



Focus on:  
**Genetics**

## Research News

- 2 RESEARCH DISCOVERIES  
IN THE NEWS
- 5 SOLVING THE  
SCHIZOPHRENIA PUZZLE  
Mary-Claire King, Ph.D.
- 10 FREQUENTLY ASKED  
QUESTIONS ON GENETICS
- 14 NEW TREATMENTS/  
THERAPIES
- 15 2014 NARSAD INDEPENDENT  
INVESTIGATOR GRANTS  
40 New Innovative Research  
Grants Funded
- 24 GLOSSARY

## Features

- 9 GENETICS FEATURE  
What Makes Some Genes  
Disrupt Brain Development?
- 12 STAVING OFF "THE DARKNESS"  
A Family Story

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## Jeffrey Borenstein, M.D.

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In a profile in *The New York Times* in February, Tom Insel, M.D., Director of the National Institute of Mental Health, said that “the only way to build a real psychiatric science is from first principles—from genes and brain biology.”

In this issue, we profile some major achievements in understanding the genetics of mental illness. We also present 40 new NARSAD Grant projects that Dr. Robert Post, Chair of the NARSAD Independent Investigator Grant Selection Committee of the Foundation’s Scientific Council describes as “cumulatively and exponentially advancing what is known about the brain and how to treat its illnesses.”

The modern era of genetic research, which has revolutionized biological science, is a scant 70 years old. It was exactly 70 years ago—in 1944—that a team of scientists at The Rockefeller Institute for Medical Research (now The Rockefeller University) reported that genes are made of DNA. Barely nine years later, Drs. Francis Crick and James Watson worked out DNA’s double helix structure, the first step toward deciphering the machinery through which genes orchestrate life. The decades since have witnessed a proliferation of discoveries of the role of genetic mutations in disease and the completion of The Human Genome Project, which successfully identified and mapped all of the genes in the human genome.

In some areas of disease, specific genetic mutations have been found to be causative, such as the breakthrough work of Dr. Mary-Claire King in breast cancer research. She discovered a mutation in a gene now known as BRCA1, the first inherited gene for breast cancer to be discovered, that is now enabling diagnosis of women at risk and development of targeted treatments. With the support of a NARSAD Grant, Dr. King has turned her focus to identifying genetic mutations that cause mental illness; we share an Interview with her on page 4.

Ongoing technological developments are now rapidly and significantly advancing the capacity to learn how the brain develops and how biology’s most complex organ works at the genetic and molecular level. Dr. Daniel Weinberger describes some groundbreaking research in this area on page 9.

Your support is crucial to advance this “real psychiatric science” that Dr. Insel speaks of. Without this support, many of the projects we fund with NARSAD Grants would never be initiated. Thank you!

Sincerely,

Jeffrey Borenstein, M.D.  
 President & CEO

# Research Discoveries in the News

## Progress in Identifying Sets of Genes Linked to Schizophrenia

A team led by scientists who have received funding from the Brain & Behavior Research Foundation has searched the protein-encoding portions of the human genome—the “exome”\*—for rare variations (so called “point mutations” and small insertions and deletions) that can help explain what goes wrong in schizophrenia. Their work adds to a growing body of evidence indicating that the disease is not caused by one single gene or mutation, but by many different genetic anomalies that occur in a large number of combinations.

Identifying genetic regions, or better, pinpointing specific genes in which mutations confer higher risk for illness, is extremely valuable to developing better diagnostic tools and treatments.

On January 22, 2014, a team that included **Shaun M. Purcell, Ph.D.**, (bottom left) recipient of a 2006 NARSAD Young Investigator Grant, and **Pamela Sklar, M.D., Ph.D.**, (bottom right) who has received three NARSAD Grants (Young Investigator in 1995 and 1998 and Independent Investigator in 2006), reported in *Nature* the results of a large study of the exome. These protein-encoding portions of our DNA, which comprise less than 2 percent of the full human genome, are thought to harbor a large majority of disease-causing mutations. This is because the protein output of such genes is so vital to all of our bodily processes and functions, including those of the brain.

Dr. Purcell, of the Broad Institute, Harvard University and

the Icahn School of Medicine at Mount Sinai, and Dr. Sklar, also at Mount Sinai, with colleagues, scrutinized the protein-coding DNA of more than 5,000 people in a Swedish sample: 2,536 had schizophrenia and 2,543 were healthy controls. The team was able to identify several small sets of genes—about 50 genes altogether—in which rare mutations were significantly more common in patients with schizophrenia than in healthy people. “We found out that the rarest, most severe mutations—the most likely to damage a protein—contribute to schizophrenia risk,” explained Dr. Sklar.

“Despite the considerable sample sizes, no individual gene could be unambiguously implicated,” commented Dr. Purcell. “Taken as a group, however, genes involved in neural function and development showed greater rates of disruptive mutations in patients. This finding suggests that many genes underlie risk for schizophrenia and so any two patients are unlikely to share the same profile of risk genes.”

The team found that the genes identified encode proteins that work together at the synapse\* to facilitate communication between neurons. It has long been suspected that schizophrenia might stem from problems at the synapse, but there has been no conclusive evidence. “Our work adds to prior work that has implicated disruption of synaptic processes in schizophrenia,” the team concluded. “Although we cannot yet use rare mutations to partition patients into more homogeneous clinical groups, this remains among our central goals.”



**TAKE AWAY:** New study identifies genetic changes in schizophrenia that manage the strength of connections and the communication between brain cells.

Shaun M. Purcell, Ph.D.; Pamela Sklar, M.D., Ph.D.



## Effective Brain Communication Impeded by “New” Genetic Mutations

One of the mysteries of schizophrenia and other neuropsychiatric illnesses with heritable genetic characteristics is that even though patients are less likely than healthy people to have children, the frequency of illness does not seem to decline. The incidence of schizophrenia, for example, is steady at about one percent of the population, over time and across human societies.

One important reason for this is that while schizophrenia has strong genetic roots, it is sometimes not an inherited genetic illness. Some unknown fraction of cases is caused by *de novo* gene mutations (new mutations that appear in a child but are not found in either parent). These mutations are the result of a normal error rate in the combining of genetic material that occurs whenever a sperm fertilizes an egg. The error rate is very small; all of us have such errors in our genome, but the key question is whether they can interrupt the work of key genes needed for normal functioning. (See also page 5, Interview with Dr. Mary-Claire King.)

In a study led by 2012 Brain & Behavior Research Foundation Lieber Prizewinners, **Drs. Michael O’Donovan** (bottom left) and **Michael Owen** (bottom right) of Cardiff University in the United Kingdom, a multi-institutional team conducted the largest study to date examining the protein-coding portions of the genome in so-called “schizophrenia trios.” These family groups are comprised of a child diagnosed with schizophrenia and parents. The study sample included 623 trios where the DNA of parents allowed the researchers to identify mutations in the

genome sequences of the affected children that were not present in either parent.

The researchers report, in a paper published in *Nature* on January 22, 2014, that they were able to identify *de novo* mutations in children with schizophrenia. This may help explain why schizophrenia persists in the human population at a constant level. Importantly, their findings also point to similar causative genetic malfunctions as the paper published by Drs. Sklar, Purcell and colleagues described on page 2. In both of these new studies, mutations identified in patients with schizophrenia were disproportionately found in genes encoding proteins needed for proper cell-to-cell communication and for regulation of the plasticity\* or strength of synapses that had been implicated in a previous study by Drs. Owen and O’Donovan.

Dr. Owen highlighted that “this degree of convergence from several studies is unprecedented in schizophrenia genetics and tells us that for the first time we have a handle on one of the core brain processes that is disrupted in the disorder.”

The findings also suggest that these mutations may be shared by other brain and behavior disorders. Dr. O’Donovan commented: “The fact we’ve been able to identify a degree of overlap between the underlying causes of schizophrenia and those in autism and intellectual disability suggests that these disorders might share some common mechanisms.”



**TAKE AWAY:** “De novo” genetic mutations—those changes in DNA sequence that are not directly inherited—are linked to altered synaptic processes in schizophrenia.

Michael O’Donovan, M.D., Ph.D.; Michael Owen, M.D., Ph.D.

\* Refer to glossary on page 24.





## Developing a Growth Chart for Brain Development

A team of scientists led by co-winners of the Foundation's 2009 Lieber Prize for Outstanding Achievement in Schizophrenia Research, **Raquel E. Gur, M.D., Ph.D., and Ruben C. Gur, Ph.D.**, (bottom left and center) and including 2010 NARSAD Young Investigator Grantee **Theodore Satterthwaite, M.D.**, (bottom right) have devised a new method called cognitive growth charting to determine when, during childhood, early symptoms of schizophrenia and psychosis can show up and with what intensity.

This new work, published online February 05, 2014 in the journal *JAMA Psychiatry*, is important for several reasons. It has been widely demonstrated that early intervention in psychiatric illness improves outcomes. In psychotic disorders in particular, if the illness can be identified and treated prior to full blown psychosis, the chances of effectively treating the illness are greatly increased. There are currently, however, no biological diagnostic tests (such as a blood test for diabetes or an EKG for heart disease) that effectively predict psychosis. It remains very challenging for parents, patients and even medical practitioners to predict and identify when psychiatric illness is in early development.

The research team at the University of Pennsylvania first conducted studies on a large sample of about 10,000 youths aged eight to 21 who were seen at the Children's Hospital of Philadelphia for general pediatric services. For this current study, they focused on over 2,000 children and adolescents with psychotic symptoms; all of the

children were genotyped and then evaluated with a one-hour computerized battery of cognitive tests. The team was able to develop a statistical measure indicating whether and by how much a given participant lagged in neurocognitive development, compared with individuals demonstrating healthy development.

The study results reveal that children who have psychotic features begin to show signs of neurocognitive delay very early. Cognitive performance suggestive of developmental delay was evident at age eight. The growth charts suggest delays across neurocognitive categories. After age 16, the divergence becomes wider.

"Our study demonstrates that both cognitive delay and psychotic symptoms co-occur and are detectable at an early age," the team reports. The developmental delays were similar in affected males and females. Those with more pronounced symptoms of psychosis showed a greater developmental lag. Females had less severe and later onset of symptoms, on average.

Much more research is needed on what is called the "prodromal"\* (early developmental) stage of schizophrenia and other brain and behavior disorders. But this work makes an important step forward in detecting irregular brain development at an early age that could greatly facilitate detection of psychiatric illness in development—rather than having to wait for the full blown illness to manifest.



Raquel E. Gur, M.D., Ph.D.; Ruben C. Gur, Ph.D.; Theodore Satterthwaite, M.D.

**TAKE AWAY:** A new method of measuring cognitive and emotional development in youth may greatly increase possibilities for early intervention in mental illness.

# Solving the Schizophrenia Puzzle

## A World-Renowned Breast Cancer Geneticist Tackles the Genetics of Serious Mental Illness

In 2006, Mary-Claire King, Ph.D, one of the world's most well-respected geneticists, was awarded a NARSAD Distinguished Investigator Grant to work on schizophrenia genetics.

"I became involved when James Watson, Ph.D. [Nobel laureate for his work with colleagues in discovering the double helix structure of DNA, life's genetic code book] and Connie and Steve Lieber [President Emerita and Chairman of the Board, Brain & Behavior Research Foundation] asked me to turn my attention to the problem of serious mental illness," she recalls. It made sense, she says, "because I'm a geneticist, and geneticists have tools to ask important questions about complex illnesses."

In her early work, beginning in the early 1970s, Dr. King began asking important questions about breast cancer genetics. After 17 years of great persistence, she proved that a specific genetic mutation, passed down from generation to generation, accounted for an important percentage of breast and ovarian cancers. The mutated gene was named BRCA1; another, called BRCA2, was found later. Women who possess a mutated version of either gene have a significantly higher risk of developing breast cancer.

For the past eight years, Dr. King and her team have been bringing their expertise to advance the understanding of genetics in schizophrenia. Like cancer, the causes and pathology of mental illness are highly complex. And like cancer, in addition to inherited genetic risk factors, environmental exposures can play a role in causation. Dr. King is interested in the genetic component of causation. She and her colleagues aim to pinpoint the kinds of genetic mutations that cause pathologies associated with schizophrenia; identify the



### Mary-Claire King, Ph.D.

Professor of Genome Sciences and of Medicine (Medical Genetics), University of Washington School of Medicine

2006 NARSAD Distinguished Investigator Grantee

Foundation Scientific Council Member

Mary-Claire King in her office examining DNA sequence data in the 1990s, after publishing the results of her 17-year quest to identify a breast cancer gene (now known as BRCA1).

*Image courtesy of Mary Levin/University of Washington*



biological consequences of these mutations at the level of cells and the entire brain; and use this knowledge to inform the development of new targeted treatments.

### DECIPHERING GENETIC VARIATIONS

When a sperm fertilizes an egg, a mother and father's genetic material combines to form the DNA of a new individual. In addition to the parental

mutations might help explain one of the deepest mysteries about schizophrenia: its persistence in the human population. If people with schizophrenia have fewer children, why does the occurrence rate of schizophrenia not decline over time?

In her NARSAD Distinguished Investigator Grant project, Dr. King began work on schizophrenia by comparing

genes that regulate functions known to be crucial in early brain development. Equally important, the researchers found that the genes being interrupted by the CNVs found in healthy people did not link to these developmental processes; in fact no particular pattern emerged from the impact of CNVs in the healthy controls.

In the past year, Dr. King and colleagues have repeated the experiment with a larger group and with much more advanced technology. Now their sample consists of DNA from entire families: "quad" sets, each with two unaffected parents and two children: one with schizophrenia, the other healthy. This made it possible to precisely study the *de novo* mutations. "We wanted to know, what are the new mutations occurring in these children with the illness, compared with their well siblings—mutations that neither parent has?"

Their results were published in *Cell* in August 2013, and again, the results were significant. "We sequenced the full genomes of all four family members in 105 families. The critical discovery: if you look only at mutations that are damaging—a minority of the total—and you ask whether there are more of these in patients, the answer is yes. Disproportionately, the mutations are found in genes affecting aspects of neurodevelopment."

Dr. King's interpretation of the importance of these results and how they suggest a path toward new therapies of the future are discussed on the following page.

**"The critical discovery: if you look only at mutations that are damaging—a minority of the total—and you ask whether there are more of these in patients, the answer is yes. Disproportionately, the mutations are found in genes affecting aspects of neurodevelopment."**

genetic material, during the process of fertilization a tiny percentage of new genetic variations occur and become a part of the baby's DNA. Thus, there is a constant stream of new mutations being introduced into human genetic material. These mutations, known as *de novo* mutations because they do not occur in either parent, account for approximately 175 DNA "letters" per person, per generation. (DNA is made up of four letters, or chemical bases, that combine in various ways to spell out the full genome.) Of the human genome's three billion letters, most variations "are biologically neutral; they have no effect on our lives at all," says Dr. King.

"The question becomes," explains Dr. King, "where do these new mutations happen, in what genes, and which ones among them actually matter?" Dr. King says that *de novo*

the DNA of healthy people ("healthy controls") with that of patients diagnosed with the illness. When they first started this work, the best technology available at the time enabled them to search for a rare kind of structural mutation of the genome called copy-number variations,\* or CNVs. These are often large stretches of the genome that contain extra DNA or missing DNA.

### THE FIRST IMPORTANT FINDINGS

Dr. King's team found rare CNVs in both healthy people and in people with schizophrenia. But these mutations were three to four times more frequent in those with schizophrenia; they were even more likely in those who had severe, early-onset illness. The results, published in the journal *Science* in April, 2008, were powerful because a pattern emerged: the researchers were able to link specific rare CNVs with the interruption of



# Next Generation Therapies for Schizophrenia: From Specific Genetic Mutations to Targeting Repair Pathways

Mary-Claire King calls it her “*Anna Karenina* Hypothesis.” Just as Tolstoy observed that “every unhappy family is unhappy in its own way,” recent results that she and colleagues have obtained suggest that someone who sustains a potentially disease-causing *de novo* gene mutation is quite possibly the only person in the world with precisely that mutation.

Incredible as this sounds, it is likely true. Dr. King describes this class of very rare disruptive mutations in her most recent schizophrenia study (published in *Cell* in 2013) as “essentially private mutations,” so specific are they to those who have them. “We found 55 affected people had 54 different disruptive mutations,” she says. That is, only 1 of the 55 was seen in more than one patient.

Does this mean that every person with schizophrenia caused by a new mutation will need a unique form of therapy to counter the mutated gene’s effects?

Almost certainly not, says Dr. King. “Many thousands of different loss-of-[biological]-function mutations\* within the *BRCA1* and *BRCA2* genes have been identified,” she says. “At the level of individuals, all of these are rare, and each one confers substantially elevated risk for breast and ovarian cancer.” But all of these rare, “severe” mutations affect the same DNA repair pathway, she explains, which makes them targets for a single class of tailored medication (now in development).

She strongly suspects there is an analogy with rare new mutations in schizophrenia

that disrupt genes and may give rise to pathologies associated with the disease. “Of those 54 disruptive mutations I mentioned, 50 of them are components of a single network of genes that we were able to identify,” says Dr. King. “That network acts within the prefrontal cortex of the brain during late gestation. Activity in the network subsides after birth, but then increases again in late adolescence.”

These facts are a source of real hope. It may be true that new mutations are unique to each person, but the genes they are affecting “seem to feed into the same pathways, ones that are important as the brain develops and years later, around the time the behavioral symptoms of schizophrenia tend to emerge,” explains Dr. King. “Once we more fully understand the pathways into which these genes are merging, then wise neurobiologists and pharmacologists will be able to find entry points into them. This is how it has worked with the *BRCA* genes: knowing the genetics led pharmaceutical researchers to develop what are called PARP inhibitors,” which effectively treat the pathology caused by the *BRCA* mutations.

Dr. King predicts that “in the future there will be new classes of psychiatric medications; I think they will be pathway-defined; I think the pathways will be gene-defined, and the genes will be mutation-defined.”

Her lab’s current project is its most ambitious so far: looking at the DNA of every person recruited into a large NIMH-curated sample of schizophrenia patients and healthy controls. After fully sequencing 7,000 patient genomes and an equal number of controls, “we’ll be looking for genes and classes of genes affected by new mutations. The more we can find, the more we can contribute to knowledge about pathways, and thus bring us closer to pathway-specific medications.”

“This is how it has worked with the *BRCA* genes: knowing the genetics led pharmaceutical researchers to develop what are called PARP inhibitors,” which effectively treat the pathology caused by the *BRCA* mutations.

\* Refer to glossary on page 24.

# Your Support Helps Improve Lives

“As a member of a family that has been partially compromised with mental illness in four generations, I am reflecting back to the early ‘80s when a son became ill after his junior year at Yale. Shortly thereafter, I heard of NARSAD [now known as the Brain & Behavior Research Foundation] and have felt a commitment ever since. Though we were immediately focused on finding the best possible care, **the need for research to find causes and treatments of these dreadful conditions was clear.** Our family has been contributing as well as informing relatives, friends and associates about the amazing work being done and the need for advocacy and financial support.

From the beginning, I have attended research symposia, galas, hosted events at my home, and served on committees. **The relationships established through these involvements have been fabulously sustaining.**”

– MS. LILIAN SICULAR on her support of the Brain & Behavior Research Foundation since its inception in 1987



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# What Makes Some Genes Disrupt Brain Development?

“It is now generally believed that an illness like schizophrenia is caused by many hundreds of genetic errors,” says Daniel Weinberger, M.D., from his office at the Lieber Institute for Brain Development at the Johns Hopkins University School of Medicine. The evidence, he says, is actually more intriguing than that. Across the human population, there may be many different genes whose malfunction can potentially contribute to pathology in the disease. But in any specific individual, “It may be that only three or four genes aren’t executing their program quite right. We tend now to think that many of the risk genes for psychiatric illnesses just introduce small biases in the programs of brain development. It’s not that they derail the brain completely. Even in someone with schizophrenia, most of the brain is functioning correctly. But these genetic flaws introduce glitches that interfere with how cells talk to their neighbors—and this can have devastating long-range consequences.”

Trained as both a neurologist and psychiatrist, Dr. Weinberger is known the world over as one of the first investigators to make a solid connection between irregularities in specific genes and the occurrence of specific psychiatric disorders. The aim of the research effort he leads at

the Lieber Institute is to develop over time a finely detailed understanding of what is different, biologically and genetically, about the brains of people with psychiatric disorders vs. healthy people. The ultimate goal is to develop more targeted medications that effectively treat, prevent or cure psychiatric illnesses.

One approach at the Institute is to study curated, postmortem brains with molecular, genetic and cellular methods. The Lieber Institute has an unmatched collection of some 1,350 postmortem human brains, about 500 of them contributed by healthy people and the remainder by people who were diagnosed with depression, bipolar disorder, schizophrenia, panic disorder, obsessive-compulsive and post-traumatic stress disorders, as well as Alzheimer’s disease.

The large sample of curated brains—of people from the 10th week of gestation to age 90—provides a wealth of data about how brains work at the genetic and molecular level, across all stages of the life cycle.

Another line of work at the Institute is to transform donated skin cells into brain cells and “to make little brains in a dish,” Dr. Weinberger explains. “Our investigators are beginning to

**Another line of work. . . is to transform donated skin cells into brain cells and “to make little brains in a dish.”**



## Daniel R. Weinberger, M.D.

Director and CEO, Lieber Institute for Brain Development, The Johns Hopkins University School of Medicine

1990, 2000 NARSAD Distinguished Investigator Grantee

1994 Foundation Lieber Prize for Outstanding Achievement in Schizophrenia Research

Foundation Scientific Council Member

take these little neurons in a dish and put them in the context of other cell types found in the brain, and create actual circuits. Incredibly, these cells in a dish take on a life of their own; they have a ‘behavior.’ Cells in the dish, like cells in the brain, link up, communicate with one another.”

The insights in models such as this come from watching how neural cells grow and assemble—according to their genetic program—as a prelude to understanding what goes wrong in an actual brain, in someone who is ill.

Within 10 years, Dr. Weinberger posits, there will be enough knowledge to develop the next generation of psychiatric medications—ones, he says, “that will interfere with the things that faulty genes make brain cells do that we want them to stop doing.”



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# Frequently Asked Questions

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## on Genetics

**Q:** Can you inherit mental illness?

**A:** The causes of mental illness are complex and not completely understood. They involve an interplay of genes and environment, which includes the environment of the womb as a fetus develops, as well as biochemical changes during brain development. Genes certainly contribute to the development of mental illness, but it's not likely that any single gene passed from parent to child is responsible. Rather, it appears that variations in many genes, combined with other factors, such as stress, work together to raise the risk of developing a brain and behavior disorder. However, even gene variations with the strongest links to mental illness only raise the risk by very small amounts.<sup>1</sup>

Forward-thinking research on the genetics of mental illness is continuing on many fronts. For example, scientists have demonstrated that a genetic component to schizophrenia involves “jumping genes”—bits of DNA that can move around and insert themselves into genes and disrupt their function. Jumping genes can either remain silent, doing nothing; they can churn out their own genetic products; or they can alter the activity of neighboring genes, sometimes with deleterious effects. This work, which is just one of many projects on the genetics of mental illness supported by NARSAD Grants, was led in part by two-time NARSAD Grantee, Tadafumi Kato, M.D., Ph.D., Senior Team Leader for Molecular Dynamics of Mental Disorders at RIKEN Brain Science Institute in Japan.<sup>2</sup>

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SOURCES:

<sup>1</sup> National Institute of Mental Health, Health and Education Publications

<sup>2</sup> *Neuron*, January 22, 2014

<sup>3</sup> *AARP Bulletin*, March 2014

<sup>4</sup> See “What Makes Some Genes Disrupt Brain Development?” on page 9

<sup>5</sup> *New York Times*, March 24, 2014

**Q:** Are there tests to find out if you have a genetic predisposition to mental illness?

**A:** There are tests on the market now that sequence all of a person's genes, or "genome" for \$1,000—inexpensive, compared to the \$400 million price tag just 10 years ago. Companies that sell these tests suggest they can provide information about a person's risk of developing specific diseases, based on variations found in their genes. But according to Francis Collins, M.D., Ph.D., Director of the National Institutes of Health, "unless you're dealing with a specific disease, these tests can be pretty hard to interpret." Dr. Collins formerly led The Human Genome Project, a massive scientific project to map and sequence all of the human DNA and determine its function.<sup>3</sup>

Genetic research might make it possible, one day, to provide a more complete picture of whether a person will develop a particular kind of mental illness based on his or her genes. That day isn't here yet, but progress is being made at research labs around the world every day. Some cutting edge research in this area is being led by two-time NARSAD Grantee Daniel R. Weinberger, M.D. at the Lieber Institute for Brain Development.<sup>4</sup>

**Q:** Are there any genetic tests to determine the best treatment for someone with a mental illness?

**A:** Doctors call this "personalized psychiatry," prescribing specific psychiatric treatments to patients based on their individual genetic makeup and biology. Currently, most psychiatrists prescribe treatments based on population-wide statistics, not individual profiles. Researchers are now focusing on identifying genetic biomarkers (biological predictors) for mental illness that will make the individualized tests possible.

Oncologists already practice personalized medicine. For instance, in breast cancer, doctors can determine the specific tumor subtype a patient has by examining tissue from the tumor and prescribing effective "targeted" treatments based on their findings. Of course, there is no way to obtain brain tissue samples from, say, a living child with autism. But research shows there is a way around this.

Shinya Yamanaka, who won the 2012 Nobel Prize in Physiology or Medicine, has been reprogramming human skin cells to become stem cells and thus all kinds of other cells, including the cells of the nervous system. By taking skin cells from an autistic child and turning them into neurons, we might be able to understand what kind of autism the child has and what chemical fixes might help.<sup>5</sup>



# Staving Off “The Darkness”

## A Family’s Struggles with Depression and their Good Fortune in Overcoming Its Grip

The Peck siblings—Wendy, Amy, and Robert—have in common a history of clinical depression, something they shared with their late mother. Fortunately, they have all found treatments that worked, and they all also benefit from a Rock-of-Gibraltar father whom Amy says “has essentially saved each of us from the darkness, at some point.”

Arthur Peck, M.D., a retired psychiatrist, and his wife, Judy, raised three intellectually gifted children who are now in their 50s. The Peck siblings took very different directions in life, but all have forged productive and fulfilling paths. They and their father have been determined not to let mental illness upend their lives.

Wendy, the older of two Peck daughters, who lives in a suburb of Philadelphia, holds an advanced degree in urban planning and works with architects and developers on major building projects. Younger sister Amy worked as a legislative assistant on the Senate Budget Committee during the eight years of the Clinton Presidency before moving to St. Louis. There she raises money and community awareness for a food bank that provides nutrition and hope to thousands of the city’s poor.

Robert, the eldest, is a motivational speaker living in New England. In his youth, after graduating *summa cum laude* from the University of Pennsylvania, he announced to his startled parents that he was going to be a juggler. And for a number of years he did just that, serving at one time as the “juggler in residence” at an exclusive private school.

Eleven years ago, when Amy moved from Washington, D.C. to St. Louis for her husband’s new job, she had to leave behind a city she loved, friends and

career, and not least, her psychiatrist. It triggered a deep depression. “I had thought I could weather the transition on my own,” she says, “that I could re-invent myself as someone without mental illness. But within a month of the move, I was in a bad way.”

Amy called her father.

Dr. Peck will not soon forget that call. One moment it was an ordinary day in his Tenafly, New Jersey home, the next moment his daughter was telling him, from a thousand miles away, that “she doesn’t know how she is going to live through the day.” Not knowing a soul in St. Louis, he called NARSAD, what is now the Brain & Behavior Research Foundation.

A supporter from the Foundation’s inception, Dr. Peck was aware early on of the importance of brain research. His 42-year career in geriatric psychiatry began in 1955 at a time when Alzheimer’s disease, a tragedy he confronted daily, was an almost compete mystery. “No one had a clue how it started or progressed or how to deal with it,” he says.

Responding to Amy’s plight, the Foundation put Dr. Peck in touch with Herbert Pardes, M.D., President of the organization’s Scientific Council. “Dr. Pardes told me he’d make sure someone in St. Louis would see Amy that day,” Dr. Peck says, “And that’s exactly what happened.”

A supporter of the Foundation since its inception, Dr. Peck was aware early on of the importance of brain research.

The “someone” was psychiatrist Dan W. Haupt, M.D. Now at Oregon Health & Science University, Dr. Haupt was then a NARSAD Young Investigator Grantee at Washington University School of Medicine in St. Louis. His NARSAD Grant study concerned the metabolic effects of antipsychotic medications, but he also treated patients in the hospital’s psychiatric service. He diagnosed Amy with bipolar depression and prescribed the mood stabilizer lamotrigine (Lamictal®)—and it worked. Amy also credits her recovery to his astute assessment of the person inside her illness and his unpatronizing and reassuring approach to her care.

The Peck children now have grown children of their own, who, like their parents, are bright, inde-

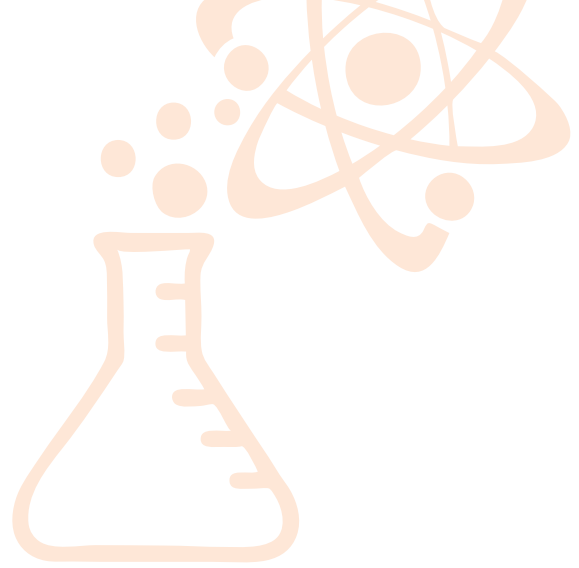
pendent and engaged in busy lives. Robert has a daughter about to graduate Smith College. Wendy has a son graduating from Lehigh University and a daughter entering Bucknell University. Amy has two sons, the older one at the University of Chicago, the younger one still in high school.

Scientists now believe that many, if not most, mental illnesses have a significant genetic component. Arthur Peck fervently hopes his grandchildren are spared the family’s struggles with depression. He crosses his fingers, saying “so far, so good” and puts his faith in the promise of research if the day should come that more of his family members will need effective treatments to treat psychiatric illness.



The Peck Family, left to right, Robert Peck, Wendy Peck, Dr. Arthur Peck, Amy Peck Abraham.

# New Treatments/ Therapies



## 2013 NARSAD Grant Supports New Genetic Insights in Schizophrenia

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Researchers have found the first direct evidence for a genetic overlap between schizophrenia risk genes and genes that regulate general cognitive ability, such as memory, attention and language skills. The team of scientists was led by three-time NARSAD Grantee and Foundation Scientific Council Member, Anil K. Malhotra, M.D., along with 2013 NARSAD Independent Investigator Grantee, Todd Lencz, Ph.D., both of Zucker Hillside Hospital. According to Dr. Lencz, these findings lead to a deeper understanding of how schizophrenia affects the brain at the molecular level and provide clues to the development of new treatments.

Source: *Molecular Psychiatry*, December 17, 2013

## Medication May Enhance Psychotherapy for PTSD

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A new study in mice suggests a class of medications called histone deacetylase (HDAC) inhibitors may help people with post-traumatic stress disorder (PTSD). When given in combination with behavioral therapy, HDACs can help reduce the emotionally upsetting aspects of well-established memories of major physical or psychological trauma. Two NARSAD Grantees contributed to this research: Rachael Neve, Ph.D., at Massachusetts Institute of Technology, and Stephen Haggarty, Ph.D., at Harvard Medical School. The researchers “extinguished” fear in mice, by giving them the HDAC inhibitors and reconditioning them to not be afraid of a chamber where they had previously experienced a mild shock to the foot.

Source: *Cell*, January 14, 2014

## EEG Test May Predict Future Psychosis

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A team of researchers at the University of California, San Francisco say that they may have found an accurate “biomarker” (a biological predictor) for psychosis. That is critical because the symptoms now used to predict future psychosis fail two-thirds of the time. This uncertainty makes the decision to prescribe or take antipsychotic medications as a preventive measure extremely difficult, since these medications carry risk of side effects. Two-time NARSAD Grantee Daniel Mathalon, M.D., Ph.D. and his team used electroencephalography (EEG) recordings to find a brain event called mismatch negativity, which was significantly reduced in those who ultimately went on to develop psychosis.

Source: *Biological Psychiatry*, March 15, 2014

# 2014 NARSAD Independent Investigator Grants

**347** ▶ **40** ▶ **4M**  
 APPLICATIONS      GRANTS      \$ FUNDED

Hailing from nine countries and 33 institutions, 40 mid-career scientists will apply powerful new technologies and new insights to study mental illnesses such as anxiety, autism spectrum disorder, bipolar disorder, depression and schizophrenia. We are delighted to be able to support their work and take pleasure in introducing them to you in the pages that follow.

Noting that more than half of these men and women received NARSAD Young Investigator Grant support early in their careers, Dr. Post stated: “All of these investigations made possible with the support of NARSAD Grants are cumulatively and exponentially advancing what is known about the brain and how to treat its illnesses. By expanding our knowledge of genetics and epigenetics, brain circuitry, neural pathways and how these impact behavior, we are steadily increasing the possibilities for those with mental illness to live full and productive lives.”



## **Robert M. Post, M.D.**

George Washington University  
 Chair, Independent Investigator  
 Grant Selection Committee  
 Brain & Behavior Research  
 Foundation Scientific Council

## INDEPENDENT INVESTIGATORS

# BASIC RESEARCH

**“We are working on an approach which mimics in vitro development of the human brain using cells derived from patients with schizophrenia. I greatly appreciate that the Foundation supports innovative ideas and the development of breakthrough technologies ... it is the best service for those suffering from mental illness.”**

**– Oleg Evgrafov, Ph.D.**



### ANXIETY

**Garret D. Stuber, Ph.D.,**

University of North Carolina at Chapel Hill, will examine circuit connectivity within the bed nucleus of the stria terminalis (BNST), a component of the amygdala,\* the brain's center for fear-related illnesses such as panic disorder, obsessive-compulsive disorder and generalized anxiety disorder. The study will determine the precise neural circuits within the BNST that selectively process threat-related stimuli.



### BIPOLAR DISORDER (BP)

**Benjamin I. Goldstein, M.D., Ph.D.,** Sunnybrook Health Sciences Centre, University of Toronto, will conduct a trial to determine how oxidative stress and blood-vessel functioning relate to cognitive problems in adolescents with BP. Oxidative stress—an imbalance between production of reactive oxygen species (free radicals) and antioxidant defenses—is increased in BP, while the proper functioning of blood vessels is reduced. These effects are associated with cognitive problems, both during episodes of depression and mania as well as during remission.



**Tracey L. Petryshen, Ph.D.,** Massachusetts General Hospital, Harvard University, will investigate the function of a gene called Ankyrin 3 (ANK3) in BP. Abnormally expressed, ANK3 is one of the strongest BP risk genes in response to stress, a major risk factor for the disorder. The study will probe ANK3 regulation of stress hormone expression in susceptible mice to pinpoint brain regions where ANK3 is believed to function.



**“Winning this prestigious grant is a great opportunity for me to continue my research that was funded with a NARSAD Young Investigator Grant. The generous contribution by the Brain & Behavior Research Foundation will allow me to study the role of a peculiar form of cortical disinhibition in an animal model of schizophrenia.”**

**– Alberto Bacci, Ph.D.**



**“The NARSAD Independent Investigator Grant is a pivotal award for me because it is my first grant to study epigenetic mechanisms. The data generated from this study will be novel and prepare me well to seek future funding to continue my research into genetic pathways of mood disorders.”**

**– Roxann Robertson-Nay, Ph.D.**

**“To me, this grant means freedom to explore some unconventional hypotheses about mental disorders, using human models that are only now being established. I hope to learn more about mental disorders in a human context.”**

**– Alysson Renato Muotri, Ph.D.**

## DEPRESSION

### **Maura Boldrini, M.D., Ph.D.,**

Columbia University, seeks to advance understanding of how inflammation influences depression. Studies of animal models of depression show that inflammation is detrimental to neurogenesis, the birth of new neurons, in the hippocampal region of the brain. Selective serotonin reuptake inhibitor (SSRI) antidepressants appear to work by spurring neurogenesis. The study will compare expression of inflammatory chemicals called cytokines in the hippocampus of postmortem brains of untreated depression patients, SSRI-treated patients and healthy controls



**Kathryn L. Evans, Ph.D.,** University of Edinburgh, seeks to clarify the effect of factors that alter gene expression in the development of major depressive disorder. The binding of chemicals such as a methyl group to a gene's DNA in reaction to environmental influences changes the amount of protein the gene produces (a field of study referred to as epigenetics, where gene expression is affected without an alteration to the underlying DNA sequence). This study will compare DNA methylation in siblings where one has depression and the other does not.

**Erika E. Forbes, Ph.D.,** University of Pittsburgh, will investigate the neural circuitry underlying the influence of inflammation on the onset of depression in a pilot study of youths at risk due to family mental health history. Recent findings with adults have shown that inflammation can lead to anhedonia (the inability to experience pleasure) and altered response to reward, responses that commonly occur in depression.



**Roxann Roberson-Nay, Ph.D.,** Virginia Commonwealth University, will examine the association between early-onset major depressive disorder and DNA methylation, a process that alters genetic activity (“epigenetics” per above). The study will examine DNA methylation in adolescent and young adult twins, with and without depression histories, to learn whether it leaves a lasting genetic imprint, if it is associated with the number of lifetime depression episodes and if it can predict depression development.

**Daniel J. Smith, M.B., Ch.B., M.D.,** University of Glasgow, aims to identify new genetic risk factors for co-morbid (co-occurring) major depressive disorder and cardiometabolic disorders. He will approach the problem by analyzing findings from the UK Biobank, in which 500,000 men and women aged 40 to 69 years were studied to learn how genetics, lifestyle, diet and environment contribute to illness.



### SCHIZOPHRENIA

**Alberto Bacci, Ph.D.**, Brain and Spine Institute, Paris, is looking into the role of cells called PV basket cells in schizophrenia. His lab previously found that PV basket cells are massively self-connected by inhibitory autapses. (Autapses are synapses

that a neuron makes with itself rather than with another neuron.) The research will examine how PV-cell autaptic self-inhibition malfunction affects cognitive functioning in schizophrenia.



**Oleg V. Evgrafov, Ph.D.**, University of Southern California, will investigate aberrations in brain development that result in noticeable differences in brain structure in people with schizophrenia. To learn how differences in gene expression of neural progenitor cells (or precursor cells) are translated into structural differences in the brain, the research will explore the effects of abnormally high expression of a calcium channel gene, CACNA1C, one of the few genes proven to be involved in the origin of schizophrenia.

**David Glahn, Ph.D.**, Yale University, will assess the influence of the glutamatergic genetic pathway on cognitive deficits in schizophrenia as a step toward clarifying how modulating glutamate neurotransmission might work as a treatment. The glutamate hypothesis of schizophrenia suggests that there is disrupted functioning of the N-methyl-D-aspartate (NMDA) receptors for glutamate, the brain's major excitatory neurotransmitter. NMDA receptors are thought to mediate cortical connectivity, which is critical for cognitive functioning.



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### MULTIPLE DISORDERS

**Kathryn Grace Commons, Ph.D.**, Children's Hospital, Boston, proposes to visualize and quantify the network of axons that controls the activity of serotonin neurons to identify features of the network that change in animal models of psychiatric illnesses. Axons are the projections that receive signals carried by neurotransmitters across the synapse, the junction between neurons. The neurotransmitter serotonin is implicated in many mental illnesses, including **depression, anxiety, obsessive-compulsive disorder** and **schizophrenia**.



**Alysson Renato Muotri, Ph.D.**, University of California, San Diego, will examine the interplay between astrocytes and neurons in psychiatric illnesses. Once believed to be passive support cells, astrocytes have been found to secrete molecules that stimulate synapse formation and function throughout the brain. The research will create and analyze stem cells derived from patients' neurons and astrocytes to explore genetic alterations that are common to **autism spectrum disorder** and **schizophrenia**.



**Anju Vasudevan, Ph.D.**, McLean Hospital, Harvard University, is investigating a signaling pathway of the neurotransmitter GABA\* that works independently of the classical, better known GABA pathway. The two pathways diverge during early embryogenesis, with far-reaching consequences for brain development. Understanding abnormalities in this novel pathway may provide new understanding of mechanisms underlying neuropsychiatric disorders such as **schizophrenia, epilepsy, autism spectrum disorder** and **mood- and anxiety-related disorders**.

### OTHER DISORDERS: EATING DISORDERS

**Benjamin R. Arenkiel, Ph.D.**, Baylor College of Medicine, will expand his examination of brain circuits underlying obesity and metabolic dysfunction and eating disorders such as anorexia and bulimia. The proposed study is based on his lab's discovery that loss of cholinergic neurons (cells of the acetylcholine neurotransmitter system) from the basal forebrain leads to increased food intake and severe obesity in mice.





# NEW TECHNOLOGIES

## BIPOLAR DISORDER (BP)

**Benicio N. Frey, M.D., Ms.C., Ph.D.**, McMaster University, Canada, will conduct a clinical trial using a novel method of magnetic resonance imaging (MRI) to determine whether patients with BP exhibit abnormalities in the myelin of the cerebral cortex. Myelin is the substance that sheathes axons, the projections on neurons responsible for receiving neurotransmission signals. The study is based on the possibility that disruptions in myelination could disrupt brain connectivity.

**Vincent A. Magnotta, Ph.D.**, University of Iowa, will apply a functional imaging tool, called T1 relaxation in the rotating frame (T1), developed in his lab, to study metabolic changes in BP; studies previously hindered by limitations in imaging technology. Preliminary findings suggest an abnormal neurovascular coupling that is contributing to observed symptoms. Results from this study may lead to novel diagnostic and therapeutic approaches.

**Dimitri Van De Ville, Ph.D.**,

Ecole Polytechnique Federale de Lausanne, Switzerland, will use functional magnetic resonance imaging (fMRI) to obtain periodic measures of brain activity in patients with BP, and apply novel analytical techniques developed in his lab to diagnose and anticipate mood changes. The guiding hypothesis is that large-scale patterns of dynamic functional connectivity can unveil the direction of mood alterations and might be a reliable predictive marker for mood fluctuations.



## MULTIPLE DISORDERS

**Adam G. Carter, Ph.D.**, New York University, will study the impact of chronic stress in mental illnesses, including schizophrenia, anxiety and depression, as it affects the prefrontal cortex, a brain structure critical in the regulation of cognition and emotion. The project will use a combination of electrophysiology, microscopy and optogenetics to explore how stress perturbs structure and function of cortical neurons in **neuropsychiatric illness**.

**David J. Foster, Ph.D.**, Johns Hopkins University, is using a rapid neural assay he helped develop to study hippocampal “replay” memory in mice. The hippocampus is a key brain memory structure. Recent rodent studies reveal a pattern across hippocampal neurons in which experiences are “replayed” at later times. Dr. Foster hypothesizes that impairments to the episodic memory and future planning functions of hippocampal replay/pre-play may be of major significance in **psychiatric disease**.

**John M. Hettema, M.D., Ph.D.**, Virginia Commonwealth University, will expand on his neuroimaging studies of brain abnormalities in **mood and anxiety disorders** by examining at-risk twins at the critical period between ages nine to 13. He will use functional magnetic resonance imaging (fMRI) brain scans to assess activation patterns in the amygdala and prefrontal cortex while subjects respond to psychological tasks. Twins are ideal subjects for determining the differential effects of genes and environment and their shared versus specific contributions.

## SCHIZOPHRENIA

**Romina Mizrahi, M.D., Ph.D.**, Centre for Addiction and Mental Health, University of Toronto, will conduct the first brain imaging studies to examine possible alterations in endocannabinoid metabolism in patients with schizophrenia. Numerous studies have shown that the use of cannabis (marijuana or hashish) is associated with increased incidence of schizophrenia. The active components of cannabis mimic the effects of endocannabinoids, brain compounds that regulate neurotransmitters, including dopamine and glutamate, which are altered in schizophrenia.

## OTHER DISORDERS: ADDICTION

**Sheena A. Josselyn, Ph.D.**, Hospital for Sick Children, University of Toronto, will explore brain mechanisms involved in the association of environmental stimuli, such as a neighborhood or song, with the rewarding properties of cocaine. The goal of the research is to determine whether disrupting the memory can prevent addiction relapse. Dr. Josselyn’s project will use molecular tools to erase reward memory in a mouse analogue of drug-seeking, as well as the new technology called CLARITY\* to examine impact on the 3-D brain-wide “cocaine map.”



\* Refer to glossary on page 24.

# NEXT GENERATION THERAPIES

**“To get the opportunity to evaluate a new brain stimulation treatment in a clinical trial will tremendously accelerate the translation of our basic science work into real-world neurotherapeutics for patients with mental illness.”**

**– Flavio Frohlich, Ph.D.**

## BIPOLAR DISORDER (BP)



**Carla Torrent, Ph.D.,** Clinica de la Salud, Spain, will test the usefulness of an online e-neurocognitive module that can be used at home as an adjunct to other remediation in the treatment of BP. Between 40 and 60 percent of patients with BP experience cognitive impairment during acute mood episodes and also during remission periods. The program, which has been used successfully with neurological and schizophrenia patients, will be altered for content specifically geared to BP.

## ANXIETY

**Rajeshwar Awatramani, Ph.D.,** Northwestern University, will study subtypes of neurons that produce dopamine, a neurotransmitter implicated in a number of neuropsychiatric disorders. Current treatments that affect the dopaminergic system lack target specificity, with often undesirable results. One subtype, DAS6, appears to project to the amygdala, the brain’s seat of fear and anxiety. The research goal is to define DAS6 involvement in fear behaviors so as to improve treatment outcomes.

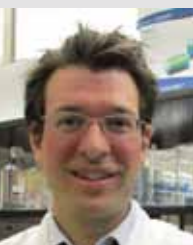


**Thomas Kash, Ph.D.,** University of North Carolina Chapel Hill, will explore the effect of the brain chemical dynorphin and its receptor, kappa opioid receptor (KOR), on the neurotransmitter glutamate and anxiety-like behavior. The aim is to demonstrate a causal role for dynorphin and KORs in a key anxiety circuit so as to identify potential targets within the system for novel treatments of anxiety and stress disorders.

## DEPRESSION

**Rodrigo A. Cunha, Ph.D.,** University of Coimbra, Portugal, will explore the effect of stress in depression, based on the hypothesis that repeated stress impairs brain circuits mediating positive emotion (reward learning), while bolstering circuits mediating negative emotion (aversion learning). The goal is to develop a therapy that targets a system regulated by a receptor for the chemical adenosine, which simultaneously corrects impaired reward and aversive behaviors.

**Flavio Frohlich, Ph.D.,** University of North Carolina, Chapel Hill, will conduct a trial of a non-invasive brain stimulation method developed in his lab for the treatment of patients with major depressive disorder. This method uniquely provides adaptive, individualized stimulation. Called “feedback transcranial alternating current stimulation,” it manipulates brain activity through a weak electric current, not detectable by the patient, applied to the scalp in response to pathological brain-activity signals measured by a standard electroencephalogram (EEG).



**Dimitris N. Kiosses, Ph.D.,** Weill Cornell Medical College, Cornell University, plans to adapt Problem Adaptation Therapy (PATH), a home-delivered psychosocial intervention, to reduce depression and prevent suicide in at-risk older adults with treatment-resistant major depressive disorder and cognitive impairment. PATH addresses patient, caregiver and home environment. The proposed pilot trial will add new cognitive, behavioral and support techniques to reduce suicide ideation (thinking about suicide) and feelings of hopelessness.





## SCHIZOPHRENIA

**Katherine E. Burdick, Ph.D.**, Icahn School of Medicine at Mount Sinai, will test the calcium channel blocker isradipine, normally used to treat high blood pressure, as a potential treatment for the cognitive deficits of schizophrenia. A variant form of the gene that encodes a subunit of a calcium channel has been shown to impair cognitive ability in schizophrenia patients, suggesting that calcium channel dysregulation may be a central feature of schizophrenia.

**Erika Jääskeläinen, M.D., Ph.D.**, University of Oulu, Finland, will utilize data from the Northern Finland 1966 and 1986 Birth Cohort population studies to determine the effects of lifetime antipsychotic medication on the course of schizophrenia, including number of symptoms and hospitalizations, recoveries, cognitive and occupational functioning, other health problems and death. The research will also examine whether outcomes differ between these two generations.



**Einat Liebenthal, D.Sc.**, Brigham & Women's Hospital, Harvard Medical School, is interested in the neural mechanisms that underlie psychotherapy's positive effects in treating schizophrenia. This study, which will explore neural response to threat words, should help determine, among other findings, the types of patients most likely to respond to psychotherapy and the aspects of therapy likely to be most effective.



**Steffen Moritz, Ph.D.**, University Hospital Hamburg-Eppendorf, will conduct a trial to assess the efficacy and feasibility of using individualized Metacognitive Therapy (MCT+) to treat psychotic symptoms of schizophrenia in patients who refuse medications or fail to take them as prescribed. MCT+ is a new form of psychotherapy that addresses reasoning biases and is derived from both individualized cognitive behavioral therapy and group metacognitive training, which has been described as "thinking about thinking."

**Yuri Rassovsky, Ph.D.**, University of California, Los Angeles, plans to try a brain stimulation method called transcranial direct current stimulation (tDCS) as a means of improving cognitive deficits in schizophrenia patients. In the clinical trial, tDCS will be applied over the dorsolateral prefrontal cortex, a brain area significantly involved in cognitive dysfunction. The research will also seek to determine whether deficits in this area involve neuronal hyperactivity or underactivity.



**Joshua Roffman M.D., M.MSc.**, Massachusetts General Hospital, hopes to determine how specific genes, abnormally expressed during fetal development, influence later development of schizophrenia. Folic acid, a B vitamin, supplies chemical precursors for gene expression regulated through a process called methylation. Folic acid deficiency is a risk factor for developing schizophrenia. Findings from the study might therefore support studies of folic acid augmentation as an early preventive measure for people at risk.



**Jason Tregellas, Ph.D.**, University of Colorado Anschutz Medical Campus, will investigate whether the anti-epileptic drug leviteracetam (LEV) will help reduce cognitive deficits in patients with schizophrenia, a problem that has eluded effective treatment. His lab recently demonstrated that the hippocampus, a brain region important for learning and memory, is hyperactive in schizophrenia. The proposed trial is based on evidence that LEV at a low dose reduces hippocampal hyperactivity and improves memory in individuals with mild cognitive impairment.

**Aristotle Voineskos, M.D., Ph.D.**, Centre for Addiction and Mental Health, University of Toronto, will conduct brain imaging studies with schizophrenia patients to study the effects on brain structure of the use of repetitive transcranial magnetic stimulation (rTMS), a promising potential treatment for impairments in working (short-term) memory. This symptom of schizophrenia is difficult to treat. Magnetic resonance imaging (MRI) before and after treatment will be used to reveal how rTMS changes the brain to improve memory performance.





## MULTIPLE DISORDERS

**Angel Barco, Ph.D.**, Institute of Molecular Biology of Barcelona, Spanish Research Council, will explore the biological mechanism of histone deacetylase inhibitors (HDACIs), a family of neuropsychiatric medications that appear to reduce cognitive deficits and degeneration in animal models of neurodegenerative diseases. How HDACIs affect neurons in illnesses such as **Alzheimer's disease, congenital and age-related cognitive impairment, mood disorders, addiction and schizophrenia** remains largely unknown; this information is needed for future treatment development.



**Benjamin Cheyette, M.D., Ph.D.**, University of California, San Francisco, will investigate a proposed biochemical feedback circuit in the brain based on his hypothesis that disruption of this circuit in neurons of the prefrontal cortex plays a part in **schizophrenia, autism spectrum disorder** and possibly other psychiatric conditions. He seeks to determine if this disruption causes changes in synapse development and function that lead to behavioral disruption. He will explore whether pharmacologic intervention that normalizes this circuit can reverse pathological changes.



**Allison D. Redlich, Ph.D.**, State University of New York, Albany, will focus on the escalating problem of the overrepresentation of people with **severe, untreated mental illnesses** in the criminal justice system. The research will analyze a large database of information on special Mental Health Courts that mandate treatment. Dr. Redlich's study will assess the validity of the rationale behind establishment of these courts—that treatment reduces crime.



**“I am delighted and extremely grateful to receive this NARSAD Independent Investigator Grant. It will allow me to devote more time to cutting-edge investigations in my lab of the molecular mechanisms underlying psychiatric disorders, something that I am passionate about.”**

**– Ben Cheyette, M.D., Ph.D.**

**“The NARSAD Grant provides me with an exceptional opportunity to study the neural mechanisms by which psychotherapeutic intervention may alleviate paranoid symptoms in schizophrenia. I am extremely excited about the prospect of shedding some light on this obscure disease!”**

**– Einat Liebenthal, D.Sc.**

**“This award is very meaningful both personally and professionally. The grant will enable us to combine advanced brain imaging with a novel clinical intervention, known as repetitive transcranial magnetic stimulation (rTMS). We are using rTMS to determine whether we can improve a type of memory performance, known as ‘working memory’ in people with schizophrenia, for which there is currently no effective treatment.”**

**– Aristotle Voineskos, M.D., Ph.D.**

# THE POWER OF A RESEARCH PARTNERSHIP



Frances and Bob Weisman

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Danielle M. Andrade, M.D.

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.

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*“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 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.”*

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

# Glossary

**amygdala:** (p.16) Almond-shaped structure located deep within the brain's medial temporal lobe (one in each hemisphere of the brain). The amygdala is part of the limbic system and is known to play a key role in the processing of emotions. Mental illnesses, including anxiety, autism, depression, post-traumatic stress disorder, and phobias are suspected of being linked to abnormal functioning of the amygdala.

**brain plasticity (or neuroplasticity):** (p.3) The capacity of the brain to respond to stimuli and stresses by forming new nerve cells and remodeling its structure, function and connections. In the past, scientists believed that once a person reached adulthood, the brain remained static, but research in the past 25 years has shown that new neurons are generated throughout human life (a process called neurogenesis). Neurogenesis can be spurred by physical activity and social and intellectual stimulation. Researchers have also found that when people recover from depression or anxiety with the help of selective serotonin reuptake inhibitor antidepressants and other treatments, new neurons form in the hippocampus, an area of the brain important to memory, learning and mood.

**CLARITY:** (p.19) A newly developed technology that renders full, intact brains transparent by replacing fatty molecules in their structures with a clear gel. Through sophisticated imaging, this technique makes it possible to study whole, preserved brains in unprecedented three dimensional detail, while still retaining an overall "big picture" view of the structure of the brain. CLARITY was developed in the laboratory of Foundation Scientific Council member Karl Deisseroth, M.D., Ph.D.

**copy-number variations (CNVs):** (p.6) Alterations of the DNA of a genome that result in the cell having an abnormal or, for certain genes, a normal variation in the number of copies of one or more sections of the DNA. CNVs correspond to stretches of the genome where there is extra DNA (sometimes forming extra copies of genes) or where DNA has been deleted (sometimes deleting entire genes from the genome). Extra genetic material can lead to overproduction of proteins made by genes; deletions prevent protein production. CNVs affecting genes active in brain development and in postnatal brain

function have been identified in people with schizophrenia and other neuropsychiatric disorders.

**exome:** (p.2) The portion of an organism's genome that contains instructions for the manufacture of proteins; referred to as the "workhorse" molecules of biological systems. Because a significant portion of human disease is thought to be traceable to mutations in genes of the exome, a quick way to discover information about the genetic roots of illness is to sequence, not the complete genome, but just the one to two percent occupied by the exome.

**GABA:** (p.18) The main chemical neurotransmitter that conveys "inhibitory" signals in the brain. Without a properly working network of GABA neurons deployed at strategic points throughout the brain, "excitatory" signals can propagate unchecked, causing overload and severe epilepsy-like seizures.

**loss-of-[biological] function mutation:** (p.7) The kind of gene mutation that prevents protein production, which affects normal biological function, whether at the level of cells, signaling networks or even entire organ systems. Other types of mutations only partially impair protein production and do not lead to the total loss of an important biological function or protein manufacture.

**prodrome/prodromal stage:** (p.4) Refers to the early stage of a brain and behavior disorder, a period just before an illness fully manifests. Researchers are particularly interested in studying the prodromal period of psychosis with the hopes of developing early intervention techniques that can prevent the damage of a psychotic break and greatly improve the chances for recovery.

**synapse:** (p.2) A tiny gap between nerve cells across which neighboring cells communicate. The human brain has trillions of synapses. These specialized connections lie between the sending and receiving nerve cells of the brain and central nervous system. Synapses can be excitatory or inhibitory—that is, they either increase or decrease activity in the target neuron.





The Hollister Family, long-time supporters of the Brain & Behavior Research Foundation

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A gift to the Foundation supports cutting-edge mental health research and future breakthroughs. There are many ways to support the Brain & Behavior Research Foundation during your lifetime and one particularly meaningful way is through planned giving.

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*100% of all donations for research are invested directly in NARSAD Grants thanks to the generosity of two family foundations.*

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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

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