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## FOCUS

on

# EARLY INTERVENTION

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# Scientific Council

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Judith L. Rapoport, M.D.

Dear Members of Our Foundation Community,

All of us who are concerned with questions of mental health know that neuropsychiatric research is flourishing. New technologies are opening new vistas to understanding the brain and neuroscientists working across disciplines and across borders are taking new approaches to improve available treatments. The once far-flung vision of prevention and cure is within our sight. We are all also keenly aware of gaps in how much is understood about the brain, how and when to appropriately intervene to treat its illnesses and how to recognize early on what is becoming a serious mental health issue.

Tragedies such as that in Newtown, CT last December have intensified awareness of this gap as well as the public dialogue around mental illness. Our point of view is that accelerating funding for neuropsychiatric research needs to be a part of this conversation. With increased focus on understanding what causes mental illness and identifying early warning signs, we will be able to intervene before the illnesses progress to a state where they are much more difficult to treat. And even more importantly, with effective early intervention, we should be able to reduce the occurrence of untreated mental illness, which sometimes presents a risk of violence—whether it is violence of the patient toward him/herself or toward others.

The projects of some of the scientists the Foundation has funded through its NARSAD Grants for work on developing diagnostic and early intervention techniques are described in this issue of *The Quarterly*. Not surprisingly, a number of these studies are focused on children and young people; exciting new methods are being explored aimed at recognizing and treating mental illnesses as early as possible so as to lessen their escalating impact over time.

It goes without saying that the Foundation's ability to fund these and many other important advances in neuroscience depends on our donors. I have been very moved over the past several months as I have stepped into the role as the new President and CEO of the Foundation to observe at first hand the dedication of our donors. The level of passion and commitment to find real answers to the complex issues presented by mental illness is quite remarkable. It is a passion shared by the researchers we fund, and together we are making significant progress. With thousands of NARSAD Grantees working everyday to find solutions, we are continually progressing to improve the lives of those still suffering with these illnesses. As the new leader of this Foundation, I commit to pursuing the funding to accelerate the rate of research and keeping you abreast of the significant and exciting progress being made.

With your continued support of the cutting edge research we fund, we can get to solutions we need—for this generation and the next.

Sincerely,



Jeffrey Borenstein, M.D.  
President & CEO

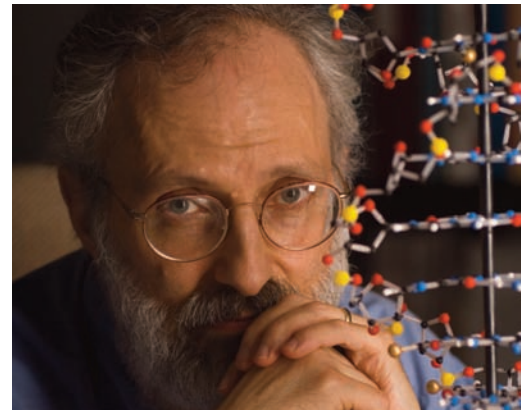


# Research Discoveries *in the News*



Jordan W. Smoller, M.D., Sc.D.  
Professor of Psychiatry, Harvard Medical School  
and Massachusetts General Hospital;  
2002 NARSAD Young Investigator Grantee

## Landmark Study Shows Common Genetic Links Across 5 Major Psychiatric Disorders



Kenneth Kendler, M.D.  
Professor of Psychiatry and Human Genetics, Medical  
College of Virginia, Virginia Commonwealth University;  
2000, 2010 NARSAD Distinguished Investigator Grantee,  
Scientific Council Member

The Cross-Disorder Group of the Psychiatric Genomics Consortium (PGC), a consortium of geneticists and neuroscientists, has released the results of a worldwide, six-year-long collaboration in the first genome-wide search for single-“letter” genetic variations (called SNPs, or single-nucleotide polymorphisms) across five psychiatric disorders. Led by Jordan W. Smoller, M.D., Sc.D. and Kenneth Kendler, M.D., as well as Nicholas Craddock, M.D., the group found genetic overlap with disorders previously thought of as distinct, including attention-deficit hyperactivity disorder (ADHD), autism, bipolar disorder, major depressive disorder (MDD), and schizophrenia.

The consortium took a novel approach by analyzing the five key disorders as if they were the same illness. The study involved researchers in 19 nations who amassed a sample consisting of 33,332 people with psychiatric illnesses and 27,888 controls.

“The major accomplishment of this collaborative effort is to begin to apply well-powered modern molecular gene-

tic techniques to attempting to answer one of the oldest questions in psychiatry: ‘What are the etiological relationships between our major psychiatric disorders?’” says Dr. Kendler.

The findings of the study were published in *The Lancet* and point to at least four locations in the human genome that appear to confer a risk that cuts across the five disorders. Two of them occur in genes that encode proteins that are important in a class of tiny pores called calcium channels that regulate the flow of calcium into cells.

“The finding that calcium channel signaling genes are involved in multiple psychiatric disorders raises the possibility that targeting this pathway might offer new opportunities for treatment,” says Dr. Smoller. He also hopes that studies like this one will lead to improved diagnostic tools for the disorders. While each of the individual genetic associations identified account for a small amount of risk for mental illness, the study opens the door for further investigation of the

overlapping areas identified. With continuing research that identifies causes of illness, diagnostics for mental illness based on neuroscience and genetics, in addition to observed behavior, become an achievable goal.❖

Also involved in the study were: **Scientific Council Members:** Huda Akil, Ph.D.; Jack D. Barchas, M.D.; Wade H. Berrettini, M.D., Ph.D.; Joseph D. Buxbaum, Ph.D.; William F. Byerley, M.D.; Robert R. Freedman, M.D.; Elliott S. Gershon, M.D.; John R. Kelsoe, M.D.; James L. Kennedy, M.D., Ph.D.; Jeffrey A. Lieberman, M.D.; Anil K. Malhotra, M.D.; James B. Potash, M.D., M.P.H.; Alan F. Schatzberg, M.D.; and **NARSAD Grantees:** Ayman Fanous, M.D.; Thomas B. Barrett, M.D.; Michael Bauer, M.D., Ph.D.; Frank Bellivier, M.D., Ph.D.; Sarah E. Bergen, M.S., Ph.D.; Joseph Biederman, M.D.; Elisabeth B. Binder, Ph.D.; Dorret I. Boomsma, M.A., Ph.D.; Jerome Breen, Ph.D.; Margit Burmeister, Ph.D.; David A. Collier, Ph.D.; Jubao Duan, Ph.D.; Nelson B. Freimer, M.D.; Pablo V. Gejman, M.D.; Elaine K. Green, Ph.D.; Tiffany A. Greenwood, Ph.D.; Hugh Gurling, M.D.; Steven P. Hamilton, M.D., Ph.D.; Witte J. Hoogendijk, M.D., Ph.D.; Stéphane Jamain, Ph.D.; Edward G. Jones, M.D., Ph.D.; James A. Knowles, M.D., Ph.D.; Todd Lencz, Ph.D.; Jun Li, Ph.D.; Chunyu Liu, Ph.D.; Falk W. Lohoff, M.D.; Patrick J. McGrath, M.D.; Melvin G. McInnis, M.D.; Andrew McIntosh, M.D.; Francis J. McMahon, M.D.; Pierandrea Muglia, M.D.; Stan F. Nelson, M.D.; Ann Olincy, M.D.; Roel A. Ophoff, Ph.D.; Urban Osby, M.D., Ph.D.; Carlos N. Pato, M.D.; Michele T. Pato, M.D.; Roy H. Perlis, M.D., M.Sc.; Shaun M. Purcell, Ph.D.; Brien Riley, M.Sc., Ph.D.; Guy Rouleau, M.D., Ph.D.; Dan Rujescu, M.D.; Alan R. Sanders, M.D.; Martin Schalling, M.D., Ph.D.; Thomas G. Schulze, M.D.; Paul D. Shilling, Ph.D.; Pamela Sklar, M.D., Ph.D.; T. Scott Stroup, M.D., M.P.H.; Robert C. Thompson, Ph.D.; Edwin J.C.G. van den Oord, Ph.D.; John B. Vincent, Ph.D.; Stanley J. Watson, M.D., Ph.D.; Myrna M. Weissman, Ph.D.; Allan H. Young, M.D., Ph.D.; Peter P. Zandi, Ph.D.

## Discovering How Adolescent Stress Can Cause Mental Illness

With the support of a NARSAD Distinguished Investigator Grant, a team of neuroscientists at the Johns Hopkins University School of Medicine has discovered a biological mechanism that helps explain the long mysterious relationship between early-life stress and the onset of severe mental illness.

In a study published in the journal *Science*, Brain & Behavior Research Foundation Scientific Council Member and NARSAD Grantee Akira Sawa, M.D., Ph.D. and colleagues show that when mice with a genetic predisposition to mental illness experience stress as adolescents they are more likely to go on to develop severe mental illnesses such as schizophrenia and depression. The mouse model mimics a form of stress—social isolation—during the mouse equivalent of human adolescence, a critical period for brain development.

In one part of their work, the team of researchers discovered that healthy young mice, when held in isolation from their parents during adolescence, were able to reintegrate without much difficulty once the isolation

period was ended. They developed no related behavioral abnormalities. Not so for “high-risk” mice, harboring a known genetic predisposition to adult illness. They failed to reintegrate and developed symptoms as adult mice—such as hyperactivity in response to psychostimulants and lack of interest in certain pleasurable activities—that are analogs of severe behavioral disorders in people.

Examinations of the affected mice revealed the absence of robust anatomical abnormalities in the brain (in the ventricles and frontal cortex) known to accompany the corresponding behavioral changes. This turned the attention of Dr. Sawa’s team to changes in the activity of brain chemicals, specifically the neurotransmitter dopamine. In mice with isolation-induced behavioral changes, levels of dopamine were found to be well below normal; the same mice also had above-normal levels of corticosterone, the main hormone in the brain that responds to elevated stress.

Dr. Sawa’s team connected these dots. By blocking corticosterone by giving

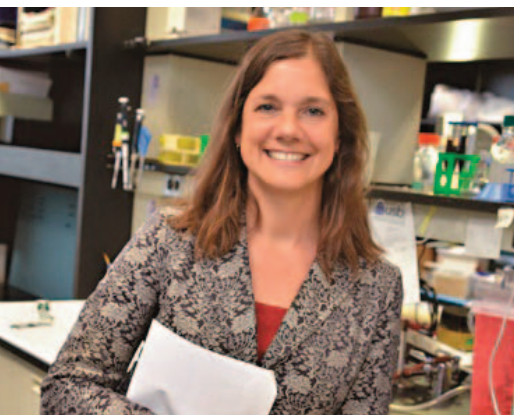


Akira Sawa, M.D., Ph.D.  
Professor, Psychiatry and Behavioral Sciences, Director of the Schizophrenia Center, Johns Hopkins University; 2002, 2004 NARSAD Young Investigator Grantee, 2011 NARSAD Distinguished Investigator Grantee, Scientific Council Member

affected animals doses of the drug RU-486 (better known as the “morning-after” birth control drug), dopamine levels returned to normal and behavioral symptoms vanished. This led them to discover a so-called epigenetic mechanism—the addition of a molecular “tag” to DNA in a specific gene—that alters gene expression and reduces dopamine production.

“We’ve shown in mice that stress in adolescence can affect the expression of a gene that codes for a key neurotransmitter related to mental function and psychiatric illness,” explains Dr. Sawa. While many genes are believed to be involved in the development of mental illness, we continue to learn more about how environmental factors are critically important to the process.”

According to Dr. Sawa, the new study highlights the need for better preventive care in teenagers who have mental illness in their families, and also sheds light on the cascade of events that occurs when cortisol levels are elevated, furthering researchers’ ability to develop new treatments with fewer side effects than RU486 has.❖



Marina Picciotto, Ph.D.  
Charles B. G. Murphy Professor of Psychiatry,  
Professor of Neurobiology and Pharmacology,  
Assistant Chair for Basic Science Research, Psychiatry,  
Yale University;  
1996 NARSAD Young Investigator Grantee,  
2004 NARSAD Independent Investigator Grantee

## Potential Root Cause of Depression Discovered by NARSAD Grantee

Marina Picciotto, Ph.D., leading a team of researchers at Yale University, has made an exciting discovery in the search for the biological causes of depression and anxiety. Their discovery points to the importance of a signaling system in the brain that was not previously believed to be central in causing depression.

For decades, many scientists have favored a theory of depression that stresses the impact of abnormally low levels of a signal-carrying chemical, called serotonin. The new research by Dr. Picciotto's team shifts attention to a different signaling chemical, or neurotransmitter, called acetylcholine.

Millions of depressed people take antidepressant drugs called SSRIs—an acronym for selective serotonin reuptake inhibitors. Prozac®, Paxil®, Celexa®, Zoloft® and other SSRI medications act to keep message-carrying serotonin molecules from being rapidly reabsorbed by nerve cells. By allowing serotonin to float for longer periods of time in the tiny spaces between nerve cells, called synapses, scientists have theorized the SSRI drugs promote signaling by compensating for abnormally low serotonin levels.

Dr. Picciotto's new research, published in *Proceedings of the National Academy of Sciences* in February, turns attention to fluctuations in levels of the neurotransmitter acetylcholine and the larger chemical signaling system it is part of, called the cholinergic system.

"Serotonin may be treating the problem," Dr. Picciotto says, "but acetylcholine disruption may be a primary cause of depression. If we can treat the root cause, perhaps we can get a better response from the patient."

Her team's experiments demonstrate that abnormally high levels of acetylcholine in the brain can cause depression and anxiety symptoms in mice. In the brains of non-depressed mice—and people—an enzyme called acetylcholinesterase (AChE) is produced to lower acetylcholine levels. The team showed that when depressed mice were given Prozac®, AChE levels were raised, and abnormally high levels of acetylcholine were thus brought under control. This adds a new dimension to understanding how and why SSRI antidepressants can alleviate depression.

Yet many depressed people do not get a therapeutic benefit from Prozac®

or other SSRI medications. Dr. Picciotto's research suggests this may be because the root problem is not, after all, low levels of serotonin, but rather, high levels of acetylcholine. By experimentally blocking the "ports," called receptors, where acetylcholine molecules "dock" with nerve cells in the brain, the team was able to reverse depression in mice.

In still other experiments, the Yale team showed how interruptions in acetylcholine signaling in the brain area called the hippocampus—important in memory and mood—promotes depression and anxiety in mice.

While the relation between the serotonin and acetylcholine signaling systems is not yet fully clear, this new research opens a new possibility to treat the cause of depression and not just its symptoms. With the new hypothesis that it is the disruption of acetylcholine, and not serotonin, that sets depression in motion, further research studies can be undertaken to determine if medications that target acetylcholine rather than serotonin, are more effective in treating depression.❖

# Interview

with

Judith L. Rapoport, M.D.

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

## Chief of Child Psychiatry at the NIMH Shares Insight



### How Studies With Children Are Helping Identify Early Developmental Links to Mental Illness

#### **Learning how genes predispose, even if they don't determine**

Over the last decade of her distinguished career in studying the genetics of brain and behavior disorders, Judith L. Rapoport, M.D., has focused on a group of children who are very sick, and whose sickness is very rare. These children, who are under the age of 13, have developed what is termed childhood-onset schizophrenia.

While their illness is uncommon, Dr. Rapoport and her colleagues at the Child Psychiatry Branch of the National Institute of Mental Health (NIMH), of which she is Chief, have learned some intriguing facts about its causation. These shed important new light on the relationship between events at the beginning of life and the subsequent emergence of schizophrenia and other serious disorders such as bipolar disorder, psychotic depression, even epilepsy.

Dr. Rapoport, whose devotion to the Brain & Behavior Research Foundation is reflected in her longtime volunteer service on the organization's Scientific Council, co-discovered the role of rare genetic mutations in schizophrenia. These gene irregularities, called copy-number variants (or CNVs), are extra copies or missing copies of genes, and, though rare, are seen much more often in people with schizophrenia, compared with healthy people.

Might CNVs serve as diagnostic markers, which have long been sought for schizophrenia and other psychiatric disorders? Not yet, Dr. Rapoport explains. It turns out that some healthy siblings of children and adults with schizophrenia also have some of the illness-linked CNVs. Also, some CNVs have been shown to be inherited from parents who do not have schizophrenia. So it's not

yet clear how or how much having disease-associated CNVs increases one's risk for actually getting sick.

While the causal relation of both rare CNVs and much more commonly seen mutations to the development of brain and behavior disorders isn't yet clear, Dr. Rapoport and colleagues have recognized that they are "non-specific" for schizophrenia. That is, mutations seen more frequently in people with schizophrenia are sometimes also seen in people with other diagnoses, particularly autism, but also intellectual disability and even epilepsy. This is promising for the development of future treatments: "The fact that these mutations are non-specific means that if and when we figure out how to counteract them, they may have benefits for patients across several illnesses, by attacking pathology common to all of them," says Dr. Rapoport.

### Tracking brain development “trajectories”

There is other encouraging news, Dr. Rapoport says. In her group’s effort to closely analyze a set of 3,000 cases of childhood-onset behavioral and mental illness, they have learned a great deal about pathologies affecting a broad array of disorders whose causes can be traced at least partly to abnormal brain development trajectories. The right and left halves of the human brain develop at different rates. As Dr. Rapoport and others have discovered, abnormal timing of developmental events in the growth and maturation of various key brain regions appears to generate pathologies that later lead to schizophrenia, psychosis, attention-deficit hyperactivity disorder (ADHD) and likely other illnesses. Such developmental abnormalities can, for instance, affect the size or volume of brain structures such as the critical cerebral cortex, the seat of higher cognitive functions.

More good news: “One truly significant discovery has been that in ADHD, we and others have found that while a big portion of hyperactive kids have abnormally slow development of their frontal lobes, say at age 7 or 8, by the time they’re 15, about half of them will be so much

better, whether or not they have had treatment.” In other words, it may be that for some, a glitch in timing corrects itself.

...abnormal timing of developmental events in the growth and maturation of various key brain regions appears to generate pathologies that later lead to schizophrenia, psychosis, attention-deficit hyperactivity disorder (ADHD) and likely other illnesses.

This makes it very clear to Dr. Rapoport what she and her colleagues need to focus on. “We’re really interested in developing diagnostics and treatments for the children who aren’t going to grow out of these timing disturbances.” Meantime, certain common genetic risks for major psychiatric illness can already be detected through prenatal screening, using specialized “gene chips” like those co-developed at Baylor University, Dr. Rapoport notes. These are designed to compare the genetic profile of the fetus with major known gene mutations. Prenatal Chromosomal Microarray Analysis (Prenatal CMA), for instance, is a diagnostic test that can detect genetic abnormalities in a fetus.

### Offering advice for parents

Dr. Rapoport offers this advice to parents with a child who has either

been diagnosed with a psychiatric disorder or whose behavior has raised warning flags. First, she suggests talking to a trustworthy pediatrician.

“They can make referrals and often have a good sense of what type of problem your child may be having. There are different things you would do if you felt it was just developmental delay, or a very focused behavioral problem.”

It also makes sense, she says, for parents to contact their local medical school to find someone in the child psychiatry department. “I am a very strong believer in psychiatric diagnoses, made by skilled clinicians. They can give parents a reasonable prediction, based on the doctor’s experience, of what sort of treatment can help; what kinds of problems one might anticipate developing within the family structure; what the child’s prognosis might be; what the chances are of outgrowing the symptoms and which treatments are likely to be the most useful.” ❖

### Ask the Researcher

#### HAVE A QUESTION?

E-mail [asktheresearcher@bbrfoundation.org](mailto:asktheresearcher@bbrfoundation.org) with questions for **Dr. Judith Rapoport**. 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.**



# Computerized Surveys Help Diagnose Depression and Suicide Risk in Youths

When he first heard about it in the late 1970s, David Shaffer, M.D., remembers being not only “skeptical” but in a state of disbelief. Just as his career in psychiatry was getting under way, an important study found that people with suicidal thoughts were least likely to give honest replies in face-to-face interviews, somewhat more likely in written questionnaires, but most likely to tell the truth in impersonal computer-administered tests.

“What emerged was that you could catch suicide; it could be suggested by various signs and clues, and thus it could be prevented.”

Dr. Shaffer’s own first groundbreaking study of youth suicides had nothing to do with computers. It was carried out in his native Great Britain using data gathered from official records. Sadly, the subjects were dead; yet the data revealed a fact which changed public attitudes. “What emerged was that you could catch suicide; it could be suggested by various signs and clues, and thus it could be prevented.”

He and other pioneers discovered that suicidal ideation is remarkably common—it’s routinely found in 25% of U.S. high school students. Actual suicides, though rare, can occur in local waves, the “cluster effect,” and this happens in part because imitation, as Dr. Shaffer discovered, plays an important role.

Dr. Shaffer’s insights, including the importance of aggressive behavior in identifying youths most at risk, as well as co-morbidities including not only depression but also alcohol use and anxiety, have been woven into the fabric of diagnostic “survey instruments” he has devised which are used across the U.S. and in many other nations. He was the lead investigator in developing the Children’s Global Assessment Scale (C-GAS), and led a team that developed the Diagnostic Interview Schedule for Children (DISC), and in the late 1990s, the Columbia Teen Screen.

Dr. Shaffer suspects that disruptions of the serotonin neurotransmitter system are important in the biological underpinnings of suicidal thinking and behavior. “Serotonin acts as a sort of shock absorber of emotion,” he says. He is deeply impressed with recent Danish studies demonstrating the importance of outpatient follow-up for youths admitted for suicidal behavior.

Dr. Shaffer notes, too, the importance of getting high schools to allow students to be screened annually for suicide risk, and says more suicides could be prevented if permission were granted—it rarely is—for brief computer-administered questionnaires seeking to identify acute anxiety and aggression. He reminds that the clearest identifier of a youth—typically an adolescent male—who might indeed carry out a self-destructive act is the admission that he has planned where and when to do the deed. “Agitation, unrest, anxiety, alcohol, and planning: these are what you want to watch out for,” Dr. Shaffer advises.



David Shaffer, M.D.  
 Irving Philips Professor of Child Psychiatry  
 College of Physicians & Surgeons, Columbia  
 University; Professor of Psychiatry and Pedi-  
 atrics and Chief, Division of Child and Adoles-  
 cent Psychiatry, Columbia University Medical  
 Center; Attending Psychiatrist and Chief, De-  
 partment of Pediatric Psychiatry, New York  
 Presbyterian Hospital;  
 1992 NARSAD Distinguished Investigator  
 Grantee,  
 2006 Brain & Behavior Research Foundation  
 Ruane Prize for Outstanding Achievement in  
 Child and Adolescent Psychiatric Research

# Frequently Asked Questions on Early Intervention

Q  
A

Are there specific techniques for early diagnosis of brain and behavior disorders that have been proven effective?

Dr. David Shaffer has been a pioneer in diagnosing depression and suicidal risk in youths. He identified the importance of aggressive behavior in identifying youths most at risk, as well as co-morbidities including not only depression but also alcohol use and anxiety. He has devised diagnostic “survey instruments” which have come to be used around the world. Such diagnostic assessments include the Children’s Global Assessment Scale (C-GAS), the Diagnostic Interview Schedule for Children (DISC) and the Columbia Teen Screen.<sup>1</sup>

In addition to these specific tools, most diagnoses require a detailed evaluation by an experienced clinician.

Q  
A

At what age or stage of obvious behavioral issues is it best to intervene—and what are the options for intervention?

Whenever behavioral warning flags are identified, it is a good idea to speak with a trustworthy pediatrician. This can be appropriate at any age. Pediatricians can make referrals and often have a good sense of what type of problem is within the “norm.” There are different ways of intervening if it is developmental delay or a very focused behavioral problem.

It also makes sense for parents to contact their local medical school to find someone in the child psychiatry department if the warning flags (behavioral issues) are persistent. Psychiatric diagnoses made by skilled clinicians can give parents a reasonable prediction, based on the doctor’s experience, of what sort of treatment can help; what the child’s prognosis might be; what the chances are of outgrowing the symptoms and which treatments are likely to be the most useful.<sup>2</sup>

**Q** What are the early warning signs of mental illness?

**A** It depends on the specific illness, but general concerning factors include difficulties in relationships with peers and behavioral or emotional problems. Parents might hear teachers complain of a child's difficulty staying in his/her seat, blurting out answers before they are called on or making frequent careless errors on homework, relative to their peers. At home, parents might see their child having more difficulty staying seated during meals or getting distracted easily, more than would be expected for a child their age.<sup>3</sup>

In psychotic disorders such as schizophrenia, early warning signs during adolescence and early adulthood can include dramatic changes in mood; changes in interests—newfound interest in the supernatural, a philosophical or religious movement, becoming superstitious or showing disinterest in activities previously enjoyed; not doing as well in school; changes in sleeping habits and/or the foods they like to eat; having illusions, slightly bizarre or unrealistic, that they're not sure are real or not; a new extreme sensitivity to sound or stimuli.<sup>4</sup>

**Q** Is it possible to predict if someone will act out suicidal ideation? Are there effective ways to intervene?

**A** Dr. J. John Mann is currently leading one of the largest studies of causes of suicidal behavior ever mounted. He hopes to develop a biological screening test to estimate the risk of suicidal behavior as well as to evaluate therapeutic interventions to relieve the desperation that leads to suicidal behavior.

Using brain-imaging technology, the team is using information they have gathered from the brains of people who died by suicide to develop brain imaging methods to test in depressed

patients, half of whom have a history of suicidal behavior and half who have never attempted suicide. After many years of mapping neurotransmitter abnormalities in the brains of people who died by suicide, Dr. Mann believes it will be possible to detect the abnormalities in brain scans and that in addition to clinical assessment, they will be able to detect depressed patients at risk for suicide.<sup>5</sup>

**Q** After being diagnosed with a particular mental illness is it “for life” or are there effective ways to curb progression or even reverse the effects of illness?

**A** There are numerous medications and behavioral therapies that have been shown to be effective in treating and alleviating symptoms of the illnesses. There is also some evidence that with therapies such as computer cognitive “brain training,” defects in brain signaling can be improved. Many researchers continue to gain insights into the underlying causes of mental illness, and with these continued advancements, more effective treatments and ultimately preventive techniques and cures will be developed.<sup>6</sup>

Sources:

<sup>1</sup> David Shaffer, M.D., NARSAD Distinguished Investigator Grantee, see p. 7

<sup>2</sup> Judith L. Rapoport, M.D., Brain & Behavior Research Foundation Scientific Council Member, see pp. 5-6

<sup>3</sup> Leslie A. Hulvershorn, M.D., M.Sc., NARSAD Young Investigator Grantee, [bbrfoundation.org](http://bbrfoundation.org)

<sup>4</sup> Jeffrey A. Lieberman, M.D., Brain & Behavior Research Foundation Scientific Council Member, [bbrfoundation.org](http://bbrfoundation.org)

<sup>5</sup> J. John Mann, M.D., Brain & Behavior Research Foundation Scientific Council Member, see p. 10

<sup>6</sup> [bbrfoundation.org](http://bbrfoundation.org)

# Using Brain Imaging Technology to Identify Brain Changes that May Predict Suicide Risk



J. John Mann, M.D.  
Paul Janssen Professor of Translational Neuroscience in Psychiatry and Radiology, Columbia University;  
Director of the Molecular Imaging and Neuropathology Division, New York State Psychiatric Institute;  
2008 NARSAD Distinguished Investigator Grantee,  
Brain & Behavior Research Foundation  
Scientific Council Member

Roughly 36,000 Americans kill themselves every year. Is it possible to develop better ways to predict and avert suicide? J. John Mann, M.D., believes the answer is “yes.”

Dr. Mann is currently leading one of the largest studies of causes of suicidal behavior ever mounted...

Dr. Mann is a pioneer in the study of factors that predispose people to depression, bipolar disorder and suicide. He is currently leading one of the largest studies of causes of suicidal behavior ever mounted, with dual goals of developing a biological screening test to estimate the risk of suicidal behavior and for evaluating therapeutic interventions that will relieve the desperation that leads to suicidal behavior.

Using brain-imaging technology, the team is using information from the brains of people who died by suicide to develop brain imaging methods that they are testing in depressed patients, half of whom have a history of suicidal behavior and half who have never attempted suicide.

The postmortem studies have revealed specific, consistent changes in certain neurotransmitter systems, and the team is trying to see if the same changes are visible in the living patients. Patients exhibiting the abnormality are being followed to see if the brain imaging findings predict outcome on different types of medication and psychotherapy treatments.

One promising intervention Dr. Mann is testing is the drug ketamine. Originally developed as an anesthetic, ketamine has the ability to ease the symptoms of major depression within a few hours, as opposed to currently available anti-depressants, which often require weeks to take effect, if at all. In current trials of ketamine with suicidal patients, about 60 percent have gotten better, a percentage that appears to be higher than achieved with other medications. These patients are then continued on other medication and followed over a period of several months.

Dr. Mann credits the Brain & Behavior Research Foundation for this research. His 2008 NARSAD Distinguished Investigator Grant afforded him the opportunity to conduct preliminary studies of the response of patients to ketamine while simultaneously scanning their brains with magnetic resonance imaging (MRI). The results of that preliminary trial led to the current ongoing studies, both of which are being funded by the National Institute of Mental Health (NIMH). “I would never have gotten initial funding from the NIMH because I had no pilot data,” he says.

“After many years of mapping neurotransmitter abnormalities in the brains of people who died by suicide,” says Dr. Mann, “we are now beginning to detect the same kinds of abnormalities in the brain scans, which means that the possibility of using a brain scan in addition to clinical assessment to detect depressed patients at risk for suicide is becoming a very real option for clinicians.”



Stamatia Pappas at the Brain & Behavior Research Foundation Women's Mental Health Conference, September 2012 in New York City

# Well Into Recovery

A family credits recovery from schizoaffective disorder to relatively early intervention, the right medication, never losing hope and a great therapist

Recalling her son's last year in high school, Stamatia Pappas can still, ten years later, feel her eyes fill with tears. What might have seemed at first to be simply a high school senior's bad case of "senioritis," turned out to be the early rumblings of an approaching cataclysm. She watched as her son, the boy who loved books, suddenly could not concentrate on reading. Until then always an able student, he came close to failing his courses. A passionate music lover, when given a senior-year "dream internship" with a music company, he sat, paralyzed, on the curb outside the company building or hid himself in the men's room.

Stamatia supported her son as best she could, even while she didn't understand what was happening. Her son somehow managed to complete the credits needed to graduate from high school and went off to college, but the following fall, two weeks before Thanksgiving, the family received a call to come and get their son. He was failing his classes and wandering the streets and needed to be taken home. By New Year's Eve of that year, he ended up in an acute care unit.

Overt psychotic symptoms typically appear in late adolescence or early adulthood. As a child spirals out of control, distraught parents often find it difficult to find appropriate help or even to get a definitive diagnosis, as happened here.

Says Stamatia: "He was discharged from the hospital with medication that clearly wasn't working and told he should just follow up with a psychiatrist. We were told that he wasn't psychotic, that the problem was his relationship with his parents. It wasn't that long ago and we were still getting this type of explanation."



Stamatia with Janet Susin, longtime Foundation supporter, at the 2012 Women's Mental Health Conference in New York City

The next episode was unambiguous—and terrifying. Home alone, with her husband off on a business trip, Stamatia tells about how her son went off to a friend's house "and spent the weekend smoking pot. When I finally reached him, he begged me, 'Mom, you have to come get me right away.' While we were driving home he was pounding his body against the dashboard."

Taking their son to be hospitalized was an excruciating choice, but there didn't seem to be any other options. Over a course of three months, the Pappas family painfully watched as their son got treatment in the hospital,

### The recovery was slow and not always steady, but eventually her son was able to go back to college ... earning his bachelor's degree.

but went through a number of antipsychotic drugs that failed to help him get better and in some cases made him considerably worse. He was finally stabilized on clozapine (Clozaril®); a second-generation antipsychotic pioneered for treatment of patients with resistant schizophrenia by Herbert Meltzer, M.D., with the support of a NARSAD Distinguished Investigator Grant. Once stabilized, their son was able to go home.

Right around when her son was released from the hospital, they also finally found the right therapist. I knew she was the right one when we met and she said to me, "Mrs. Pappas, we're all going to dance at your son's wedding."

In September of 2012, when Stamatia Pappas was invited to tell her story at the Women's Mental Health Conference hosted by the Brain & Behavior Research Foundation, she was able to open her presentation with the news that her son, now 27 years old, is "well into recovery."

The recovery was slow and not always steady, but eventually her son was able to go back to college, not far from

The Pappas family supports the Brain & Behavior Research Foundation because of the work funded to better understand what causes mental illness and to develop effective early intervention and diagnostic techniques.

the family's home, beginning as a part-time student and then completing the program and earning his bachelor's degree. He completed a certificate program in art therapy, is working at an organization where he is helping two young men with autism spectrum disorders, and hopes to eventually earn a master's degree in music therapy.

Stamatia has also found support for herself as she continues to support her son's recovery. She is a member of NAMI, the National Alliance on Mental Illness, where she is currently President of a chapter and an instructor in its Family-to-Family program. The conference session

in which Stamatia shared her story was titled "Early Intervention, Rehabilitation and Reintegration." The NARSAD Grant-supported scientists who spoke on the panel with her described what researchers are now learning about the crucial importance of treatment early on in the course of mental illness for preventing or minimizing the progression of disease. (See pages 22–23.)

While the process of dealing with her son's illness has been painful and perplexing, rife with setbacks early on, Stamatia considers her family lucky. They were able to find the right treatments relatively soon after the onset of illness and she believes this has been crucial to the whole family's recovery. She has heard so many stories of other, less fortunate families. "What has helped our son is a combination of things," says Stamatia. "He is on the right medication, he is determined to stay well, has a family that never gave up hope and a great therapist. I look forward to dancing at his wedding!"

The Pappas family supports the Brain & Behavior Research Foundation because of the work funded to better understand what causes mental illness and to develop effective early intervention and diagnostic techniques. ❖

# NARSAD Independent Investigator Grantees in 2013



**Robert M. Post, M.D.**  
Chair, NARSAD Independent Investigator Grant Selection Committee,  
Brain & Behavior Research Foundation Scientific Council;  
Head, Bipolar Collaborative Network  
Professor of Psychiatry,  
George Washington School of Medicine



Forty mid-career scientists from 10 countries and 34 institutions will pursue innovative research related to depression, bipolar disorder, schizophrenia and anxiety disorders like obsessive-compulsive and post-traumatic stress disorders. We are very proud to present them to you here.

Dr. Post said: “The range of project proposals this year was exceptional in its variety of new approaches to understand and treat mental illness. Tackling the illnesses of the brain remains science’s most daunting challenge and requires these cutting-edge approaches that the Brain & Behavior Research Foundation has been supporting for 25 years with its NARSAD Grants. Each year we build upon the growing body of knowledge about the brain and its functioning and come closer to finding cures.”

## Basic Research

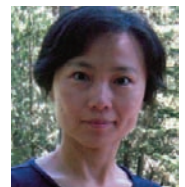
### BIPOLAR DISORDER



**Anabel Martinez-Aran, Ph.D.**, of the Institut D’investigacions Biomèdiques August Pi i Sunyer in Spain, will conduct a clinical trial to examine the role of the growth factor BDNF (brain-derived neurotrophic factor) in cognitive impairment and long-term functioning in bipolar disorder to determine the efficacy of cognitive remediation. The study will compare BDNF levels in 100 patients in an euthymic (nondepressive, nonmanic) state after half received a neurocognitive intervention and half received a pharmacological treatment-as-usual.

based on findings that reduced astrocyte cell density is seen in several brain regions in postmortem studies of depression. The resultant findings may be applicable to other cell types as well.

**Qin Wang, M.D., Ph.D.**, of the University of Alabama at Birmingham, will explore the link between a molecule called  $\alpha 2AAR$  and depression. The  $\alpha 2AAR$  is a key receptor involved in regulating brain neurotransmitter systems thought to be disrupted in depressive disorders. The research will use transgenic mice to observe cellular and molecular alterations in the brain associated with  $\alpha 2AAR$  over-expression in depressive behaviors, and the possibilities for corrective therapy targeting  $\alpha 2AAR$ .



### DEPRESSION



**Robert C. Thompson, Ph.D.**, of the University of Michigan, will investigate how stress affects gene expression in different brain cell types to contribute to depression. Using animal models, the research will begin by determining the impact of stress on cells called astrocytes,

## Basic Research *(continued)*

### POST-TRAUMATIC STRESS DISORDER (PTSD)



**Julia A. Chester, Ph.D.**, of Purdue University, is exploring the role of stress in genetic risk for co-occurring (co-morbid) post-traumatic stress disorder and alcohol abuse toward the goal of developing new treatments. Utilizing mice bred for high or low alcohol preference she has found that high-alcohol preference mice show greater anxiety-related behavior than low-alcohol preference mice, suggesting that common genetic mechanisms influence the two behaviors.

### SCHIZOPHRENIA



**Alessandro Bertolino, M.D., Ph.D.**, of the University of Bari in Italy, is studying epigenetic risk for schizophrenia. Epigenetics refers to environmentally induced events that alter gene activity. Having demonstrated that methylation of the gene COMT (Catechol-O-methyltransferase) affects the functioning of dopamine, a brain chemical involved in schizophrenia, the Bertolino lab plans to now evaluate DNA methylation interaction with genes controlling dopamine pathways.



**Peng Jin, Ph.D.**, of Emory University, proposes to expand testing his hypothesis that malfunction of a genetic regulator of neurodevelopment, microRNA-137 (miR-137), contributes to the development of schizophrenia. Postmortem brain-tissue studies suggest that miR-137 is down-regulated in schizophrenia. To explore its activity in a living organism, Dr. Jin's team have bred mice with a disabled miR-137 gene.



**Carsten Korth, M.D., Ph.D.**, of the University of Düsseldorf in Germany, is examining the interaction of DISC1, a key risk gene for schizophrenia, and dopamine, a chemical neurotransmitter of messages between nerve cells. The Korth lab has identified a novel function of DISC1 in modulating the dopamine transporter, the molecule critical to reuptake of released dopamine following neural communication. The lab will now conduct animal studies to characterize DISC1 and dopamine transporter interaction.



**Antonietta Lavin, Ph.D.**, of the Medical University of South Carolina, will explore the underlying mechanisms of the decreases in release of the brain chemical glutamate and the role of the protein dysbindin in relation to the cognitive deficits associated with schizophrenia. Brain tissues from schizophrenia patients show decreases in both glutamate and dysbindin, and decreases in glutamate release also appear in dysbindin-deficient mice that the Lavin lab will use as experimental models.

**Todd Lencz, Ph.D.**, of The Feinstein Institute for Medical Research, aims to identify rare genetic variants associated with schizophrenia by utilizing DNA from an Ashkenazi Jewish population, in which there is much less genetic variation than in the general public. Preliminary testing of a small number of Ashkenazi subjects with schizophrenia identified a set of possible candidate genes that Dr. Lencz now intends to pursue in a larger number of participants.



**Daniel J. Mueller, M.D., Ph.D.**, of the Centre for Addiction and Mental Health in Canada, is exploring the genetics of the weight gain caused by antipsychotic medications. Commonly prescribed drugs for schizophrenia like clozapine and reserpine induce substantial weight gain in up to half of patients, posing risks for serious illness and for treatment noncompliance. Dr. Mueller and colleagues are working to identify the responsible gene variants and their role in antipsychotic-induced weight gain and possibly in obesity generally.



**Brien P. Riley, Ph.D.**, of Virginia Commonwealth University, proposes to sequence all protein-coding DNA in the genomes of a group of Irish patients with schizophrenia in multiple affected families in order to identify rare, damaging genetic variations. Such families have a substantially higher risk of illness than the general population, and likely harbor gene variations with greater impact in the causation of a disease in which hundreds of variants have been implicated.



### MULTIPLE DISORDERS

**Alon Chen, Ph.D.**, of the Weizmann Institute of Science in Israel, is studying the role of microRNAs, molecules that repress gene expression, in regulating the brain chemical serotonin in **depression and anxiety**. Levels of brain microRNAs are affected by behavioral and pharmacological manipulations. In-depth understanding of mechanisms regulating serotonin function may contribute to more effective, faster-acting antidepressant and anti-anxiety medications with fewer negative side effects than now available.



**Todd Denton Gould, M.D.**, of the University of Maryland, will study changes in a gene called CACNA1C that appear to confer susceptibility to mental illness, primarily **bipolar disorder and depression**. The goal is first to identify CACNA1C variants expressed in adult and fetal brains to assess whether the mechanism regulating gene expression is specific to developmental stages, and then to determine the mechanisms of gene expression that lead to illness susceptibility.







**Andrew L. Gundlach, Ph.D.**, of the University of Melbourne in Australia, will investigate the involvement in **anxiety and depressive disorders** of a molecule called RXFP3. Acute RXFP3 activation reduces levels of anxiety-like behavior in genetically engineered ‘anxious’ mice and increases their social interactions. The proposed study will elucidate the targets of RXFP3, which may uncover new targets for treatment.



**Yasushi Nakagawa, M.D., Ph.D.**, of the University of Minnesota, will examine interactions in the brain between the thalamus and the prefrontal cortex. Defects in these interactions are implicated in **many brain and behavior disorders, including schizophrenia, bipolar disorder and autism**. Projections from the thalamus to the cortex play a central role in conveying visual and auditory information. Projections from the mediodorsal area are important for learning and memory.

## New Technologies

### BIPOLAR DISORDER



**Manon H. J. Hillegers, M.D., Ph.D.**, of Utrecht University in The Netherlands, is looking for biomarkers for bipolar disorder in adolescence, which is peak time for bipolar onset. The project will apply magnetic resonance imaging studies to compare the brains of unmedicated adolescents at high genetic risk with healthy controls to observe how vulnerability for bipolar disorder affects brain function.

I am very grateful that the Brain and Behavior Research Foundation continues to fund important clinical science that has the potential to make a direct impact on the lives of people with mental illness and their family members. More understanding of brain function abnormalities as a possible illness predictor in adolescents at high (familial) risk for bipolar disorder can only be gained when this type of support is provided.

Manon Hillegers, M.D., Ph.D.



**Beny Lafer, M.D., Ph.D.**, of the University of Sao Paulo in Brazil, proposes to conduct a trial of creatine monohydrate, a medication that boosts energy metabolism, as a treatment strategy for bipolar depression, based on the hypothesis that creatine improves depressive symptoms through changes in the brain levels of metabolites of energy production. Via a technology called phosphorus magnetic

resonance spectroscopy, the trial will examine relevant brain events before and after creatine treatment.

### DEPRESSION

**Christopher G. Beevers, Ph.D.**, of the University of Texas at Austin, wants to determine the role of genetic variation in how individuals respond to treatment for depression. Single nucleotide polymorphisms, or SNPs (pronounced “snips”), are variations in the DNA sequence of a gene. Dr. Beevers will apply a newly developed technique, genome-wide complex trait analysis, to assess 500,000 SNPs associated with rare and common genetic variations as predictors of treatment response.



### SCHIZOPHRENIA

**Dost Öngür, M.D., Ph.D.**, of Harvard University, is investigating reduced brain energy production in people with schizophrenia. Mitochondria are the energy-producing factories within cells. Dr. Öngür and colleagues have developed a specialized MRI tool that can follow changes in levels of energy molecules within the living brain. To rule out the influence of medication or chronic psychosis, the research will examine brain mitochondrial processes in unmedicated patients undergoing their first psychotic episode.



## Next Generation Therapies

### DEPRESSION



**Charles L. Raison, M.D.**, of the University of Arizona, will conduct a trial of whole body hyperthermia—raising the body temperature—to treat depression. A preliminary trial showed rapid, lasting improvement after a single session. Animal research suggests hyperthermia affects a neural pathway from the skin to specific brain cells. The research will try to confirm whole body hyperthermia as a safe,

fast-acting new antidepressant and evaluate the relevance of peripheral neural pathways.

**Jonathan P. Roiser, Ph.D.**, of the University of London in the UK, will examine the neural mechanisms affected by transcranial direct current stimulation (tDCS), a brain stimulation treatment for depression, and its ability to boost



### Next Generation Therapies

#### DEPRESSION (continued)

the effectiveness of cognitive behavioral psychotherapy. Treatment with tDCS stimulates the left dorsolateral prefrontal cortex region of the brain, which is involved in higher cognitive functions.



**Gabrielle Rudenko, Ph.D.**, of the University of Michigan, will test a protein called  $\Delta$ FosB as a target for treatment of intractable depression. In normal responses to stress,  $\Delta$ FosB accumulates in specific brain regions and spurs resilience mechanisms that enhance the body's ability to cope with stress.  $\Delta$ FosB levels appear dramatically reduced in postmortem brain tissue of depressed patients. By clarifying mechanisms and function of  $\Delta$ FosB, Dr. Rudenko hopes to exploit and enhance the protein's antidepressant action.



**John A. Wemmie, M.D., Ph.D.**, of the University of Iowa, will explore the contribution of a particular ion channel, ASIC1a, to mood and behavior, and its potential as an antidepressant target. Ion channels are proteins on cell membranes that control ion flow in to and out of the cell. The lab's prior animal research showed that disturbed ASIC1a contributes to depression and anxiety behaviors and that inhibiting the ASIC1a gene in the brain reduced these behaviors.

#### SCHIZOPHRENIA



**Christopher R. Bowie, Ph.D.**, of Queen's University Belfast in the UK, will test a new online application of cognitive remediation for people with schizophrenia. Cognitive remediation is psychotherapy that improves schizophrenia-associated deficits in cognitive functions such as attention, memory and planning, but many patients lack access to it. Online delivery, if effective, may provide patients the ability to achieve even better, more consistent skill development than is achievable with weekly face-to-face psychotherapy.



**Ariel Graff, M.D., Ph.D.**, of the Centre for Addiction and Mental Health in Canada, will conduct a pilot trial to see whether levels of the brain chemical glutamate are increased in schizophrenia patients who do not respond to antipsychotic medications. If increased glutamate can be linked to lack of treatment response, it should facilitate development of new treatments aimed at normalizing glutamate levels.

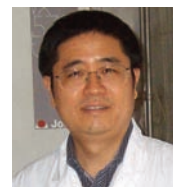
**Gregory A. Light, Ph.D.**, of the University of California, San Diego, is working to improve cognitive ability in people with schizophrenia. The cognitive impairments that affect schizophrenia patients are not helped by current medications, but are helped by cognitive training. One promising approach, Targeted Cognitive Training, sharpens auditory information processing. The study will ascertain utility of this intervention and provide possible biomarkers to predict which individuals are most likely to respond to it.



**Alessandro Usiello, Ph.D.**, of Ceinge Biotechnologie Avanzate in Italy, will explore the possible role of an amino acid, D-aspartate, in schizophrenia and its potential as a schizophrenia treatment. Amino acids are small compounds that can perform as chemical messengers in the brain. Postmortem brain studies suggest altered metabolism of D-aspartate in schizophrenia, and animal research has shown that D-aspartate can induce effects similar to those of the antipsychotic haloperidol.



**Xiang Yang Zhang, M.D., Ph.D.**, of the Baylor College of Medicine, will conduct a trial to see if the apparent cognitive benefits of smoking for people with schizophrenia can be pharmacologically mimicked. Nicotine appears to improve cognitive function through nicotinic receptors in the brain, but the effect is short-lived and has toxic consequences. The antiemetic drug tropisetron also interacts with a nicotinic receptor and Dr. Zhang's preliminary studies indicate that tropisetron also improves cognitive deficits.

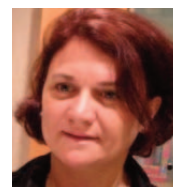


#### MULTIPLE DISORDERS

**Elizabeth W. Twamley, Ph.D.**, of the University of California, San Diego, hopes to develop and test a mobile application of a quick, low-tech intervention that improves cognitive impairment, which is a common feature of **schizophrenia, bipolar disorder, and major depression**. If the method, called Compensatory Cognitive Training, can be adapted for smartphones and tablets, it would greatly increase access to therapy while decreasing cost.



**Analia Bortolozzi Ph.D.**, of the Institut D'Investigacions Biomèdiques August Pi i Sunyer in Spain, is seeking new therapeutic targets for **mood and cognitive disorders**. This study will test the hypothesis that selective suppression of the activity of two potassium channels in the brain's hippocampal region induces resilience to stress, evoking antidepressant-like effects and improved cognitive function. Potassium channels are structures on cell membranes that regulate the flow of substances in and out of cells.



# NARSAD Independent Investigator Grantees in 2013 with a focus on **Early Intervention**

## BIPOLAR DISORDER



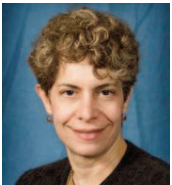
**Mark A. Ellenbogen, Ph.D.**, of Concordia University in Canada, and a Canada Research Chair, will test a program aimed at heading off mental illness in children of parents with bipolar disorder. These children show high levels of the stress hormone cortisol and are more biologically sensitive to stress. The study will apply a program called Reducing Unwanted Stress in the Home (RUSH), developed in the Ellenbogen lab, which includes stress management techniques for the children and family-based interventions.

Recent evidence of gene-environment interplay supports the need for environmental interventions, even for highly heritable disorders. We hope our research will provide the groundwork to conduct a larger multi-site study of early prevention in the children of parents with bipolar disorder, and will elicit a greater focus among practitioners on children growing up with parents who struggle to cope with a debilitating mental disorder.

Mark A. Ellenbogen, Ph.D.



**Michael F. Grunebaum, M.D.**, of Columbia University, hopes to lower the high rate of suicide risk in people with bipolar disorder. Studies have demonstrated rapid improvement in suicidal ideation in patients after infusion of the anesthetic ketamine. To learn how ketamine works to curtail suicide, Dr. Grunebaum proposes a pilot study to compare ketamine's effects versus midazolam, a similarly sedative medication not known to reduce suicidal thoughts.



**Vivian Kafantaris, M.D.**, of the Feinstein Institute for Medical Research, is seeking an early biomarker of response to lithium in adolescents with bipolar disorder to sort out those who will and will not benefit from lithium treatment. Increased volume in specific brain regions following lithium use suggests that one of lithium's effects is to increase the volume of cell connections. Dr. Kafantaris is investigating volume increases in the hippocampus, the most neuroplastic brain area.

## DEPRESSION



**Heather C. Abercrombie, Ph.D.**, of the University of Wisconsin, will examine the role of the stress hormone cortisol in women with depression. Early life experience can alter gene expression into adulthood through so-called epigenetic changes caused by non-genetic, environmental factors such as stress. Dr. Abercrombie wants to determine whether childhood adversity is predictive of epigenetic changes related to altered cortisol functioning in depressed women, a potentially reversible process.

A variety of interventions may reverse and/or compensate for epigenetic changes due to early adverse experiences. [This] research is important because further understanding of the (epigenetic) mechanisms that link early adversity with stress-related pathology in adulthood is an essential stepping stone toward development of targeted early intervention strategies.

Heather C. Abercrombie, Ph.D.



**James E. Swain, M.D., Ph.D.**, of the University of Michigan, will conduct a trial to identify hormonal biomarkers of risk for and resilience to postpartum depression and anxiety. His lab has identified regional brain responses in depression, during parenting behaviors, and in responses to the stress hormone cortisol. The lab will now focus on responses in trial participants at one month postpartum, and their mood and behavior at three and six months postpartum. The researchers aim to improve early detection of and intervention for postpartum mental health issues.

### POST-TRAUMATIC STRESS DISORDER (PTSD)



**Ananda B. Amstadter, Ph.D.**, of Virginia Commonwealth University, will test a form of psychotherapy called Risk Reduction Family Therapy to treat adolescents who have been exposed to sexual abuse and suffer from subsequent post-traumatic stress disorder and drug abuse. The study aims to examine the biological mechanisms of response to the treatment, results of which may then inform other treatment approaches to trauma-induced illness.

Childhood sexual abuse is a major public health problem in the United States. It is associated with devastating rates of PTSD and substance use and abuse among the victims. Ultimately, the goal of this research is to elucidate the pathophysiology of PTSD, with a focus on environmental (i.e., psychosocial treatment) and biologic interplay, which will inform further treatment developments for the post-trauma context.

Ananda B. Amstadter, Ph.D.

### SCHIZOPHRENIA



**Deepak C. D'Souza, M.D.**, of Yale University, is interested in the consequences of chronic cannabis exposure and schizophrenia. Evidence suggesting a link between marijuana use and psychosis has relied mostly on self-reporting. Participants in this study will be members of a group whose early, unrestricted use of cannabis is central to their beliefs. Preliminary data show that these subjects underperform non-cannabis using controls on cognitive tests and have higher measures of schizophrenia symptoms.



**Stephen J. Glatt, Ph.D.**, of the State University of New York, will study a risk gene for schizophrenia, DRD2, which encodes receptors for the brain chemical dopamine. How variant forms of DRD2 impart susceptibility to schizophrenia remains unclear. Dr. Glatt is focused on answering that question to gain further insight of the underlying pathology of schizophrenia and to identify better targets for new medications and earlier interventions.

This avenue of research will be critical for the development of early screening tools that might make it easier for clinicians to diagnose the disorder and start treatment sooner, and we know that earlier detection and treatment lead to better outcomes for patients. It may even become possible to identify biomarkers that are expressed at the time of first symptoms, before the disorder is even diagnosable based on traditional methods.

Stephen J. Glatt, Ph.D.



**Christine I. Hooker, Ph.D.**, of Harvard University, hopes to improve the future of young people at risk for psychosis as it affects their cognitive skills. Research has shown that intensive cognitive and social skills training improve functioning in people with schizophrenia. In the proposed project, a group of youths at high risk will participate in a randomized trial of a computerized intervention targeting functions compromised in schizophrenia such as attention, memory and problem solving.



**Oliver D. Howes, M.D., Ph.D.**, of King's College London in the UK, wants to determine whether changes in behavior of the brain chemical dopamine occur with the onset of psychosis. Dopamine dysfunction is linked to schizophrenia, but only a third of those thought at risk develop psychosis. Confirming a dynamic process of dopamine deregulation would advance understanding of the neurobiology of psychotic disorders and could lead to interventions targeted on dopamine synthesis regulation to prevent onset of psychosis.

# Help improve the lives of those living with mental illness



Lilian Sicular at the Brain & Behavior Research Foundation 2012 Women's Conference

## Ms. Lilian Sicular speaks of why she has supported the Brain & Behavior Research Foundation since its inception.

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 the Sicular family was focused on finding the best possible care, the need for research to find causes and treatments of these dreadful conditions was clear. The 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.



Lilian Sicular at the 2010 Klerman/Freeman Awards Dinner

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.

## Make a donation today to the Brain & Behavior Research Foundation

- Accelerate the support for cutting-edge research to develop early intervention techniques, preventive strategies, and next generation treatments and therapies
- Invest in the most promising brain and behavior research on disorders including depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder and anxiety disorders like obsessive-compulsive and post-traumatic stress disorders

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

For more information, please **call (800) 829-8289**, or **visit [bbrfoundation.org](http://bbrfoundation.org)**.



## With a Will

### There's a Way to Help

**Philanthropy can change your life from making a donation to making a difference.**

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.

*Gifts which benefit the Foundation also personally benefit its donors by helping to fulfill important family and financial goals and insure that our scientists, today and tomorrow, will have the resources to continue making advances in mental health research.*

Please consider making a gift to provide for a loved one and help make a difference to the Brain & Behavior Research Foundation.

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

[bbrfoundation.org/planned\\_giving](http://bbrfoundation.org/planned_giving)

## New Treatments

# New Treatments

### Folic Acid in Early Pregnancy May Significantly Reduce Autism Risk

A team of researchers, including NARSAD Grantees Mady Hornig, M.D., Kari Kveim Lie, M.D., W. Ian Lipkin, M.D., and Ezra Susser, M.D., Dr.P.H., led a large birth-cohort study in Norway that found folic acid (Vitamin B9) administered from four weeks before and 8 weeks into pregnancy may reduce the infant's risk of developing autism by as much as 40 percent compared to children of mothers who did not take folate. Folic acid is required for DNA synthesis and repair, and is found in beans, eggs and many vegetables. Norway does not enrich flour with folate, but recommends it in early pregnancy for protection against birth defects.

**Source: Journal of the American Medical Association**

### Vitamin B12 & Folate Supplements May Reduce Schizophrenia Symptoms

NARSAD Grantees Joshua Roffman, M.D., M.MSc., Donald C. Goff, M.D., (study senior author) and Jordan Smoller, M.D., Sc.D. (a study co-author) found that adding supplements to antipsychotic medication alleviated some negative symptoms in patients with schizophrenia, especially those carrying specific genetic variants. Adding folate and Vitamin B12 to treatment with antipsychotic medication in their study of 100 patients showed a mild to significant improvement in the following symptoms: apathy, social withdrawal and lack of emotional expressiveness. Earlier research by members of this team associated low blood folate levels with more severe negative symptoms among patients with schizophrenia.

**Source: Journal of the American Medical Association Psychiatry**

### An Antioxidant May Reduce Neuron Loss in Schizophrenia & Bipolar Disorder

NARSAD Grantee Kim Q. Do, Ph.D., and her team found that the antioxidant named N-acetylcysteine appears to protect from stress a subtype of neurons that is believed to play a role in the development of mental illnesses, especially schizophrenia and bipolar disorder. N-acetylcysteine proved its protective qualities when given to mice that were deficient in glutathione, a molecule that normally protects against oxidant stress (excessive levels of oxidants or "free radicals"). This new finding shows promise for a possible preventative role for at-risk infants to guard against the effects of stress during a critical phase of brain development that could otherwise result in life-long psychological impairment.

**Source: Biological Psychiatry**

# Meet the **Scientist** A Virtual Q&A Discussion



Please join us by phone or on the web  
the second Tuesday of every month @ 2:00 P.M. Eastern Time

## Leading Experts Present the Latest in Mental Health Research

**Moderated by Jeffrey Borenstein, M.D.**

President & CEO, Brain & Behavior Research Foundation  
Host of the public television series "Healthy Minds"

### **May 14** **OCD & Anxiety: Symptoms, Treatment & How to Cope**

**Helen Blair Simpson, M.D., Ph.D.**

Director, Anxiety Disorders Clinic, New York State Psychiatric Institute/Columbia University  
NARSAD Grantee

### **June 11** **Depression in Children and Adolescents**

**Karen Dineen Wagner, M.D., Ph.D.**

Director, Division of Child & Adolescent Psychiatry, University of Texas Medical Branch at Galveston  
Brain & Behavior Research Foundation Scientific Council Member

### **July 9** **Resilience: The Science of Mastering Life's Greatest Challenges**

**Dennis S. Charney, M.D.**

Professor of Psychiatry and Neuroscience, Mount Sinai Hospital  
NARSAD Grantee, Brain & Behavior Research Foundation Scientific Council Member

### **August 13** **Ketamine and Next Generation Therapies**

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

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

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# Women's Mental Health Conference: The Art & Science of Caring

On September 14, 2012 in New York City, the Brain & Behavior Research Foundation hosted the Women's Mental Health Conference: The Art & Science of Caring. The event included a panel discussion on Early Intervention, Rehabilitation and Reintegration; small group discussions with leading researchers across mental illnesses; and a final panel discussion on overcoming stigma and the future of public policy and research. The following pages contain highlights of some of the presentations. Full transcripts of the talks are available at [bbrfoundation.org/2012-WMHC](http://bbrfoundation.org/2012-WMHC).



Rachel Loewy, Ph.D.  
Associate Professor, Department  
of Psychiatry,  
University of California, San Francisco;  
2007 and 2009 NARSAD Young  
Investigator Grantee

## Intervening in Early Psychosis with Computer-Based Brain Training Rachel Loewy, Ph.D.

The changes to brain function that schizophrenia effects, the cognitive deficits that inflict the most devastating long-term disabilities, are difficult to reverse and can worsen with recurring psychotic episodes. Recent research strongly indicates that the earlier the intervention to prevent or minimize the brain changes caused by schizophrenia, the better the long-term functional results.

Although a person's predisposition for schizophrenia is likely determined even before birth, the disorder does not usually manifest itself until late adolescence or early adulthood. Dr. Loewy and her colleagues, among them NARSAD Grantee Sophia Vinogradov, M.D., have been working to develop computer-based early interventions aimed at preventing or reversing the cognitive damage of schizophrenia. They have been conducting trials with two specific groups of young people. Those in the first group are in what is called the prodromal, or pre-onset, stage; that is, they have exhibited behaviors that point to risk for schizophrenia but have not yet displayed full-blown psychosis. Those in the second group have recently experienced their first psychotic break.

Among the critical thinking skills that can be affected by schizophrenia is information processing, the ability to pick out and retain with speed and accuracy what is important in a particular situation and respond appropriately as, for example, in negotiating traffic, holding a conversation or reading the emotion on someone's face. Progressive brain changes and inefficient information processing have been observed to occur during the early phases of psychosis.

Dr. Loewy and team have created software specifically aimed at strengthening information processing, beginning with a focus on auditory processing: information about sounds. Participants in the lab's trial are asked to spend an hour a day, five days a week, for eight weeks with laptop computers, listening to differing sounds and making distinctions among the sounds. The first signals they hear are simple, and they must note, simply, if the sound is going up or going down. As the trial progresses, the tasks become increasingly more difficult, requiring greater effort. The program is designed to maintain an 80 percent accuracy rate, which keeps the participants having to push their efforts.

Early results with a small trial sample lead Dr. Loewy to feel hopeful that this kind of cognitive training can be effective in averting long-term brain impairment for people with schizophrenia. The question still needing to be pursued is whether this method of changing cognitive function can improve their real-world functioning.



## Early Diagnosis and Intervention Techniques for Children

Rachel G. Klein, Ph.D.

Attention-deficit hyperactivity disorder (ADHD) is the most commonly diagnosed neurobehavioral disorder in children, but its diagnosis has been controversial. Without specific biological markers, diagnosing mental illness in children is difficult. ADHD diagnosis has traditionally depended on the presence of particular behavioral traits, mainly hyperactivity, impulsivity and inattention, but these traits can differ at different ages and can be different in boys and girls.

Dr. Klein, a founding member of the Brain & Behavior Research Foundation Scientific Council, is a leader in research on childhood mental health. Her long-term studies have helped to confirm ADHD as a true brain disorder, and point to the need for tailored approaches to prevent and effectively treat disorders in children.

How can actual brain disease be sorted out from normal variations in children's behavior? ADHD usually has a family history. A strong genetic component has been demonstrated in landmark twin studies; twins raised by adoptive parents have a considerably higher than average percentage of ADHD if a biological parent had the disorder.

The advent of powerful methods of brain imaging has revealed alterations in the brains of patients with ADHD. Dr. Klein and colleagues recently completed an imaging study of people now 41 years old who had been diagnosed with ADHD at age eight. Compared to controls followed for the same period of years, all of them showed smaller brain volumes whether or not they were still diagnosed with ADHD.

ADHD is currently treated with either stimulant drugs or behavioral therapy, or a combination of the two. Amphetamines and methylphenidate (Ritalin), have been in use for many years, but they were not systematically evaluated until the 1960s and 1970s. Previously, their main disadvantage was that they were short-acting. Long-acting, oral and patch-delivery forms are now available, and are effective for the majority of ADHD patients. By contrast, behavior therapy for ADHD, introduced in the 1960s, has not been shown to be as effective as medication and involves intensive application and considerable cost. A collaborative study in which Dr. Klein participated showed that outcomes for patients treated with medication combined with two years of intensive psychosocial therapy worked no better than medication alone.

With regard to concern about potential dangers of long-term use of stimulant medications, Dr. Klein's follow-up studies of children taking these medications for periods of up to five years has yielded no evidence of negative effects.



Rachel G. Klein, Ph.D.  
Fascitelli Family Professor of Child and Adolescent Psychiatry,  
New York University Child Study Center;  
1995 NARSAD Distinguished Investigator Grantee,  
2004 Brain & Behavior Research Foundation Ruane Prize for Outstanding Achievement in Childhood and Adolescent Psychiatric Research,  
Scientific Council Member

Go to [bbrfoundation.org/2012-WMHC](http://bbrfoundation.org/2012-WMHC) to read the full transcripts of presentations made at the Women's Mental Health Conference.

# Glossary

## Helpful definitions of terms used in this issue

**acetylcholine** (p. 4): a neurotransmitter that is part of the cholinergic chemical signaling system in the brain; abnormally high levels of acetylcholine in the brain have recently been found to cause symptoms of depression and anxiety in mice. If proven in humans, this represents a new target for depression treatments, offering a possibility of addressing a potential root biological cause of depression rather than treating its symptoms.

**acetylcholinesterase (AChE)** (p. 4): an enzyme produced by the body to lower acetylcholine levels.

**attention-deficit hyperactivity disorder (ADHD)** (pp. 2, 6, 13, 23): the most commonly diagnosed brain and behavior disorder in children, research indicates that ADHD may be caused by alterations in the brain and the way it functions and there may be predisposing genetic factors. ADHD diagnosis depends on clinical observation of behavioral traits, mainly hyperactivity, impulsivity and inattention, but these traits can differ at different ages and can be different in boys and girls. A person with ADHD is so inattentive or impulsively hyperactive—or both—that daily functioning at home, school and work is compromised. ADHD usually becomes apparent in children during preschool and early school years.

**cholinergic system** (p. 4): a neurotransmitter system which is stimulated, activated, or transmitted by the neurotransmitter acetylcholine and is believed to be involved in the regulation of memory and learning. Abnormal cholinergic neurotransmission linked to psychiatric disorders is a relatively new area of study, being pursued in areas such as depression and schizophrenia research as well as research on Alzheimer's disease.

**copy-number variants (CNVs)** (p. 5): CNVs are extra or missing segments of DNA in a person's genome. Many CNVs result in a person having multiple copies of genes that fall within the "duplicated" region; or no copies at all, if the region in question is deleted rather than copied. The average person has several dozen CNVs. Only rarely do these extra or missing segments of DNA include genes that play roles in diseases such as schizophrenia or autism.

**epigenetics** (pp. 3, 14, 17): the study of changes in gene expression caused by non-genetic factors that influence the development of an organism but do not alter the underlying DNA sequence. DNA, the genetic material, is "bookmarked" or "tagged" with various molecules, which have the effect of helping to determine whether a given gene is switched "on" or "off," or the degree to which a gene that is switched on "expresses" itself (by giving a cell instructions to manufacture more or less of a specific protein).

**ketamine** (pp. 10, 17): approved for use as an anesthetic and analgesic, this drug has been found to relieve symptoms of treatment-resistant depression in people, sometimes within hours. It is used only experimentally and is not approved for use in patients because of its serious side effects, including hallucinations. Efforts are under way to design medications that will have ketamine's benefits without the side effects.

**prodromal** (pp. 18, 22): the stage of illness before onset of full-blown disease symptoms.

**single-nucleotide polymorphisms (SNPs)** (p. 2): (pronounced "snips") single-letter variations in the 3-billion-letter genetic code that differ between individuals. They are the most frequent type of variation in the genome. Their causal relation to illness is currently debated.

**Selective Serotonin Reuptake Inhibitors (SSRIs)** (p. 4): currently the most popularly prescribed class of antidepressant medications. SSRIs keep the neurotransmitter serotonin in the synaptic gaps between nerve cells in the brain by preventing their rapid reabsorption into the neurons that release them, thus promoting signaling between cells.

**translational neuroscience** (p. 10): a process in which "basic research" about how the brain and its component parts function is "translated" into clinically valuable treatments.

# Save<sup>the</sup> Date

## October 25, 2013

Join us to meet the 2013

Outstanding Achievement Prizewinners  
Productive Lives Awardees and  
NARSAD Young Investigators at our



## National Awards Dinner

Friday Evening

and attend



## The 25th Annual New York City Mental Health Research Symposium

Friday Morning and Afternoon

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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 families and friends.

### HOW WE DO IT:

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

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