

The Quarterly

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FOCUS on ANXIETY

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NARSAD
The Brain and Behavior Research Fund

This issue of *The Quarterly* demonstrates remarkable achievements by scientists who had early career support from NARSAD grants. When Jonathan A. Javitch, M.D., Ph.D., (page 1) was awarded his first NARSAD Young Investigator grant in 1990, he was selected because of his promising insights on brain systems in schizophrenia, which he wanted to develop further. Now that he has received four NARSAD grants, culminating in a Distinguished Investigator grant, he has found new therapeutic potentials for novel drug treatments.

Bryan L. Roth, M.D., Ph.D., (page 2) was another Young Investigator funded by NARSAD first in 1992, then in 1998 with an Independent Investigator grant, and in 2008 Dr. Roth was awarded a Distinguished Investigator grant for his innovative work on brain circuitry. His research has broadened the knowledge base aimed to develop therapies to treat addiction.

W. Ian Lipkin, M.D., (page 3) was awarded a Young Investigator grant in 1991. His early research was focused on a discovery of viral disease infection in patients with bipolar disorder. This discovery led him into an accomplished 20-year career in the field of viral disorders.

John H. Krystal, M.D., (see page 4) received his first NARSAD grant as an Independent Investigator in 1997, to study the impact of amphetamines on psychosis. In 2000 he received a Distinguished Investigator grant to study signaling issues in the brain's cortex, and then, in 2006, a Distinguished Investigator grant for work on the glutamate receptor in the cortex. Beyond his extraordinary laboratory accomplishments, Dr. Krystal has become chair of Yale University's Psychiatry Department and Chief of Psychiatry at the renowned Yale-New Haven Hospital.

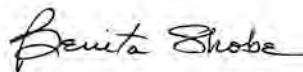
When you turn to the last page, you will see that Helen S. Mayberg, M.D., built a career of innovative accomplishment on a series of NARSAD grants and obtained significant subsequent funding to greatly expand her remarkable contribution to the field.

These gifted, dedicated scientists, and now more than 3,000 others awarded NARSAD grants, illustrate the goal of the NARSAD Scientific Council and its supporters – driving research from discovery to recovery. NARSAD began 24 years ago with the goal of achieving better treatments and cures. Great progress has been made and greater is expected from remarkable scientists such as those mentioned in this issue.

Sincerely,



Herbert Pardes, M.D.
President, NARSAD Scientific Council



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President and CEO



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NARSAD Research Discoveries in the News

NARSAD Scientific Council Member Discovers Key Dopamine Receptor Structure



Jonathan A. Javitch, M.D., Ph.D.

NARSAD Scientific Council member Jonathan Javitch, M.D., Ph.D., of Columbia University, is part of a team that recently determined the structure of one of the five dopamine receptors in the human brain — the culmination of three years of study and experimentation.

Expressed widely throughout the brain, dopamine is a message-carrying molecule called a neurotransmitter, which is involved in a number of regulatory processes related to movement and aspects of cognition such as attention, memory and learning. Dopamine depletion is characteristic of Parkinson's disease, while increased dopamine levels in the brain are thought by many to play a role in psychotic symptoms such as delusions and hallucinations in schizophrenia. Significant increases in dopamine levels are also thought to play a central role in drug abuse and addiction.

Dr. Javitch is seeking to obtain a finely detailed understanding of the different types of dopamine receptors and their specific impacts in disease, including their properties as pharmacological targets. Using a technique called x-ray crystallography, a method used widely in molecular biology in which an x-ray beam is fired at a crystallized form

of a given molecule, Dr. Javitch and colleagues at Weill Cornell Medical College, the National Institute of Drug Abuse and the Scripps Research Institute recently were able to capture a detailed three-dimensional atomic structure of the dopamine-3 receptor (D3R).

D3R is implicated in schizophrenia, Parkinson's disease, depression and drug addiction. Antipsychotic drugs used to treat schizophrenia activate receptors on nerve cells in the brain that inhibit dopamine. This lowers dopamine levels and can thereby reduce symptoms. However, antipsychotic drugs that target D3R are known for side effects, such as reduced motivation and pleasure, fatigue, weight gain, and diabetes. Patients taking these drugs over a long period of time sometimes also develop even more severe side effects such as the movement disorder tardive dyskinesia.

The new data on D3R, published in the journal *Science* this past November, is important in part because each of the five dopamine receptors is unique in structure, and likely also in function. Knowledge of their differences as well as similarities at the level of atoms and molecules is vital if scientists are to better understand how dopamine is regulated.

The work also directly informs efforts to develop more effective drugs that interact with the dopamine receptors to produce therapeutic effects in illnesses in which dopamine regulation plays an important role.

The hope is that this new, detailed view of the receptor will provide the basis for the design of new drugs that will target the receptor more accurately. New drugs could possibly provide a therapeutic advantage over existing drugs that block the receptor and perhaps also cause fewer side effects.

Members of the team now intend to use this same method to determine the structure of another dopamine receptor, D2R, which is similar although, importantly, not structurally identical to D3R. As with the work just completed, subtle differences between the two receptors will inform efforts to build more accurate models of the human dopamine system and predict the therapeutic potential of novel drug treatments, not only for schizophrenia and Parkinson's, but also for addiction.

Dr. Javitch received NARSAD Young Investigator grants in 1990 and 1992, an Independent Investigator grant in 2003 and a Distinguished Investigator grant in 2010.



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

NARSAD Supports Innovative Technologies That Improve Treatment of Mental Illness

Bryan L. Roth, M.D., Ph.D., NARSAD Scientific Council member, is a well known expert on psychopharmacology. In recent years, he has developed several experimental technologies that are now paying dividends in research that is explaining some of the mysteries of brain circuitry involved in addiction, schizophrenia and other neuro-behavioral disorders. The NARSAD investment of a 2008 Distinguished Investigator grant has made this work possible.

In the January issue of the journal *Nature Neuroscience*, Dr. Roth's lab at the University of North Carolina Chapel Hill Medical School, in collaboration with scientists from the University of Washington, Seattle, reported success in what they called "deconstructing" the contributions of specific neural pathways to addiction-related behavior. Other members of the team include NARSAD Young Investigator Susan M. Ferguson, Ph.D., and NARSAD Independent Investigator John Neumaier, M.D., Ph.D., both from the University of Washington.

The experimental methods developed by Dr. Roth and initially funded solely by his NARSAD Distinguished Investigator award enable neuroscientists to follow the pathways taken by messages sent between neurons in complex networks in the brain. This has always been a very difficult feat to accomplish, in part

because molecules used to stimulate or inhibit nerve cells have a tendency to be able to "dock" with a variety of receptors, found on the surfaces of various types of cells. Because of this, "off-target effects" are hard to tease out from intended ones when neuroscientists try to tweak a circuit experimentally to see how it functions.

In the study just published, Dr. Roth and colleagues focused on a part of the brain well known to be important in addiction, called the dorsal striatum. This part of the brain acts as a cohesive functional unit, and is involved, among other functions, in the control of movement. Parkinson's disease, as well as the movement-related aspects of obsessive-compulsive disorder and Tourette's syndrome are traced partly to problems in this part of the brain, in addition to some of the behavioral phenomena associated with drug addiction.

The team set out specifically to untangle the roles of two types of neurons in the dorsal striatum. One type, called striatopallidial neurons, form part of what neuroscientists call an "indirect" pathway in the striatum and adjacent brain areas. The other cell type, striatonigral neurons, is associated with a corresponding "direct" pathway. It has been theorized that these pathways have opposite effects in the regulation of movement.

In rats, Dr. Roth and colleagues looked at the activity of neurons in the direct and indirect pathways as the animals were becoming "sensitized" to amphetamines, an addictive drug. Sensitization is a progressive and persistent increase in an addicted person's (or in this case, rat's) behavioral response. Dr. Roth's team was able to confirm experimentally what had only previously been theorized: direct and indirect pathway neurons do indeed have opposing roles. Striatonigral neurons promoted sensitization to amphetamines; striatopallidial neurons suppressed it.

This discovery will help inform ongoing attempts to develop therapeutic means to treat addiction. Additionally, Dr. Roth reports, the technologies used in this work will be used by other scientists, including John Allen, Ph.D. a NARSAD Young Investigator being mentored by Dr. Roth. He seeks to identify the neuronal circuits responsible for symptoms of schizophrenia.

Dr. Roth is a recipient of NARSAD Young, Independent and Distinguished Investigator grants in 1992, 1998 and 2008 respectively.

New York Times Profiles NARSAD Investigator as ‘Master Virus Hunter’



W. Ian Lipkin, M.D.

In 1991, NARSAD awarded a Young Investigator grant to W. Ian Lipkin, M.D., then at the University of California, Irvine, for a study of the Borna disease virus (BDV). His interest came from a surprising report of BDV infection in patients with bipolar disorder. Borna virus got its name from a German town where, a century earlier, it famously caused an outbreak of equine encephalitis, but in all the years thereafter no one had been able to isolate the virus. Bypassing established methods, Dr. Lipkin created his own method, captured the virus and went on to become one of the most inventive and renowned virus hunters in the world.

Today Dr. Lipkin is applying his vast expertise to the baffling questions surrounding the growing prevalence of autism: Is infection a trigger? Is the measles-mumps-rubella (MMR) vaccine a risk factor?

A virus is a very small entity, a handful of genes wrapped in protein, which survives by invading a living cell and basically taking over the cell's functioning. Small size and the ability to hide in cells make viruses often hard to find.

Dr. Lipkin developed an ingenious molecular probe to tease out the BDV genes from the brains of infected animals. In the 20 years since, he and his colleagues have created ever more sophisticated techniques. While still at Irvine he identified

West Nile Virus, not seen before on this continent, as the cause of the 1999 outbreak of encephalitis in New York. Now the John Snow Professor of Epidemiology and professor of neurology and pathology at Columbia University, Dr. Lipkin directs the Center for Infection and Immunity. Since his arrival in 2002, he and his team have examined tens of thousands of viruses and identified several hundred new ones.

Recently, his focus returned to the question of the role of viruses in brain disorders. While neither he nor anyone else has been able to replicate the original report of BDV infection associated with bipolar disorder, there is a growing body of research suggesting infection as a trigger for schizophrenia and autism in people with a genetic susceptibility. Autism is among the most heritable of neurodevelopmental disorders, but its pathogenesis remains unclear.

Dr. Lipkin's team is now participating in a large multi-institutional project that includes the Norwegian Institute of Public Health and the U.S. National Institute of Neurological Disorders and Stroke, among others. A recent paper in *Molecular Psychiatry* titled “The Autism Birth Cohort: A Paradigm for Gene-Environment-Timing Research” describes the study, which takes advantage of the more than 100,000 children regularly screened through the Norwegian Mother and Child Cohort.

The Autism Birth Cohort (ABC) was designed to focus on prenatal or postnatal infection, diet, other environmental exposure to potential toxins and general obstetric risk factors that may contribute to the development of autism.

The idea that the MMR vaccine could induce autism in children was based on a British study conducted in 1998 that claimed measles in the vaccine released into the intestines might move to the brain. Numerous researchers have tried and failed to duplicate the initial study. Dr. Lipkin recently entered the fray and went on the hunt for measles' viruses. He found no difference in virus levels in the intestines of autistic and normal children with gastrointestinal problems. The finding, which confirms other reports, is of major significance. As he explains, by failing to vaccinate their children, parents inadvertently run the greater risk of measles outbreaks.



Interview

with John H. Krystal, M.D.

NARSAD Scientific Council Member
Chair, Department of Psychiatry, Yale University
Chief of Psychiatry, Yale-New Haven Hospital
Director, NIAAA Center for the Translational Neuroscience
of Alcoholism
Director, Clinical Neuroscience Division,
VA National Center for PTSD
Director, VA Alcohol Research Center
Medical Director, VA Schizophrenia Biological Research Center

Linking Brain and Behavior:

Gifted researcher advances understanding of the brain's biology that leads to breakthroughs in treatment of anxiety and other disorders

“I think we have arrived at a tipping point in the maturation of psychiatry,” says John H. Krystal, M.D., NARSAD Scientific Council Member. “In terms of drug discovery, it is fair to say that we’ve moved from a pre-scientific mode to a scientific mode. Insights about how the brain works provided by basic and clinical science have already led to new and in some cases unexpected treatments for a number of psychiatric disorders, and more are on the way. That’s what makes this one of the most exciting eras in the history of the entire field.”

These are words to remember, for Dr. Krystal is one of the most accomplished and well-respected figures not only in psychiatry, but in the related areas of neurobiology and neuropsychopharmacology – the science that studies how drugs

interact with the biology of the brain. Having earned his M.D. at the Yale School of Medicine in 1984, he is today the chair of Yale’s psychiatry department and is chief of psychiatry at Yale-New Haven Hospital.

But there is much more, and therein lies an important story about Dr. Krystal and about the value of basic research into the brain supported by NARSAD grants. In addition to his duties at Yale, Dr. Krystal is Director of the Center for Translational Neuroscience at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), one of the National Institutes of Health. He is also, remarkably, Director of the Clinical Neuroscience Division at the Veteran Administration’s (VA) National Center for Post-Traumatic Stress Disorder (PTSD); Director of the VA Alcohol Research Center; and

Medical Director of the VA Schizophrenia Biological Research Center.

Dr. Krystal, therefore, does not merely treat patients and conduct research at Yale, but also directs the work of teams of scientists and physicians at major national institutes and centers dedicated to studying and treating illnesses running the full gamut: anxiety disorders such as PTSD and OCD (obsessive-compulsive disorder); substance abuse disorders such as alcoholism; and the devastating illnesses of schizophrenia and major depression. One naturally wants to know: what unites these wide-ranging activities? What is the scientific thread that connects them?

Discoveries enable broad psychiatric advances

There is indeed a thread between these varied brain and behavior disorders, and as Dr. Krystal relates, it can be traced back to a subject that captured his interest at the very beginning of his career: the neurobiology of the glutamate system in the brain.

Glutamate is a message-carrying molecule, the most important and

“Insights about how the brain works ... have already led to new and in some cases unexpected treatments for a number of psychiatric disorders ... That’s what makes this one of the most exciting eras in the history of the entire field.”

prevalent of the class of excitatory neurotransmitters, which stimulate the brain. When glutamate that has been released by one nerve cell “docks” with a receptor on a neighboring nerve cell, it increases the chance that the receiving cell will fire an impulse to yet another nearby nerve cell. Beyond a certain threshold of excitation, a cell will indeed fire, and the process repeats. This is how messages, the building blocks of our thoughts and actions, are conveyed – over the span of milliseconds – across the vast tangle of neural circuits in the brain.

Dr. Krystal’s interest in the glutamate system came at a moment when surprising observations linking brain and behavior in the 1960s were beginning to make scientific sense. It had been noted that a drug called PCP (also known as “angel dust”) produced symptoms in people resembling those of schizophrenia. This was mysterious. By the 1980s, scientists knew PCP’s molecular target: the NMDA receptor, a type of “docking port” found on the surface of a subset of neurons in the brain. In the late ‘80s, Dr. Krystal and colleagues began to study a relative of PCP called ketamine, which also produced schizophrenia-like symptoms in people. This line of research has informed efforts to develop a new class of drugs to treat schizophrenia.

What makes these recent developments in treatment applications for schizophrenia possible is the basic science that Dr. Krystal and other pioneers have accomplished. This is part of a larger process in which, as

he notes, neuropsychiatry has become progressively more scientific, and able to explain the mechanisms that underlie the clinical phenomena of illnesses like schizophrenia and anxiety. Dr. Krystal’s first NARSAD grant, a 1997 Independent Investigator award, used ketamine as a tool for studying aspects of psychosis in schizophrenia, specifically the impact of amphetamines on psychosis. In his second NARSAD award – a 2000 Distinguished Investigator grant – he focused on several aspects of how glutamate signals are sent and in some cases inhibited in the brain’s cortex. And in his most recent award, a 2006 Distinguished Investigator grant, Dr. Krystal’s basic research was

among the studies that shed new light on how the NMDA glutamate receptors work in the cortex.

This story runs in parallel to one that explains how Dr. Krystal, during the same years, became involved in research that has since borne fruit in anxiety disorders. While still in medical school at Yale, he and Dr. Eugene Redmond were studying the effects of stress in monkeys. “We were studying a system in the brain called the noradrenergic system, which releases an adrenaline-like substance called norepinephrine,” he remembers. “When we activated this system, I noticed that some of the behaviors the monkeys exhibited resembled symptoms I was seeing in



VA National Center for PTSD building in West Haven, Conn., where Dr. Krystal is director of the Clinical Neuroscience Division, which specializes in researching the physical basis of how the brain receives and processes traumatic stress, including neurobiology, brain imaging, genetic epidemiology, resilience, and treatment. Courtesy of VA Public Affairs

my clinical training involving soldiers who had come back from Vietnam.”

Just as PCP and ketamine provided a path for Dr. Krystal and other scientists to learn about the biology of schizophrenia, the noradrenaline system offered a path into PTSD. With distinguished collaborators including Drs. Dennis Charney and Stephen Southwick, Dr. Krystal performed studies on veterans at the VA National Center for PTSD, one of the centers Dr. Krystal now directs. “We found that if you activate the noradrenaline system, you can produce the arousal symptoms associated with PTSD.

“At the time, we didn’t really understand much at all of the neurobiology of PTSD symptoms. We’d have a veteran in a quiet room start saying, all of a sudden, ‘Look over there – the helicopter’s going down! I can hear people screaming!’ Very vivid,

very intense memories of trauma. We also had people describing feeling detached from what was going on around them, feeling like time had slowed down, feeling numb and other kinds of bodily distortions.”

In a telling glimpse of how the discovery process works in science, Dr. Krystal, when faced with the mystery of these symptoms’ biological origins, thought of work he was doing around the same time on ketamine. “In addition to producing some of the cognitive impairments associated with schizophrenia, ketamine also produced some symptoms of this kind that we were seeing in PTSD, which I would call ‘dissociative.’”

The upshot of this observation was Dr. Krystal’s hypothesis that some of the different sets of symptoms produced by ketamine contained clues about “disorders other than schizophrenia, in which the glutamate

system might be involved.” Since 1980, when PTSD was acknowledged by psychiatry as a distinct illness – a landmark moment that reflected an increasingly scientific, as opposed to purely anecdotal understanding of it – there have been only two drugs approved to treat its symptoms. Both are antidepressants of the SSRI (selective serotonin reuptake inhibitor) class: paroxetine (Paxil) and sertraline (Zoloft). But Dr. Krystal, while frustrated to note that neither drug helps a majority of patients, was able to draw on his much earlier work on the noradrenaline system to come up with a new treatment idea.

“NARSAD is the most remarkable acted with,” Dr. Krystal says. “It on not only my career, but on gen NARSAD is an organization that oment of young scientists and innovation in psychiatry since its

Dr. Krystal on the Vital Role of NARSAD

As a member of the NARSAD Scientific Council, Dr. John H. Krystal knows the organization intimately. But he first came to know it in the way that thousands of other scientists have over a quarter-century – as one whose career in research was given a key boost by a NARSAD grant.

“NARSAD is the most remarkable organization that I’ve ever interacted with,” Dr. Krystal says. “It has had such a profound impact on not only my career, but on generations of young investigators. NARSAD is an organization that has been a catalyst

to the development of young scientists and through that mechanism has fueled innovation in psychiatry since its inception.

“In my own experience, I was able to undertake studies that I couldn’t have otherwise initiated because they were very high-risk – and, I hoped, high-gain – studies.

“NARSAD grants provided a chance to build on preliminary data so that we were able to carry out other studies to move the work forward. It’s now pretty much at the point where

in order to initiate a career in psychiatry and neurobiology that’s really innovative, you need a NARSAD Young Investigator award. And at a time when funding rates are very low and our young investigators as a result have become very vulnerable, NARSAD is more important now than it’s ever been to sustaining the vitality of the research pipeline.

“I’ve personally had many students get funded, and now as chair of the Department of Psychiatry at Yale, I count on the continued support of NARSAD for our young investigators

He asked, “What about some of the older antidepressants?” He had in mind drugs that blocked the molecule that transports noradrenaline between nerve cells. Zoloft and Paxil block the transporter for serotonin, another neurotransmitter. But if noradrenaline was involved in PTSD, then perhaps the antidepressant desipramine (Norpramin) might help. With colleagues, Dr. Krystal performed a study involving 88 veterans with PTSD. The results were surprising, but productively so. While Norpramin worked no better than Paxil in reducing PTSD symptoms, it had the completely unexpected

effect of helping the patients control co-morbid alcoholism.

“I love in research when something turns out to work in an unexpected or paradoxical way,” Dr. Krystal says.

The Norpramin surprise is by no means the only time Dr. Krystal experienced this phenomenon, which each time marks a moment when our understanding of how the brain works takes a leap forward. Perhaps the most outstanding example in Dr. Krystal’s work relates to the concept of neuroplasticity, which can be defined as the response of cells and circuits in the brain to a person’s experiences.

“This idea of neuroplasticity is extremely important,” Dr. Krystal says. “The natural progression within an organism when it is ill is to try to heal itself. Paradoxically, sometimes the healing process itself can get in the way of recovery. That’s why we take

aspirin, for instance – to reduce the pain of inflammation that is caused by the body trying to heal itself.

“Where the brain is concerned, sometimes in order to get better, it is necessary to restore the capacity of the neural circuit to remodel itself. Sometimes it is the deficit in that capacity – neuroplasticity – that is part of what we think of as the illness. In the case of stress disorders, we’ve learned that traumatic stress can cause the retraction of knob-like input centers called dendritic spines, which are the places where signals come into nerve cells. This is particularly true in glutamate neurons in the brain.”

Dr. Krystal points out that there is evidence of spine retraction in symptoms seen in stress and anxiety disorders: impaired memory function, and, importantly, impaired capacity to learn to respond to stressors in new and therapeutic ways.

organization that I’ve ever interacted with has had such a profound impact on the development of young investigators. It has been a catalyst to the development of that mechanism that has fueled inception.”

to help supplement the resources we have in the department. There’s nothing more important for the vitality and for the progress in science than to sustain these young investigators who invariably are developing new technologies and approaches to the field.”

Dr. Krystal makes clear that his remarks about NARSAD are connected directly to the themes about research

he discusses in the accompanying story. “We began our discussion by talking about the evolution of psychiatry and why this is such an exciting time. We are just beginning to get insights into how what’s happening in the brain and what’s happening in the body are connected – there is no divide between mind and body. Psychiatric illnesses have biological causes. This opens up all kinds of new and exciting possibilities.

“Because there are so many opportunities to make a big difference, I feel it is so important that we not lose this generation of young investigators coming up in the ranks today, and we enable them to pick up the baton from their mentors and move this field forward into the future. I am certain NARSAD is going to play an important role in the process.”

“In order to initiate a career in psychiatry and neurobiology that’s really innovative, you need a NARSAD Young Investigator award.”



Dr. Krystal's work with veterans has led him to advance research into better treatments for PTSD. Above: Members of the United States Army salute during a ceremony honoring a fallen soldier and police officer. Photo credit: Shutterstock

The scientific leap came when the insight about neuroplasticity was linked with psychotherapy, which, Dr. Krystal points out, “works by changing the capacity of neural circuits to adapt.”

“If your capacity for neuroplasticity is impaired, in other words, the capacity of these networks to learn and adapt is compromised.”

Pre-scientific to scientific mode in psychiatry

Indeed, Dr. Krystal says every change in brain function and in behavior – “as far as we know” – has an underpinning in brain function. “Sometimes the change could be new connections; sometimes it could be elimination of existing connections, and sometimes it might be the fine-tuning of connections, either strengthening or weakening them.”

In an elegant example of how science can radically change the way we look at something we thought we understood, Dr. Krystal and colleagues have recently reported their success in a preliminary test using neuroplasticity as the target for a new class of treatments for anxiety disorders, mood disorders and schizophrenia. Rather than design a new treatment to address one or more observed symptoms of, say, panic disorder, the idea would be to find a way to correct a neuroplasticity impairment – the reduced capacity of a neural circuit to modify itself in response to stress or trauma.

This was attempted in 2009 on a pilot basis in patients with panic disorder. Researchers used a well-known drug called D-cycloserine (DCS) in combination with a short course (only five sessions) of cognitive behavioral therapy, a form of so-called exposure therapy that aims at conditioning someone repeatedly experiencing extreme fear or panic to learn new responses to thoughts, sensations or feelings. The success observed in this trial, Dr. Krystal notes, is not due to the capacity of DCS to address symptoms of panic. Rather, he hypothesizes, DCS performs work within the neural circuitry that then enhances

the ability of psychotherapy to produce functional changes in circuitry that amount to the patient's therapeutic learning.

Importantly, this preliminary positive outcome is the product of several layers of solid biological knowledge about the brain and brain chemistry – knowledge obtained in the last decade or two, as psychiatry has moved into a genuinely scientific era. From much prior work, it was known that DCS enhances activity at NMDA glutamate receptors. And those receptors, it is now understood, thanks to basic research, are fundamental facilitators of neuroplasticity – the process central to adaptation and new learning, which in this instance includes unlearning maladaptive responses to traumatic or other stressful memories.

“The idea of targeting plasticity deficits by facilitating neuroplasticity or harnessing it in novel ways is a concept I think has quite broad implications,” Dr. Krystal says. “What we must do next is move from these exploratory types of studies in panic disorder, OCD and PTSD, to larger-scale, more definitive studies, which I think will happen.”

Go to:
www.narsad.org
 to hear interviews with
 Dr. Krystal about PTSD
 recovery.
 Click on “disorders”

Ask the Researcher

We welcome your questions about the latest in brain and behavior research! Please e-mail asktheresearcher@narsad.org with questions for Dr. Krystal. Select questions and answers will be published in the next issue of *The Quarterly*.

We are pleased to introduce this new column: “Ask the Researcher.” It is intended to give you the opportunity to ask questions of the NARSAD researcher profiled in “Interview with a Researcher” and give us the opportunity to bring our mission to life.

NARSAD is committed to alleviating the suffering of mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. As part of this mission, we believe it is necessary to bring science to families. We do this through our website, free publications, symposia open to the public led by leading experts in the field – and now this “Ask the Researcher” column.

Please note that this column is intended to provide answers to questions related to scientific research and discoveries leading to better treatment of a broad range of mental illnesses. 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.

Frequently Asked Questions on Anxiety Disorders

Q

What are the five types of anxiety disorders that are well known?

A

1. Generalized Anxiety Disorder
2. Obsessive-Compulsive Disorder (OCD)
3. Panic Disorder
4. Post-Traumatic Stress Disorder (PTSD)
5. Social Phobia (or Social Anxiety Disorder)

Q

What is generalized anxiety disorder?

A

Generalized Anxiety Disorder (GAD) is an exaggerated anxiety and tension that persists for months on end and affects approximately 6.8 million Americans or about 3.1 percent of the population. GAD causes people to anticipate catastrophe and worry excessively about many things, from overarching concerns such as health, money or work to more routine concerns such as car repairs or appointments. GAD affects twice as many women as men, and the anxiety becomes so severe, normal life and relationships become impaired.

Worries can be accompanied by physical symptoms, such as fatigue, headaches, muscle tension and aches, difficulty swallowing, trembling, twitching, irritability, sweating, and hot flashes. The disorder usually develops gradually and may begin anytime during life, although the risk is highest between childhood and middle age. It is diagnosed when someone spends at least six months worrying excessively without a specific focus of the fear and an inability to control the anxiety.

Q What is Obsessive-Compulsive Disorder?

A Obsessive-Compulsive Disorder (OCD) is an anxiety disorder marked by fearful ideas and ritualistic behaviors. Obsessions are repetitive thoughts or impulses, such as a fear of getting infected from someone else's germs or hurting a loved one. These obsessions create excessive anxiety and stress for the person affected. Although the thoughts are intrusive and unwanted, the person with OCD cannot stop them. Compulsions are repetitive behaviors people with OCD feel compelled to perform in an attempt to control or decrease the anxiety created by the obsessions. This can include things like constantly checking that an oven is off to prevent a fire, or frequent cleaning or hand-washing to avoid contamination.

Q What is Panic Disorder?

A Panic disorder is characterized by unexpected and repeated episodes of intense fear accompanied by physical symptoms that may include chest pain, heart palpitations, shortness of breath, dizziness or abdominal distress. It is characterized by sudden attacks of terror, usually accompanied by a pounding heart, sweatiness, weakness, faintness or dizziness. During these attacks, people with panic disorder may flush or feel chilled; their hands may tingle or feel numb; and they may experience nausea, chest pain or smothering sensations. Panic attacks usually produce a sense of unreality, a fear of impending doom or a fear of losing control. Panic attacks can occur at any time, even during sleep. An attack usually peaks within 10 minutes, but some symptoms may last much longer.

Q What is Post-Traumatic Stress Disorder?

A Post-Traumatic Stress Disorder (PTSD) is an anxiety disorder that can develop after exposure to a terrifying event or

ordeal in which grave physical harm occurred or was threatened. After traumatic events, such as death, an earthquake, war, car accidents, floods or fires, it is not uncommon for people to experience feelings of heightened fear, worry, sadness or anger. If the emotions persist, however, or become severe, or the person gets triggered into reliving the event in their daily life, this can affect the person's ability to function and may be a sign of PTSD.

Q What is Social Phobia?

A Social Phobia, or Social Anxiety Disorder, is an anxiety disorder characterized by overwhelming anxiety and excessive self-consciousness in everyday social situations. Social phobia can be limited to only one type of situation, such as a fear of speaking in formal or informal situations, or eating or drinking in front of others. In its most severe form, social phobia may be so broad that a person experiences symptoms almost anytime they are around other people.

Q How are anxiety disorders diagnosed?

A Primary care physicians and psychiatrists diagnose someone as having an anxiety disorder if symptoms occur for six months on more days than not, and significantly interfere with the person's ability to function at home, work or school.

Doctors perform physical and psychological evaluations to rule out other causes for the symptoms of anxiety. Cardiovascular disease, thyroid problems, menopause, substance abuse and/or drug side effects, such as from steroids, may cause symptoms similar to those of an anxiety disorder.

(Source: National Institute of Mental Health)

Anxiety Disorders

Ongoing Research Improves Lives

As more is understood about the genetics and brain regions involved in an exaggerated fear response, improved diagnostic tools and treatments will be developed for generalized anxiety and related disorders.

NARSAD invests in the most promising projects in brain and behavior research related to anxiety disorders. Here are some examples of the latest research:

- **NARSAD Young Investigator Stephanie Bissiere, Ph.D.**, and a team of researchers at UCLA successfully made a “long-shot” discovery about the behavioral relevance for electrical communication and gap junctions in the adult brain. The team found that blocking electrical synapses, which couple inhibitory neurons and enable them to synchronize their firing, can prevent fear memories to a place or context from forming. This new discovery has major implications for new treatment targets for PTSD and other anxiety disorders. (Source: *Science*)
- **NARSAD Independent Investigator Mikhail V. Pletnikov, M.D., Ph.D.**, has found that male mice born with a genetic mutation believed to make humans more susceptible to schizophrenia developed behaviors that mimic mood and anxiety disorders. This research is another step toward understanding the causes and developing better treatments for a broad range of mental illnesses. (Source: *Biological Psychiatry*)
- Researchers led by **NARSAD Investigators Francis Lee, M.D., Ph.D.**, and **Sergey Shmelkov, M.D.**, have discovered that a single omitted gene is responsible for symptoms of a certain type of OCD in mice, helping scientists better understand the disorder and enabling development of possible treatments. (Source: *Nature Medicine*)

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The Mortimer D. Sackler Foundation sponsors Dr. Mikhail Pletnikov's research uncovering the genetic links between anxiety disorders and schizophrenia. The foundation generously funds his research grant that is leading toward prevention of a broad range of mental illnesses.

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Research Gives People Hope

Multiple family illnesses inspire a couple's life-long commitment to the mental health cause

N

o one knows better than the Garatt family how far research in mental illness has come – and how far it still has to go. Thirty-three years ago, when Sean Garatt was diagnosed with schizophrenia, his mother, Marcia, was told that she was the cause. The “bad mothering” theory eventually collapsed under an avalanche of research pointing to schizophrenia as a biological illness, opening the door for more treatment options.

Sean was 17 years old at the time of his first psychotic break. He remained seriously ill, his life a shambles, until the age of 31, when he was given clozapine, an antipsychotic drug developed in the late 1980s under the leadership of NARSAD Scientific Council Member Herbert Meltzer, M.D. With medication

Sean got better; not totally well, but mostly free of mind-imprisoning psychosis and able to live an ordered, if limited, life. “Now, he knows what day it is,” Marcia says.

Even before Sean’s diagnosis, the Garatts were no strangers to mental illness. Paul, Marcia’s husband of 53 years, has been battling anxiety and depression most of his life, including a close brush with suicide. The family’s experience has made them outspoken advocates for better understanding of mental illness and ardent supporters of NARSAD.

Young couple faces mental illness together

Absent mental illness, the Marcia and Paul story would have read like the quintessential American dream: idyllic rural childhood, committed marriage, good jobs, two wonderful, devoted sons. The couple grew up in the small farming community of Candor, in upstate New York, dated in high school and married after finishing college. That is, Marcia finished college. Paul dropped out. Although bright and articulate, with a wide range of interests and abilities, Paul’s “noisy brain,” as he calls it, made it impossible for him to focus on his studies. “I married him anyway,” Marcia says. “We were so young and innocent, and he was so enjoyable and funny.”

“When I read what their scientists are doing, I’m just amazed. As I try to keep up with things that are going on in research, I get the feeling that NARSAD is way ahead of the curve.” Says Paul: “Research gives people hope.”

Without work or prospects, Paul joined the Navy and thoroughly enjoyed seeing the world while chasing Russian submarines. On entry, he had tested so well that he had his choice of specialty. He chose electronics, and military structure and discipline kept him on task. After his four-year tour of duty, Paul’s training served him well when he returned to civilian life.

Marcia, who had majored in social work, became a probation officer, working with child offenders the courts were trying to keep out of prison; children that others in the system were convinced couldn’t be helped. Marcia saw it as “a wonderful challenge.” She set up a volunteer program that over the years provided many such youngsters the chance to do things they’d never done before: farm, swim, fish. Her 18 years of service earned her an award from the state of New York and

the satisfaction of knowing she had helped turn around some very troubled young lives.

Despite these triumphs, mental illness always hovered over the Garatts’ lives. When Paul’s early jobs in computer testing and quality control became boringly routine, he taught himself computer programming. In a burgeoning industry, he soon landed a very good, more demanding job in North Carolina. As it turned out, it was too demanding. He went to bed at night worrying about work and woke up to the same worries.

“I just could not, as the saying goes, lock my toolbox,” he remembers. “I had taken a job I couldn’t do, I hadn’t enough training for. The pain went on and on and I couldn’t unhook my brain. So one day I stopped my car on the railroad tracks. I knew the train would be coming soon, and then it would be over. But what happened instead, other cars pulled up, and when the guy behind me honked, I drove on.” He drove home, and when he told Marcia what had happened, she said, “We’re going to the hospital.”

They went to Duke University Medical Center, where Paul received state-of-the-art treatment that included both medication and cognitive behavioral therapy. When back on his feet but concerned about his future,

a therapist encouraged him to go back to his boss and ask for a less demanding job. To Paul’s surprise, the boss agreed. Later, when the company was downsizing, they made him the proverbial offer he couldn’t refuse, and he took early retirement.

From denial to action

Paul is ever conscious of and grateful for Marcia’s steadfastness through many trying years. Marcia acknowledges that she has often felt pushed to the edge of despair. Both admit they were, for a long time, “in denial” about their son Sean.

Scientists are now pretty certain that genetic predisposition combined with some environmental factor – possibly maternal infection or trauma during pregnancy – triggers schizophrenia in many instances.



*Marcia, Sean
and Paul Garatt.
Courtesy of Patt Blue
Photographer*

Despite its early seeding, however, full-blown symptoms typically don't erupt until adolescence or early adulthood. There can be a gray period before then – what's called the prodrome – when the child's behavior begins to become worrisome. But when dealing with a rebellious adolescent, how is a parent to know, except in hindsight, whether, as Marcia says, “you have a bad child or a mad child?”

By the age of 14, the once cheerful, responsible Sean had grown angry and argumentative, hiding away in his room. The Garatts could later recall some startling earlier clues to his – and their – impending reality. They remember a day when 12-year-old Sean, browsing in the Encyclopedia Britannica, looked up and said, point blank, “I have schizophrenia.” More painfully unforgettable, at the age of five he told them that he felt “like I have a tangled Slinky toy in my head.”

Sean's years in the wilderness, until he was finally stabilized, were marked by earnest if futile efforts to live a normal life: failed attempts to hold a job, an ill-advised and short-lived marriage, a baby son neither he nor his violent, addicted wife could handle. (The child was subsequently raised by his maternal grandmother.)

Seven years ago, Marcia and Paul moved to Paducah, Kentucky, to be near their younger son, Geordie, an attorney, and his family. Sean moved with them, but lives on his own. Each morning he calls his parents to reassure them he has taken his meds. He takes halperidol (Haldol), an older, so-called typical antipsychotic, in combination with clozapine. Among the things clinicians and researchers have learned is the importance of tailoring medications to the individual patient. One

size does not fit all. Once, when a new doctor took Sean off halperidol, he crashed.

Atypical antipsychotics like clozapine can have some serious side effects. A common side effect is metabolic syndrome, marked by weight gain, high blood pressure and the risk of diabetes and cardiovascular illness. Because Sean has put on weight, every day he and Marcia go to a fitness center. He also attends diabetes prevention classes. Looking toward the time when they will no longer be there for Sean, Marcia and Paul update a plan every year, a list for Geordie of his older brother's needs.

In addition to helping NARSAD, the Garatts have been active for many years with NAMI, the National Alliance on Mental Illness, a grassroots, self-help, support and advocacy organization. Paul and Marcia both taught a course for caregivers of people with severe mental illness in NAMI's family-to-family program. They were instrumental in establishing NAMI in North Carolina, and Paul served as its second president. Currently, Marcia and Sean have been working with their local NAMI, teaching people how to set up a crisis plan: the steps to take when a family member with mental illness encounters difficulties.

While teaching for NAMI, the Garatts often clipped items of interest from NARSAD publications to distribute to the class. “We're most appreciative of NARSAD,” Marcia says. “When I read what their scientists are doing, I'm just amazed. As I try to keep up with things that are going on in research, I get the feeling that NARSAD is way ahead of the curve.” Says Paul: “Research gives people hope.”

2010 Young Investigators

FUNDING YOUNG SCIENTISTS ON THE QUEST TO FIND BREAKTHROUGHS



Herbert Y. Meltzer, M.D.
Bixler/May/Johnson Professor
of Psychiatry
Professor of Pharmacology
Vanderbilt University

A founding member of the NARSAD Scientific Council, Dr. Meltzer directs the NARSAD Young Investigator grant reviews. He received the NARSAD Lieber Prize for Outstanding Achievement in Schizophrenia Research in 1992 and NARSAD Distinguished Investigator Awards in 1988, 1994, 2000 and 2007.

“The 214 designated NARSAD 2010 Young Investigator awardees are the very best young basic and clinical scientists from throughout the world who are starting research careers devoted to basic and clinical neuroscience. Each submitted an exciting, innovative research plan, which the NARSAD Scientific Council – made up of 124 of the world’s leading brain researchers – believes will add substantially to the effort to prevent and alleviate devastating brain and behavior disorders. Experience has demonstrated that support for the NARSAD Young Investigator program is the most effective way for the private sector to further the massive effort needed to conquer these disorders that plague humanity. This is especially important now because of the reduced ability of governments, industry and academic medical centers to fund research and treatment programs.”

Dr. Herbert Meltzer

NARSAD Young Investigators represent a new generation of researchers who will pioneer breakthroughs in mental health research. Young Investigator grants are catalysts for additional funding, providing researchers with “proof of concept” for their work. The Young Investigator program is a hallmark of NARSAD grants. On average, NARSAD Young Investigators have used their grants to leverage an additional 19 times their original grant amount and some have gone on to receive much more than that after proving initial hypotheses with their first NARSAD grant support. Receiving up to \$60,000 over two years, Young Investigators pursue brain and behavior research related to disorders occurring in children and adults such as schizophrenia, depression, bipolar disorder, autism, ADHD, and anxiety disorders, such as OCD and PTSD.

NARSAD awarded a total of \$12.6 million to its 2010 Young Investigators, strengthening its investment in the most promising ideas to lead to breakthroughs in understanding and treating mental illness. Two-hundred fourteen brilliant researchers from leading research institutions on six continents were selected from more than 1,000 applicants to receive Young Investigator grant awards to support their innovative research. The 124-member NARSAD Scientific Council, a volunteer group of preeminent mental health researchers leads the rigorous and competitive process of identifying the most promising ideas for NARSAD to fund in grant awards each year. The Young Investigator selection process was led by Scientific Council member Dr. Herbert Meltzer of Vanderbilt University, a founding member of the council.

Meet the Grantees

214 of the world's finest young neuroscientists receive NARSAD grants

Anxiety Disorder

Stephanie Bissiere, Ph.D.

University of California, Los Angeles

Brian R. Cornwell, Ph.D.

National Institute of Mental Health

Thomas L. Kash, Ph.D.

University of North Carolina at Chapel Hill

Attention-Deficit Hyperactivity Disorder

Eleanor J. Dommert, Ph.D.

The Open University, U.K.

Susan M. Ferguson, Ph.D.

University of Washington

Yanli Zhang-James, M.D., Ph.D.

State University of New York, Upstate Medical University

Autism

Kristi A. Clark, Ph.D.

University of California, Los Angeles

Denis Jabaudon, M.D., Ph.D.

University of Geneva, Switzerland

Roger J. Jou, M.D., M.P.H.

Yale University

Xiao Ching Li, Ph.D.

Louisiana State University

Rhiannon J. Luyster, Ph.D.

Harvard University

Ming Meng, Ph.D.

Dartmouth College

Jennifer B. Wagner, Ph.D.

Harvard University

Lauren A. Weiss, Ph.D.

University of California, San Francisco

Bipolar Disorder

Dean T. Acheson, Ph.D.

Veterans Medical Research Foundation

Xavier Caseras, Ph.D.

Cardiff University, U.K.

Richard Cameron Craddock, Ph.D.

Baylor College of Medicine

Liz Forty, Ph.D.

Cardiff University, U.K.

Tobias Gerhard, Ph.D.

Rutgers University

Alison Gilbert, Ph.D.

Zucker Hillside Hospital

Katrina C. Johnson, Ph.D.

Emory University

Christopher A. Lowry, Ph.D.

University of Colorado, Boulder

Jon M. Madison, Ph.D.

Broad Institute of MIT and Harvard

Donel M. Martin, Ph.D.

University of New South Wales, Australia

Alessandra M. Passarotti, Ph.D.

University of Illinois at Chicago

Theodore D. Satterthwaite, M.D., M.A.

University of Pennsylvania

Jens R. Wendland, M.D.

National Institute of Mental Health

Depression

Mohamed K. Aly, M.D.

Columbia University

Pauline Belujon, Ph.D.

University of Pittsburgh

Daniel Blumberger, M.D.

University of Toronto, Canada

Alexandre Bonnin, Ph.D.

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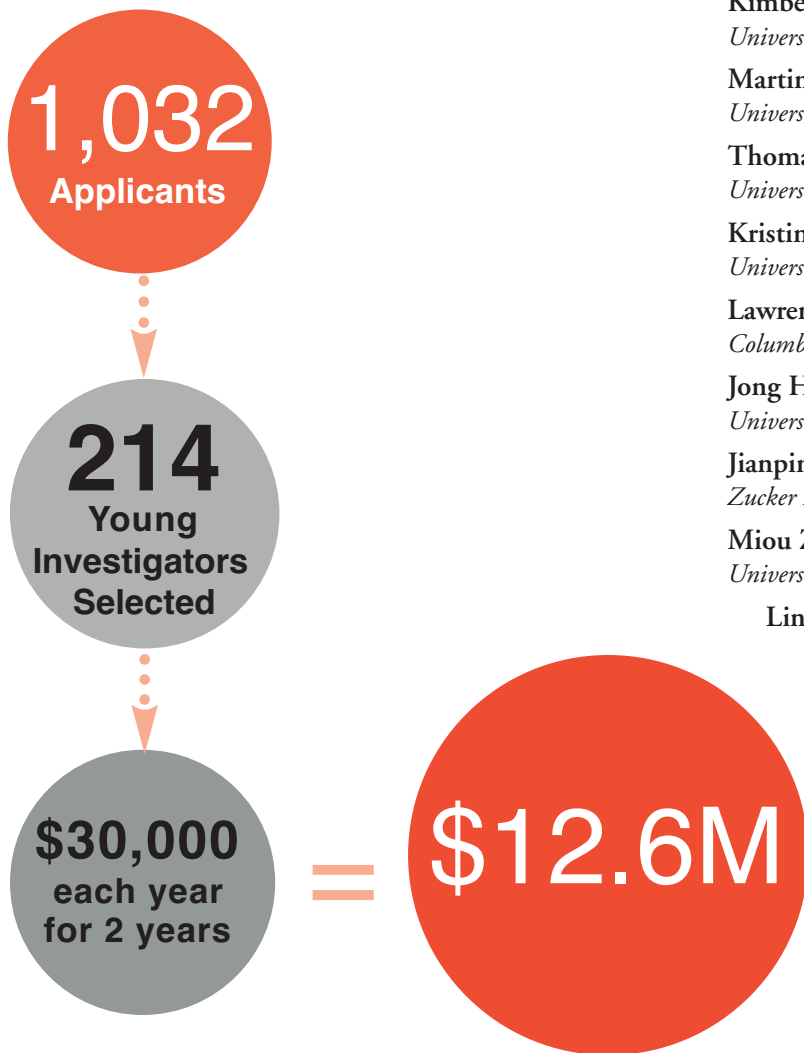
Schizophrenia

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Laura E. Wise, Ph.D.

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Tracy L. Young-Pearse, Ph.D.

Harvard University

Qi Zhang, Ph.D.

Vanderbilt University Medical Center

Xiangzhong Zheng, Ph.D.

University of Pennsylvania

Xianjin Zhou, Ph.D.

University of California, San Diego

Annual Young Investigator Grants Awarded by NARSAD



Glossary

Helpful definitions of terms used in this issue.

Dissociative Symptoms (page 6): Dissociative symptoms are found frequently in people with psychiatric disorders, including depression, schizophrenia, anxiety disorders and personality disorders. Dissociative symptoms include:

- Depersonalisation – a feeling that your body doesn't quite belong to you or is disconnected from you
- Derealisation – a feeling that you are disconnected from the world around you or “spaced out”

Glutamate and the glutamate system (page 4): Glutamate is a message-carrying molecule, the most important and prevalent of the class of excitatory neurotransmitters, which stimulate the brain. Glutamate is believed to be involved in cognitive functions like learning and memory. When glutamate that has been released by one nerve cell “docks” with a receptor on a neighboring nerve cell, it increases the chance that the receiving cell will fire an impulse to yet another nearby nerve cell. Beyond a certain threshold of excitation, a cell will indeed fire, and the process repeats. This is how messages, the building blocks of our thoughts and actions, are conveyed – over the span of milliseconds – across the maze of neural circuits in the brain.

Dopamine and the dopamine system (page 1): Dopamine is a neurotransmitter in the brain that can activate five types of dopamine receptors (D1, D2, D3, D4, D5) located on neurons. It is a key element of the brain's reward system and is also believed to play a central role in the learning of new motor skills. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to ADHD and some symptoms of schizophrenia.

Neuroplasticity (page 7): Neuroplasticity is the capacity of cells and circuits in the brain to change in response to a person's experiences. Neural circuits are “remodeled” throughout life, allowing for adaptation and learning, although a variety of cellular and biochemical anomalies are thought to impair this critical capacity of the brain, perhaps in post-traumatic stress disorder (PTSD) and other anxiety disorders, as well as in schizophrenia and depression.

Noradrenergic system (page 5): The noradrenergic system involves norepinephrine, or noradrenaline, in the transmission of nerve impulses. This adrenaline-like molecule is released from noradrenergic neurons and binds to adrenergic receptors. In addition to its role as a neurotransmitter, norepinephrine can also act as a hormone. It affects parts of the brain, such as the amygdala where attention and responses are controlled. Along with epinephrine, norepinephrine also underlies the fight-or-flight response.

New Treatments/ Therapies

As research breakthroughs continue to be made, new treatments and therapies for people living with mental illness point toward recovery

THREE STEPS TO MENTAL HEALTH

Step 1:

DISCOVERY

Understanding malfunctions
in the brain

Step 2:

TREATMENT

Reducing symptoms
and retraining the brain

Step 3:

RECOVERY

Supporting rehabilitation
to enable full, productive lives

NARSAD-Funded Research Uncovers New Antidepressant Treatment

NARSAD Independent Investigator Marina Picciotto, Ph.D., has found that combining two types of antidepressants may help the approximately 50 percent of patients non-responsive to SSRI medications. Dr. Picciotto found that when drugs that alter two mood-regulating brain chemicals – serotonin and acetylcholine – are combined, they produce a greater antidepressant response. Dr. Picciotto presented this research at the annual meeting of the Society of Neuroscience in November 2010. SSRIs, which increase serotonin levels in the brain and are common treatments for depression, help to regulate moods. Recent studies have suggested that the brain chemical acetylcholine also plays an important role in regulating mood. By combining the SSRI fluoxetine (Prozac) with cystine, a drug that limits the effects of acetylcholine, Dr. Picciotto found the drugs together produced greater antidepressant-like properties in mice than when the drugs were used alone. Results suggested that serotonin plays a significant role in cystine's antidepressant-like effects.

Source: Society for Neuroscience

Stopping Depression Relapse with Mindfulness-Based Cognitive Therapy

Mindfulness-based cognitive therapy appears to be similar to maintenance antidepressant medication for preventing relapse or recurrence among patients successfully treated for major depressive disorder. Patients in this type of therapy learn to alter their automatic reactions associated with depression by examining their thinking patterns when they feel sad. Patients complete daily homework that includes guided exercises on raising awareness of their thoughts and feelings, learning self-compassion and developing strategies for responding to any signs of depression relapse. Scientists studied 84 patients in remission from major depressive disorder who had experienced at least two episodes of depression. Patients in remission were randomly assigned to one of three treatment groups: 28 continued taking their medication; 30 had their medication slowly replaced by placebo; and 26 tapered their medication and then received mindfulness-based cognitive behavioral therapy. During the 18-month follow-up period, relapse occurred among 38 percent of those in the cognitive behavioral therapy group, 46 percent of those in the maintenance medication group and 60 percent of those in the placebo group, making both medication and behavioral therapy effective at preventing relapse.

Source: *Archives of General Psychiatry*

Radiosurgery May Be the Hope When Other Treatments for Severe OCD Fail

A study in the January issue of *Neurosurgery* reports that a procedure called radiosurgery may improve the lives of people living with severe obsessive-compulsive disorder (OCD). Results of radiosurgery in three patients with very severe OCD that didn't respond to medications were promising to researchers. Further research is needed, but radiosurgery appears to be a new alternative to medications to treat OCD. Despite taking multiple medications to treat OCD, all patients continued to have disabling factors. During the procedure a gamma knife delivers an intense beam of radiation to a specific area of the brain (the anterior cingulate cortex) where OCD symptoms originate. Radiosurgery's original use was to destroy brain tumors. Patients were closely evaluated before and after radiosurgery. Patients continued taking medication after surgery and "All patients noted significant functional improvements and reduction in OCD behavior," the paper's authors wrote. More research is needed before it becomes widely recommended.

Source: *Neurosurgery*

Momentum

Event Calendar and Updates

S	M	T	W	T	F	S
NARSAD ANNUAL EVENTS						
NARSAD Annual Mental Health Research Symposium in New York City Tuesday, October 25, 2011						
NARSAD National Awards Dinner Wednesday, October 26, 2011						
UPCOMING TEAM UP FOR NARSAD EVENTS						
Let the Sun Shine: 2.2 Mile Run/Walk for Mental Health April 30, 2011 St. Boniface Parish Center Cold Spring, Minn. www.letthesunshinerun.com						
Benefit Concert for Mental Health with Tracy Grammer May 13, 2011 Daylesford Abbey in Paoli, Penn. www.benefit4mentalhealth.org						
Taking Strides Against Mental Illness Walk May 15, 2011 Wild Duck Pond Saddle River Country Park in Ridgewood, N.J. www.againstmentalillness.org www.facebook.com/takingstrides						
Fifth Annual Chrissy's Wish Memorial Golf Outing July 22, 2011 Rock Hill Golf & Country Club in Manorville, N.Y. Featuring BBQ Lunch and Dinner www.chrissyswish.com www.causes.com/causes/79714						
Go to www.narsad.org/events for a complete listing.						



Spotlight:

Taking Strides Against Mental Illness Walk

This year will mark the fourth annual Taking Strides Against Mental Illness Walk to help support NARSAD-funded research in depression, mood disorders and schizophrenia. "We do the walk to raise money for research and the more research we do, the closer we get to helping people with mental illness," said Rebecca Ehrlich, organizer of Taking Strides Against Mental Illness Walk.



Rebecca Ehrlich

"It's important to have an event like this because mental illness needs to be recognized as an illness. This event is important to me because I live with a mental illness and I know what it's like to live in a group home and to be treated in a hospital." Rebecca's passion for raising awareness and eliminating stigma motivates her to support research.

Get involved with the Taking Strides Against Mental Illness Walk and join Rebecca in making a difference.

Announcements

March 9 - 11: Advancing Drug Discovery for Schizophrenia



The goal of this New York City conference is to facilitate the translation of discoveries in basic neuroscience into the development of innovative pharmacological agents for the treatment of schizophrenia by convening and encouraging dialogue among clinical, translational and basic neuroscientists. Sponsored by The New York Academy of Sciences. Go to www.nyas.org for details.

April 2011: Wiring the Brain Conference in Ireland



This conference will bring together scientists from diverse disciplines to explore brain connectivity and its role in mental illness and neurological disease. Go to www.wiringthebrain.com for details.

May 26: Frontiers in Mental Health

This symposium will explore frontiers in mental health research with a focus on genomics and neurocircuitry. Sponsored by The Gairdner Foundation and The Graham Boeckh Foundation. Location: Montreal, Quebec. Go to www.gairdner.org/calendar for details.



How You Can Help Fund Breakthrough Research

Team Up for NARSAD and hold a fundraiser for brain and behavior research!

1. Choose the type of event your team will host
2. Sign-up with **Team-Up** for NARSAD at www.narsad.org/teamup or e-mail teamup@narsad.org
3. Plan your event with the **Team-Up** for NARSAD Tool Kit available online

Funding brain and behavior research means funding new breakthroughs and future discoveries that will improve the lives of those affected by mental illness. Get started today! **Team Up** for NARSAD!

Team Up for NARSAD at www.narsad.org/teamup



HEALTHY MINDS ACROSS AMERICA

Discovery to Recovery through Science

More than 40 institutions across the United States and Canada partnered with NARSAD in presenting its “Healthy Minds Across America” series of public talks in 2010. Each event helped to bring science to families seeking hope for better treatments of a broad range of mental illnesses. The following pages contain highlights of presentations from various venues in the series. Full transcripts of the talks are available at www.narsad.org/events. Click “Past NARSAD Events.”

NARSAD

In partnership with

Columbia University



H. Blair Simpson, M.D., Ph.D.

NARSAD Young, Independent Investigator
Associate Professor of Psychiatry,
Columbia University
Director, Anxiety Disorders Program,
New York State Psychiatric Institute

The patient, guided by the therapist, confronts the feared thing and stays in the anxious moment until the fear is lessened or extinguished.

Is Fear Extinction Possible in Treating OCD?

H. Blair Simpson, M.D., Ph.D.

Obsessive-compulsive disorder (OCD), the most severe of the anxiety disorders, is typified by intrusive, distressing thoughts that lead to compulsive, repetitive behaviors that can greatly diminish quality of life and curtail normal activity. Medication or psychotherapy, specifically a form of cognitive behavioral therapy called exposure and response prevention, can reduce OCD symptoms, but not for every patient and not permanently, and treatments are often difficult to sustain or have negative side effects.

Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine (Prozac) and paroxetine (Paxil), which are antidepressant drugs that target the serotonin neurotransmitter system, can be effective in treating OCD, but only at very high doses. Adding low doses of antipsychotic medications helps in about half of cases, but can have serious side effects. New research is testing the usefulness of medications that modulate glutamate, a different neurotransmitter system.

Exposure and response prevention is a psychotherapeutic rather than a pharmacological intervention. In this therapy, the patient, guided by the therapist, confronts the feared thing and stays in the anxious moment until the fear is lessened or extinguished. For the technique to work it requires time, patience, a skilled therapist and a willing patient.

Motivational interviewing, a therapy used for treating substance abuse, is being tested to see whether it can improve patient adherence in OCD treatment. Researchers are also examining a new use for an old drug, D-cycloserine, developed to treat tuberculosis, which can be added to exposure therapy to speed the fear extinction process.

Among laboratory technologies exploring the neurobiology of OCD, advances in imaging methods have made it possible to examine the living brain in real time. Imaging studies have shown that people with OCD

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Yale University



Joan Kaufman, Ph.D.

NARSAD Young Investigator
Associate Professor of Psychiatry and
Director of the Child and Adolescent
Research and Education Program,
Yale University School of Medicine

Research is also showing that having an adult in their lives that they can count on, can help to promote resiliency in high-risk children.

have abnormal activity in a brain circuit involved in planning and organization, which includes the thalamus, a main role of which is to filter incoming information. One theory about OCD is that the thalamus is not gating incoming information appropriately. The need to learn whether everyone with OCD has the same brain abnormality has now led to expanded efforts to develop better animal models for study.

How the Early Environment May Trigger Susceptibility and/or Teach Resiliency

Joan Kaufman, Ph.D.

A key environmental factor contributing to and highly predictive of psychiatric illness is stress. Children with a history of trauma or maltreatment are at enormous lifetime risk for anxiety, depression, PTSD, suicide, substance abuse and other mental health problems.

Many, if not most, psychiatric disorders arise from the interplay of genes and environment. Current research looks at gene and environmental predictors of risk and resiliency. Among the challenges of such research is the fact that most psychiatric disorders involve many different genetic anomalies. Also, individuals vary significantly in their genetic vulnerability. Further, there is a large percentage of patients with co-morbidity – co-existence – of anxiety with depression or other disorders.

Molecular mechanisms have recently been identified that show how gene-environment interaction can affect DNA structure and function. A seminal study a few years ago appeared to show that the serotonin transporter gene, part of the system regulating the neurotransmitter serotonin, could moderate the effects of stress on major depression. The gene has two common forms. *S* is the short form, and people who have it are believed to be more affected by stress and susceptible to mental illness. *L* is the lower risk form of the gene. Researchers are also looking at what is called brain-derived neurotrophic factor (BDNF). The BDNF system and the serotonin system interact on multiple levels.

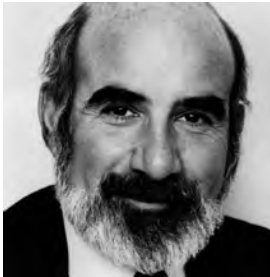
Not surprisingly, maltreated children with the highest-risk genetic profiles tend to show the greatest vulnerability to psychiatric disorders. But as research is revealing, these effects are not necessarily fixed. Studies with animals have shown, for example, that maternal behavior can influence, for better or worse, the brain development of their offspring.

Research is also showing that psychiatric ill effects can be reversed with environmental and pharmacological interventions, the earlier the intervention, the better. For example, social support, especially having an adult in their lives that they can count on, can help to promote resiliency in high-risk children. In pharmacological research, current experiments are testing a range of drugs that influence gene expression and DNA structure toward the goal of individualized treatments to optimize efficacy and minimize side effects.

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Mount Sinai School
of Medicine



Larry J. Siever, M.D.

Professor of Psychiatry,
Director of the Special Evaluation
Program for Mood and Personality
Disorders, and Vice-Chair
for VA Affairs,
Mount Sinai School of Medicine

While personality disorders can change, they tend to change slowly and require psychosocial treatment and in some cases medication.

Brain Circuitry in Personality Disorders

Larry J. Siever, M.D.

Personality disorders, while less known about than some other psychiatric conditions, nonetheless pose serious mental health problems. Researchers are gaining new insights into the brain-circuitry malfunctions that are believed to underlie personality disorders.

Simply stated, people with personality disorders are held back by approaches to life that don't work, for example, extreme emotions and unstable behavior that constrain their ability to engage others or be effective in the workaday world. Among the various categories of these disorders, borderline personality disorder is characterized by excessive anger, impulsiveness and distorted relationships. People with schizotypal personality disorder are isolated, locked away in their own world. A category called anxious cluster personalities is characterized by people so fearful of and stressed by rejection that they avoid social interactions.

In the human brain, the cortex, which is the region of higher mental function, modulates the more "primitive," emotional limbic system to create a balance necessary for normal functioning. In psychiatric disorders, including many personality disorders, whether caused by trauma or by abnormal brain-structure development, these systems are not in balance.

Current research is exploring all the elements of brain circuitry that may be disturbed in personality disorders:

- Key anatomical structures, including the cortex and the all-important amygdala, the limbic brain's alarm center;
- Neurotransmitters, principally serotonin, as well as other molecules of brain-cell communication; and
- Genes that initiate and orchestrate these processes.

Among research findings, PET imaging has revealed a reduction in volume in cortical structure in people with personality disorders. Studies of genes associated with suicide risk, which appear also to be associated with borderline personality disorder, suggest that trauma may amplify the risk for aggression among people with this gene signature.

While personality disorders can change, they tend to change slowly and require psychosocial treatment and in some cases medication. Researchers are exploring therapies such as dialectical behavioral intervention that appears to target the amygdala to help build impulse control and improve emotional processing. Researchers have also been experimenting with the antidepressant fluoxetine (Prozac), which acts on the serotonin system to enhance cortical activity.

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Case Western Reserve
University



David E. Kemp, M.D.

NARSAD Young Investigator
Assistant Professor of Psychiatry and
Director, Mood and Metabolic Clinic,
Case Western Reserve University

In a small pilot study, patients with altered insulin sensitivity and depression were treated with pioglitazone, commonly used to treat diabetes. They showed improvement in metabolic symptoms, and correlated improvement in symptoms of depression.

Can Treatment for Diabetes Treat Depression?

David E. Kemp, M.D.

Mental illness is a major risk factor for cardiovascular disease and early death. People with depression and diabetes experience very high rates of stroke, heart attacks and renal failure. Current research is focused on finding novel ways to treat people with this double threat to their health and happiness before trouble begins.

Major risk factors for diabetes and heart disease are insulin resistance and obesity, the key components of the so-called metabolic syndrome. Interestingly, recent studies have shown that depression and diabetes travel a two-way street: each is a risk factor for the other. Researchers have found that patients displaying full-blown metabolic syndrome go on to develop depression at a rate 140 percent higher than average. Based on these and other observations, researchers are trying a reverse approach that attempts to treat depression by treating the metabolic syndrome.

Most current antidepressant medications target neurotransmitters in the brain, such as dopamine, serotonin and norepinephrine, whose dysfunction is believed to be involved in depression. Yet many patients with depression who are given these medications fail to improve fully or at all. Research is aimed at going beyond or around the current paradigm, based on findings that suggest targeting insulin-signaling pathways directly affects the activity of the neurotransmitters.

Pioglitazone is a drug used in the treatment of type 2, adult-onset diabetes to decrease metabolic syndrome and obesity. It also decreases some immune-system chemicals involved in inflammation that are abnormally activated in diabetes. In a small pilot study, the effectiveness of pioglitazone has been tested in patients who do not have diabetes, but do have altered insulin sensitivity or insulin resistance and depression. As expected, they showed improvement in metabolic symptoms, including reduced insulin levels. They also showed correlated improvement in symptoms of depression: those who had the largest decrease in insulin resistance also experienced the greatest abatement of depression severity. Additionally, patients with the most improvement in depression symptoms showed the largest drop in inflammatory markers.

While this pilot study with pioglitazone is in its very early stages, it will lead to support for expanded studies to confirm the efficacy of this approach.

Go to www.narsad.org and click on 'Past Events' to read the full transcripts of presentations made at Healthy Minds Across America venues.

Tune in to the webcast at Columbia University or view the video of the Vanderbilt University event!

NARSAD Scientific Council

The 124-member NARSAD Scientific Council, a volunteer group of preeminent mental health researchers, leads the rigorous and competitive process of identifying the most promising ideas for NARSAD to fund in grant awards each year.

With a focus on excellence, they ensure that NARSAD grant awards cover the broadest range of brain and behavior research across communities and institutions.

The NARSAD Scientific Council includes:

- 2 Nobel Prize winners
- 4 former directors of the National Institute of Mental Health
- 23 Chairs of Psychiatry Departments at leading universities and medical schools
- Current President, Herbert Pardes, M.D., President and CEO of NewYork-Presbyterian Hospital

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How I turned a **\$60,000 NARSAD grant** into more than **\$8.5 million** worth of additional **depression research funding**

Helen S. Mayberg, M.D., NARSAD grant recipient in 1991, 1995 and 2002



Helen Mayberg's success as a researcher can be attributed, in part, to her first NARSAD grant, which enabled her to demonstrate the feasibility and practical application of Deep Brain Stimulation on treatment-resistant patients with depression. Dr. Mayberg, one of the world's leading authorities on neurology and depression, went on to receive numerous NIMH and institutional grants thanks to NARSAD funding her work with a seed grant.

Dr. Mayberg's story is a familiar one to us at NARSAD as many NARSAD-funded scientists have received additional grant support equaling, on average, 19 times their original NARSAD grants. And 100% of NARSAD grants go directly to our researchers thanks to the generosity of two family foundations that underwrite NARSAD operating costs.

No other mental health research organization can say this.

To learn more about how you can invest in the most promising brain and behavior research like that of Dr. Mayberg's, please call us at (516) 829-0091 or visit our website at www.narsad.org.



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Investing in Breakthroughs — To Find a Cure

MISSION: NARSAD is committed to alleviating the suffering of mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

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

OUR CREDENTIALS: For a quarter of a century, we have awarded more than \$274 million worldwide to over 3,000 scientists carefully selected by our prestigious Scientific Council.

To find out more about NARSAD, the research it supports and how you can become involved, please call us at 800.829.8289 or visit www.narsad.org.

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