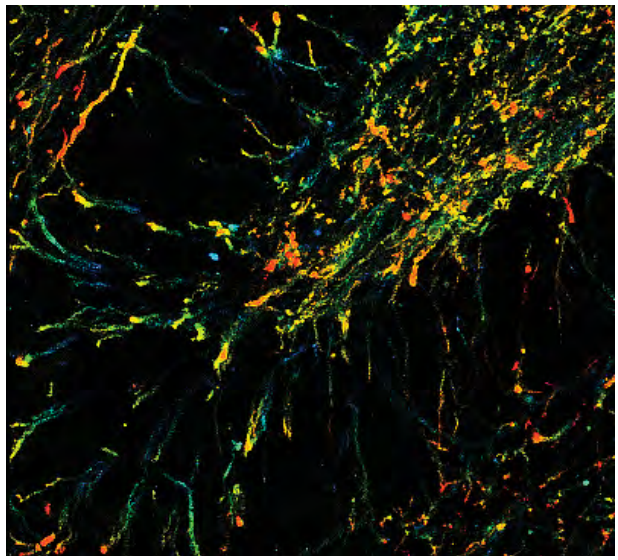
The Quarterly

Summer 2014

BRAIN & BEHAVIOR RESEARCH FOUNDATION

Awarding **NARSAD** Grants



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Jeffrey Borenstein, M.D.
President & CEO
Brain & Behavior Research Foundation

Whether because of our nation's recent involvement in two long wars in the Middle East and the toll that has taken on the mental health of our armed services personnel or the horrendous episodes of violent shooting sprees across the country, Americans have become increasingly aware of post-traumatic stress disorder (PTSD). Tragically, the debilitating symptoms of PTSD—the unremitting reliving of a traumatic event—can persist for years, and even decades, as has been seen with many veterans of the Vietnam War.

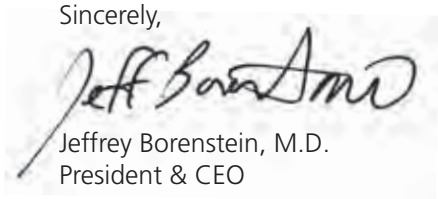
It is especially heartbreaking when PTSD strikes children. Two articles in this issue, found on pages 6 and 21, address the impact of everyday violence on the developing brain. As Dr. Kerry Ressler, Foundation Scientific Council member and PTSD expert, explains in the Interview with a Researcher piece, childhood trauma is, in fact, the strongest predictor of risk for PTSD in adulthood. Dr. Ressler, of Emory University, has found rates of PTSD in inner city neighborhoods "as high as those seen in Vietnam vets."

The tools to effectively address and lessen the disheartening prevalence and impact of PTSD are being developed by an increasing number of bright, young minds, many supported by NARSAD Grants, who are determined to get to the roots of the illness and develop better treatments. They are making significant progress in identifying risk factors for PTSD that can make early intervention and even prevention a possibility, and they are beginning to identify what causes the disorder to develop.

Summer is the time when the Foundation awards its Klerman and Freedman Prizes in recognition of exceptional research by NARSAD Young Investigator Grantees in both basic and clinical research. The 2014 Prizewinners, selected by Committees of the Foundation's Scientific Council, were honored at a special dinner celebration on July 25th in New York City. See pages 13 to 17 to learn more about their exciting work, made possible by the generosity of Foundation supporters. The prizes are often predictive of future prominence; Dr. Ressler, for example, was the winner of the 2009 Freedman Prize.

Across the spectrum of mental illnesses, NARSAD Grantees are making continual and important progress to effectively address and curb the impact of mental illness once and for all. This is made possible through your generous contributions. Thank you.

Sincerely,



Jeffrey Borenstein, M.D.
President & CEO

Research Discoveries in the News

Surprising Way to Promote Resilience from Stress

Can too much of a bad thing lead to a good outcome? In new research at the Icahn School of Medicine at Mount Sinai, this paradoxical question is at the heart of a surprising new discovery that could lead to a novel approach for treating stress-induced depression.

Working with mice, the research team, led by 2007 NARSAD Young Investigator Grantee **Ming-Hu Han, Ph.D.** and including 2010 NARSAD Young Investigator Grantee **Vincent F. Vialou, Ph.D.,** found that by boosting overactive neuronal activity during a simulation of "social defeat stress"—a behavioral situation akin to repeated bullying—a self-stabilizing response was eventually triggered in animals susceptible to developing depression. By accentuating the flaw in activity, they found that it eventually corrected itself. Out-of-balance electrical activity in the brain was stabilized and behavioral symptoms of depression, such as social withdrawal, anxiety and listlessness were reversed.

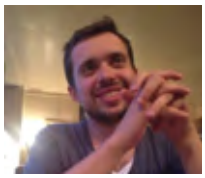
The results of this new work were published online April 18th in the journal *Science*. Dr. Han and his team knew from prior studies that in mice naturally susceptible to developing stress-induced depression, the electrical current is elevated in cation channels, which enable positively charged ions to enter dopamine neurons*. This is thought to contribute to pathology. When susceptible mice are bullied they become depressed.

But the first unexpected finding made by Dr. Han's team was that in mice naturally resilient to bullying—mice that don't get depressed after experiencing social defeat stress—the level of current in cation channels was even higher than that seen in the susceptible mice. Oddly enough, these neurons were stable; unlike those of the depression-prone mice, they fired at a normal rate. A counterintuitive idea was born: perhaps if cation channels in dopamine neurons* were even more highly activated in susceptible mice, the neurons would become hyperactive, but then stabilize.

Using beams of laser light to control individual dopamine neurons* in the mice susceptible to developing depression—with the new technology optogenetics*—the team increased the overactive neuronal activity in these mice. This produced the second surprise: not only did the firing of the neurons stabilize; depression-related behaviors were "completely reversed." At a certain point, the elevated neuronal activity triggered its own compensatory ion channel* adaptation to stabilize the out-of-balance electrical activity and produced resilience.

Dr. Han and his colleagues believe that if a medication could accentuate this neuronal hyperactivity until it self-corrects, essentially pushing depressed individuals past a certain tipping point, it could work as a more natural antidepressant by promoting resilience and cause fewer side effects.

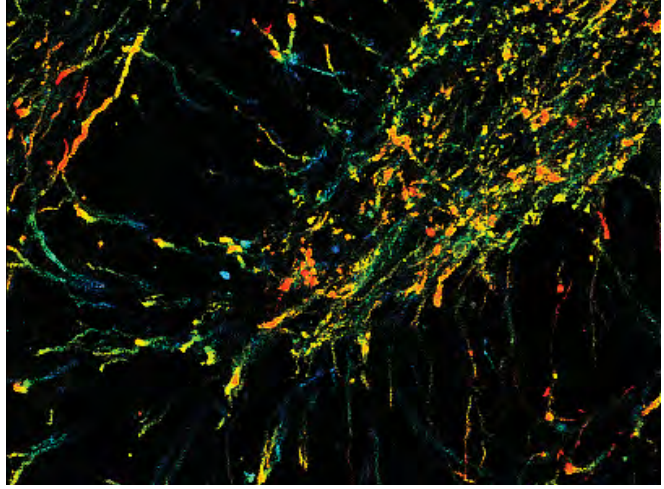
Foundation Scientific Council member Eric Nestler, M.D., Ph.D., Chair of the Department of Neuroscience at Mount Sinai, praised the research, saying the team "reveals a highly novel mechanism that controls an individual's susceptibility or resilience to chronic social stress. The discoveries have important implications for development of new treatments for depression and other stress-related disorders."



TAKE AWAY: Using laser light to accentuate nerve cell activity, Foundation-funded scientists may have found a novel way to treat depression.

Ming-Hu Han, Ph.D.; Vincent F. Vialou, Ph.D.

** Refer to glossary on page 28.*



Identifying How Early Stress Impacts the Brain

Above: Imaging of myelinated nerve fiber tracts converging in the hilus area of the rat hippocampus. Chetty et al. found that the production of oligodendrocytes, the myelinating cells of the brain, is increased after stress, providing new evidence that dysregulation of myelin may contribute to stress-related mental illness.

For years, psychiatrists and scientists who study the brain have noted that a highly stressful experience or periods of chronic stress early in life not only can cause behavioral and emotional problems at the time of the stress, but also make many people vulnerable to developing stress-related disorders into adulthood.

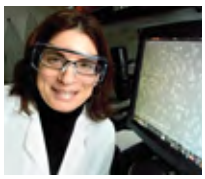
The biological explanation for this lingering susceptibility is one of brain science's great mysteries. A team of researchers—led by **Daniela Kaufer, Ph.D.,** of the University of California, Berkeley, a recipient of a NARSAD Young Investigator Grant in 2009—tested a theory that they report has held up well in experiments. Their findings were explained in a paper appearing in *Molecular Psychiatry* on February 11, 2014.

The team, which also included 2004 NARSAD Distinguished Investigator Grantee **Robert M. Sapolsky, Ph.D.,** of Stanford University, set out to determine if stress alters the process by which the adult brain and central nervous system produce an essential class of cells called oligodendrocytes. These "helper" cells manufacture the fatty coating that insulates nerve sheaths in much the same way that a rubber coating protects copper wires. "White matter" in the brain gets its name from the abundance of this light-colored nerve fiber coating, called myelin.

In multiple sclerosis, oligodendrocytes die or are unable to make myelin; the lack of nerve insulation profoundly affects the normal function of both the brain and connected motor systems. The question Dr. Kaufer and colleagues explored was whether oligodendrocyte production was affected by stress. They were able to demonstrate that environmental stress caused an abnormally high production of oligodendrocytes in the dentate gyrus* (DG) region of the brain. This part of the brain's hippocampus is central in memory and emotion, and one of the few places in the brain where new neurons are generated in adults.

Stress (as well as direct injections of stress hormone) caused fewer new nerve cells to be born in the DG in experiments with rats. For the first time ever, the team was able to show that stress (and stress hormone injections) also increased oligodendrocyte production in the DG. In test tube experiments, Dr. Kaufer's team went on to show that stress hormone injection caused stem-like cells that usually give rise to neurons to turn on a transcriptional program that increases the rate at which oligodendrocytes are generated. By blocking these cells' docking ports for stress hormone—disabling their capacity to take it in—the overproduction of mature oligodendrocytes was prevented.

Taken together, these experiments provide an intriguing potential explanation for why adults who were traumatized or regularly stressed as youths carry an abnormally high risk of developing stress-related disorders. "Stress may alter how the hippocampus functions, by promoting the production of oligodendrocytes," the scientists say. "We suggest that this alters the composition of cells in that region and changes its white-matter structure. This may create a persistent, white matter structural vulnerability to mental illness."

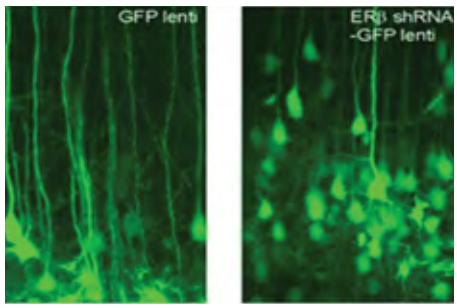


TAKE AWAY: Scientists have now shown that stress may change the structure of the brain's white matter, creating a vulnerability to mental illness.

Daniela Kaufer, Ph.D.; Robert M. Sapolsky, Ph.D.

* *Refer to glossary on page 28.*

How Estrogen Protects Females Against Detrimental Stress



Above: Neurons of the prefrontal cortex region of the brain (green) are particularly sensitive to the effects of stress, and limiting estrogen action in these cells reduces estrogen's protective effects in females.

This May, Francis Collins, M.D., Ph.D., Director of the National Institutes of Health, co-authored a much-discussed commentary in the journal *Nature* reminding scientists of the need to test their theories on both males and females, in experiments ranging from animal models of disease to human clinical trials. More studies will now be required to include females in their study samples to be approved for funding.

For researchers who study the impact of stress on the brain, this came as a welcome message. For years, their observations have shown striking differences in the response of males and females to stress. It is well known that male rodents are more likely than females to be adversely affected by low to moderate levels of repeated, "subchronic" stress.* But why?

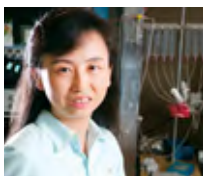
A major step forward in understanding the biology behind this phenomenon has been taken by a research team led by **Zhen Yan, Ph.D.,** of the State University of New York, Buffalo (1999 and 2004 NARSAD Grantee). The team included Foundation Scientific Council member **Bruce S. McEwen, Ph.D.**, of The Rockefeller University (also a 1998 NARSAD Distinguished Investigator Grantee) and **Ilia N. Karatsoreos, Ph.D.,** a 2013 NARSAD Young Investigator Grantee at Washington State University, Pullman.

In the May 2014 issue of *Molecular Psychiatry*, the team reported a series of clear distinctions in the responses of male and female rats to a week of repeated, subchronic stress.* As expected, females showed no impairment in a memory test given at the end of the stress period, while males were clearly impaired. The test measured the function of a cognitive system centered in the brain's prefrontal cortex (PFC),* and specifically the integrity of nerve transmission in excitatory neurons,* activated by the neurotransmitter glutamate.

But when the team then blocked receptors, or docking ports, for the hormone estrogen located on the surface of PFC excitatory neurons* (or eliminated them altogether), female rodents no longer were protected against the ill-effects of repeated stress. They showed memory impairments just as stressed males did. Conversely, when a version of the female hormone was injected into stressed males, they experienced no memory impairments, just as normal stressed females had.

"The results suggest that estrogen protects against the detrimental effects of repeated stress" in glutamate-activated neurons, in tasks centered in the PFC, the scientists concluded. Important though this sex difference is, it is specific to subchronic stress. For, as the team notes, over the lifespan, women are more likely than men to experience major depression.

Both phenomena are the consequence of biological differences. Women's lifetime vulnerability to major depression is understood to be a result of hormonal fluctuations related to the reproductive cycle and child-bearing. As for the biological difference accounting for female protections against at least some forms of stress, the new study points to hormones, but specifically to the ability of brain cells to locally synthesize estrogen—an ability confirmed in this study. It would be one of the fundamental brain differences among the sexes that Dr. McEwen has devoted much effort to studying throughout his celebrated career. (See *The Quarterly,* Fall 2013, pp. 5-6.)



TAKE AWAY: New research shows that estrogen supports nerve transmission in the prefrontal cortex to protect against detrimental effects of stress.

Zhen Yan, Ph.D.; Bruce S. McEwen, Ph.D.; Ilia N. Karatsoreos, Ph.D.

* *Refer to glossary on page 28.*

Unraveling How Trauma Converts to PTSD

Bright Mind Focuses On Identifying the Risk Factors and Biological Roots of PTSD

Kerry Ressler, M.D., Ph.D., is one of America's leading authorities on the psychological and behavioral impacts of trauma—not just trauma suffered by soldiers on the battlefield but also by civilians, here at home. "Post-traumatic stress disorder," or PTSD, was first coined as a term after the Vietnam War and acknowledged as an illness when it was added to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980.

Kerry Ressler, M.D., Ph.D.

Professor, Psychiatry and Behavioral Sciences, Emory University School of Medicine

Co-Director, Trauma Clinic, Fulton County Behavioral Sciences

Investigator, Howard Hughes Medical Institute

2002, 2005 NARSAD Grantee

2009 Freedman Prize for Exceptional Basic Research by a Young Investigator

Foundation Scientific Council Member

"The first thing people should know about PTSD is that it happens after a trauma, and is caused by unwanted intrusions of terrifying memories into our conscious thoughts and even our dreams," says Dr. Ressler. "It can happen to anybody, yet some people are more prone to it than others, and our research is beginning to explain who is more at risk. A second thing we know about PTSD is that the more trauma you have experienced, the more at-risk you are. So, multiple battlefield deployments like we saw in the Iraq war definitely put people at greater risk. But this applies just as much to sources of risk found in our own cities, especially the most violent inner cities. In Atlanta, we see rates of PTSD as high as those seen in Vietnam vets."

Dr. Ressler is Co-Director of the Grady Trauma Project, based at Atlanta's Grady Hospital, whose aim is to better understand the specific risks of post-traumatic injury in places where violence in the streets and within families (in the form of sexual abuse, spousal and child battery and abandonment, for example) is far above average. "Almost half of the 8,000 people we've interviewed in Atlanta know someone who has been murdered. Two-thirds have been attacked. One-

> "PTSD is very prevalent; it can happen to anybody. Yet some people are more prone to it than others, and our research is beginning to explain who is more at risk."

Kerry Ressler, M.D., Ph.D., in his laboratory at Emory University where he studies genes in mice linked to the fear and stress response in an effort to better understand the human experience of PTSD.
Image courtesy of Dr. Ressler

third has been sexually assaulted."

In a 2012 paper suggesting the value of early intervention, Dr. Ressler and colleagues said that while "most people will experience symptoms of post-traumatic stress in the immediate aftermath of a trauma, these reactions typically extinguish over time." What's perplexing is why some people can purge these memories and others cannot. Aside from having unwanted traumatic memories, those who suffer from PTSD often avoid places or people associated with the trauma, have an overly sensitive startle response (called hyper-arousal), are emotionally numb and tend to have angry outbursts.

In the first years of the Grady Trauma Project, Dr. Ressler realized that in Atlanta he was "well equipped to study resilience. We interview people who have had an enormous amount of lifetime trauma and we see that they are reasonably happy, able to hold a job, trying their best to be a good parent, getting on with life with very few symptoms."

This, he says, is "the flip side" of seeing very high rates of PTSD in violent inner-city neighborhoods: "We actually see more people who don't have PTSD or depression (which often co-occurs with it), people who have every reason in the world to be overwhelmed."

Doctors know that childhood trauma or abuse is the biggest risk factor for developing PTSD. In fact, someone who experiences trauma as a child is more at risk for adult PTSD than an adult who experiences trauma. The impact for those who happen to be vulnerable extends far into the future. But why? And, in biological terms, who and how?

Here is where research is answering key questions that should lead to better therapies. "Until quite recently," says Dr. Ressler, "an expert would say that PTSD was about the trauma exposure itself," and not about a person's biological make-up. But studies in identical twins now suggest that 30 to 40 percent of a person's risk for developing PTSD is genetic.

Very little is known about gene variations that increase a person's PTSD risk. By studying the fear response in rodents, Dr. Ressler and others in the field have made some progress in identifying specific mutations. But the evidence won't be persuasive until much larger population samples are analyzed.

Other PTSD studies by Dr. Ressler and colleagues have yielded many new insights. In the last three years alone they have made a number of important findings:

- Different versions (polymorphisms) of genes associated with the fear and stress response in mice are also associated with abnormalities in the human brain's amygdala and hippocampus—an increased reaction to threat stimuli and a decrease in connectivity between the two regions. These two brain areas are central to memory, the fear response and learning.
- In adults who were abused as children, those resilient to stress and trauma are less likely to misuse alcohol and drugs.
- PTSD may function "as a pathway" between childhood abuse exposure and development of pain-related conditions in adulthood.
- Childhood trauma exposure may contribute to increased risk of heart disease through its influence on lipid levels, in males but curiously not in females.
- Estrogen may contribute to differential PTSD vulnerability for women with trauma histories.

Dr. Ressler credits the Foundation with "doing a terrific job in giving scientists the flexibility they need to follow where their research goes. In terms of getting new ideas off the ground, no program does it as well as the NARSAD Grant program."

Optimism about New Treatments: Acting Quickly, in the "Golden Hours"

It's called "the golden hour:" the first hour after a severe trauma when medical intervention has the greatest chance of saving a victim. Dr. Kerry Ressler, who spent some of his medical training in emergency rooms (ER) and still devotes time to seeing trauma patients, says evidence suggests there is a similar golden period after a trauma during which PTSD can be minimized or even prevented.

Dr. Ressler and colleagues published results of a double-blind study combining virtual reality exposure therapy with a promising medication called D-cycloserine (DCS). This paradigm-shifting work suggests that DCS may improve the effectiveness of exposure therapy by enhancing the biological processes that lead to memory extinction.

This window of intervention is probably a number of hours, although research is still determining how much longer it may be, by which time the trauma memories are formed after a traumatic experience. Whenever possible, clinicians need to act quickly. But doing so for every person reporting a trauma would be logistically daunting, not to mention impossibly costly. This is why Dr. Ressler is determined to identify risk genes, so that in the future, a simple blood test can identify the trauma victim in the ER whose genetic profile makes the chance of PTSD more likely.

While the search for risk genes goes forward, doctors know that it pays to treat trauma victims with a behavioral method called "exposure" therapy. The most effective kind has been tested in clinics with both civilians and veterans, where trauma victims receive a course of psychotherapy that includes virtual reality. By virtually recreating the scene of the trauma in a safe, non-threatening environment, doctors often succeed in desensitizing the victim to cues that set off PTSD symptoms.

Earlier this year, Dr. Ressler and colleagues published results of a double-blind study combining virtual reality exposure therapy with a promising medication called D-cycloserine, or DCS. Designed as an antibiotic, DCS selectively stimulates NMDA receptors* in the brain. The medication is thought to help victims extinguish unwanted trauma memories. Dr. Ressler's trial showed no advantage post-treatment for soldiers who received virtual exposure therapy combined with DCS vs. placebo. But it showed that those getting DCS had lower levels of cortisol, the stress hormone, during therapy, as well as better scores in the "startle-response" test. This paradigm-shifting work suggests that the medication DCS may improve the effectiveness of exposure therapy by enhancing the biological processes that lead to memory extinction. Although more tests will follow, DCS remains a strong candidate for combination treatment.

Another possible treatment-enhancing medication involves the nerve growth factor BDNF (brain-derived neurotrophic factor). In the fear center of the brain called the amygdala, memories cannot be extinguished without BDNF. This suggests BDNF or a medication that acts just like it might be given to people who are undergoing exposure therapy. In the "golden hours," a BDNF-blocker also might be given to prevent the formation of a traumatic memory.

"I think PTSD is going to be tractable," Dr. Ressler says. "I expect medications similar to BDNF or DCS will be given in a targeted way, and infrequently, to coincide with the time of memory formation or specific subsequent attempts to extinguish traumatic memories. More generally, everyone in the field agrees this is a time when discoveries are happening quickly. I'm quite optimistic they will lead to better ways of taking care of people with PTSD and even, in some cases, preventing it altogether."

HAVE A QUESTION?

Send questions for Dr. Ressler to **asktheresearcher@bbrfoundation.org**. Select questions and answers will be in the next issue of *The Quarterly.*

Please note that the researcher cannot give specific recommendations or advice about treatment; diagnosis and treatment are complex and highly individualized processes that require comprehensive face-to-face assessment.

** Refer to glossary on page 28.*

ANSWERS TO:

Ask the Researcher

Carlos A. Zarate, M.D.

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

Clinical Professor of Psychiatry and Behavioral Sciences, The George Washington University

1996 & 2005 NARSAD Grantee

Foundation's 2011 Bipolar Mood Disorder Outstanding Achievement Prize (renamed the Colvin Prize in 2012)

Has brain research scientifically proven that major depression is a brain disorder?

The short answer to this is yes. Research suggests that major depression is a brain disorder associated with a wide range of peripheral biological effects, including changes in endocrine, cardiovascular, stress response, inflammatory, and metabolic functions.

I have severe anxiety and depression and have tried over a dozen medications with little benefit. Is there progress being made in figuring out what is different between those who respond to medications and those who don't?

Significant progress has been made in identifying clinical and biological predictors of antidepressant response or non-response for different classes of antidepressants, though more work is needed to translate our findings into practice. In general, better response to currently available antidepressants has been associated with fewer past depressive episodes, absence of family history of mood and psychotic disorders, and lower anxiety levels. My group has been studying predictors of response to ketamine and other new treatments, which are typically given to individuals with treatment-resistant depression. Our preliminary findings suggest that response to ketamine is associated with family history of alcohol dependence, specific genetic polymorphisms, and neuroimaging changes in areas such as the anterior cingulate cortex.

Does the research on ketamine as an effective and fast-acting treatment for depression tell us anything about the brain that could lead to treatments for other kinds of mental illness?

Our studies of ketamine have yielded useful information regarding the pathophysiology of depression and bipolar disorder and the role of the glutamatergic system (which regulates glutamate, an abundant neurotransmitter) and its downstream therapeutic targets. We are using ketamine in a wide variety of ongoing studies that we hope will ultimately lead to better and more effective treatments for depression; for instance, 1) as a prototype for developing rapid-acting treatments, 2) in the search for biomarkers of treatment response, and 3) in investigations of the neurobiology of treatment response.

Are there concerns about the long-term safety of using ketamine?

Although a single infusion of ketamine has promising and rapid antidepressant and anti-suicidal effects, we know very little about its potential long-term effects. Concerns regarding long-term ketamine use include risk of abuse, problems with cognition, risk of cystitis and other as yet unknown side effects. Ongoing studies are investigating the long-term safety profile of ketamine.

How close are we to having "personalized" treatments for mental illness?

A considerable amount of research is being conducted to identify biomarkers of treatment response that would one day enable us to match a particular individual with the best treatment based on their underlying biology. However, we are not there yet. Although our preliminary findings suggest that it is possible to differentiate between groups of individuals who will or will not respond to a particular therapy, actually doing so will require the development and identification of biomarkers through a wide range of technologies (brain imaging, peripheral imaging, pharmacogenomics, metabolomics, etc). Recent advances have identified predictors of response to mood stabilizers and antidepressants, but given the complexity of the human brain and polygenic basis of psychiatric disorders, this field is still in its infancy.

Frequently Asked Questions *on* PTSD

Q: **Is post-traumatic stress disorder (PTSD) something that only affects combat veterans?**

A: A significant number of veterans suffer from PTSD: up to 20 percent of those who served in the Iraq and Afghanistan wars and up to 30 percent of those who served in Vietnam.[1] But PTSD can result from a variety of traumatic or life-threatening incidents such as sexual assault, child abuse, accidents, bombings, or natural disasters such as tornadoes, for example. Even witnessing a traumatic event can cause PTSD.[2] In the United States, about seven or eight out of every 100 people will have PTSD at some point in their lives. During a given year, some five million adults are coping with PTSD.[1]

Q: **What are the symptoms of PTSD?**

A: In the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, published in 2013, the American Psychiatric Association (APA) updated its list of PTSD symptoms. They include: recurrent, involuntary, and intrusive memories of a traumatic event; nightmares; "dissociative reactions" (also called flashbacks); intense or prolonged distress after exposure to traumatic reminders; trauma-related thoughts or feelings; alterations in mood; distorted and negative beliefs about oneself (for example, "I am bad."); persistent emotions of fear, horror, anger, guilt, or shame; feeling alienated or detached from others; behavior that is irritable, aggressive, self-destructive, or reckless; problems concentrating or sleeping; feeling edgy or easily startled. According to the APA, if such symptoms persist for more than a month, the person experiencing them most likely has PTSD.[3]

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Q: Are there effective ways to treat PTSD?

A: A number of treatment techniques, sometimes combined with one another, are being used with varying degrees of success:

- Cognitive behavioral therapy, to help people recognize their ways of thinking, or "cognitive patterns," that keep them stuck
- Exposure therapy, to help people safely face what they fear, in order to learn to cope with it (virtual reality devices are often used to simulate a situation or setting in which the trauma took place)
- Eye movement desensitization and reprocessing, or EMDR, which combines exposure therapy with a series of guided eye movements that help people process traumatic memories and change the way they respond to those memories[4]
- Anti-anxiety medications and antidepressants can also ease the symptoms of PTSD; some people with PTSD whose symptoms include insomnia or recurrent nightmares find relief with a medication called prazosin that blocks the effect of adrenaline in the body[4]
- Osanetant, a medication that has been tested in humans to treat schizophrenia, and was found to be safe but ineffective, has recently been found to block fear memories in mice shortly after exposure to a trauma; it targets a distinct group of cells in the brain that controls the formation and consolidation of fear memories. According to Foundation Scientific Council member Kerry Ressler, M.D., Ph.D., who led the research at Emory University, osanetant shows potential to aid in preventing PTSD from developing if administered in the emergency room or battlefield, for example, before traumatic memories consolidate.[5]

Q: What are the characteristics of resilience?

A: In their 20 years of treating and studying trauma survivors, Dennis S. Charney, M.D., of the Icahn School of Medicine at Mount Sinai and Steven M. Southwick, M.D., of Yale School of Medicine identified ten common practices in people who have shown resilience in the face of extreme stress[6]:

- Maintaining an optimistic but realistic outlook
- Facing fear (ability to confront one's fears)
- Relying upon one's own inner, moral compass
- Turning to religious or spiritual practices
- Seeking and accepting social support
- Learning from and imitating sturdy role models
- Staying physically fit
- Staying mentally sharp
- Cognitive and emotional flexibility (finding a way to accept that which cannot be changed)
- Looking for meaning and opportunity in the midst of adversity

SOURCES:

1 U. S. Department of Veterans Affairs
2 National Institute of Mental Health
3 American Psychiatric Association (2013), *Diagnostic and Statistical Manual of Mental Disorders*, (5th ed.). Washington, DC
4 MayoClinic.org, April 15, 2014
5 "A Role for Tac2, NkB, and Nk3 Receptor in Normal and Dysregulated Fear Memory Consolidation," published online in *Neuron*, June 26, 2014
6 Steven M. Southwick, M.D. and Dennis S. Charney, M.D.: *Resilience: The Science of Mastering Life's Greatest Challenges,* Cambridge University Press, 2012

American Psychiatric Association (APA) Honors Brain & Behavior Research Foundation President Emerita **Constance Lieber** and Board Chair **Stephen A. Lieber**

A Special Presidential Commendation was presented to Mr. and Mrs. Lieber by APA President Jeffrey A. Lieberman, M.D., at its 167th Annual Meeting on May 5, 2014 in New York City. Dr. Lieberman, Psychiatrist-in-Chief at New York-Presbyterian Hospital/Columbia University Medical Center and Chair of the Department of Psychiatry at Columbia University College of Physicians and Surgeons, said the award was in recognition of the Liebers' "passionate and generous philanthropy and support of psychiatric research."

For more than a quarter of a century, Connie and Steve Lieber have provided unwavering moral and material support to unravel the mysteries of the brain, and to better understand and treat mental illness. Their frustration with the limited treatments available for their daughter, exacerbated by the stigma associated with mental illness, instilled in them the overwhelming conviction that what was needed above all was more scientific discovery into these illnesses. Since that time they have mobilized every resource imaginable to fund cutting-edge research and educate the public.

From the beginning, they believed that research was the best avenue to find meaningful and lasting solutions to alleviate the suffering caused by mental illnesses. Their work to support psychiatric research began in the early 1980s through their family foundation, the Essel Foundation. The Essel Foundation is one of two family foundations to fund the organization's overhead, so that 100 percent of donations for research are invested directly into scientific grants.

After attending one of Columbia University's early schizophrenia conferences in the early 1980s, they met Herbert Pardes, M.D., who was in the early stages of helping launch the Brain & Behavior Research Foundation and creating its Scientific Council. Mrs. Lieber joined the Foundation's Board of Directors in 1986 (the Foundation was then known as NARSAD or the National Alliance for Research on Schizophrenia and Depression) and went on to serve as its President for 18 years; she is now President Emerita. Mr. Lieber serves as Chair of the Foundation's Board of Directors.

The Liebers initiated prizes for outstanding achievement in psychiatric research with the Lieber Prize for Outstanding Achievement in Schizophrenia Research in 1987; two Lieber Prizewinners, Arvid Carlsson, M.D., Ph.D., and Paul Greengard, Ph.D., have gone on to win Nobel Prizes. They co-founded the Schizophrenia Research Center at Columbia University Medical School; the Learning Center at Columbia University, known as the Lieber Clinic; the Neuroscience program at Williams College, and the Lieber Institute for Brain Development at Johns Hopkins University.

2014 Klerman-Freedman Prizes

for Exceptional Research by NARSAD Young Investigator Grantees

Six Young Investigators received the Annual Klerman and Freedman Prizes on Friday, July 25th in New York City, in recognition of their exceptional research.

These two prizes pay tribute to Drs. Gerald L. Klerman and Daniel X. Freedman, whose legacies as researchers, teachers, physicians and administrators have indelibly influenced neuropsychiatry. They recognize exceptional clinical and basic research by young scientists who have been supported with NARSAD Young Investigator Grants—our hallmark program that enables aspiring young scientists with innovative ideas to garner pilot data and many times to go on to receive further funding once they have "proof of concept" for their work.

The prizewinners are selected by committees of the Foundation Scientific Council, a volunteer group of 146 distinguished scientists across brain and behavior research disciplines. This early recognition of their work by the Foundation's Scientific Council often serves as a precursor to further accomplishments, awards and prizes as well as to their establishment as Independent Investigators at their institutions.

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University of North Carolina School of Medicine

2014 Klerman Prizewinner for Exceptional Clinical Research

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

"The support provided by the NARSAD Young Investigator Grant has been critical in promoting my research career, allowing me to implement a study of my own design at a very early stage of my career. Furthermore, the award provided protected time for research during the vulnerable period of transition from clinical training; this support has allowed me to compete successfully for additional funding and progress to become an independent scientist."

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

Theodore D. Satterthwaite, M.D., M.A., an Assistant Professor of Psychiatry at the University of Pennsylvania School of Medicine, in Philadelphia, and an attending physician in the university's hospital, is being honored for his work using neuroimaging to identify the biological roots of major mental illness. For his NARSAD Grant project, Dr. Satterthwaite used neuroimaging to study impairment of the brain's reward system in both bipolar and unipolar depression. His findings identify specific dysfunctions that may represent distinct biomarkers (biological predictors) for future treatment interventions and also make it possible to distinguish between the two disorders, which are often hard to tell apart in the early stages of illness.

Unipolar and bipolar depression overlap in depressive symptoms, such as lack of enjoyment in normal pleasurable activities, but bipolar disorder also involves the presence of mania. This suggests that while dysfunction of the brain's reward system may be important in both illnesses, there are most likely both common and distinctive processes occurring in the brain.

In collaboration with Daniel Wolf, M.D., Ph.D, a 2005 NARSAD Young Investigator Grantee and recipient of the Foundation's 2009 Syndey R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research, Dr. Satterthwaite used functional magnetic resonance imaging (fMRI) to examine reward-system activation and connectivity. In the scanner, patients and healthy comparison subjects played a card-guessing game, winning or losing money on each guess, driving activation of the reward system. The brain's connectivity patterns at rest were also examined.

The study revealed that regardless of whether patients were diagnosed with unipolar or bipolar depression, greater levels of depressive symptoms were associated with diminished activation and resting connectivity of the reward system. This suggests that depression may have similar mechanisms of action in the brain regardless of clinical diagnosis. However, patients with bipolar depression had higher levels of reward-system activation and connectivity than those with unipolar depression, which is blunted in depressive episodes. It is this difference in reward responsiveness that has the potential to be a useful biomarker in the context of early diagnosis and potential new and differing therapies for relieving symptoms of both unipolar and bipolar depression.

Dr. Satterthwaite earned a master's degree in biology and an M.D. at Washington University in St Louis. He completed residency in psychiatry and postdoctoral training in neuropsychiatry at the University of Pennsylvania before joining the Penn faculty in 2012.

2014 Klerman Prize Honorable Mentions

Elena I. Ivleva, M.D., Ph.D.

Elena I. Ivleva, M.D., Ph.D., Assistant Professor of Psychiatry at the University of Texas (UT) Southwestern Medical Center at Dallas, is being honored for her NARSAD Grant project work that identified underlying mechanisms of schizophrenia and related psychotic disorders that may aid in future development of objective biomarker-based diagnostic tools.

In her 2010 NARSAD Young Investigator Grant project, Dr. Ivleva sought to characterize heritable brain alterations underlying the two main symptoms of schizophrenia, psychosis and cognitive dysfunction, specifically memory deficits. To learn how alterations in the system may contribute to psychosis, she used advanced brain imaging to examine the circuitry of both the hippocampus and the hippocampal–cortical system, which is known to mediate memory formation and is implicated in psychosis. She sought to identify how alterations in the system may contribute to psychosis. Her research revealed an overall decrease in activation in the circuitry during memory challenge in patients with schizophrenia and schizoaffective disorder as well as in their first-degree relatives, and extensive volume reductions in cortical and subcortical gray matter.

"The support from BBRF ... has moved me one step forward in devoting my effort to helping patients with psychotic illness and their families."

Dr. Ivleva completed an M.D. degree, psychiatry residency and a Ph.D. in neuroscience at the Voronezh State Medical Academy, in Russia, and a postdoctoral fellowship at UT Southwestern before being appointed to the UT faculty. She received the Foundation's 2011 Sidney R. Baer, Jr. Prize for Innovative and Promising Schizophrenia Research.

Aristotle N. Voineskos, M.D., Ph.D., FRCPC

Aristotle N. Voineskos, M.D., Ph.D., FRCPC is an Assistant Professor of Psychiatry at the University of Toronto and Koerner New Scientist and Head of the Kimel Family Imaging-Genetics Laboratory at the university's Centre for Addiction and Mental Health. He is being recognized for his NARSAD Grant project that demonstrated that repetitive transcranial magnetic stimulation (rTMS) substantially improved working memory performance in patients with schizophrenia.

Currently, there is no approved treatment for the cognitive impairments associated with schizophrenia, notably working memory deficits, which are an important predictor of functional disability. (Working memory is the short-term memory that makes it possible, for example, to remember phone numbers or other information needed for normal day-to-day activities.) In his 2010 NARSAD Grant research, Dr. Voineskos conducted a trial that showed significant improvement in working memory in 13 patients randomized to receive rTMS compared to 14 subjects who received inactive, or sham, treatment. A non-invasive treatment, rTMS applies magnets to the skull to stimulate brain sites associated with specific functions. The improvement of the rTMS-treated patients after four weeks of treatment rose to the level of healthy controls. Dr. Voineskos has been awarded a 2014 NARSAD Independent Investigator Grant to help confirm and extend these findings.

Dr. Voineskos earned M.D. and Ph.D. degrees at the University of Toronto, where he did a residency in psychiatry. He completed a research fellowship at Harvard University.

2014 Freedman Prizewinner for Exceptional Basic Research

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

"The NARSAD Young Investigator Grant gave me the support I needed to turn a daring project into reality. It allowed me to focus my efforts on a fundamental biology endeavor—the reprogramming of neurons and the circuits they form—while maintaining a long-term, disease-related perspective."

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

Denis Jabaudon, M.D., Ph.D., is an Assistant Professor of Neurosciences at the University of Geneva, Switzerland, and Senior Attending Physician in the Neurology Outpatient Clinic of the Department of Clinical Neurosciences at Geneva University Hospital. He is being honored for his NARSAD Grant project work that provides a first proof-of-principle for the postnatal reengineering of neuronal circuits in vivo. This work may have clinical relevance to repair or even prevent the "faulty wiring" of circuits that happens during very early brain development and underlies a variety of neurological disorders, including some forms of autism spectrum disorder.

Dr. Jabaudon's research focus is on the genetic mechanisms that control the identity of the wide variety of neuron types that make up the cerebral cortex and assemble to form circuits in an elaborate choreography during brain development. These precisely wired circuits allow us to perceive, understand, and interact with the world. He seeks to understand how genes instruct neurons to play a particular role and why that process sometimes dysfunctions. For example, cortical circuits mis-assemble in some forms of autism spectrum disorder (ASD) and genetically reprogramming neurons to reassemble into normal circuits could provide new therapeutic avenues for these disorders.

For the grant project work, Dr. Jabaudon and colleagues developed a novel gene delivery technique that triggered an "identity switch" in functional brain circuits in vivo. Using a combination of in vivo and ex vivo approaches, including the use of optogenetics,* they demonstrated that directed gene expression can reassign the "circuit identity" of cortical neurons. This work reveals that neurons and the circuits they form are not only more plastic than previously thought, but can in fact be manipulated to reverse-engineer specific functional circuits well after neuronal identity has been assigned.

Dr. Jabaudon's ultimate goal is to develop cell-based strategies for manipulating these programs to promote re-wiring and functional recovery from neurodegenerative diseases or after injury. One of his objectives is to identify molecular targets for the treatment and ultimate prevention of autism.

Dr. Jabaudon obtained his M.D. and Ph.D. degrees from the Universities of Lausanne and Zurich in Switzerland, where he studied mechanisms controlling synaptic transmission, the transmission of messages between nerve cells across the synapse, the narrow gap between neurons. After a neurology residency at Geneva University Hospital, he completed a postdoctoral fellowship at Harvard University, where he began his investigation of genetic control of cortical development.

* *Refer to glossary on page 28.*

2014 Freedman Prize Honorable Mentions

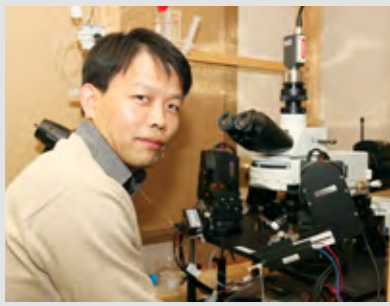
Mazen Kheirbek, Ph.D.

Mazen Kheirbek, Ph.D., is an Assistant Professor of Clinical Neurobiology at Columbia University and a Research Scientist at the New York State Psychiatric Institute. He is being recognized for findings on how circuits within the brain's hippocampal region contribute to emotional behavior and how they may be disrupted in anxiety disorders. His research has elucidated impairments in hippocampus function that appear to underlie the inability to discriminate among stimuli, often seen in anxiety disorders such as post-traumatic stress disorder and panic disorder. His findings offer a possible new approach to treatment.

In his 2010 NARSAD Young Investigator Grant project, Dr. Kheirbek used genetic tools to modulate the excitability of hippocampal neurons believed to play a role in how the brain distinguishes subtle differences between similar representations. He then targeted cell subpopulations in a region of the hippocampus called the dentate gyrus. He found that different parts of the dentate gyrus respond differently. The dorsal portion was required for encoding spatial information; the ventral portion was not needed for memory formation, but its activation robustly reduced anxiety. These results provide the first causal link between dentate gyrus activity and emotion. Moreover, they suggest that strategies to modulate the excitability of the ventral dentate gyrus may help to alleviate anxiety disorders.

Dr. Kheirbek received his Ph.D. in neurobiology from the University of Chicago and conducted postdoctoral studies at Columbia University.

Bo Li, Ph.D., M.Sc.



Bo Li, Ph.D., M.Sc., an Associate Professor at Cold Spring Harbor Laboratory, in New York, is being honored for his studies exploring the link between neural circuits and behavior. His research is helping to define the synaptic and neural-circuit mechanisms in the brain that regulate cognitive functions such as attention, learning and memory, and the dysfunctions in these mechanisms that may underlie major mental illnesses, including schizophrenia, depression and anxiety. Findings from his 2010 NARSAD Young Investigator Grant project revealed in exquisite detail the role of synaptic plasticity and neural circuitry in fear regulation and anxiety disorders.

The synapse is the tiny gap between neurons across which the cells dispatch and receive neurotransmitters, the brain's messengers. Synaptic plasticity* is the ability of the synapse to change in strength in response to stimuli. Synaptic plasticity is believed to serve as a cellular mechanism for learning and memory. Dr. Li worked with animal models to probe and manipulate fear response. He discovered and dissected synaptic plasticity induced by fear stimuli, and pinpointed a central neural circuit in the amygdala* that appears to store fear memories and control fear expression.

Dr. Li earned a Ph.D. in molecular and neuroscience at the University of British Columbia and did postdoctoral research at Cold Spring Harbor Laboratory and the University of California at San Diego.

"My NARSAD Young Investigator Grant has enabled me to investigate the link between genetic deficits, neural circuit changes and behavioral abnormalities that are associated with major psychiatric disorders."

** Refer to glossary on page 28.*

Finding a Way to Help and Heal

An Annual Event Honors a Beloved Son and Supports the Foundation's Research

Toward the end of his freshman year at the University of Minnesota, where he had hoped to lay the foundation for a career in architecture, Jonathon Robbins began to experience symptoms of schizophrenia. He didn't make it through his sophomore year.

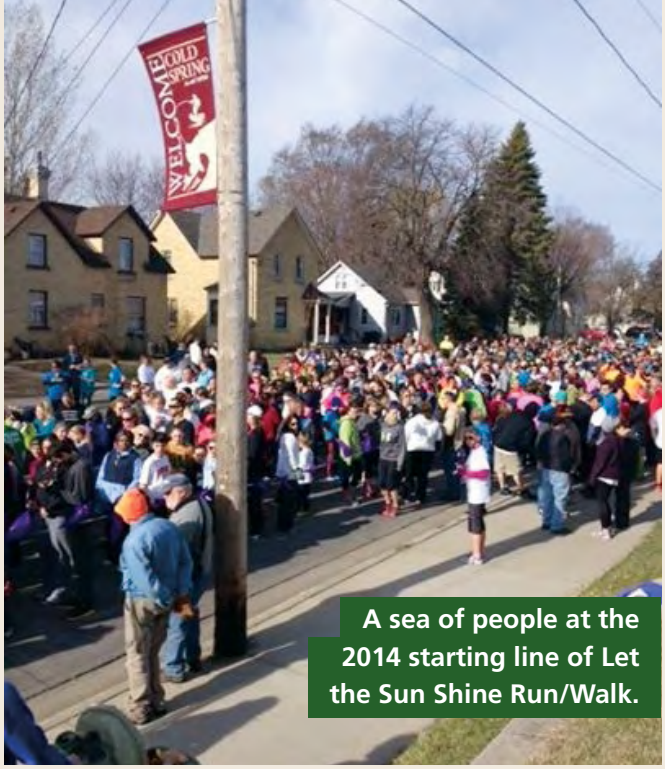
"He had everything going for him until his illness took hold," says Kathy Robbins of her son. "He went from being an outgoing, honor-roll student to a young man who didn't want to leave the house."

Jonathon began his struggle with delusions and depression. Heartsick at the worry he was causing his parents, Kathy and Curt, his younger sister, Arianna and younger brother, Jordan, Jonathon cut himself off from the people he loved most for a time. Until one night, after driving to Texas, presumably on the instruction of his voices, he came back home—a 48-hour round trip—and asked for help.

"When we took him to the hospital," Kathy says, "they told us he had caffeine-induced psychosis. I remember thinking, 'Well, I suppose there is such a thing.' But of course it was ridiculous."

The family at our daughter's graduation. We can't take a family picture without Jonathon. So our Jonathon bear wore a suit for the special occasion.

How does one cope with the death of a child? For the Robbins, their goal became finding a way to honor Jonathon and to help other families struggling with mental illness.



A sea of people at the 2014 starting line of Let the Sun Shine Run/Walk.

The hallucinations worsened. "One time when we were in church he became convinced the priest was telling him that he was bad," Kathy says. "He'd think the neighbor was talking about him, saying he was bad."

Such thoughts hounded Jonathon, despite his family's ceaseless efforts to dispel them. The family doctor put him on aripiprazole* (Abilify®), which helped reduce the symptoms but made him feel "weird," and he stopped taking it. Hospitalized once more, he finally received a definitive diagnosis. When the doctors thought Jonathon was stabilized, they released him. That day he went home and took his life. Jonathon was 22 years old.

"I kept wondering what would have helped Jonathon," Kathy says. "I thought maybe better medicine would have." She searched the Internet to learn more, and discovered the Brain & Behavior Research Foundation. "I knew we had to raise money for their research," Kathy says.

The Robbins are not wealthy people. Curt is a hospital maintenance worker and Kathy runs a day care center in her home. But they are rich in relatives and friends, whom they counted on to pitch in when they came up with the idea of holding a walk/run event. (Jonathon and Kathy had run marathons together.)

"My family's huge," says Kathy, the youngest of 12 children. "We were hoping 200 people would participate, maybe 100 of my family and 50 or so of our friends. We went from house to house asking them. We ended up with over 600 people taking part the first year."

The race, now an annual event, covers a 2.2 mile course, the distance selected to honor Jonathon's age when he died. The Robbins named it "Let the Sun Shine," because, says Kathy, "Jonathon was the sunshine in our lives."

The first event, held April 28, 2011, the anniversary of Jonathon's death, brought in more than $14,000, and it has grown each year. This past April, more than a thousand people converged on the Robbins' little home town of Cold Spring, Minnesota, where the race is held, raising $27,000. The money is donated to the Foundation's Research Partners program, which matches donors to scientists working in areas of the donors' particular interest.

Kathy Robbins adds a distinctive touch to "Let the Sun Shine." She makes signs for participants that honor the loved ones they are racing for, many of whom, like Jonathon, died as a result of mental illness. These "memory signs," as Kathy calls them, show the loved one's name, photo and perhaps some words of tribute: "Perfect granddaughter," "Your smile brought so much joy." The signs line the entire route of the race.

"I have to make sure I work on the signs on a day I feel strong," Kathy says. "I look at these people and I wonder why this had to happen." Her own consolation, she says, is the certainty that "Jonathon died knowing how much we loved him."

** Refer to glossary on page 28.*

In Memoriam: Paul H. Patterson, Ph.D.

FOUNDATION SCIENTIFIC COUNCIL MEMBER

The Foundation mourns the loss of a pioneer in neuroimmunology—the study of interactions between the nervous and immune systems and their links to mental illnesses, such as autism, depression and schizophrenia. Dr. Paul Patterson, who was the Anne P. and Benjamin F. Biaggini Professor of Biological Sciences at California Institute of Technology (Caltech), died at his home on June 25, 2014. He was 70 years old.

Instead of relying primarily on genetic alterations to study behavioral models of these mental illnesses, Dr. Patterson studied the role of environmental triggers. He developed groundbreaking animal models of maternal immune activation, models that are now widely used by dozens of laboratories.

An article in *The New York Times* on August 25, 2012—"An Immune Disorder at the Root of Autism" by Moises Velasquez-Manoff—cited Dr. Patterson's groundbreaking research: "The lesson here isn't necessarily that viruses and bacteria directly damage the fetus. Rather, the mother's attempt to repel invaders—her inflammatory response—seems at fault. Research by Paul Patterson, an expert in neuroimmunity at Caltech, demonstrates this important principle. Inflaming pregnant mice artificially—without a living infective agent—prompts behavioral problems in the young. In this model, autism results from collateral damage. It's an unintended consequence of self-defense during pregnancy."

Dr. Patterson is the author of the book "Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia and Depression" and he wrote a blog entry to bbrfoundation.org describing the book on Nov. 30, 2011: "… The heart of the book concerns the involvement of the immune systems of the pregnant woman and her fetus, and a consideration of maternal infection as a risk factor for schizophrenia and autism. … In the course of this discussion, I … explain how the immune system influences behavior, and how the brain regulates the immune system, looking in particular at stress and depression. Finally, I describe the promise shown by recent animal experiments that have led to early clinical trials of postnatal and adult treatments for patients with autism and related disorders.

My association with the Brain & Behavior Research Foundation, then known as NARSAD, started many years ago when I received the first of two grants to begin work on mental illness. These grants were particularly important to get projects going because the application did not require extensive preliminary results. This is unlike applications to the National Institutes of Health, where the research practically has to be already finished to get funding to do it!"

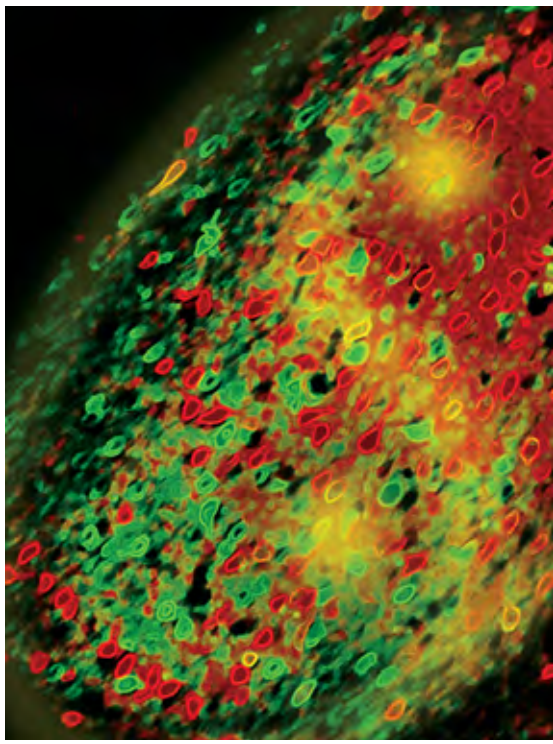
Dr. Patterson's group also tested various types of gene therapy for treatment of mouse models of multiple sclerosis and Huntington's disease, including novel viral vectors for delivery to the brain.

Dr. Patterson grew up in Chicago, attended Grinnell College in Iowa, and obtained his Ph.D. at The Johns Hopkins University in biochemistry. He then completed his postdoctoral appointment in neurobiology at Harvard Medical School before joining its faculty in 1973. Dr. Patterson joined Caltech as a biology professor in 1983 and became the Anne P. and Benjamin F. Biaggini Professor of Biological Sciences in 2005.

Creating New Possibilities for Treating Post-Traumatic Stress Disorder

NARSAD Grantees on the Leading Edge

Impressive progress is being made by Foundation-funded scientists to understand and more effectively treat post-traumatic stress disorder (PTSD). These researchers are addressing the relationship between traumatic experiences and the creation of long-lasting memories of the experiences that cause behavioral problems. Because of the "plasticity" of the brain ("neuroplasticity") as it constantly adapts to new experiences, a trauma can cause long-lasting changes to brain structures. Memories of the experience can be stored and then persistently retriggered, leading some traumatized individuals to overreact to slight stressors or unexpected events. Scientists are working hard—and making great progress—to understand how this happens within the brain and what makes some people more prone (or others more resilient) to developing a "post-traumatic stress" response.



Above: Specific neurons (here, colored red) located in the brain's central amygdala encode fear memory. Dr. Bo Li, who pinpointed these neurons, is learning how these memory traces are read out and translated into physical fear responses.

Victor Carrion, M.D., (following page) who received a NARSAD Young Investigator Grant in 2000, leads an innovative program of research at Stanford University Medical Center that focuses on the vulnerabilities of children and adolescents to stress and trauma. As the head of Stanford's Early Life Stress and Pediatric Anxiety Program, Dr. Carrion and his team have established a special relationship with the Caesar Chavez Academy in East Palo Alto, California, a middle school in a highly distressed urban setting (as featured in a segment of the PBS "News Hour" on March 4, 2014). Many pupils are homeless and most

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have witnessed or been the victim of domestic and/or street violence. Dr. Carrion estimates nearly a third of children from low-income, high-crime neighborhoods have symptoms of traumatic stress.

"Here, 'adverse childhood experiences' means suicide, drugs, sexual abuse, starving," Dr. Carrion says. "This is the constant life of these children. Not only do they live it, they have reminders of it in their own school."

In addition to working with the youth, he and his colleagues have been using functional magnetic resonance imaging (fMRI) brain scans to examine how stress can alter brain structures in the young, developing brain. They have confirmed that anomalies in the prefrontal cortex* (the brain's center for decision-making and high-level information processing) and in vital brain structures such as the amygdala and hippocampus (central in learning and memory) develop in some youths who have experienced trauma and/or chronic stress.

While the family situation of at-risk children is not something doctors can directly change, Dr. Carrion says children "can learn to cope if we teach them how." In the face of much skepticism, Dr. Carrion's team has shown that biofeedback (learned control over breathing or heart rate, for example) and "mindfulness" training can have a real impact.

Mindfulness training seeks to teach young people to stay in the present moment. This involves being actively aware of one's feelings (for example, through group "check-ins" in a therapy session) while also remaining focused on something specific and physiological, such as breathing in and out. In 2010, Dr. Carrion and colleagues published a treatment protocol called CCT, or Cue-Centered Therapy, for traumatized youths.

A key concept in CCT derives from the word "cue." It points to what doctors and researchers understand to be the brain mechanism underlying post-traumatic stress. In PTSD it is not the trauma itself, but the memory of it, that is causing harm. Over millions of years, we (and other mammals) have evolved a response to stress that features the release of stress hormones such as cortisol. This induces the "fight-or-flight" response. It's a healthy response to danger—but only when the danger represents a real threat.

For people with PTSD it is often difficult to "extinguish" traumatic memories. When a car backfires, it's normal to be startled, but not normal to fall to the ground and begin crawling on your belly, as a traumatized war veteran suffering from PTSD might do. One way of approaching the problem is to deal directly with the "cue" (or trigger) that touches off the traumatic memory—to "sensitize" a person to it through repeated exposure, effectively replacing the "fear" memory with a memory of these exposures that involve no harm or threat.

Over the last two years, **Bo Li, Ph.D., (opposite, bottom)** of Cold Spring Harbor Laboratory, 2014 Freedman Honorable Mention Prizewinner and 2010 NARSAD Young Investigator Grantee, has published remarkable findings that trace fear memories to a precise group of neurons in the central amygdala. Dr. Li was able to pinpoint these cells by training mice to respond to a harmless auditory cue in "Pavlovian" fashion. Whenever they hear a certain sound, which they are trained to associate with a mild foot shock, the mice freeze with fear. Once trained, the mice freeze whenever they hear the sound cue—even when they are not given a foot shock or exposed to any other discomfort. They are acting on the basis of their memory of the unpleasant experience. Dr. Li and other neuroscientists, including **Richard L. Huganir, Ph.D., (opposite, top)** a 1999 NARSAD Distinguished Investigator Grantee, want to know much more about the neural mechanisms behind this reaction, with an eye to moving beyond exposure therapy in attempting to counter it.

Using genetic techniques to "tag" the neurons specifically involved in the fear response in the mouse brain, Dr. Li and his team have recently shown precisely how these neurons in the central amygdala are connected via long-range nerve fibers

* *Refer to glossary on page 28.*

to the brainstem where the signal is translated into action: mouse muscle cells fire thousandths of a second after the cue is sounded. Precise neural and anatomical knowledge like this is very challenging to identify in the brain, and greatly advances the possibilities for more targeted and effective therapies.

In a bold program of research, Dr. Huganir, of Johns Hopkins University and an Investigator of the Howard Hughes Medical Institute, has been working since 2010 on ways to completely erase fear memories. Dr. Huganir notes that "erasure," for all practical purposes, is what occurs in people with PTSD when "exposure" therapy succeeds: cues for an unwanted traumatic memory are effectively reprogrammed or replaced, so that they are associated with unthreatening thoughts.

This reprogramming is possible because of the brain's plasticity, as mentioned in the opening of this article. As we move through life, second by second, day by day, our brain is constantly being reshaped, in a way that directly reflects our experiences. "By sculpting connections between neurons, learning creates new circuits, making new connections, strengthening some, weakening or removing others," Dr. Huganir explains. "We've found that you can remove receptors from a synapse or add them to a synapse, and that this affects the strength of the connection. Or, if you remove a specific mechanism for adding receptors to a synapse, you can affect the ability of mice to retain a memory. They become forgetful."

This is the train of thought that has led to Dr. Huganir's remarkable work since 2010 on erasing fear memories. When the brain learns something, nerve cells are adding receptors around the synapses that connect neighboring cells, making connections stronger. Fear memories are learned by neurons in the amygdala. Dr. Huganir has learned in his mouse studies that a window in time opens about a day after a fearful memory is encoded and closes, usually within a week. During this period, a common type of glutamate receptor on nerve cells in the amygdala is replaced with a rare receptor subtype. (Both are variants of so-called AMPA receptors.) The rare subtype is unstable, and Dr. Huganir's experiments show it can be removed entirely by activating another brain receptor called mGluR1.* When this happens, the mechanism by which a fear memory is encoded is reversed and the fear memory is erased.

Dr. Huganir has found that when behavioral therapy works in recently traumatized animals, it activates the mGluR1* pathway. He suspects that when this happens in the human brain, as in the mice in his experiments, the rare AMPA receptor subtype is destabilized, keeping the linkage between external cues that trigger a memory of a trauma and cause an overreaction in the stress system from fully forming. The caveat, he notes, is that the intervention must occur within that narrow window after a traumatic or stressful event—a day to a week after.

Dr. Huganir's team is looking for ways to re-open or extend that very specific time window. He envisions a time when behavioral therapy can be combined with medications to activate the mGluR1* pathway, even beyond the brief time after a traumatic event, to prevent bad memories from forming.

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At a private dinner on April 30th at Christie's auction house, the Brain & Behavior Research Foundation honored four individuals with Productive Lives Awards. These awards are presented to remarkable people who have devoted their energy and formidable talents within their respective professions to help those living with mental illness realize their potential and live full, productive lives.

bbrfoundation.org/2014-productive-lives-awards


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This year's recipients are:

Francis S. Collins, M.D., Ph.D., Director of the National Institutes of Health (NIH)

Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH)

Eric R. Kandel, M.D., University Professor and Fred Kavli Professor and Director of the Kavli Institute for Brain Science at Columbia University and a Senior Investigator at the Howard Hughes Medical Institute

Judy Collins, Award-winning Singer/Songwriter and Social Activist

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1. Susan Lasker Brody, Member of the Foundation's Board of Directors
2. Dr. Thomas R. Insel recieving his award from Dr. Jeffery Borenstein, President & CEO of the Foundation
3. Dr. Francis S. Collins and Judy Collins, both recipients of the Productive Lives Awards
4. Dr. Herbert Pardes, President of the Foundation's Scientific Council, addressing the guests

5/8. Foundation information alongside Christie's artwork

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New Treatments/ Therapies

Molecule Found That Could Help Diagnose and Treat Mental Illness

Alon Chen, Ph.D., of the Weizmann Institute in Israel, and a 2013 NARSAD Independent Investigator Grantee, has led a team that identified the unique "fingerprints" of a molecule called miR135, which acts on serotonin-producing nerve cells in the brain. The researchers found that people who suffered from depression had unusually low miR135 levels in their blood. This suggests that miR135 could be a useful therapeutic molecule—both as a blood test for depression and related anxiety disorders, and as a target whose levels might be raised in patients. Based on this research, a pharmaceutical company is already working on developing a medication and diagnostic technique for testing in clinical trials.

Source: *Neuron,* June 19, 2014, online

Insight on Brain Wiring May Help Treat Autism and Schizophrenia

At McGill University, a team of scientists led by Edward Ruthazer, Ph.D., a 2007 NARSAD Young Investigator Grantee, found surprising new information about how the brain rewires and fine-tunes its connections. By studying tadpole brains, which are transparent, the team could clearly see that when flashes of light were pulsed out of sync, the brain cells lost their ability to make other cells fire. This also caused neurons to dramatically increase the growth of new branches in search of better "partners." An increased understanding of the rules that control healthy brain wiring will help advance treatments for brain injuries and developmental disorders such as autism and schizophrenia.

Source: *Science*, May 27, 2014

Pediatric-Specific Treatment for Children with Bipolar Disorder

A new study co-led by Daniel Dickstein, M.D., a 2006 NARSAD Young Investigator Grantee at Brown University, has found that children with bipolar disorder have greater activation in the right amygdala—a brain region important for emotional reaction—than adults with bipolar disorder have when viewing emotional faces. The research suggests that children might benefit from treatments that target emotional face identification, such as computer-based "brain games" or group and individual therapy. This is the first study to directly compare brain changes between children and adults with bipolar disorder, using data from 100 functional MRI (fMRI) brain scans, and may point toward crucial early intervention techniques.

Source: *JAMA Psychiatry*, June 18, 2014, online

Glossary

aripiprazole (Abilify®): *(p.19)* A second-generation antipsychotic medication often used for the treatment of schizophrenia and bipolar disorder; also used as an add-on treatment for depression.

dopamine neurons: *(p.3)* Neurons specifically activiated by dopamine, a neurotransmitter in the brain that can activate five types of dopamine receptors (D1, D2, D3, D4, D5). Dopamine 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.

excitatory neurons: *(p.5)* Most neurons in the human brain are excitatory: beyond a given threshold, a stimulus conveyed by a neurotransmitter (for instance, glutamate, the most common) will cause such a cell to fire. If not for their modulation by a much smaller number of inhibitory neurons, the brain would "seize up," as it does in major epileptic episodes.

ion channel: *(p.3)* A large, pore-like protein lodged in the membrane of a cell, whose opening and closing enables charged atoms (of, for example, sodium, potassium or calcium) to flow into and out of the cell. In brain cells, this influences when and for how long nerve cells "fire."

mGluR1: *(p.23)* A type of nerve-cell receptor that enables the excitatory neurotransmitter glutamate to interact with the cell. One set of experiments in mice has suggested that after a fear memory has formed in the amygdala, activation of mGluR1 can reverse the process in which the fear memory is encoded, leading to erasure of the memory.

NMDA (N-methyl-D-aspartate) receptors: *(p.8)* Nerve-cell receptors or docking ports located on the surface membrane of a class of neurons in the brain that are sensitive to excitatory neurotransmitters, mainly glutamate. NMDA receptor dysfunction may be linked to impaired brain plasticity, memory formation and the negative symptoms of schizophrenia.

optogenetics: *(pp.3, 16)* A new technology developed at the lab of Karl Deisseroth, M.D., Ph.D., with the early support of a NARSAD Grant. Optogenetics enables research scientists to use colored laser light to switch individual neurons "on" and "off" in the brain and to observe the corresponding effects on behavior in living animals. This technology makes possible a new generation of experiments aimed at identifying specific circuits involved in brain and behavior disorders.

prefrontal cortex: *(pp.5, 22)* A vital region of the brain that is responsible for executive function: orchestration of thoughts and actions in accordance with internal goals; ability to differentiate among conflicting thoughts—determine good and bad, better and best, same and different, future consequences of current activities, prediction of outcomes, expectation based on actions, etc.

subchronic stress: *(p.5)* Minor or moderate stress that persists over a period of time but does not cause adverse behavioral or psychiatric symptoms in most individuals. In animal models of human brain and behavior disorders—for instance rodent models of human depression or anxiety—researchers sometimes find it valuable to compare the impact of a small or moderate source of stress with the impact of severe stress. This sheds light on levels of stress that are sufficient to cause behavioral symptoms in particular individuals.

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