was then in the NIMH Mood and Disorders program, reported positive results of a clinical trial in which ketamine



“You see people who have been depressed solidly for 30 years, and all of a sudden they feel they can work, they speak more confidently, as if a life-weight had been removed. These are quite exciting times!”

was given, not just to patients who had been diagnosed with major depressive disorder (MDD), but to those for whom other therapies had failed (“treatment resistant” patients who had tried on average at least six other antidepressants). The onset of response for these patients was within two hours. “Ever since, the field has moved rapidly forward,” Dr. Zarate says.

With continued NARSAD Grant support, Dr. Zarate was able to push his line of research further. He was able to demonstrate for the first time that patients with treatment-resistant bipolar depression can respond to ketamine within one hour. Subsequently, Dr. Zarate’s team was able to replicate this finding in bipolar depression. “The Brain & Behavior Research Foundation has had an important impact on my career and permitted me to pursue a line of research that will hopefully help the field in developing next-generation treatments for our patients that are more efficacious and work more rapidly than existing treatments.”

Dr. Zarate and his colleagues believed that if ketamine was given under carefully controlled hospital conditions, and to depressed people who had run out of treatment options, it might prove to be beneficial. “The

key in generating interest in the study of ketamine was when we replicated the 2006 results some time later, and then again in a third study,” says Dr. Zarate. “People really started believing in ketamine’s rapid antidepressant efficacy.” Then, in early 2013, a larger NIMH-funded study with ketamine in treatment-resistant depression was completed and essentially confirmed the results of these earlier studies.

Dr. Zarate’s work has moved to incorporate a diversity of technologies to identify biomarkers of response to rapid-acting antidepressants and to identify the neurobiological changes that are involved in this response. His group employs technologies such as structural and functional neuroimaging, genetics, polysomnography and electrophysiology studies in patients taking part in clinical trials who are being treated with ketamine and scopolamine (Scopace®). Also being studied are other medications that regulate the glutamate system, as does ketamine. These other medications appear to cause fewer or less severe side effects than ketamine, while still acting quickly to bring relief to patients with MDD. (See page 7.)

Dr. Zarate’s team and others have already begun to identify several biomarkers, which will become very im-

portant for developing other rapidly-acting treatments and possibly for personalizing treatments when such antidepressants become available for clinical use.

Further testing will offer more details on how the medications perform in different patient populations. For example, are there patients whose depressive symptoms are alleviated by ketamine but not by scopolamine and vice versa? How do the side effects of the two medications compare in different subgroups of patients?

“We know ketamine and scopolamine work rapidly in depressed people, and in people with treatment-resistant depression,” says Dr. Zarate. “It’s now a matter of understanding how they do this, and we are well on our way. These are not miracle drugs. Not everyone gets better. But when they do, it’s remarkable, dramatic.

You see people who have been depressed solidly for 30 years, and all of a sudden they feel they can work, they speak more confidently, as if a life-weight had been removed. These are quite exciting times!” ❖



## Developing Antidepressants That Go Beyond the “Serotonin Theory”

“It’s very likely that there are many different ways of getting an antidepressant response,” Dr. Zarate hypothesizes. For decades, most depressed people have been prescribed medications of the SSRI (selective serotonin reuptake inhibitor) class, such as fluoxetine (Prozac®) and others. One-half to two-thirds of patients don’t have a full response; those who do can wait weeks or months to see an effect. SSRIs affect levels of the neurotransmitter serotonin, which helps conduct messages between brain cells. Dr. Zarate says that some people might be biologically resistant to this form of therapy.

Research has shown that ketamine works through an entirely different mechanism than serotonin—in the glutamate neurotransmitter system. Ketamine blocks one of the key receptors for glutamate in brain cells, called NMDA receptors. “Ketamine causes a massive presynaptic release of glutamate,” Dr. Zarate explains, in part by activating other glutamate receptors, called AMPA receptors. Scopolamine also appears to have similar effects on glutamate release. Both medications appear to target the same protein within the brain cell called mTOR. So far, research has shown that this protein is crucial to the mechanism of both ketamine and scopolamine. Dr. Zarate believes the key to the rapid antidepressant response in ketamine and scopolamine is their ability to quickly increase plasticity, including the formation of connections between brain cells.

The big question is long-term safety. Even though ketamine is now being used in clinics around the country by experienced doctors, Dr. Zarate believes that long-term efficacy and safety studies are needed. Another problem is duration of the effect: relief from ketamine may last only a few weeks, and there is still not enough data on whether repeated doses are safe. This is why Dr. Zarate and others are working on substitutes for ketamine—similar molecules that modulate glutamate targets in other ways than ketamine, for instance. These other molecules appear to have milder effects, but may be longer lasting and safer. Meantime, the pharmaceutical industry has taken notice and is investing in rapid-acting ketamine-like compounds. Johnson & Johnson and AstraZeneca, among others, have ketamine variants in active clinical trials.

“These medications are not yet ready for prime time,” Dr. Zarate says, “but hopefully in several years, pending FDA approval, there could be a medication available for our patients.”

Dr. Zarate discussed his work when he won the Foundation’s Bipolar Mood Disorder Prize (now known as the Colvin Prize for Outstanding Achievement in Mood Disorders Research) in 2011. Watch the video at [bbrfoundation.org/prizewinner-zarate](http://bbrfoundation.org/prizewinner-zarate).

Watch Dr. Zarate’s ‘Meet the Scientist’ webinar from August, 2013 at [bbrfoundation.org/august-2013-webinar](http://bbrfoundation.org/august-2013-webinar).



“The Brain & Behavior Research Foundation has had an important impact on my career and permitted me to pursue a line of research that will hopefully help the field in developing next-generation treatments for patients that are more efficacious and work more rapidly than existing treatments.”

# Answers to Ask the Researcher

from

## Bruce S. McEwen, Ph.D.

Alfred E. Mirsky Professor, The Rockefeller University  
1998 NARSAD Distinguished Investigator Grant  
2005 Goldman-Rakic Prize for Outstanding Achievement  
in Cognitive Neuroscience  
Foundation Scientific Council Member



**Aside from physical exercise and socializing, which you mentioned in your article, are there other things a person can do to increase his or her brain plasticity? Do “brain games” have any effect?**

Besides regular physical activity and a supportive social network, it's also important to get adequate sleep and maintain a sensible diet. So-called “brain games” appear to be gaining some credibility, although the jury is still out. Probably the most important factor is “eudemonic well being”—that is, doing things that have meaning and purpose, including doing things that benefit other people such as volunteer activities like the Executive Volunteer Corps or the Experience Corps. Expanding one's mind by reading and engaging in enjoyable hobbies also provide relaxation and diversion. Studies now show that this is protective against dementia and has positive effects on physiology and brain function.

**If some people are inherently more able to bounce back from stress, can those traits be acquired by others, or is this just an ability people possess at birth?**

Resilience is an active process that helps one achieve positive outcomes in the face of adversity. Resilience is not a trait at birth but a foundational capacity of an individual. This capacity is built by positive factors in early life involving a nurturing and positive upbringing that fosters the development of healthy brain architecture and good self-regulatory skills.

**My sister lives with depression and seems to be having increasing issues with her memory as well. You say that stress and depression can “shrink” the brain. Can antidepressants and/or other treatments reverse that?**

Chronic depression is associated with shrinkage of brain areas that are involved in memory. Regular physical activity,

such as walking an hour a day, enlarges these brain areas and improves function—probably the best antidepressant of all!

**Can one be measured for brain plasticity and/or brain “damage” resulting from stress?**

Not really, except in cases of stroke or head trauma. Neuropsychological tests of memory and executive function are best to reveal deficits, which in many cases may be due to a sedentary life style and lack of adequate rest and may be reversible with physical activity, as I describe above.

**What are you most hopeful about in your research?**

The potential of harnessing brain plasticity and the power of behavior in changing brain structure and function, aided in some cases by pharmacological agents which will not do the job by themselves.

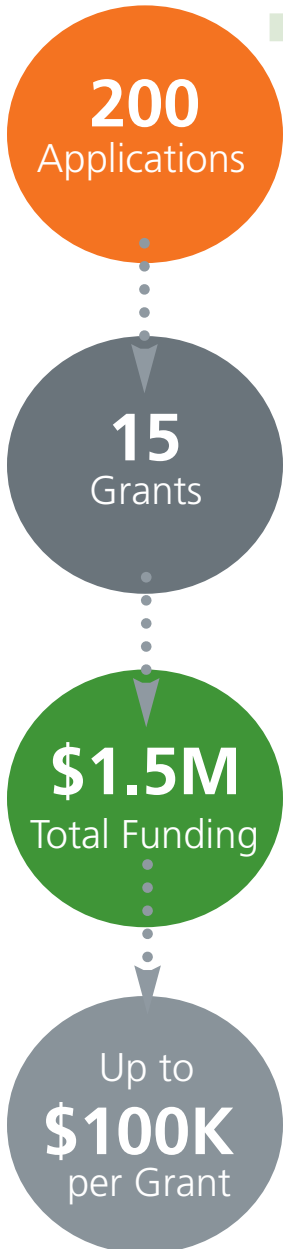
### Ask the Researcher

#### HAVE A QUESTION?

E-mail [asktheresearcher@bbrfoundation.org](mailto:asktheresearcher@bbrfoundation.org) with questions for **Dr. Carlos Zarate**, featured on pages 5 through 7. 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 Distinguished Investigator Grants in 2013



The NARSAD Distinguished Investigator Grants provide support for experienced investigators (full professor or equivalent) conducting neurobiological and behavioral research. One-year grants of \$100,000 each are provided for established scientists pursuing particularly innovative project ideas.

The current grantees were selected by members of the Foundation's Scientific Council, a volunteer group of 146 leaders in brain and behavior research. This year's 15 established investigators, selected from 200 applicants, include a number utilizing new technologies, such as advanced brain imaging, optogenetics and stem cell technology. Others will work toward identifying new targets for next-generation therapies, through greater understanding of genetic risk factors and dysregulation in brain circuitry. Yet another novel project aims to collect data on firearms injury and mortality among adults with schizophrenia, bipolar disorder or depression in an effort to spur public policy reform with regard to gun violence among the mentally ill.

**"An exciting aspect of the awards is the degree to which they either attempt to answer an important question or help to identify new potentially game-changing targets for treatment. Even in the best of funding times they have been extremely important ... Now they are absolutely essential for seed funding for new directions that would otherwise be impossible."**

Jack D. Barchas, M.D.  
Weill Cornell Medical College,  
Chair, Distinguished Investigator Grant Selection Committee,  
Foundation Scientific Council

### Also Awarded in 2013:

**NARSAD Independent Investigator Grants** to support mid-career scientists during the critical period between initiation of research and receipt of sustained funding: **40 grants awarded in March for \$4M**

**NARSAD Young Investigator Grants** to help researchers launch careers in neuroscience and psychiatry and gather pilot data to apply for larger federal and university grants: **200 grants awarded in August for \$11.8M**

NARSAD Grants fund **Basic Research** to understand what happens in the brain to cause mental illness

### BASIC RESEARCH

#### AUTISM SPECTRUM DISORDER (ASD)



**Eric Klann, Ph.D.**

New York University

Dr. Klann will test the hypothesis that exaggerated protein synthesis affecting a subpopulation of nerve cells called medium spiny neurons (MSNs)

may lead to ASD by causing synaptic dysfunction in the striatum region of the brain. Using mice models of ASD, the research will determine the subtype of MSNs that exhibit altered synaptic plasticity and identify their dysregulated proteins. The experiments should provide new insight into the molecular mechanisms linked to dysregulated protein synthesis in the striatum that results in the behavioral symptoms of ASD.



**Stuart A. Lipton, M.D., Ph.D.**

Sanford Burnham Medical Research Center

Dr. Lipton will follow up on evidence from his lab that some cases of ASD may result from interaction of genetic and toxic environmental factors.

Previously, the lab reported that a process that mediates nitric oxide called S-nitrosylation can regulate the activity of specific proteins that contribute to neurodegenerative conditions such as Parkinson's disease. The current goal is to determine whether many sporadic cases of ASD result in part from environmental factors that induce protein S-nitrosylation which mimics a relatively rare genetic mutation believed to cause ASD.

**This grant should allow us to look for a new pathway to neuronal synaptic damage in autism spectrum disorders that involves aberrantly oxidized proteins. These altered proteins may serve as biomarkers for the disease and could lead to new therapeutic strategies.**

Stuart A. Lipton, M.D., Ph.D.

#### SCHIZOPHRENIA



**Joel E. Kleinman, M.D., Ph.D.**

Lieber Institute for Brain Development

Dr. Kleinman will further his study of postmortem human brains, including fetal brains, in the search for the molecular biology of increased

risk for schizophrenia. One hypothesis about the molecular biology mechanisms by which genetic variation increases risk for schizophrenia involves expression of specific alternative transcripts critical for early brain development. Most of these alternative transcripts are common variants found widely throughout the population, making it possible for initial studies to be conducted

in normal postmortem human brain so as to then help pinpoint transcript changes that lead to schizophrenia.

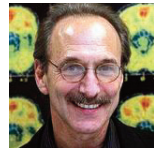
**This grant will allow our research group to use our postmortem human brains to elucidate the mechanisms by which genetic variation increases risk for schizophrenia.**

Joel E. Kleinman, M.D., Ph.D.

**Steven G. Potkin, M.D.**

University of California, Irvine

Dr. Potkin aims to achieve a more integrated understanding of schizophrenia by combining already collected data—from brain imaging, cognitive and clinical examination and DNA sequencing—with gene expression data from 180 schizophrenia patients and 180 healthy controls. In addition, he and his colleagues will investigate the role of the miR-137 locus, or gene site, and its genetic variant, which is believed to be involved in schizophrenia, in order to determine miR-137's functional role in the disorder.



#### MULTIPLE DISORDERS

**Charles D. Gilbert, M.D., Ph.D.**

The Rockefeller University

Dr. Gilbert will test a theory of brain-circuit interactions underlying re-entrant processing as a way of understanding behavioral disorders. Re-entry refers to a concept of how brain regions interact to interpret stimuli. Dr. Gilbert's theory involves disruption of normal brain interactions, and considers **schizophrenia and autism** "disconnection syndromes," whereby re-entrant signals between cortical areas are not operating properly. Instead, internally generated sounds, thoughts or movements, rather than being communicated within the brain as self-generated, are misidentified as coming from an external source.



**James L. Kennedy, M.D.**

Centre for Addiction and Mental Health,  
University of Toronto

Dr. Kennedy's study is based on the proposition that variants in mitochondrial genes increase susceptibility for major psychoses, and that **schizophrenia and bipolar disorder** may be, at least in part, due to the inability of neuronal mitochondria to keep up with the brain's energy demands. (Mitochondria are the cellular organelles responsible for energy production.) If so, identification of mitochondrial risk factors for these disorders should help shed light on the causes of psychosis and address the urgent need for new therapeutic targets.



NARSAD Grants fund **New Technologies** to advance or create new ways of studying and understanding the brain

## NEW TECHNOLOGIES

### ANXIETY



**Vadim Bolshakov, Ph.D.**  
Harvard University

Dr. Bolshakov will combine optogenetics with electrophysiological recordings and behavioral testing to address questions about the brain circuits of fear conditioning and fear extinction. Focusing on auditory fear conditioning, the research will investigate whether extinction is associated with synaptic plasticity, the ability of synapses to strengthen or weaken in response to changing conditions. The hypothesis of this research is that fear extinction may involve decreased efficacy in the system regulating transmission of the neurotransmitter glutamate from a region of the medial prefrontal cortex to targets in the amygdala, a brain center critical for processing memory and emotions, including fear.

**“The Foundation’s award will greatly enhance my ability to address important new questions about synaptic and neuronal mechanisms mediating fear-related behavioral processes.”**

Vadim Bolshakov, Ph.D.

### DEPRESSION



**Deanna M. Barch, Ph.D.**  
Washington University

Dr. Barch will integrate state-of-the-art neuroimaging with behavioral approaches to identify the risk trajectory for major depressive disorder in a group of pre-pubertal children whose mothers live with depression. Maternal depression is a highly predictive risk factor for children. The processes associated with depression likely influence brain development long before clinical signs appear, suggesting early childhood as a unique time window for preventative interventions. A co-investigator on the Human Connectome Project at Washington University, Dr. Barch uses equipment that will allow unprecedented high-resolution imaging of the children’s brain circuitry.

**“Receiving the NARSAD Distinguished Investigator Grant is an extremely important step in helping push forward what we believe is a very novel and important line of research to identify early predictors of risk for mood disorders in children.”**

Deanna M. Barch, Ph.D.

### SCHIZOPHRENIA

**Fred H. Gage, Ph.D.**

Salk Institute for Biological Studies

Dr. Gage will use stem-cell technology to probe the causes and underlying neuronal pathology of schizophrenia. Induced pluripotent stem cells engineered from non-stem cells obtained from schizophrenia patients and controls will be reprogrammed to become neurons. Applying this method, Dr. Gage and his team previously demonstrated deficits in neural connectivity and neurotransmission in schizophrenia, studies that also highlighted several genes and neuronal processes that may play a central role in the pathophysiology of schizophrenia.



**Vivian Hook, Ph.D.**

University of California, San Diego

Dr. Hook will model schizophrenia by means of human-induced pluripotent stem cells (hiPSC) differentiated into neurons. Her preliminary data show that schizophrenia hiPSC neurons show changes in amounts of secreted catecholamine neurotransmitters compared to normal controls and also that the antipsychotic loxapine (Loxitane®) reverses some of these changes. The project will assess the hypothesis that changes in profiles of secreted neurotransmitters occur in schizophrenia compared to controls and will also evaluate the effects of antipsychotic drugs on secreted neurotransmitter profiles.



**“Findings from this project will lay the foundation for defining new biomarkers and drug targets for future treatment of schizophrenia.”**

Vivian Hook, Ph.D.

**Douglas F. Levinson, M.D.**

Stanford University

Dr. Levinson will conduct studies of synaptic function in induced pluripotent cell lines created from cells taken from three schizophrenia patients with deletions in the neurexin-1 (NRXN1) gene and from matched controls. The aim is to characterize the phenotype, or specific traits, associated with NRXN1 deletions (loss of some of the genetic material) and schizophrenia. NRXN1 deletions are the only known single-gene mutation with a large effect on schizophrenia risk. The research should produce a profile of synaptic dysfunction in NRXN1 deletion carriers with schizophrenia.



**“With this award, I and my colleagues are hopeful that our work on reprogrammed cell models will provide critical information about the physiological mechanisms that underlie vulnerability to psychotic disorders.”**

Douglas F. Levinson, M.D.

NARSAD Grants fund **Next Generation Therapies** to reduce symptoms of mental illness and retrain the brain

### NEXT-GENERATION THERAPIES

#### BIPOLAR DISORDER



**Andrew A. Nierenberg, M.D.**

Harvard University

Dr. Nierenberg will conduct a clinical trial of a treatment for bipolar disorder based on a newer concept of bipolar pathophysiology. This concept proposes that bipolar disorder results from dysregulation of mitochondria, the structures in cells responsible for cellular energy production. Bezafibrate, a widely used anti-cholesterol medication, targets mitochondrial master switches called peroxisome proliferator-activated receptors. Dr. Nierenberg's study will assess the safety and tolerability of bezafibrate added to lithium for bipolar depression, especially with regard to worsening manic symptoms and suicidal ideation.

#### DEPRESSION



**Danny G. Winder, Ph.D.**

Vanderbilt University

Dr. Winder seeks to explore how ketamine treatment produces its rapid antidepressant effect. GluN2B-containing NMDARs in a brain region called BNST (bed nucleus of the stria terminalis) appear to be key sites for ketamine's antidepressant action. (NMDARs are receptors for the neurotransmitter glutamate and GluN2B is an NMDAR subunit.) In addition to glutamate, prior studies have also suggested an important role of the stress-related chemical corticotropin-releasing factor (CRF) in the BNST region. Dr. Winder will use optogenetic brain mapping in mice models to test whether ketamine produces antidepressant actions by GluN2B-dependent suppression of BNST CRF signaling, which would suggest new therapeutic targets.

#### DEPRESSION



**Jon-Kar Zubieta, M.D., Ph.D.**

University of Michigan

Dr. Zubieta will examine the neurobiology of the placebo effect in the treatment of depression. Recent research into the placebo effect in pain treatment has shown the endocannabinoid system to be among the brain systems involved, as reflected by the concentration of cannabinoid receptors (CBR1) in response to placebo. Hypothesizing that this response could cross diagnostic boundaries, Dr. Zubieta will study CBR1 involvement in antidepressant response in a clinical trial of placebo with a sample of unmedicated patients who have major depressive disorder.

**“This grant will allow us to examine for the first time novel markers associated with treatment responses in Major Depression and therefore advance our understanding of this devastating illness and potential new treatment options.”**

Jon-Kar Zubieta, M.D., Ph.D.

#### MULTIPLE DISORDERS

**Jeffrey Wallace Swanson, Ph.D.**

Duke University



Dr. Swanson's goal is to provide concrete information that will spur public policy reform with regard to gun violence among the mentally ill. His team will collect data on firearms injury and mortality, including firearms-related suicide and violence, among 23,000 adults with schizophrenia, bipolar disorder or depression, who received services in Florida's health care system between 2002 and 2012. Gun-disqualifying mental health adjudications and criminal disqualification from firearms will also be examined, as well as patterns of psychiatric hospitalization and outpatient mental health services and their effectiveness.

**“Receiving the 2013 NARSAD Distinguished Investigator Grant is a great honor, and will be a huge boost to my research program devoted to understanding the causes of violence and suicide in relation to mental illnesses in the population.”**

Jeffrey Wallace Swanson, Ph.D.

**“Now they [NARSAD Distinguished Investigator Grants] are absolutely essential for seed funding for new directions that would otherwise be impossible.”**

Jack D. Barchas, M.D.  
Chair,

Distinguished Investigator Grant Selection Committee,  
Foundation Scientific Council

# Fine-Tuning the Circuitry in the Brain and Intervening Early On: Exciting Next-Generation Treatment Possibilities

This is a time of great insight and creativity in brain and behavior research. With the invention of innovative technologies in genetics and brain imaging, new understanding about the brain's functioning and circuitry is now possible. These developments, along with studies offering a better understanding of the course of mental illnesses in different subsets of patients, are opening possibilities for a new generation of treatments.

Interestingly, many treatment approaches now coming of age are not pharmacological therapies. Some innovative investigators are studying treatments that share the objective of literally “putting energy back into the brain.” That is how **Kafui Dzirasa, M.D., Ph.D.**, winner of the Foundation's 2013 Sidney R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research, characterizes his work to repair malfunctioning brain circuits by using focused magnetic fields. **Paolo Cassano, M.D., Ph.D.**, 2012 NARSAD Young Investigator Grantee, is using light waves to treat people with depression.

“Schizophrenia is an illness that involves problems in communication, not in a single area but between different brain regions.”

Dr. Dzirasa says he and his colleagues at the Laboratory for Psychiatric Neuroengineering at Duke University are trying to “understand the brain's language,” which he likens to music. “We're trying to learn the timing and frequency of this music,” he says.

Taken together, all the billions of neurons in the brain and the countless circuits they form have an electrical output that Dr. Dzirasa compares to the sound of a symphony orchestra “if all the instruments were told to play notes without a score, at the same time.” To make music, a real orchestra's instruments have to sound at particular moments in time, for specific durations and at specific pitches and levels of intensity. “If all the instruments play without pattern, you lose the music,” he points out.

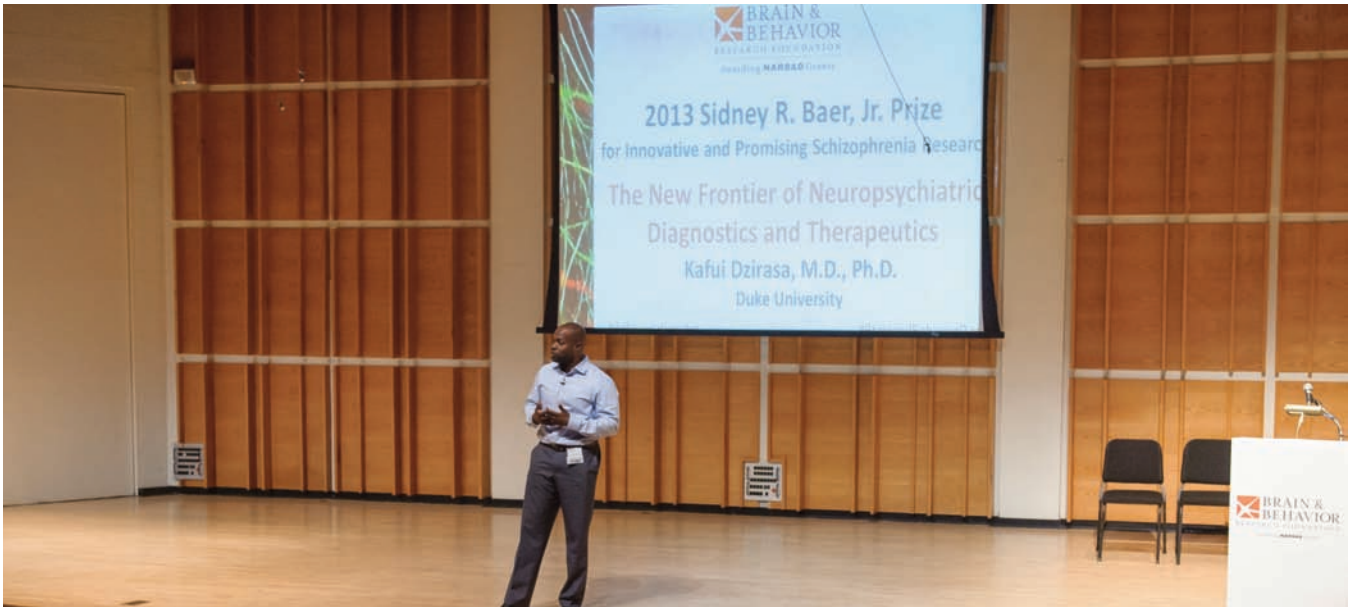
Dr. Dzirasa learns the patterns that form the brain's “musical line” by making electrical recordings in the mouse brain. He and his colleagues record more than a dozen brain areas simultaneously. The resulting data provide a baseline in healthy animals with which to compare patterns from the same areas in mice that have been genetically engineered to model a mental illness such as schizophrenia.



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

Dr. Dzirasa aims to develop “neural prosthetics”—electrical devices that act something like pacemakers in the heart, “putting energy back into the brain”—to fix gaps in communication.

“Schizophrenia is an illness that involves problems in communication, not in a single area but between different brain regions. We're looking to create a kind of codex, or a Rosetta Stone, that will enable us to relate changes in the functioning of illness-related genes to *places* in the brain where problems in communication are occurring,” Dr. Dzirasa explains.



Dr. Dzirasa addresses the audience at the Brain & Behavior Research Foundation 2013 New York City Mental Health Research Symposium

He aims to develop “neural prosthetics”—electrical devices that act something like pacemakers in the heart, “putting energy back into the brain”—to fix gaps in communication.

The idea of using pacemakers to aid broken brain circuits is not far-fetched. Other methods already in use have demonstrated the principle of applying electromagnetic energy to the brain to achieve therapeutic results. Some apply this energy from outside the body. Transcranial magnetic stimulation (TMS) is one such method, developed in the last decade by Dr. Mark George with NARSAD Grant support. It uses focused magnetic fields to therapeutically change electrical properties in particular brain regions. A non-invasive technique, it does not induce seizures, and in this respect is unlike a much older treatment called electroconvulsive therapy, or ECT. TMS has proven effective in some people with treatment-resistant depression and was approved by the FDA in 2008.

Deep brain stimulation (DBS), pioneered by Foundation Scientific Council Member Helen Mayberg, M.D., applies electrical energy, via a pacemaker-type device, to a very small area in the brain to treat patients with depression who have not responded to other treatments. It remains experimental and is an invasive approach, requiring surgery, but the results are promising for those patients without other treatment options.

At Massachusetts General Hospital, Dr. Cassano uses a kind of laser light, noninvasively, to treat people with depression. Light therapy has been used for many years

to treat people with seasonal-affective disorder. The light employed in such treatments is “white light” from the visible part of the spectrum. Dr. Cassano uses a special kind of light called near-infrared, generated by lasers. Patients who receive the therapy, which is carefully focused toward two brain areas, must wear protective glasses during treatment.

This treatment has proved to be safe and effective in experimental treatments of more than 400 people who have had a stroke.

Dr. Cassano explains that the depressed brain has an abnormal metabolism: PET imaging studies have shown that energy levels are abnormally low. A technique called magnetic resonance spectroscopy has also demonstrated that when depressed people recover, they have elevated levels of a molecule called NTP (nucleoside triphosphate), which helps cells produce energy.

Near-infrared light produced by the lasers Dr. Cassano uses penetrates the skin and bodily tissues, and their energy is absorbed inside cells by tiny structures called mitochondria. This additional energy, he theorizes, supplements glucose, brain cells’ main source of energy,



Paolo Cassano, M.D., Ph.D.





2012 NARSAD Young Investigator Grantee Paolo Cassano, M.D., Ph.D. explains how near-infrared light enhances the brain's metabolism at the Brain & Behavior Research Foundation 2013 New York City Mental Health Research Symposium

**“Depressed patients we have tested with near-infrared light maintain a better mood over time, have quicker reaction times, and retrieve memories more rapidly,” Dr. Cassano says.**

to yield antidepressant results in many patients. Near-infrared light also has been found to increase levels of BDNF (brain-derived neurotrophic factor) proteins, which spur the birth of new nerve cells and enhance the formation of synapses (connections between neurons).

“Depressed patients we have tested with near-infrared light maintain a better mood over time, have quicker reaction times, and retrieve memories more rapidly,” Dr. Cassano says.

**Boris Birmaher, M.D.**, of the University of Pittsburgh, winner of the Foundation's 2013 Colvin Prize for Outstanding Achievement in Mood Disorders Research, has focused his efforts on children with early signs of bipolar disorder (BP) and finding ways to delay the arrival of the full-blown illness.

After spending many years observing children, adolescents and young adults with BP, he has learned that it is very difficult to diagnose the illness in small children. As Dr. Birmaher points out, some of its hallmarks, such as “euphoria” and “irritability,” are concepts that don't mean anything to small children; unlike adults with BP, they are unable to report such symptoms.

Even when a diagnosis is made, treatment is especially challenging. Medications commonly used to manage the manic highs and frightening lows of adults with BP are powerful, have side effects, and are therefore problematic to use in the youngest patients—children who may be only six, seven, or eight years old.

Dr. Birmaher's novel approach to the problem emerged from a commitment he and colleagues at the University of Pittsburgh, University of California, Los Angeles, and Brown University made to closely follow a large group of children diagnosed with BP. The researchers were able to follow 367 children for at least four years after they enrolled in the study. Dr. Birmaher's insights about treatment emerged gradually, as the data from the study group trickled in over a decade.



Boris Birmaher, M.D.

Unlike most studies that focus on adults with BP, the scientists focused, not on the most ill children, but rather on those who fared the best. In fact, about 45 percent of the 367 children in the study were found, after four years, to be “doing well, or relatively well,



Dr. Birmaher speaks on early signs of bipolar disorder (BP) in youths and finding ways to delay the arrival of the full-blown illness at the Brain & Behavior Research Foundation 2013 New York City Mental Health Research Symposium

**"If we can delay onset, say, from age 10 or 12 to age 18 or 20, we will be giving children and their brains the chance to mature physically, emotionally, cognitively and socially."**

at least in terms of their bipolar symptoms," Dr. Birmaher says. Some of the children did have difficulties with other aspects of their functioning, but their BP was notably absent.

"The fact that nearly half the kids with BP were doing well is good news for families of kids who have bipolar," he says. "It is often assumed, from studies in adults, that bipolar disorder is 'forever'—once you have it, you will always have it. But based on our observations, this is not necessarily so."

Compared to those who fared poorly, children who were relatively symptom-free after four years had a later age-of-onset of illness; when symptomatic, the relatively symptom-free group experienced depressions that were less severe and manic phases that were less pronounced. They also had fewer suicidal thoughts, less history of sexual abuse, more stable families, and tended to come from the middle or upper classes.

The most important implications for treatment, says Dr. Birmaher, is that all efforts must be made to delay onset of the illness. "If we can delay onset, say, from

age 10 or 12 to age 18 or 20, we will be giving children and their brains the chance to mature physically, emotionally, cognitively and socially." To some degree, being more developed in these ways appears to be protective and predictive of a better outcome.

How to delay the onset of BP is not clear-cut. Dr. Birmaher points to things we do know how to do: involve symptomatic children as early as possible in psychotherapy and give them medications where indicated. Efforts also must be made to treat family pathology, especially ongoing family discord and sexual abuse. Substance abuse or untreated attention-deficit hyperactivity disorder, in addition to chronic family dysfunction, can cause chronic stress and destabilize a vulnerable child's mood. Whenever possible, these issues must be addressed.

Dr. Birmaher is encouraged by the research findings. Even in young children who will go on to develop BP, he says, simply delaying the arrival of the full-blown illness seems to make it much more likely that as young adults they will be among the 45 percent who appear either to recover within a few years, or enjoy a long remission that could last many years. ❖

### The Takeaway

The Foundation supports novel approaches to better treat mental illness, including electromagnetic techniques and interventions to delay onset of illness.

# The Power of Partnership

## A Personal Connection



My son's long and heartbreaking struggle with mental illness began when he was barely in his teens (see our Family Story on page 20). Four decades later, I am profoundly grateful for the treatments now available that are making it possible for him to enjoy a more fulfilling and productive life. Over the years, through my participation in the Foundation's Research Partners Program, I have had the opportunity to view up close how brilliant young neuroscientists conduct the search for solutions to brain dysfunctions. It has filled me with optimism that mental illness can and will be conquered.

Ms. Martha ("Marty") Atherton has Research Partnerships with NARSAD Grantees Peter G. Enticott, Ph.D. of Monash University, Stephanie L. Barrow, Ph.D. of the University of California, Davis, James C. McPartland, Ph.D. of Yale University and Marjorie Solomon, Ph.D. of the University of California, Davis.



**Uniting  
Donors**

**with**

**Researchers**

## How the Research Partner Program works:

- Select a scientist in your area of interest, at a particular institution or in a specific geographic region
- Develop a relationship with your scientist and learn more about their work through personal communications
- Receive progress reports that outline their research findings
- Have your support recognized in published work resulting from the research

# Frequently Asked Questions on Next Generation Therapies



What are some of the latest improvements in treatment of depression?

**Rapid-acting Antidepressants:** For several years now, mental health researchers have been studying new rapid-acting antidepressants such as ketamine (Ketalar®) and scopolamine (Scopace®) to treat severe depression. The benefit of these medications is that they treat depression symptoms in hours as opposed to weeks, as is typical for most antidepressants currently available. NARSAD Grants have supported several of these studies and it is now anticipated that there will be a new medication ready for patients within the next several years based on this work.<sup>1</sup>

Stephanie Dulawa, Ph.D., at the University of Chicago, has discovered a different biological mechanism that may offer a new target for fast-acting antidepressant medications. With NARSAD Grant support, she studied different subtypes of serotonin receptors and found that when 2C receptors were selectively blocked in mice, a reduction in depression-like behaviors in five days was observed. This compared to a minimum of two weeks to take effect for a control antidepressant medication.<sup>2</sup>

**Neuromodulation:** Mark S. George, M.D., of the Medical University of South Carolina, developed transcranial magnetic stimulation (TMS) for treatment of resistant depression with the support of NARSAD

Grant funding, and received FDA approval for its use in 2008. The technique uses electrical and magnetic stimulation to modulate brain circuits and change brain activity.

Helen S. Mayberg, M.D., of Emory University, with her first NARSAD Grant 20 years ago, identified the subcallosal cingulate—or Brodmann Area 25—as a locus of pathology in depression. She went on to pilot the use of deep brain stimulation (DBS) to target Area 25 with further Foundation support and this technique is showing promise in clinical trials for the treatment of resistant depression.

Cognitive computer brain training is also being developed to correct malfunctions in brain signaling and is showing promise to treat the cognitive symptoms of schizophrenia. The Foundation has supported several investigators in this area.<sup>3</sup>

## Q Can electrical stimulation improve cognition in people living with schizophrenia and bipolar disorder?

A method called transcranial direct current stimulation, or tDCS, has already been used to help stroke victims recover, and has been studied in patients with Alzheimer's and Parkinson's diseases. tDCS is a non-invasive technique in which a very weak direct electrical current is passed through the cerebral cortex via electrodes placed on the scalp. Donel M. Martin, Ph.D., of the University of New South Wales, who used a 2010 NARSAD Young Investigator Grant to conduct studies with tDCS, says the method "can potentially help the brain to relearn through facilitating local brain activity and inhibiting competing brain regions." More studies are needed to determine if cognition related to psychiatric illness can be improved beyond the treatment sessions themselves.<sup>4</sup>

## Q Can brain scans guide treatment for depression?

A Psychiatric brain imaging has confirmed the biological nature of many psychiatric illnesses over the past twenty years. Yvette Sheline, M.D., in the mid 1990s, used functional magnetic resonance imaging (fMRI) to identify structural brain changes in depressed patients and established depression as a brain disease.<sup>5</sup>

Using positron emission tomography (PET) scan images, Dr. Helen Mayberg of Emory University identified, in 2013, specific brain activity that can potentially predict whether people with major depressive disorder will best respond to an anti-depressant medication or psychotherapy. This important new work offers a first potential imaging biomarker for treatment selection.<sup>6</sup> A team of researchers including NARSAD Grantees Stefan G. Hoffman, Ph.D., of Boston University and Frida E. Polli, Ph.D., of Massachusetts Institute of Technology have used brain imaging to predict the success of cognitive behavioral therapy, a specific type of talk therapy often used to help treat a wide range of mental illnesses including anxiety disorders, depression and schizophrenia.<sup>7</sup>

J. John Mann, M.D., a 2008 NARSAD Distinguished Investigator Grantee, is using brain-imaging methods to study suicidal behavior. He and his team have found specific and consistent changes in the brains of people who died by suicide. They are testing depressed patients to see whether the same changes are visible in brain scans of living people.<sup>8</sup>

### Sources:

- <sup>1</sup> See "Interview with a Researcher," pages 5-7
- <sup>2</sup> See "Research Discoveries in the News," page 2
- <sup>3</sup> See *The Quarterly*, Fall 2012, page 2 and Winter 2013, page 7
- <sup>4</sup> See "New Treatments/Therapies," page 22
- <sup>5</sup> *Proceedings of the National Academy of Sciences*, April 1996
- <sup>6</sup> *JAMA Psychiatry*, June, 2013
- <sup>7</sup> *JAMA Psychiatry*, January, 2013
- <sup>8</sup> See *The Quarterly*, Spring 2013, page 10

# Inexpressible Gratitude

A mother beams as her son, living with Asperger's syndrome and schizophrenia, courageously lives his dream to become an inventor

John Atherton is a 53-year-old electronics whiz and inventor living in Portland, Oregon. At the time of this writing, he was busy preparing a prototype of one of his inventions for presentation to potential investors at the Consumer Electronics Show, held every January in Las Vegas. The device, one of several he has patented, is a hand-held voltage indicator that determines whether a power cord is alive or dead.

John also lives with schizophrenia and Asperger's syndrome (an illness "on the spectrum" of autism). His mother, Martha Atherton, explains that it took years for John to get the right combination of medications to alleviate his debilitating symptoms. She has been his unwavering supporter and a trusted companion during many dark periods when John questioned whether his life was worth living. Today, Martha plans to join John at the convention in Las Vegas and can hardly contain the pride she feels in her son's success.

Martha, John and the rest of the Atherton family have faced what seems like more than a family's fair share of hardship. A happily married couple, Martha and Robert Atherton worked side-by-side at Robert's successful company in Chicago for more than 50 years until his death in 2009. They had three sons, and lost two of them to cystic fibrosis. John, the middle son, began showing signs of psychiatric illness in his teens.

John never knew his older brother, who died in early childhood, but he was very close to his younger brother, whose death at age 12, when John was 14, triggered a severe depression. John was later diagnosed with



John Atherton with one of several inventions he has patented—a hand-held voltage indicator that determines whether a power cord is alive or dead.

John wanted to challenge himself, to do “something that would express my creativity.”

schizophrenia. Although he had shown some early signs of difficulty with socialization, he was in his late thirties before he was also diagnosed with Asperger's syndrome.

As is often the case in children with Asperger's, John was an outstanding student. He tried to cope with the loss of his brother by burying himself in his books. Toward the end of high school, he says, “I began to unravel.” John struggled through three years of electrical engineering studies at the University of Illinois, but could not complete his degree. By that time, he says, “I was down and out. I thought about suicide.”

After a long and agonizing period marked by disappearances from home, hospitalizations and trial-and-error treatments, he finally found some relief with the antidepressant fluoxetine (originally sold as Prozac®). Today, John is stabilized on a combination of antipsychotic and antidepressant medications.

John had moved to Portland when he was 18, drawn by its mountains, which he used to love climbing. He has lived there on and off ever since, returning to Illinois to attend college and for other brief periods. He gradually put on a great deal of weight, which can be a side effect of some of his medications, and had a near-fatal fall while leaping to safety as his house went up in flames. John was bedridden for two years with multiple fractures and still has trouble walking more than short distances.

During his extended recuperation, John became determined to turn his life around. He realized that what he wanted most was to challenge himself, to do “something that would express my creativity.” Inventing,

which he now pursues full time, has filled a “great inner void.”

As for Martha, it is hard for her to articulate the pride she feels in her son's courage and the joy she shares in his success as an inventor.

Although his family has seen to it that he is financially secure, John is eager for his inventions to pay off—partly for his own self-satisfaction, but mainly, he says, to be able to help others. From his own struggles with mental illness, he has great compassion for others' suffering, particularly for homeless people. Having learned from his parents' example of philanthropy and charitable giving, John supports the Portland Rescue Mission that offers services for the homeless. Like his parents, he supports cystic fibrosis research and donated all the funds raised when he climbed Mount Denali in Alaska in memory of his brothers.

As for Martha, it is hard for her to articulate the pride she feels in her son's courage and the joy she shares in his success as an inventor. She and her late husband are longtime supporters of the Brain & Behavior Research Foundation, through which she says she has developed a better understanding of autism and schizophrenia and a strong conviction that research will eventually lead to the alleviation of suffering caused by mental illness. She says the Foundation “is a blessing in her life” and she knows the treatments John eventually found have helped save his life. For that, no gratitude can possibly be adequately expressed.

# "Healthy Minds" TV Series

Healthy  
minds

The initial results of a PBS-WLIW  
December 2013 viewer survey rate

**"Healthy Minds"**  
the most-loved show!



**Hosted by**  
**Jeffrey Borenstein, M.D.**  
President & CEO  
Brain & Behavior Research Foundation

### **Featuring:**

Crucial mental health topics through in-depth interviews with the foremost experts on brain science and prominent voices in mental health advocacy

Visit [bbrfoundation.org/TVstations](http://bbrfoundation.org/TVstations) to find a listing of local stations airing "Healthy Minds"

### **Examples of guests include:**

Nobel Prize winner Eric Kandel, M.D.; Former Chairman of the Joint Chiefs of Staff Admiral Michael Mullen (U.S. Navy, Retired); Brain & Behavior Research Foundation Scientific Council Members, Board Members, Prizewinners and NARSAD Grantees

### **Topics:**

Program topics range from early warning signs to prevention strategies to breakthrough treatments for a broad range of mental illnesses

**WLIW21**

"Healthy Minds" is produced by WLIW21 for WNET New York Public Media.

## New Treatments/Therapies

### **Can Fast-Acting Antidepressants Also Reduce Anxiety?**

Important progress has been made on the development of a medication that can quickly alleviate the symptoms of both depression and anxiety. Known as RS67333, this medication shows a therapeutic effect in animal models after only seven days of treatment. Scientists found that the rapid-acting anti-anxiety effects of RS67333 do not depend on the birth of new neurons, suggesting that it acts in a previously unknown way. The team of researchers was led by two-time NARSAD Distinguished Investigator Grantee René Hen, Ph.D., of Columbia University, and included NARSAD Young Investigator Grantee Denis J. David, Ph.D.

**Source: *Neuropsychopharmacology*, November 28, 2013**

### **Oxytocin May Help Treat Autism**

Researchers at the Yale Child Study Center—former NARSAD Grantees Professor James F. Leckman, MD., and Assistant Professor Ruth Feldman, Ph.D.—found that brain areas involved in empathy and reward (less active in children with ASD) showed more activity after taking oxytocin (Pitocin®) than placebo. It appears that oxytocin reduced certain symptoms of the disorder, temporarily normalizing activity in areas of the brain known to have atypical activity in children with ASD. These findings show that oxytocin can stimulate brain activity, providing some evidence that these brain regions may not be irrevocably damaged in children with ASD.

**Source: *Proceedings of the National Academy of Sciences*, December 2, 2013**

### **Electrical Stimulation May Help in Schizophrenia, Bipolar Disorder**

Tests have shown that a non-invasive technique called transcranial direct current stimulation, or tDCS, may be able to enhance the brain's working memory, processing speed, executive function and reaction time, all of which can be diminished in mental illnesses such as schizophrenia and bipolar disorder. According to Donel M. Martin, Ph.D., of the University of New South Wales, who studied tDCS using a NARSAD Young Investigator Grant, the method "can potentially help the brain to re-learn through facilitating local brain activity and inhibiting competing brain regions." Dr. Martin and his colleagues conclude that the benefits of tDCS may extend beyond the improvements observed during treatment sessions.

**Source: *International Journal of Neuropsychopharmacology*, October, 2013**



# What Would You Give to Have a World Without Mental Illness?

The Brain & Behavior Research Foundation is a driving force in advancing what is known about mental illness and how to better treat, prevent, and ultimately cure it.

A few examples of research progress in 2013 include:

- **CLARITY**, a new technology developed at the lab of Dr. Karl Deisseroth at Stanford University, enables researchers for the first time to image a whole, intact brain in three dimensions and obtain a virtually transparent view of its inner structure. Dr. Deisseroth and his team also developed the groundbreaking technology “optogenetics” with the early support of a NARSAD Grant.
- NARSAD Grantee Dr. Kirsty Spalding of Karolinska Institutet in Sweden, used an innovative methodology to **quantify the number of brain cells renewed throughout human life**. Researchers were able to identify the “birth date” of neurons in deceased human brains and found that more than one-third of neurons are regularly renewed throughout life.
- The discovery of a **potential root cause of depression**—two-time NARSAD Grantee Dr. Marina Picciotto and team at Yale University uncovered the importance of a signaling system in the brain not previously believed to be central in causing depression. This opens the possibility to treat the cause of depression and not just its symptoms.
- New treatment approach shows potential to **reverse symptoms of schizophrenia** and restore healthy brain function in adult animal models. Research led by two-time NARSAD Grantee Dr. Joseph T. Coyle of Harvard Medical School offers the possibility that D-serine, a simple compound that boosts signals of the brain chemical glutamate, may be able to remedy debilitating symptoms of schizophrenia.

Please support the **cutting-edge brain research** supported by NARSAD Grants. As always **100% of your donation will go directly to fund research** thanks to the far-sightedness of two family foundations that underwrite operational expenses at the Foundation.



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# New York Mental Health Research Symposium

On Friday, October 25, 2013, the Brain & Behavior Research Foundation held its 25th Annual New York Mental Health Research Symposium at The Kaufman Music Center in New York City. Seven 2013 Brain & Behavior Research Foundation Outstanding Achievement Prizewinners and two especially promising NARSAD Young Investigator Grantees reported on recent innovations and insights that are revolutionizing the ability of neuroscientists to explore the brain and apply new information to prevent or reverse the course of mental illness. The following summaries are from three of the Outstanding Achievement Prizewinners who presented.

## Integrated Approaches to Develop Improved Schizophrenia Therapies



Dr. Caron

*From the Chair of the Lieber Prize Selection Committee:*

Dr. Caron is a remarkable scientist. He has published over 700 papers, including landmark studies relevant to schizophrenia, and is one of the most highly cited researchers in neuroscience and neuropsychopharmacology.

William E. Bunney, Jr., M.D.  
Distinguished Professor  
and Della Martin Chair,  
Department of Psychiatry  
and Human Behavior  
University of California, Irvine

### Marc G. Caron, Ph.D.

James B. Duke Professor of Cell Biology  
and Professor of Medicine and of Neurobiology  
Duke University Medical Center

**2013 Lieber Prize for Outstanding Achievement in Schizophrenia Research**  
Brain & Behavior Research Foundation Scientific Council Member  
2005 NARSAD Distinguished Investigator Grant

The symptoms of schizophrenia have been managed for the past half-century through the use of antipsychotics, but the medications that currently exist are not adequate to treat all the symptoms of this complex disease and they also have serious side effects. All clinically effective antipsychotics block the actions of the neurotransmitter dopamine by interacting with dopamine D2 receptors, which are members of a large family of proteins, called G protein-coupled receptors (GPCR). Activation of a GPCR by a neurotransmitter generates a cellular signal and response that is rapid and robust and must be carefully turned off in a process called de-sensitization.

In his presentation, Dr. Caron described research in his laboratory that has shown that these GPCR de-sensitization mechanisms carry out previously unrecognized cellular signaling events. Also, GPCR can be activated to one pathway and block another, or vice versa, giving rise to the notion of functional selectivity. The lab's further work with genetically engineered mice has revealed that antipsychotics can target the molecular de-sensitization machinery of dopamine D2 receptors in a preferential fashion. This had led Dr. Caron to the idea that it might be possible to separate the beneficial and negative effects of antipsychotics on the basis of functional selectivity.

To validate the concept of GPCR signaling as potentially relevant to the development of schizophrenia and the actions of antipsychotics, the Caron team has shown that genetic manipulations of components of this signaling pathway recapitulate schizophrenia-like symptoms in mouse models. Dr. Caron and colleagues are now leveraging the concept of GPCR functional selectivity to develop novel, more efficacious antipsychotics.

A graduate of Laval University, in Quebec City, Dr. Caron earned his Ph.D. in biochemistry at the University of Miami. After a postdoctoral fellowship at Duke he first returned to Laval as an Assistant Professor in the Department of Physiology and then joined the Duke faculty, where he was also a Howard Hughes Medical Institute Senior Associate and Investigator.

## The Teen Brain: Insights from Neuroimaging

### Jay N. Giedd, M.D.

Chief, Brain Imaging Section, Child Psychiatry Branch  
National Institute of Mental Health (NIMH)  
Adjunct Professor of Family and Reproductive Medicine  
Johns Hopkins Bloomberg School of Public Health  
**2013 Ruane Prize for Outstanding Achievement  
in Child and Adolescent Psychiatric Research**

Few parents are surprised to hear that the brains of teens are different. The teen brain is not a broken or defective adult brain. It has been exquisitely forged by evolution to have properties distinct from those of a child or an adult—differences that have been instrumental in our survival. A protracted period of dependence is related to prolonged brain plasticity, which confers both vulnerabilities and opportunities. Opportunities include the ability to master a wide range of vocational skills and enormous educational potential. Vulnerabilities include the consequences of impulsive behavior or poor decision making.

Adolescence is also the peak time for the emergence of several classes of psychiatric illness including psychosis, mood and anxiety disorders, eating disorders and substance abuse. In fact, the majority of all mental illnesses emerge during this time. Understanding the neurobiology of typical and atypical teen brain development may help optimize treatments or preventive efforts.

Dr. Giedd's presentation described the research he leads to explore the path, mechanisms and influences on brain development in health and illness. He highlighted findings from his team's 22-year longitudinal studies of the relationships of genes, brain and behavior, and discussed deviations from typical development related to illnesses and the implications of his research for children, teens, parents, educators, clinicians and society.

A summa cum laude graduate of the University of North Dakota, Grand Forks, Dr. Giedd earned his M.D. degree at the University of North Dakota School of Medicine. He completed an 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 before joining the NIMH.



Dr. Giedd

### *From the Scientific Council Ruane Prize Selection Committee:*

“Dr. Giedd has done groundbreaking work establishing normal changes in the brain during childhood and adolescence. His highly cited work has investigated the effects of age, gender and genetics on regional brain trajectories. Dr. Giedd also has a national reputation for his unique ability to communicate these and other scientific advances to the general public.”



Dr. Nierenberg

*From the Chair of the Scientific Council Colvin Prize Selection Committee:*

Dr. Nierenberg has focused on new approaches to patients with difficult-to-treat illness and conducted large-scale practical clinical trials. One is the comparative assessment of lithium and quetiapine, two of the major treatments of the illness. In another recent study, he found that adding moderate doses of lithium to treatment-as-usual was no more effective than adding placebo, but did result in the need for lower doses of adjunctive atypical antipsychotics. The secondary findings of this study importantly documented the relatively low response rates in either group indicating the great need for further treatment studies of this illness.

Robert M. Post, M.D.  
Head, Bipolar Collaborative Network  
Professor of Psychiatry  
George Washington University

## Making the Impossible Possible: The Challenges of Practicing Evidence-Based Psychiatry with a Focus on Bipolar Depression\*

### Andrew A. Nierenberg, M.D.

Professor of Psychiatry  
Harvard Medical School  
Director, Bipolar Clinic and Research Program  
Associate Director, Depression Clinical and Research Program  
Massachusetts General Hospital

#### 2013 Colvin Prize for Outstanding Achievement in Mood Disorders Research

Brain & Behavior Research Foundation Scientific Council Member  
2002 NARSAD Independent Investigator Grant

The treatment of bipolar disorder, and especially bipolar depression, continues to challenge patients and doctors. Many people with bipolar depression experience difficult-to-treat, recurring depressive episodes.

In his talk, Dr. Nierenberg discussed the challenges clinicians face in treating bipolar depression, and how studies undertaken by his team have informed clinical practice.

Dr. Nierenberg and his colleagues have conducted clinical trials to determine the effects of short- and long-term treatments and what treatments appear to work best. He presented findings from some of the largest studies of bipolar disorder ever conducted: the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and the Lithium Moderate Dose Use Study (LiTMUS). STEP-BD results raised questions as to the efficacy of the use of antidepressants for bipolar depression while LiTMUS showed that low doses of lithium in addition to other medications do not appear to improve outcome.

Dr. Nierenberg also discussed a recently completed study, Bipolar CHOICE, that compares benefits and risks of lithium compared to quetiapine (Seroquel®), a second-generation mood-stabilizing antipsychotic. He not only reviewed the available evidence for treatments for bipolar depression, but also critiqued the structure of the evidence and the challenge of practicing and implementing evidence-based psychiatry.

Dr. Nierenberg earned his M.D. from the Albert Einstein College of Medicine of Yeshiva University and completed residency in psychiatry at New York University/Bellevue Hospital. He studied clinical epidemiology at Yale University as a Robert Wood Johnson Clinical Scholar, then joined the faculty at Harvard Medical School, at McLean Hospital, before assuming his current posts.

#### \*The 2013 Gloria Neidorf Memorial Lecture

The late Gloria Neidorf struggled with and succumbed to bipolar disorder in 1989. Her family established the Gloria Neidorf Memorial Lecture in hopes to inspire and educate others.

Wednesday  
November 13, 2013

# Women Breaking the Silence About Mental Illness

Metropolitan Club  
New York, NY



l-r: Ellen Levine and Swanee Hunt engage in intimate conversation

“What a positive way to move research, discussion and support forward!”

“Thanks to both of these outstanding women for their candid and courageous sharing of their personal experiences.”

First-time women’s luncheon attracted a crowd of 300 supporters and featured guest speakers, **Ellen Levine**, Editorial Director of Hearst Magazines, and **Swanee Hunt**, former Ambassador to Austria and now serving as Harvard University’s Eleanor Roosevelt Lecturer in Public Policy. These extraordinary women captivated the “full house” audience with a direct and personal conversation on how to deal with mental illness without being afraid to speak up and seek help.



Brain & Behavior Research Foundation President & CEO, Jeffrey Borenstein, M.D., addressing the luncheon

“The most moving approach for gaining support for a philanthropic cause I’ve ever been exposed to!”

“I was absolutely blown away by this luncheon: such powerful stories, such compelling people, such an important topic.”



l-r: Co-Chairs of the Women’s Luncheon Committee and Foundation Board Members Barbara Streicker and Carole Mallemont

“This kind of leadership will move mental illness out of the closet and into the open.”



For information on upcoming events visit:  
[bbrfoundation.org/events-programs](http://bbrfoundation.org/events-programs)

# Glossary

**AMPA receptor** (p. 7): amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is a docking port for glutamate that mediates fast synaptic transmission in the central nervous system and is important in brain plasticity.

**amygdala** (pp. 3, 11): Almond-shaped structures located deep within the brain (there is one on each side of the brain) known to perform a primary role in emotional regulation, emotional memory and responses to emotional stimuli.

**Asperger's syndrome** (pp. 20, 21): An autism spectrum disorder characterized primarily by social impairment, with good verbal and language skills. Many people with Asperger's syndrome are exceptionally talented or skilled in a particular area such as music or math.

**BDNF (brain-derived neurotrophic factor)** (p. 15): Proteins that spur the birth of new nerve cells and enhance the formation of synapses (connections between neurons), a process important in brain plasticity, or the capacity of the brain to repair and adapt to change.

**deep brain stimulation (DBS)** (pp. 14, 19): An experimental form of therapy for treatment-resistant depression in which a surgically implanted probe applies current to a specific spot in the brain.

**dissociative side effects** (p. 5): A sense of detachment from one's surroundings, ranging from mild to severe. Can be caused by hallucinogenic drugs, and by abuse of ketamine.

**dopamine** (pp. 2, 24): A neurotransmitter that is a key element of the brain's reward system and is also believed to play a central role in the learning of new motor skills. It has been demonstrated that dopamine plays a role in mental illnesses such as autism, bipolar disorder and schizophrenia.

**extinction therapy** (p. 3): A form of talk therapy where the patient recalls a fearful memory/ies in a safe environment such as the therapist's office, and learns to make new associations with the memory. This technique has been shown to de-activate memories as "triggers" and is often used to treat post-traumatic stress disorder.

**magnetic resonance spectroscopy (MRS)** (p. 14): Also called NMR (nuclear magnetic resonance) imaging. This imaging technology is used to determine the structure of molecules in the brain. Like positron emission tomography (PET) imaging, MRS can be used to study brain metabolism.

**neural prosthetics** (p. 14): Man-made devices that might be surgically implanted in the brain, to correct cell or circuit malfunctions thought to cause brain and behavior disorders such as depression.

**optogenetics** (pp. 4, 9, 11, 23): A new technology developed with the early support of a NARSAD Grant by Dr. Karl Deisseroth and colleagues that enables research scientists to switch "on" and "off" individual neurons in the brain. This technology makes possible a new generation of experiments aimed at identifying specific circuits involved in brain and behavior disorders.

**seasonal affective disorder** (p. 14): A form of depression brought on by declining levels of light with the onset of winter.


**selective serotonin reuptake inhibitors (SSRIs)** (pp. 2, 4, 7): Medications that increase brain levels of serotonin, a neurotransmitter long known to play a key role in depression and other mood and anxiety disorders, including social phobia.

**serotonin 2C receptors** (p. 2): Proteins that bind to the neurotransmitter serotonin and dispatch the neurotransmitter's message within the brain's neural system. Serotonin has been shown to play a role in affective disorders such as depression.

**striatum** (p. 10): An area of the brain that contributes directly to decision making and is involved in inhibiting behavior in social interaction.

**transcript changes** (page 10): Transcription is the biological process of making a working copy of the body's DNA blueprint. Some errors or changes that can occur during this process may lead to dysfunction or illness, including mental illness.

# Meet the Scientist Monthly Q&A Webinars

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

## 2014 Webinar Series

**FEBRUARY 11**

**William T. Carpenter, Jr., M.D.**  
University of Maryland School  
of Medicine



**New Approaches for  
Therapeutic Discovery  
in Schizophrenia**

**MARCH 11**

**Rachel G. Klein, Ph.D.**  
New York University Child Study Center



**ADHD:  
Neurodevelopmental  
Disorder Through the Ages**

**APRIL 8**

**Bruce S. McEwen, Ph.D.**  
The Rockefeller University



**Brain Plasticity:  
What Is It and  
Why Is It Important?**



**Moderator: Jeffrey Borenstein, M.D.**  
President & CEO, Brain & Behavior Research Foundation  
Host of the PBS TV series "Healthy Minds"

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## Investing in Breakthroughs — To Find a Cure

### OUR MISSION:

The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

### OUR VISION:

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, schizophrenia, anxiety, autism, and bipolar, attention-deficit hyperactivity, post-traumatic stress and obsessive-compulsive disorders.

### OUR CREDENTIALS:

For more than a quarter of a century, we have awarded over \$300 million worldwide to more than 3,700 scientists carefully selected by our prestigious Scientific Council.

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