

CLARITY – 3-D BRAIN IMAGING

Page 2

## FOCUS

on

# NEW TECHNOLOGIES

### RESEARCH NEWS

- 2 RESEARCH DISCOVERIES IN THE NEWS
- 5 INTERVIEW WITH A RESEARCHER  
Karl Deisseroth, M.D., Ph.D.
- 7 BRAIN Initiative
- 8 REMEMBERING ROBERT S. WARSHAW
- 9 ASK THE RESEARCHER
- 14 FREQUENTLY ASKED QUESTIONS  
ON NEW TECHNOLOGIES
- 23 NEW TREATMENTS
- 24 GLOSSARY

### FEATURES

- 10 EMERGING NEW TECHNOLOGIES  
New Technologies Open New Horizons  
for Brain Research
- 17 A FAMILY STORY  
Heartache and Hard-Won Progress
- 19 2013 KLERMAN-FREEDMAN PRIZES  
Recognizing Exceptional Clinical and Basic Research  
by NARSAD Young Investigator Grantees

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Dear Members of Our Foundation Community,

From the earliest microscopes to modern MRIs, from the moonwalk to the Human Genome Project, I never cease to marvel at how many life-altering advances in science and medicine have depended on—indeed, been sparked by—advances in technology. Now more than ever, remarkable new technologies are beating a path into the sanctum of the brain.

I had the honor of representing the Foundation at the White House this Spring when President Obama announced a bold new research initiative—the BRAIN Initiative (Brain Research Through Advancing Innovative Neurotechnologies)—to “unlock” the mysteries of the brain and map its activity and functioning. The Initiative calls for public and private collaboration to support a multi-year, broad-based research program to help researchers find new ways to treat, cure, and even prevent brain disorders.

This exciting new Initiative acknowledges what we all as members of the Brain & Behavior Research Foundation community take as an article of faith: that accelerated brain research is the key to conquering the psychiatric illnesses that continue to plague mankind. One of our current NARSAD Distinguished Investigator Grantees, Rafael Yuste, M.D., Ph.D., is one of the six authors of “The Brain Activity Map Project” paper published in *Neuron* in June, 2012 that is cited as having influenced President Obama’s team to launch this Initiative. You can read about his current NARSAD Grant work on page 12.

Karl Deisseroth, M.D., Ph.D., a Foundation Scientific Council Member featured in this issue, is one of fifteen leading neuroscientists and biologists selected to serve on the Advisory Committee to the Director of the National Institutes of Health on the BRAIN Initiative. Optogenetics, the groundbreaking technology developed in his lab at Stanford in 2005 with the support of a NARSAD Young Investigator Grant, was cited by the White House as one of the “landmark discoveries that now create the opportunity to unlock the mysteries of the brain.”

With our track record of funding researchers with “out of the box” ideas, we are poised to play a significant role in this Initiative. By funding Young, Independent and Distinguished Investigators with innovative ideas, we can provide critical support. As you read about Drs. Deisseroth and Yuste and others whose NARSAD Grant support is enabling the development of powerful new technologies, remember that you, as donors, are the crucial piece that makes them possible.

I hope you will consider how you can help us take a leadership role on the “private” side of this public-private collaboration to accelerate the funding for brain research.

Thank you, as always, for your continued support.

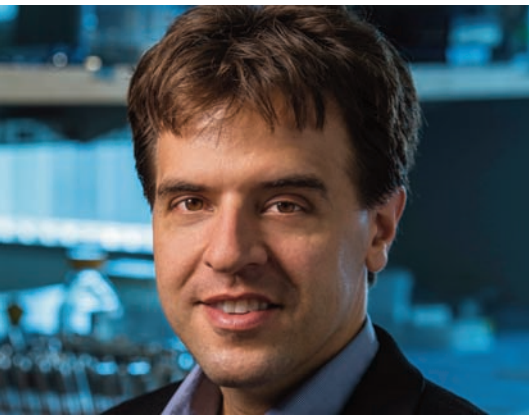
Sincerely,



Jeffrey Borenstein, M.D.  
President & CEO



# Research Discoveries *in the News*



**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

## Breakthrough Technology—CLARITY— Offers 3-D View of Inner Structures of the Brain

Thanks to many years of work by a determined and talented team, researchers are able for the first time to image a whole, intact brain in three dimensions and obtain a virtually transparent view of its inner structure. The new technology, called CLARITY, involves an intricate process of replacing the brain's fatty molecules, and their role of holding the brain together, with a clear transparent gel (called a hydrogel). Once complete, after about 9 days, researchers are then able to use 3-D imaging technology to see all the brain's important structures—from single neurons to populations of neurons and how they project, to axons, dendrites, synapses, etc.

This groundbreaking technique was developed by a multidisciplinary team led by Brain & Behavior Research Foundation Scientific Council Member and NARSAD Grantee Karl Deisseroth, M.D., Ph.D. (see Interview with a Researcher, p. 5). The research was reported online on April 10th in the journal *Nature*.

"Studying intact systems with this sort of molecular resolution and global scope—to be able to see the fine detail and the big picture at the same time—has been a major unmet goal in biology, and a goal that CLARITY begins to address," said Dr. Deisseroth. "It enables researchers to study complex biological systems with high resolution without taking them apart." The new imaging technology can be used to make any organ transparent, but it was the challenges of imaging the brain that motivated Dr. Deisseroth. He hopes the technology will lead to identification of brain malfunctions that lead to psychiatric disorders such as schizophrenia, depression and autism.

The research in this study was performed primarily on mouse brains, but the team also analyzed post-mortem brain tissue from a patient with autism spectrum disorder (ASD). They were able to see dendrites of neurons in the cortex joining together in ladder-like patterns in the ASD patient, a pattern not seen in typical brains.

Within a week of publication, the Deisseroth lab was abuzz with requests from dozens of labs wanting to learn about the new technology. And, as the lab did with their groundbreaking development of optogenetics technology, they intend to share it openly and widely. This kind of open sharing of breakthrough new approaches to understanding the brain and how it functions—and can malfunction—gives great reason for hope that improved treatments and even possibilities for prevention of mental illnesses are on our horizon. ❖

### The Takeaway

A technique named CLARITY that makes it possible for researchers to see through an intact, preserved brain and into its structures in exquisite detail is being openly shared with research labs around the world.

## Serotonin Discovery via X-Ray Crystallography Points Toward More Precise Treatments

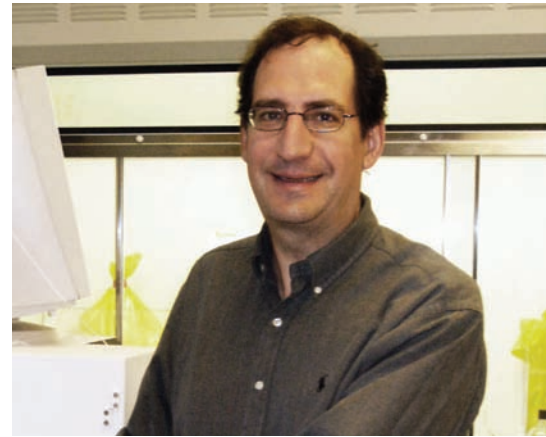
Bryan L. Roth, M.D., Ph.D., Foundation Scientific Council Member, received a NARSAD Young Investigator Grant in 1992 to study the structure and function of serotonin receptors. At the time, he was having difficulty securing funding for his idea that understanding these receptors would be crucial for the development of safer and more effective psychiatric medications. Serotonin receptors are molecules on nerve cells that bind to the neurotransmitter serotonin and are the targets for many medications prescribed for a variety of ailments, including, importantly, depression and schizophrenia.

This year, Dr. Roth, in an international collaboration with colleagues at The Scripps Research Institute in California and the Chinese Academy of Sciences, identified the structures of two of 14 known serotonin receptors (the two are known as 5-HT1B and 5-HT2B). The research team used X-ray crystallography, a technology in which X-ray beams are fired at crystals of the compound in question to deduce the atomic structure from the scatter pattern of the beams. The researchers

also investigated how differences in binding affected chemical signaling in the serotonin pathway. The results of their work were published in back-to-back papers in the May 3rd issue of the journal *Science*.

The two receptors were found to have very similar structures in the areas where serotonin docks, but in one area of the 5-HT1B receptor, the binding pocket was wider, a tiny difference but enough to explain why the two receptors bind differently to certain compounds. The distinction may be relevant to the safety of medications: some medications that activate 5-HT2B are thought to cause heart problems and have been withdrawn from the market.

“Nearly all psychiatric drugs—including virtually all drugs which treat schizophrenia—affect serotonin receptors to some extent. These receptors also mediate a host of effects outside the brain, for example, on blood coagulation, smooth muscle contraction and heart valve growth,” explained Dr. Roth.



**Bryan L. Roth, M.D., Ph.D.**

Chair Protein Therapeutics and Translational Proteomics; Director, National Institute of Mental Health Psychoactive Drug Screening Program, University of North Carolina School of Medicine; 1992, 1998 and 2008 NARSAD Young, Independent and Distinguished Investigator Grantee  
Foundation Scientific Council Member

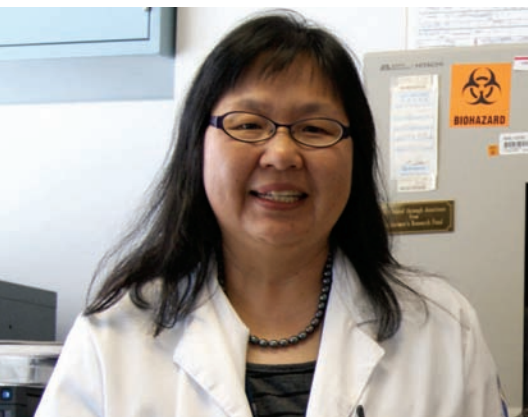
“These new findings will facilitate the development of more precise medications that avoid potentially harmful “off-target” effects with greater beneficial actions.”

An editorial accompanying the *Science* papers explains the importance of the work: “Experimental methods developed by Bryan Roth enable neuroscientists to follow the pathways taken by messages sent between neurons in complex networks in the brain—here used to identify structure and function of serotonin receptors. The work offers a valuable framework for designing safer and more effective medications.”

### The Takeaway

An international team of scientists is working to decode the actions in the brain of widely used medications for depression and schizophrenia, knowledge that can be used to design more precise treatments.





**Debby W. Tsuang, M.D.**

Professor of Psychiatry and Behavioral Science, University of Washington School of Medicine; Director of the Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System;  
2001 NARSAD Young Investigator Grantee  
2009 NARSAD Independent Investigator Grantee

## New Schizophrenia Genes Discovered Through Innovative Genetic Sequencing Approach

With the support of a NARSAD Independent Investigator Grant, Debby W. Tsuang, M.D., and her colleagues at the University of Washington have applied an innovative approach to uncover elusive, genetic variants associated with schizophrenia susceptibility. Their findings, published online on April 3rd in *JAMA Psychiatry*, provide a new tool in the search to understand how aberrant genes undermine molecular pathways in the brain to cause schizophrenia and related mental illnesses and suggest possible new targets for treatment.

Schizophrenia is an extremely complex, highly heritable genetic disorder. The more commonly used genetic methods through which causative genes have been identified in many disorders have been less successful for finding candidate genes for schizophrenia, and the identification of specific causative genes has been elusive. The genetic variants so far identified as being associated with schizophrenia, Dr. Tsuang points out, “only account for slightly increased risks. It is likely that the majority of patients carry multiple genetic variants, along with environmental risk factors to develop the disorder.”

On the other hand, there may be unique families who carry rare novel genetic variants that have eluded discovery until recently. One novel method for gene identification is genomic sequencing, to detect any genetic variants in the entire DNA sequences—the genome—of an organism. DNA is composed of smaller units called nucleotides. When looking for very rare variants, Dr. Tsuang explains, “sequencing every one of the three billion nucleotides in the human genome is still expensive. However, it is feasible to sequence the exome, the areas that contain the coding regions or exons, of all genes. Exons make up less than 5% of the genome but are believed to harbor disease-causing mutations.”

For her NARSAD Grant-funded project, Dr. Tsuang selected five large families enrolled in the National Institute of Mental Health Center for Collaborative Genomic Studies on Mental Disorders Initiative. Each family had multiple affected members: among the 41 subjects, 18 had schizophrenia, four had schizoaffective disorder or depression and two had unspecified psychosis. Seventeen were unaffected.

In all five families, exome sequencing detected rare variants unique to each family in one of three genes that are in the N-methyl-D-aspartate (NMDA) receptor pathways. The NMDA receptor is involved in transmitting glutamatergic signals. Glutamate is one of the brain’s most important inhibitory neurotransmitters. These genes, mGluR5, PPEF2, and LRP1B, may represent novel targets for medications to treat schizophrenia.

Dr. Tsuang says, “Our findings suggest that exome sequencing in multiplex pedigrees can be an effective strategy to gene discovery in complex disorders like schizophrenia. Because of the generous funding of the NARSAD Grant, we were able to uncover new genes associated with the risk of developing schizophrenia.” ❖

### The Takeaway

Applying a novel technique to study families in which many members have mental illness is uncovering previously unidentified risk genes, primarily for schizophrenia.

# Interview

with

## 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

## Revolutionary New Technologies to Understand the Brain



## Fueled by Compassion, Brilliant Psychiatrist / Neuroscientist / Bioengineer Sets Out to Transform Treatment of Mental Illness

If understanding how the brain works is biology's "final frontier"—and its toughest challenge—then Dr. Karl Deisseroth is without a doubt one of its foremost contemporary explorers. He's a psychiatrist, neuroscientist and bioengineer whose human compassion, experimental imagination and technological brilliance lie behind his invention, just in the last decade, of two of the most important new methods of learning about brain function.

Boosted by a NARSAD Young Investigator Grant in 2005, Dr. Deisseroth invented a technology called optogenetics that is used today by thousands of neuroscientists in laboratories all over the world.

With optogenetics, scientists can switch individually targeted brain

cells on and off, one at a time, using colored beams of laser light and then observe the impact on behavior in living animals. The beams of light are transmitted into the brains of animals via the equivalent of fiber optic cables, thin as human hairs. Their ability to switch neurons on and off is the result of a genetic "trick": inducing brain cells to express light-sensitive proteins found in species such as light-sensing microbes from lakes and ponds.

If this sounds like science fiction, Dr. Deisseroth's latest invention, called CLARITY, may be even more amazing. It enables scientists to see right through whole, intact brains by removing all the fatty molecules that hold the brain together and replacing them with a substance called hydrogel (see page 2).

Why do this? Because the fatty cells make the brain optically opaque—so dense that until now it had to be cut into hundreds or thousands of razor-thin slices in order to see its detailed structures in even the most powerful microscopes.

What do these amazing technologies enable scientists to do? By manipulating specific brain cells optogenetically, scientists are on the road to discovering how particular brain circuits work, and what happens when they do not work. CLARITY does something equally important in non-living brains, such as those collected in "brain banks" holding precious human brain samples. Their fully intact contents can be revealed and observed with perfect clarity, down to fine structures such as the dendrites, axons, and

synapses connecting individual neurons—one of the long-sought objectives of brain research and until now the stuff of fantasy.

I can tell you that the level of need, the urgency of our patients' conditions, is a constant source of motivation and inspiration for me. It helps guide what I do with my team in the lab.

"We've been helping labs all over the world get things going with CLARITY, and we're already receiving images sent by teams reporting their successes," Dr. Deisseroth reports. And despite his great achievements in technology development, Dr. Deisseroth still regularly treats psychiatric patients. "We use medications, we do brain stimulation therapies, and I can tell you that the level of need, the urgency of our patients' conditions, is a constant source of motivation and inspiration for me. It helps guide what I do with my team in the lab."

Dr. Deisseroth's direct involvement in and empathy for the problems faced by his patients, most of whom have serious and persistent illnesses such as treatment-resistant major depression and schizophrenia, makes him a uniquely insightful and persuasive authority on the connection between patient-based clinical research and lab-based basic research.

"It is really important to explain to Foundation (and NARSAD Grant) supporters how these two things relate to one another," he says. "You could easily take the wrong lesson, for instance, from the two tracks of my work in mental health. I'm deeply committed to patients, yet it would be a serious mistake to insist that in the research we do, that we limit it to work that has immediate applications for those who suffer.

"That kind of applied work is called 'translational research,' and it is extremely important. It involves taking existing ideas, existing technologies, and using them with patients, directly, in the clinic. This has to be done. But it can only go so far, by definition—it can take us

places made possible by what we now understand and know about the brain. And we desperately need a great deal of new, additional knowledge about how the brain works if we want to make treatments that are better in revolutionary ways."

It is possible to use optogenetics to manipulate the activity of specific neurons in mice which model various aspects of complex disorders like autism, anxiety, or depression. "But even if we had a way to control every neuron in the human brain—which we don't, yet—we frankly would not know what to do in a clinical setting today. We absolutely must do the basic research: study the brain in its normal functioning and separately, and comparatively, in disease states," Dr. Deisseroth says.

My team is building technologies needed to probe the structure and functioning of the brain—not only for the abstract purpose of understanding its complexity but also to make it possible to better understand diseases and to come up with new ideas for truly precise treatments.

"The brain is wonderfully, mysteriously complex. We have a lot of work to do. And I believe that patients know that. Family members know that. They know how devastating the symptoms are, but they also are painfully aware that the medications we have are problematic. They're not specific enough. They have side effects. They are not effective enough.

"Psychiatric disorders are the leading cause of disability in the adult age groups. They are immensely costly, in terms of dollars and suffering and lives not lived to their fullest. On the research side, my team is building technologies needed to probe the structure and functioning of the brain—not only for the abstract purpose of understanding its complexity but also to make it possible to better understand diseases and to come up with new ideas for truly precise treatments." ♦



## The BRAIN Initiative: Public-Private Partnership to Map the Function of the Human Brain

On April 2, President Barack Obama announced a bold new research initiative—the BRAIN Initiative (Brain Research Through Advancing Innovative Neurotechnologies)—to “unlock” the mysteries of the brain and map its activity and functioning. Being compared to the Human

Genome Project, the Initiative calls for public and private collaboration to support a multi-year, broad-based research program to help researchers find new ways to treat, cure, and even prevent brain disorders.

With the Foundation’s track record of funding researchers who need support to pursue “out of the box” ideas, we are poised to play a significant role in the success of this Initiative.

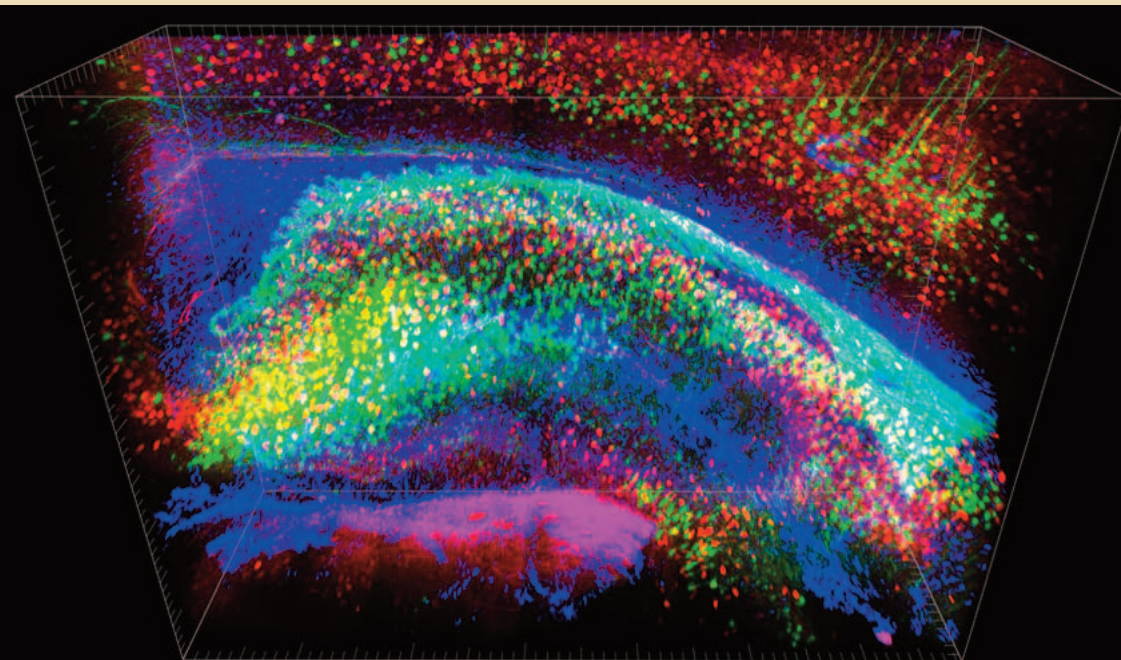
The new Initiative acknowledges the great progress being made in neuroscience and also emphasizes the crucial role of new technologies in advancing what we can know about how the brain functions. The White House cited optogenetics, developed by Dr. Karl Deisseroth with the early support of a Foundation NARSAD Grant, as one of the “landmark discoveries that now create the opportunity to unlock the mysteries of the brain.”

Dr. Deisseroth, an active Foundation Scientific Council Member, is one of the 15 leading neuroscientists and biologists tapped to serve on the Advisory Committee to the Director of the National Institutes of Health (NIH) on the BRAIN Initiative. The Committee is currently working to flesh out the aims and approaches of the project. Dr. Francis Collins, head of the NIH, will funnel the group’s findings directly to President Obama. Dr. David Anderson, a 2007 NARSAD Distinguished Investigator Grantee, is also serving on the Advisory Committee. The Defense Advanced Research Projects Agency (DARPA) and the National Science Foundation (NSF) are also being consulted.

“We’re actually a pre-advisory group,” Dr. Deisseroth explains, “and we’re collecting information from the neuroscience community and helping to think about what would be a useful direction for this project to go in.”

“The brain is a very complex structure; it’s data-rich; and it’s hard to access. If we can figure out how to build technologies that are needed to probe that structure, we’ll learn many interesting things. We’ll not only understand ourselves better, but understand the brain and behavioral disorders that affect so many of us better—and on this basis be able to come up with new ideas for treatments.”

By funding NARSAD Young, Independent and Distinguished Investigators with innovative ideas to support the BRAIN Initiative, we can provide critical support. The President has earmarked \$100 million for the project for fiscal year 2014 and we hope to have a record-breaking year of fundraising to substantially augment this amount with private contributions.



**CLARITY – 3D Brain Imaging:** an intact mouse brain stained with fluorescent labels for different proteins. Each color represents a different molecular label.

“...this is exactly the type of technology one would hope to develop for the BRAIN Initiative” – Dr. Michelle Freund, Program Manager, National Institute of Mental Health

This technique “is a giant step forward...” – Dr. Cori Bargmann, Rockefeller University, co-leader of President Obama’s BRAIN Initiative

Photo:  
Courtesy of Karl Deisseroth, M.D., Ph.D.

# Remembering Robert S. Warshaw, Esq.

## *Visionary Philanthropist*

### April 18, 2013

*The Brain & Behavior Research Foundation mourns the passing of long-term member of the Board of Directors, Robert S. Warshaw. Bob Warshaw provided support and guidance in our program to enhance the lives of people suffering from mental illness through research. He was honored with our 2010 Visionary Philanthropist Award, especially for his work with the Hofmann Trust. His leadership role went beyond offering his skills as a lawyer to his articulate reviews of our staff and structure. He will be missed as a vital force for our mission.*

*— Jeffrey Borenstein, M.D., President & CEO,  
Constance E. Lieber, President Emerita, and  
Stephen A. Lieber, Chairman, Board of Directors*

Robert S. Warshaw was a friend, inspiration and example of someone interested in helping people living with mental illness who embraced the Foundation mission. Mr. Warshaw passed away on April 18, 2013 at the age of 88.

Bob was born in Boston and received degrees from Harvard College, Graduate School and Law School. He served in the United States Army in WWII in Europe. His legal career began at the law firm of Donovan Leisure. He then became a founding member of Javits, Moore and Trubin with New York Senator Jacob K. Javits. He later practiced independently, managing the estates of several well-known artists, including the renowned German-born American abstract expressionist Hans Hofmann.

At the Brain & Behavior Research Foundation 2010 Klerman-Freedman Awards, Bob, a Trustee of the Renate, Hans and Maria Hofmann Trust, was honored with the "Visionary Philanthropist Award." The award recognized his dedication in pursuing Renate Hofmann's desire to improve the lives of those living with mental illness.

Renate Hofmann, Hans Hofmann's widow, personally suffered from schizophrenia. Her will designated that residual funds from the Hofmann estate—monies generated in addition to what was needed for support of the artistic legacy—be given to homeless and outcasts of society. The Trustees chose to concentrate their annual grants to research into the causes and treatment of brain and behavior disorders. Bob's guiding influence most assuredly played a key role in the Trustees' decision to begin funding NARSAD Grants in 1992. Since then the Hofmann Trust has made annual grants and has contributed more than \$2.3 million to date.

Robert S. Warshaw will be remembered as a man of strong conviction and one who gave generously of his time and talents to ensure others had opportunity to lead productive lives.



*Robert S. Warshaw, Esq.  
Brain & Behavior Research Foundation  
Board of Director 2006 - 2013*

# Answers to Ask the Researcher

from

## Judith L. Rapoport, M.D.

Chief, Child Psychiatry Branch  
National Institute of Mental Health  
2002 Foundation Ruane Prize for Outstanding Achievement  
in Child and Adolescent Psychiatric Research  
2009 NARSAD Distinguished Investigator Grantee  
Foundation Scientific Council Member



**Do you recommend finding out if your children carry the risk genes that can predispose to different mental illnesses? Is it better to know—and if so, what does one do with that information?**

There are genes in general which so far have not been helpful to measure in most situations, except on a research basis. There are starting to be discoveries of several different, missing or duplicated pieces of chromosomes, called copy number variants or CNVs (which may contain 1-40 genes), that are associated with autism, schizophrenia, intellectual disability and epilepsy—that is they are not specific. Research is addressing how great a risk these are for illness, but it is too soon to tell.

**Is there any way to prevent suspect genes from causing mental illness or to prevent the development of these 'copy-number variants' (CNVs) that have been linked to schizophrenia? Is that a current focus of research?**

So far, there is no known way to stop copy number variants (CNVs) from forming. But stress can effect how genes are expressed and this is an area of very active research.

**Are there clear, identifying characteristics of the “abnormal timing of developmental events” that can lead to the illnesses you mention in the article (schizophrenia, psychosis, attention-deficit hyperactivity disorder, etc.)?**

**How can parents know if their child has experienced this abnormal development?**

This is a top research question. Probably there are very early abnormalities even before birth that “decide” whether the child will have autism, schizophrenia or the other disorders. But this is still a question for research.

**What are the most promising areas of research today—and how close are we getting to prevention and cures?**

Certainly, brain imaging and genetics have the greatest attention in clinical research, with epidemiology a close second. We are not yet close to prevention, but neuroscience is providing new tools and fascinating new findings, and therein lies hope for many people.

### Ask the Researcher

#### HAVE A QUESTION?

E-mail [asktheresearcher@bbrfoundation.org](mailto:asktheresearcher@bbrfoundation.org) with questions for **Dr. Karl Deisseroth**. 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. This Q&A forum is not meant to serve as a substitute for that, but rather to share insights.



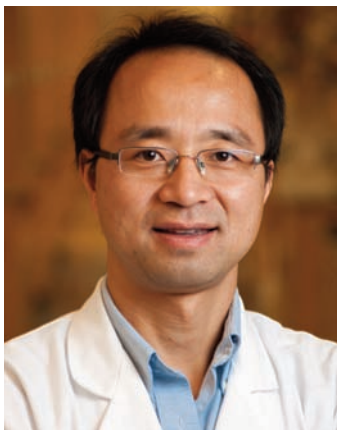
## New Technologies Open New Horizons for Brain Research

An important new phase of research on the brain has begun and the Brain & Behavior Research Foundation is playing a critical role, funding NARSAD Grants for investigators with innovative ideas for developing new technologies.

What are these new technologies and what will they enable doctors and scientists to do?

The answers are so remarkable it almost makes them seem like science fiction. But these projects are already under way, with the potential to transform knowledge about the brain and treatments for brain and behavior disorders. In this feature, we highlight a few examples.

### Stem Cell Technology: New Window Into Diseased Cells, Cell Therapy and Regenerative Medicine



Zhiping Pang, Ph.D.  
Assistant Professor  
Child Health Institute of New Jersey  
Dept. of Neuroscience and Cell Biology  
Robert Wood Johnson Medical School  
2008 and 2010 NARSAD Young  
Investigator Grantee

**Zhiping Pang, Ph.D.**, a two-time NARSAD Young Investigator Grantee, and others, are developing a technology that enables ordinary skin cells to be genetically reprogrammed to an earlier stage of cellular development, or transformed into other cell types, including brain cells, for scientific research and potential therapeutic purposes.

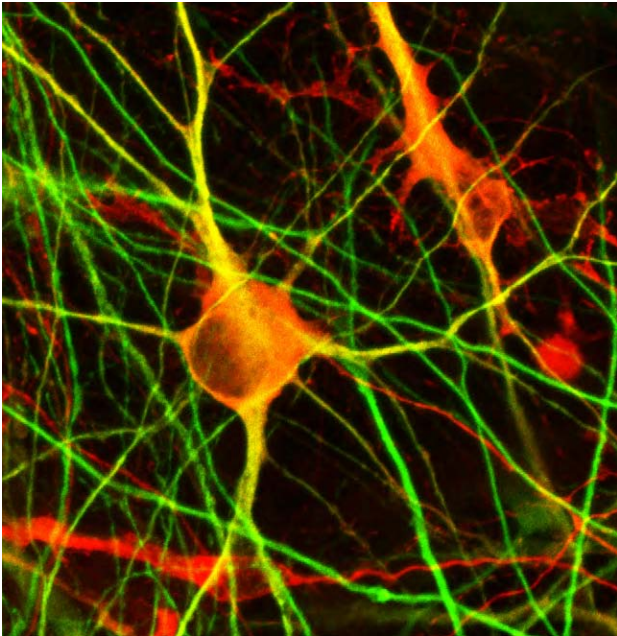
Dr. Pang, on the faculty of the Robert Wood Johnson Medical School in New Brunswick, New Jersey was awarded the Foundation's Freedman Prize in 2012. With the support of his first NARSAD Young Investigator Grant in 2008 he figured out how to genetically induce mouse and human skin cells to change into cells functionally similar to an

authentic neuron. The converted "iN" (induced neuronal) cell forms communication junctions called synapses with other nerve cells. It can generate the electrical impulses (action potentials) that "real" neurons use to do their communicating.

*Dr. Pang is excited about several possibilities, each of which could be transformative.*

What can be done with such a technology? Dr. Pang is excited about several possibilities, each of which could be transformative. In one scenario, patients with a serious illness such as depression or schizophrenia might donate a few harmless skin cells that would then be "induced" to become neural-like cells. Dr. Pang hopes that such a converted cell would manifest all or at least some of the defects found in neurons native to that patient's own brain. This could work similarly to how a biopsy works with physical diseases of the body in living patients and might provide otherwise unobtainable insights into brain disease pathology (where biopsies are too dangerous to perform).





Induced Neuronal (iN) cells: functional neurons that help create models of mental illnesses “in a petri dish”

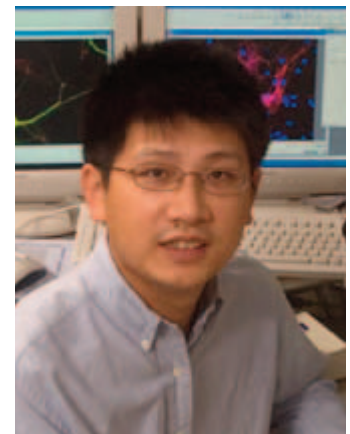
Another approach is to use iNs, or another “induced” cell type called iPS cells, to perform cell therapy. iPS cells (induced pluripotent stem cells), often skin cells, are reprogrammed to the pluripotent state, a primitive developmental state in which they can be coaxed to mature into any one of a number of different cell types, including brain cell types. Diseased cells or neurons might be replaced with newly manufactured cells of the same type, made from these reprogrammed skin cells. This could slow or halt progression of the disease and might even have promise in reversing damage caused by illness. Dr. Pang stresses that this work is in its early stages and clinical applications aren’t ethical in people until more is understood about the biological properties of reprogrammed cells.

NARSAD Independent Investigator Grantee **Hongjun Song, Ph.D.**, meanwhile, is studying stem cells in the brain to determine how they generate different kinds of brain cells in adulthood. These include neurons as well as “helper” cells (glia), which provide essential support for neurons.

Dr. Song is intrigued about niches in a brain structure called the hippocampus where stem cells live and can give rise to new neurons, a process called neurogenesis.

With the support of his first NARSAD Young Investigator Grant in 2008, Dr. Pang figured out how to genetically induce mouse and human skin cells to change into cells functionally similar to an authentic neuron. The converted “iN” (induced neuronal) cell forms communication junctions called synapses with other nerve cells.

With the support of a 2008 NARSAD Independent Investigator Grant, he and colleagues discovered that any single stem cell is capable of both replacing itself and of giving rise to both neurons and glia. They also discovered that a lone stem cell can generate two new stem cells; that is, stem cells don’t just maintain the numerical status quo, or



Hongjun Song, Ph.D.  
Professor of Neurology  
Johns Hopkins University  
Institute for Cell Engineering (ICE)  
Director, Stem Cell Program at ICE  
2008 NARSAD Independent Investigator Grantee

“If we can cash in on this newly discovered property of stem cells in the brain, and find ways to intervene so they divide more, then we might actually increase their numbers instead of losing them over time...”

deplete in number, they can amplify their number. This was an unexpected finding, about which Dr. Song says: “If we can somehow cash in on this newly discovered property of stem cells in the brain, and find ways to intervene so they divide more, then we might actually increase their numbers instead of losing them over time, which is what normally happens, perhaps due to aging or diseases.”

These findings have significance for understanding processes involved in depression and schizophrenia, among other illnesses. The hippocampus is one area of the adult brain where neurogenesis is known to occur, and it’s also intimately involved in learning, memory and mood regulation. Research on stem cells opens a new window to understand how these illnesses may affect the development of new neurons in the adult brain. And this emerging technology and capacity may also lead to the development of regenerative medicine opportunities for patients with these illnesses.

## Photon Lasers and Calcium Imaging

NARSAD Distinguished Investigator Grantee **Rafael Yuste, M.D., Ph.D.**, has begun a highly innovative project that seeks to manipulate the activity of a rare class of brain cells whose malfunction is thought to generate pathologies seen in schizophrenia.

The cells in question, called chandelier cells, look very much like old-fashioned candelabras (see image, left on p. 13) whose ‘branches’ connect with numerous excitatory neurons called pyramidal cells. These excitatory cells are the main type of neuron throughout the cortex, and mediate essentially all neuronal signals and commands involved in perception, memory and language. One chandelier cell connects with up to 500 excitatory neurons, and has the capacity to powerfully inhibit each one of them, in whole or in part. This could make them crucial switches in the cortex.

There is evidence suggesting chandelier cells are dysfunctional in schizophrenia, and Dr. Yuste is using a technology his team developed to modulate the activity of these cells in living animals. The technique

employs a light-sensitive chemical derived from the metal ruthenium and ultrafast two-photon lasers to activate chandelier cells. The group combines this ruthenium photo-activation with calcium imaging, a technique, also developed by Dr. Yuste, which enables the team to monitor the activity of all cortical neurons simultaneously. “We’ve been working on these technologies for years,” says Dr. Yuste, “and now we’re using them together in this important project. By changing the firing pattern of chandelier cells, we hope to see if indeed they can control cortical activity. Their dysfunction could be the cause of the pathophysiology in schizophrenia.”

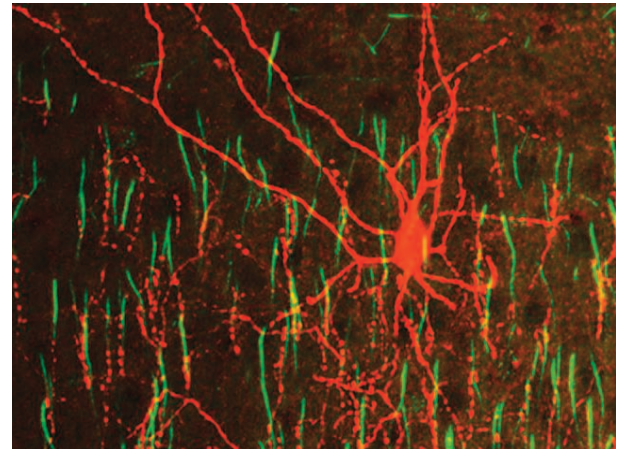
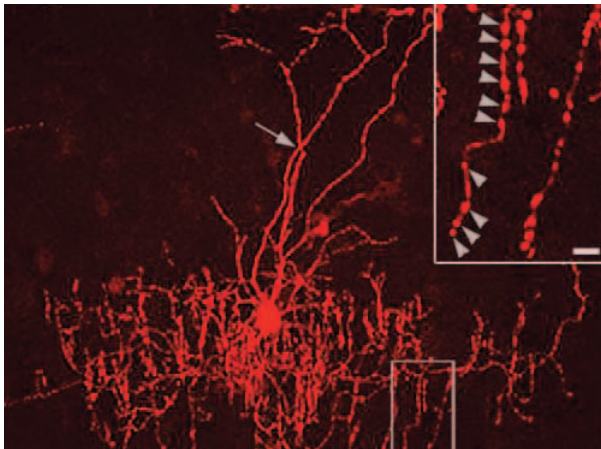


Rafael Yuste, M.D., Ph.D.  
Professor, Biological Sciences  
and Neuroscience  
Co-director, The Kavli Institute for Brain  
Science  
2012 NARSAD Distinguished Investigator  
Grantee

There is evidence suggesting chandelier cells are dysfunctional in schizophrenia and Dr. Yuste is using a technology his team developed to modulate the activity of these cells in living animals.

## Nanotechnology

Some advanced technologies seem downright magical, including several in the research prospectus of NARSAD Distinguished Investigator Grantee **Brian Litt, Ph.D.** Dr. Litt’s interests range across the disciplines, from neuroscience, biology and chemistry to physics, computer science and materials science. Dr. Litt is pioneering a new field called electroceuticals. These are medicines—devices—that use electrical impulses to modulate the body’s neural circuits.



**Image, left:** shows the likeness of chandelier cells to old-fashioned candelabras. **Image, right:** one chandelier cell connecting with many excitatory neurons (green segments). Each one of these green lines is a connection with a different excitatory cell. This shows how chandelier cells are the "circuit breaker" switches that can modulate or even shut off as many as 500 excitatory cells at a time.



Brian Litt, Ph.D.  
 Professor, Neurology and Bioengineering  
 Penn Engineering  
 University of Pennsylvania  
 2012 NARSAD Distinguished  
 Investigator Grantee

Unlike pacemakers and defibrillators, electroceuticals will be devices on the nanoscale, far too small to be visible to the naked eye. As now conceptualized, they would be ingested and would come into being as functional therapeutic units only after self-assembling once inside the body.

Dr. Litt's lab "translates neuro-engineering research directly into patient care."

His current NARSAD Grant-supported project of creating an implantable nanoscale device is no pipe dream. He intends for the implanted device to deliver therapy for neurological illness. The device under development will be coated with antibodies, enabling it to find and bind to surface receptors in a specific type of nerve cell. Dr. Litt intends to pre-program the first generation of such devices to

His current NARSAD Grant-supported project of creating an implantable nanoscale device is no pipe dream. He intends for the implanted device to deliver therapy for neurological illness.

activate upon receiving a light or radio signal from outside the body.

According to Dr. Litt, such an approach could one day make feasible a unique class of non-invasive treatments for brain disorders. Nanodevices could be used to control or induce electrical signals in specific neuronal types or in specific spots in brain circuits, to correct or compensate for existing pathologies. ❖

### The Takeaway

NARSAD Grants are funding many researchers developing new technologies to advance brain research who have difficulty getting funding support before their ideas are proven.

# Frequently Asked Questions on New Technologies

## Q

What kind of new technologies are helping advance brain research?

## A

There are many kinds of technologies that are significantly advancing our understanding of the brain. Here are a few examples:

- **Genetic sequencing:** Since the completion of the Human Genome Project just over ten years ago, researchers have had unprecedented opportunity to study and identify genes and genetic mutations associated with various mental illnesses. The cost to sequence the human genome has plummeted and researchers are increasingly sharing DNA research and clinical information to gather the statistical power for comprehensive genomic analyses. Scientists from around the world have joined consortia, such as the Psychiatric GWAS Consortium, allowing collaborative analysis of over 10,000 samples from people with schizophrenia. A similar effort for autism is supporting full exome (the protein coding parts of the genome) sequencing in roughly 2,000 DNA samples. This rapidly advancing genetic work can lead to possibilities for early intervention and prevention strategies, as well as the potential for personalized medicine approaches in treatment plans for individual patients.<sup>1</sup>
- **Positron Emission Tomography (PET):** Dr. Helen Mayberg pioneered the use of PET scans to study the neurology of depression with a NARSAD Young Investigator Grant in 1991. She developed an important model of depression through this work and identified a key locus of depression pathology in the brain (Brodmann Area 25). The work led to a mapping of brain changes mediating different depression treatment strategies and is leading to the development of imaging biomarkers for treatment response.



- **Functional Magnetic Resonance Imaging (fMRI):** Dr. Yvette Sheline used another type of neuroimaging (fMRI) to learn about depression in the 1990s. She identified structural brain changes in the hippocampus and amygdala in patients with depression that established depression as a brain disease.
- **Optogenetics** is a groundbreaking technology that combines genetic bioengineering, fiber optics and light technology to stimulate or inhibit specific neurons in the brain, allowing for observation of the corresponding behavior in living animals as well as monitoring of their brain activity. Optogenetics was developed with the support of a NARSAD Grant to Karl Deisseroth, M.D., Ph.D. of Stanford University in 2005 (see Interview p. 5) and is now being used in thousands of research labs around the world. Using the technology, researchers are able to tease apart the complex circuits that compose the brain so they can be studied one by one, and they are identifying precise neural circuits underlying symptoms of a wide range of psychiatric disorders as well as potential new treatment targets to alleviate the symptoms.<sup>3</sup>
- **Stem Cell Technology, Nanotechnology, Photon Lasers:** See our 'Emerging New Technologies' feature on pp. 10-13 for more about these technologies

## Q Can brain imaging assist in the diagnosis of mental illness?

A Research using brain imaging is helping researchers identify abnormalities in brain function linked to a wide range of psychiatric illnesses and is pointing toward biomarkers for treatment response (as per above answer), but is not yet used to diagnose mental illnesses. Dr. Helen Mayberg recently published study results (in *JAMA Psychiatry* online on June 12, 2013) that suggest that specific patterns of brain activity identified in PET scans may help predict which people do better on antidepressant medication and which would benefit most from cognitive behavioral therapy instead. This offers a first

step towards personalized medicine treatment decisions for major depression.<sup>2</sup> Other researchers have used PET scans to predict which antidepressant would work for individual patients. Dr. Yvette Sheline, with the support of a 1998 NARSAD Grant, used fMRI scans to identify how antidepressants correct abnormal brain function to alleviate symptoms of depression.<sup>3</sup> See our article on CLARITY 3-D brain imaging on p. 2 for the latest example of brain imaging advancing understanding of the brain, how it may malfunction and what possibilities there may be to remedy the malfunctions.

## Q Are there other technologies that may aid in diagnosing mental illness?

A The ideal diagnostic test for mental illness would be simple and inexpensive. This could be a blood test (such as a glucose test for diabetes); researchers are working with different methodologies to identify differences in proteins, immune factors, growth factors and genes in the blood that are associated with mental illnesses. Other diagnostic possibilities include electroencephalography or EEG, which measures the brain's electrical activity, similar to how an electrocardiogram or EKG identifies problems with the electrical activity of the heart. Magnetoencephalography or MEG is another tool being developed to map brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain. Behavioral and cognitive tests, measuring a person's thinking, reaction time and memory may also support diagnosis.<sup>2</sup>

### Sources:

- <sup>1</sup> Dr. Thomas Insel, National Institute of Mental Health Director's Blog: "Genomics: The Future is Bright," March 2011
- <sup>2</sup> National Public Radio, June 13, 2012: 'Could Brain Scans Reveal The Right Treatment For Depression?' by Nancy Shute
- <sup>3</sup> bbrfoundation.org

# The Power of Partnership

## A Personal Connection



Frances and Robert Weisman



Danielle M. Andrade, M.D.

*"Supporting research is essential in order to advance our knowledge as to how the brain works and what can go wrong to cause mental illness. Focused research is certain to lead to relief and comfort for the millions who struggle daily with these illnesses. Our participation for over 20 years with the Brain & Behavior Research Foundation, and as Research Partners for the past 13 years, gives us the opportunity to support and motivate the endeavors of the Young Investigators who are focused on these complex issues."*

Frances and Bob Weisman have a Research Partnership with Danielle M. Andrade, M.D., of the University Health Network at the University of Toronto, a 2010 NARSAD Young Investigator Grantee.

## Partner with a NARSAD Grantee:

- Select a scientist in your area of interest, an institution or geographic area
- Develop a personal relationship with your scientist and learn more about their work through personal meetings and conversations
- Receive progress reports that outline their research findings
- Your support will be recognized in published work resulting from the research

**For information on becoming a Research Partner or to support research in other ways, please call (800) 829-8289 or (516) 829-0091, or visit our website at [bbrfoundation.org](http://bbrfoundation.org)**

# Heartache and Hard-Won Progress

Love, support, and good education:  
not enough to preclude mental illness in this family,  
but enough to help them cultivate recovery

Miriam Katowitz and Arthur Radin were able to provide their children with a good home and excellent education, as well as their own personal examples of achievement. Arthur is a partner of longstanding in a well-respected Manhattan accounting firm, and Miriam, also a Certified Public Accountant (CPA), has worked in both the private and nonprofit spheres, and is currently acting controller of the 24-campus City University of New York (CUNY) system.

Their parental care has been rewarded. Their daughter is a construction project manager and their younger son, a recent Ph.D. graduate from the Massachusetts Institute of Technology (MIT), is a postdoctoral fellow in political science at the University of Southern California.

What Miriam and Arthur discovered they could not provide was a bulwark against mental illness. Their older son, David, has schizophrenia. He had barely begun his first semester at college when he had his first psychotic episode. "He couldn't get to classes, couldn't keep up," Miriam recalls, "and within a week or two, he was hospitalized."

David is now 44, and over the ensuing years, he and his family have experienced both heartache and hard-won progress. David is luckier than some. After a harrowing beginning in which he was treated with haloperidol (Haldol®), which worsened his condition and left him with traces of tardive dyskinesia, a side effect that causes involuntary, tic-like movements, he was stabilized on risperidone (Risperdal®), one of the atypical antipsychotics. The development of this class of medications was sparked by the work of Brain & Behavior Research Foundation Scientific Council Member Herbert Meltzer, M.D. with the support of a 1988 NARSAD Grant. He tested clozapine with patients with treatment-resistant schizophrenia and received FDA approval in 1989. Although not effective for all patients, this class of antipsychotics has been life-saving for the millions of patients who respond positively to them.

When these medications were first introduced, many psychiatrists were unaware of them. David was lucky in that his psychiatrist was aware of the newly available medications, and



Miriam Katowitz and Arthur Radin, Foundation Board Member

What Miriam and Arthur clearly do understand is that scientific research offers the best hope for families like theirs.

they helped alleviate his symptoms. The downside is the side effect experienced by many: significant weight gain leading to diabetes, what doctors call metabolic syndrome, which David lives with.

Nonetheless, compliance with his medication, along with psychotherapy and the unwavering support of his family, has made it possible for David to live an independent life. After two years at a residential mental health facility in Baltimore, and shorter stays in halfway houses, he is now in his own apartment in Baltimore. Remaining in Baltimore provides continuity with the health professionals who have been treating him over the years. He does volunteer work in a hospital, filing records for medical practices.

David lives independently, but not without limitations. Schizophrenia can be socially isolating. The child who grew up in Brooklyn Heights, hanging out with friends and playing soccer and basketball, as an adult with schizophrenia has had difficulty relating to people. While in the hospital, and later, in a supportive housing program, he had people around him. His current situation, although positive in terms of his ability to take care of himself, is isolating, a situation his family and therapists are trying to improve.

For a long time David had difficulty even being with those he loves. In that regard, Miriam reports, there has recently been significant improvement. "He's able to spend more time with us and to converse a little more. We don't have to drag him out of his room when he comes to visit."

Schizophrenia effects cognitive function, the ability to think clearly, to make decisions and act upon them. Another recent improvement: David has begun reading the newspaper again, mostly the sports section, and his old interest in basketball has revived.

Remembering the boy who shortly before becoming ill had graduated from an elite, highly competitive high school, Miriam remarks, wistfully, that of the three children David "might have been the brightest."

The onset of David's illness coincided with the founding, in 1987, of NARSAD, now the Brain & Behavior Research Foundation. Miriam and Arthur learned of its existence through "an ad in the paper," Miriam recalls. "We gave a little money, and then we thought, 'what else can we do?'"

It turns out, quite a lot. Their involvement grew as the organization grew, as generous contributors in time and money. Arthur has served on the Foundation's Board of Directors for five years, the last three years as its Treasurer. And, since 1997, as participants in the Research Partners program, which pairs donors with scientists working in a field of interest to the donors, the couple has supported 11 NARSAD Young Investigator Grantees working on various aspects of schizophrenia, including the use of new technologies, such as brain imaging, to explore brain function abnormalities.

Miriam enjoys getting to know the scientists she sponsors. "I like being able to hear them speak and to talk to them," she says, "although I admit I don't always understand what they say." What Miriam and Arthur clearly do understand is that scientific research offers the best hope for families like theirs.

Miriam and Arthur have seen at firsthand how important NARSAD Grants are for getting scientists with good ideas to enter the field—and for ultimately making important advances in understanding and treating mental illness. Knowing full well that not every idea pans out, Miriam acknowledges: "It's a gamble, but if you don't try, you won't ever succeed. ❖"



## Klerman-Freedman Prizes

### Recognizing Exceptional Research by NARSAD Young Investigator Grantees

Seven young scientists will be recognized with the Foundation's Annual Klerman and Freedman Prizes on Friday July 26, 2013 in New York City. These prizes pay tribute to Drs. Gerald L. Klerman and Daniel X. Freedman, whose legacies as researchers, teachers, physicians and administrators have indelibly influenced neuropsychiatry. The prizewinners are selected by committees within the Foundation's Scientific Council, a volunteer group of 138 distinguished scientists across disciplines in brain and behavior research.

### 2013 Klerman Prizewinner for Exceptional Clinical Research

*The Klerman Prize was established in 1994 by Myrna Weissman, Ph.D., in memory of her late husband, Gerald Klerman, M.D.*

**James McPartland, Ph.D.**, Assistant Professor of Child Psychiatry and Psychology and Director of the Developmental Disabilities Clinic at Yale University, is being honored for his discovery of a novel electrophysiological 'marker' of eye contact that predicts social ability in children and is disrupted in children with autism spectrum disorder (ASD). The new marker may enable early intervention techniques in very young children to slow progression of the illness and possibly even offer preventive possibilities.

In research initiated with his 2009 NARSAD Young Investigator Grant, supported by his Research Partnership with the Atherton Foundation, Dr. McPartland and colleagues have been measuring electrophysiological indices of social perception during the first months of life in infants at risk for developing ASD. The research team uses electro-

*"The NARSAD Young Investigator Grant offered essential support at a critical juncture in my career. By ensuring research time and resources to invest in a lab, it empowered me to develop a program of research and advanced my goal of bettering the lives of children and families affected by neurodevelopmental disabilities."*

encephalography (EEG) to record electrical activity in the brain and coordinates it with eye tracking measurements of eye

position and movement. To conduct their experiments, the team developed a set of computer-generated faces capable of producing controlled, realistic gaze changes and emotional expressions.

The researchers measured brain activity in subjects during face-to-face interactions to measure eye contact as a predictor of social ability. They found diminished eye contact in children with ASD and their data showed abnormal developmental trajectories by six months of age. The team is currently assessing whether this marker can advance the objective of prevention by referring children before the onset of behavioral symptoms. They are also interested in using the marker to assess treatment outcome.

A graduate in psychology, magna cum laude, from Harvard University, Dr. McPartland earned a Ph.D. in child psychology at the University of Washington, Seattle, and completed clinical training at the Yale Child Study Center, where he began his independent research.



## 2013 Klerman Prize Honorable Mentions



**Andrea Danese, M.D., Ph.D.**, Associate Professor at the Institute of Psychiatry, King's College London, is being recognized for his findings that maltreated children are at heightened risk for treatment-resistant depression, and for providing the first evidence that inflammation contributes to the development of depression among this group.

Dr. Danese studies stress and stress-related psychopathology in young people. He discovered immune and metabolic abnormalities in individuals with a history of childhood maltreatment. These often overlooked abnormalities are now showing great promise as targets for treatment of difficult-to-treat cases of affective and psychotic disorders. It was with his 2009 NARSAD Young Investigator Grant research project, supported by his Research Partnership with Vital Projects Fund Inc., that he linked inflammation in those maltreated as children with later development of treatment-resistant depression.

Dr. Danese trained in medicine and adult psychiatry at the University of Pavia School of Medicine, Italy, and in child and adolescent psychiatry at King's College London, where he earned a Ph.D. He also studied epidemiology at the London School of Hygiene and Tropical Medicine.



**Carmen Andreescu, Ph.D.**, Assistant Professor of Psychiatry at the University of Pittsburgh, is being honored for identifying neural markers of treatment response in late-life generalized anxiety disorder (GAD). Although the most prevalent anxiety disorder in the elderly, and more prevalent than depression, GAD has been the least studied, least understood and probably least treated mental illness in the elderly.

In her 2009 NARSAD Young Investigator Grant project, Dr. Andreescu administered the antidepressant citalopram (Celexa®) to a group of previously untreated elderly GAD patients. Post-treatment brain scans revealed significant changes in the neural networks involved in emotion regulation, including greater prefrontal connectivity. (The prefrontal cortex regulates complex cognitive, emotional and behavioral functioning.) However, a persistent problem with GAD is its high rate of post-treatment relapse. Dr. Andreescu

is now applying her findings toward developing more personalized strategies so as to improve treatment response rates.

Dr. Andreescu is a graduate of the University of Medicine and Pharmacy "Carol Davila" in Bucharest, Romania. She was a fellow in geriatric psychiatry at the Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, before her faculty appointment at the University.



**Daniel J. Mueller, M.D., Ph.D.**, Associate Professor of Psychiatry and Head of the Pharmacogenetics Research Clinic at the University of Toronto's Centre for Addiction and Mental Health, is being recognized for his work to develop genetically-based algorithms in patients to optimize individual treatment plans (personalized medicine).

In his 2009 NARSAD Young Investigator Grant project, Dr. Mueller and his team identified important gene variants associated with excessive weight gain induced by antipsychotic medications, which can lead to symptoms that shorten life span. Genetic predictors of negative metabolic effects would help to avoid trial-and-error switches of medication, improve patient compliance and help prevent premature death.

Dr. Mueller earned his M.D. at the University of Bonn, Germany, and his Ph.D. at Charité University Medicine Berlin. He completed postdoctoral fellowships at Bonn and at the Centre for Addiction and Mental Health at the University of Toronto. The research supported by his NARSAD Grant has been cited in 28 published papers (to date) by Dr. Mueller and his colleagues.

## 2013 Freedman Prizewinner for Exceptional Basic Research

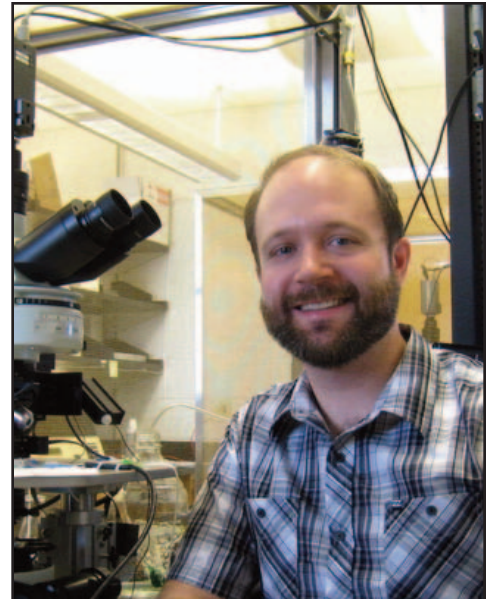
*The Freedman Prize was established in 1998 in honor of the late Daniel X. Freedman, M.D., a founding member of the Foundation's Scientific Council.*

**Garret D. Stuber, Ph.D.**, Assistant Professor of Psychiatry and Cell Biology and Physiology at the University of North Carolina School of Medicine, is being honored for his research to dissect the role of dopamine and non-dopamine neurons in the midbrain. Dopamine is a neurotransmitter involved in the transmission of messages between nerve cells, and midbrain dopamine neurons have been thought to play a major role in regulating behavioral responses in addiction, anxiety, depression and other neuropsychiatric illnesses. Little to date has been known about the mechanisms that control their activity, so the Stuber laboratory engaged a variety of cutting-edge technologies in an attempt to identify their role in mediating behaviors that might lead to new treatment targets.

...the Stuber laboratory engaged a variety of cutting-edge technologies in an attempt to identify their [dopamine neurons] role in mediating behaviors that might lead to new treatment targets.

A major boost in understanding dopamine neurons came with the lab's application of a revolutionary new technology called optogenetics, which was developed by Brain & Behavior Research Foundation Scientific Council Member Karl Deisseroth, M.D., Ph.D., while he, himself, was a 2005 NARSAD Young Investigator Grantee (see p. 5 Interview). Optogenetics combines optical and genetic methodologies to allow researchers to manipulate neural circuits and control behavior in laboratory animals with exquisite precision. Dr. Stuber states that his use of optogenetics has been "incredibly fruitful" and that "with the support of the NARSAD Grant, I was able to generate data that was essential for many other successful grant applications, including one from the National Institute on Drug Abuse."

Dr. Stuber earned a B.S. degree in Psychology at the University of Washington, Seattle, in 2000, and a Ph.D. in Neurobiology at the University of North Carolina at Chapel Hill in 2005. After a turn as a visiting scientist at the Netherlands Institute of Neuroscience, in Amsterdam, he completed a postdoctoral fellowship at the University of California at San Francisco, where he began his NARSAD Grant-supported research. He returned to the University of North Carolina as a member of the faculty in 2010.



"with the support of the NARSAD Grant, I was able to generate data that was essential for many other successful grant applications, including one from the National Institute on Drug Abuse."

## 2013 Freedman Prize Honorable Mentions



Research by **David J. Foster, Ph.D.**, Assistant Professor of Neuroscience at Johns Hopkins University School of Medicine, is being recognized for his work, and the innovative tools he developed, to study the neural basis of memory. Nerve cells of the hippocampus region in the brain play important roles in the formation of memory and their dysfunction has been linked to disorders such as schizophrenia.

Dr. Foster combines advanced electrophysiological, computational and behavioral approaches in his research studies. In his NARSAD Grant-supported project, in order to investigate the coordinated activity of hippocampal neurons in mouse models of mental illnesses, he and his team developed tools that have allowed them to record and examine the simultaneous activity in large groups of hippocampal neurons in normally behaving mice.

“The hippocampus has been shown to be overactive in schizophrenia patients, exactly mirroring the mouse-model results we found ... These insights have the potential to drive new therapeutic approaches.”

Explaining the significance of his NARSAD Grant research, Dr. Foster says: “Our basic research promises to have a large impact on the future understanding of schizophrenia since we can now examine the neural mechanisms of functions such as memory and planning in precise spatial and temporal detail, and examine impairments to these functions in the huge array of genetic mouse models which are available.”

Dr. Foster is a graduate of Imperial College, in London and he earned a Ph.D. in computational neuroscience at Edinburgh University, Scotland. He joined the faculty at Johns Hopkins University School of Medicine in 2009.



**Hiroki Taniguchi, Ph.D.**, a Research Group Leader at the Max Planck Florida Institute for Neuroscience, is being recognized for research toward understanding what causes the dysfunction in the GABAergic system that has been implicated in schizophrenia and autism. (GABA is a neurotransmitter that slows down activity in the nervous system.) Unraveling the development and function of different types of GABAergic neurons is critical to understanding how the normal brain works and how it loses normal functions in disease states. This has been extremely difficult due to the lack of reliable strategies to manipulate various subtypes of GABAergic neurons. This lack is what Dr. Taniguchi’s research is helping to address.

Postmortem brains of schizophrenia patients show changes in a class of GABAergic neurons called chandelier cells. Dr. Taniguchi and his colleagues developed the first mouse-genetic model to identify spatial and temporal origins of chandelier cells, as well as strategies to study the life cycle of these cells, from development to function, in normal and abnormal brains. His results now make it possible to examine the hypothesis that selective deficits in GABAergic chandelier cells disrupt function in other cells called pyramidal neurons, leading to dysfunction in working memory, a condition typical in schizophrenia. These results now make it possible to ask many different questions about development and functions in the GABAergic system.

A graduate of Osaka University, Dr. Taniguchi earned a Ph.D. in Developmental Neurobiology from the National Institute for Basic Biology in Japan. Of his NARSAD Grant project, conducted as a research investigator at Cold Spring Harbor Laboratory in New York, he says: “the generous support of the NARSAD Grant ... had a significant impact on my grant acquisition and career development. I won the most prestigious grant in Japan ...” Dr. Taniguchi’s research was supported by a Research Partnership with The Essel Foundation.



# New Treatments

## FDA Expedites New Psychosis Treatment Developed by Scientific Council Member

Herbert Meltzer, M.D., Foundation Scientific Council Member, NARSAD Grantee and Foundation Lieber Prizewinner, has dedicated 25 years to researching and developing pimavanserin, a new medication for the treatment of psychosis associated with Parkinson's disease. The U.S. Food and Drug Administration is expediting approval of the therapy as there are currently no approved treatments for this debilitating psychiatric condition experienced by almost 60% of patients with Parkinson's disease. Dr. Meltzer, Professor at Northwestern Feinberg School of Medicine, developed pimavanserin with ACADIA Pharmaceuticals. He says pimavanserin "can be expected to have a big impact shortly in the treatment of all types of psychosis, especially schizophrenia and psychotic mood disorders."

**Source:** Herbert Meltzer, M.D. and *Schizophrenia Research*

## Doctor's Order:

### Exercise for Treatment of Depression

In a first-of-its-kind effort, specific exercise guidelines stating the type, intensity and duration of physical activity recommended for patients with major depressive disorder have been developed by NARSAD Grantees Chad Rethorst, Ph.D. and Madhukar Trivedi, M.D. of the University of Texas Southwestern Medical Center. To truly deliver the desired antidepressant effect, the doctors suggest 45-60 minutes of aerobic exercise three to five times a week at 50-85% of the patient's maximum heart rate, and suggest lower and upper body weight training (three sets of eight repetitions using weights that are 80% of the maximum the patient can lift).

**Source:** *Journal of Psychiatric Practice*, May 2013

## Brain's Cannabinoid Receptors Have Potential Role in PTSD Treatment

NARSAD Grantees Alexander Neumeister, M.D., Daniele Piomelli, Ph.D. and Marc N. Potenza, Ph.D. are among researchers who conducted the first human study using brain imaging to confirm the role of endocannabinoids (a protein produced by the brain) and their receptor cannabinoid type 1 ("CB1") in post-traumatic stress disorder (PTSD). Their comparison of brains of people with and without PTSD revealed that PTSD patients had lower concentrations of the neurotransmitter anandamide (a neurotransmitter associated with pleasure, motivation and memory) and more CB1 receptors in brain areas associated with fear and anxiety. Building on these neurobiological findings may lead to the first medication designed specifically to treat PTSD.

**Source:** *Nature - Molecular Psychiatry*, May 2013, online



**With a Will**

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A gift to the Foundation supports cutting-edge mental health research and future breakthroughs.

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For more information on planning your gift, please contact our Planned Giving office at (800) 829-8289 or (516) 829-0091.

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# Glossary

**anandamide** (p. 23): a neurotransmitter associated with pleasure, motivation and memory; targets cannabinoid receptors in the brain and central nervous system, which also are the target of marijuana and the body's naturally occurring endocannabinoids.

**atypical antipsychotics** (p.17): a class of medications, also called second-generation antipsychotics, used to treat schizophrenia. Two examples include Clozapine (Clozaril®) and Aripiprazole (Abilify®). They are "atypical" in that they do not generally cause the involuntary movements often caused by earlier, first-generation antipsychotic medications. This class of medications were developed following the breakthrough NARSAD Grant-supported research of Dr. Herbert Meltzer in 1988 to test clozapine on patients with treatment-resistant schizophrenia and led to FDA approval of the treatment in 1989.

**endocannabinoids** (p. 23): compounds produced by the body which interact with and activate cannabinoid receptors in cells in various parts of the body, including the brain.

**exome** (p. 4): the comparatively tiny portion of a complete genome (less than 2% of the human genome) that contains only the genes that issue instructions for manufacturing proteins. Sequencing only the exome saves time and money in studying genes and proteins implicated in illness.

**exons** (p. 4): portions of immature messenger-RNA (m-RNA) molecules that contain code for the production of proteins. These are preserved, while enzymes splice out non-essential non-coding portions, called introns, to make a mature m-RNA.

**genome** (p. 4): the complete DNA sequence of an organism, which includes its full set of protein-coding genes in addition to a vast amount of regulatory DNA.

**genomic sequencing** (p. 4): determining the order of the chemical units, called bases or nucleotides, that comprise a full genome. The human genome contains about 3 billion pairs of bases.

**metabolic syndrome** (p.18): a cluster of symptoms that can include obesity, abnormal cholesterol and triglyceride levels, and diabetes that can lead to cardiovascular disease and premature death; a common side effect of antipsychotic medications.

**nucleotides** (p 4): the four chemical bases, or "letters," of the DNA "alphabet": adenine (A), guanine (G), cytosine (C), and thymine (T).

**serotonin** (p. 3): a neurotransmitter, or chemical messenger, which, when improperly produced and/or regulated, is thought to be involved in a range of mental illnesses, including depression.

**serotonin receptors** (p.3): molecules on neurons, or nerve cells, that bind the neurotransmitter serotonin.

**translational research** (p. 6): research designed to apply concepts and technologies developed in basic research in the clinic, often in projects involving patients.

**working memory** (p. 22): temporary or transitory memory needed for a short time to complete a task.

**X-ray crystallography** (p.3): a technology in which X-ray beams are fired at a crystallized form of a protein, revealing, via refraction patterns, the protein's atomic structure. An important tool in medication development and basic research.

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**August 13**  
2:00 p.m. ET

**Rapid-Acting Antidepressant (Keta-  
mine) and Next Generation Therapies**

**Carlos A. Zarate, M.D.**

Chief, Section on the Neurobiology and Treatment of  
Mood Disorders and Experimental Therapeutics, and Patho-  
physiology Branch, National Institute of Mental Health;  
NARSAD Grantee



**September 9**  
2:00 p.m. ET

**Childhood-Onset Schizophrenia:  
The Study and Treatment**

**Judith L. Rapoport, M.D.**

Chief, Child Psychiatry Branch, National Institute of Mental  
Health; NARSAD Grantee, Foundation Scientific Council  
Member



**October 8**  
2:00 p.m. ET

**Molecular Mechanisms  
of Drug Addiction**

**Eric J. Nestler, M.D., Ph.D.**

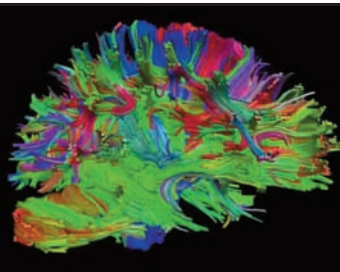
Nash Family Professor of Neuroscience, Chair, Department  
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**Evening**  
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## Investing in Breakthroughs — To Find a Cure

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

### OUR CREDENTIALS:

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