

The Quarterly

Winter
2011



Page 13

FOCUS on ANXIETY

RESEARCH NEWS

- 1 NARSAD RESEARCHERS IN THE NEWS
- 4 INTERVIEW WITH A RESEARCHER
John H. Krystal, M.D.
on Advancing Treatments for Anxiety Disorders
- 10 FREQUENTLY ASKED QUESTIONS
ON ANXIETY DISORDERS
- 16 YOUNG INVESTIGATOR GRANT AWARDS
214 of the finest young neuroscientists receive
NARSAD grants
- 23 GLOSSARY
- 24 NEW TREATMENTS/THERAPIES
Breakthroughs continue to be made
- 26 MOMENTUM
NARSAD Events Calendar and Updates
A sampling of Healthy Minds Across America Symposia

FEATURE

- 13 RESEARCH GIVES PEOPLE HOPE
Multiple family illnesses inspire a couple's life-long
commitment to the mental health cause

NARSAD

The Brain and Behavior Research Fund



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.

NARSAD

60 Cutter Mill Road, Suite 404
Great Neck, NY 11021
516.829.0091 • 800.829.8289
www.narsad.org

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.

ON THE WEB:



Facebook



Twitter



NARSAD Blog and eNewsletter