

Mood Disorders:  
Restoring a Delicate Balance

Understanding and  
Preventing Suicidal Behavior

# Brain & Behavior

M A G A Z I N E

DECEMBER 2019



BBRF Grants that Helped Build a Foundation  
for Rapid-Acting Antidepressants

# PRESIDENT'S LETTER



This issue of *Brain & Behavior Magazine* features a number of articles that highlight the impact that science funded by BBRF is having on the field, with broad implications for improved treatments, methods of prevention, and potentially, cures for brain and behavior disorders.

At our recent fall Symposium and Awards Dinner, BBRF honored nine outstanding scientists for their contributions to the advancement of our understanding and treatment of depression, ADHD, bipolar disorder, and schizophrenia. Their work is distinguished by their devotion to finding innovative new therapies that will improve care for those living with mental illness, as well as their efforts to seek preventive and diagnostic tools for the future. Read about these special events on page 10.

A wonderful example of the impact of BBRF can be found in our *Transformative Grants* article (page 4), which shows the value of our grants over an extended period of time. Most importantly it shows that real progress is being made. Over the past 20 years BBRF awarded 90 grants totaling more than \$6.5 million which helped build the scientific foundation for rapid-acting antidepressants, the first two of which were approved by the FDA this year. Because of the remarkable expertise of our Scientific Council and our ability to nurture the best people at the beginning of their careers, the funds we direct to them have a huge multiplier effect. We expect the search for rapid-acting antidepressants to continue—and we share the aspiration of researchers to develop a number of such agents that carry minimal side effects and can work in people with a range of psychiatric conditions.

This issue's *Pathways to the Future* article (page 16) profiles the work of Dr. Hilary Blumberg, who is passionate about caring for patients living with psychiatric conditions as well as conducting cutting-edge research to get to the bottom of why they are ill. By studying subtle brain changes that imaging has revealed in mood disorders, she is hoping to develop ways to predict suicide risk. While this research is still in developmental stages, it could pave the way to better diagnosis and treatments.

Our *Advice* article (page 27) conveys valuable information for parents, relatives, and friends who may be worrying about loved ones who they believe are either contemplating suicide or who have engaged in suicidal behavior. We interview Dr. David Brent of the University of Pittsburgh, a 2001 BBRF Distinguished Investigator and winner of the 2006 Ruane Prize. He is one of the nation's leading experts on suicide.

This issue's *Research Partners* story on page 22 focuses on how giving through the Research Partners program and supporting science through your alma mater can help advance mental health research. This article once again shows how an impressive list of grantees, carefully selected by our Scientific Council, accomplished amazing things over time.

We are deeply grateful for your ongoing support. Together, we will continue to fund innovative and impactful research that will drive the field forward. Our shared goal of a world free from debilitating mental illnesses relies first and foremost upon you, our donors—in partnership with the numerous scientists chosen by the BBRF Scientific Council—who are working to transform your donations into improved treatments, methods of prevention, and ultimately cures for our loved ones.

I am inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing generous support.

Sincerely,

A handwritten signature in black ink that reads "Jeff Borenstein". The signature is written in a cursive, flowing style.

**Jeffrey Borenstein, M.D.**

*100% percent of every dollar donated for research is invested in our research grants. Our operating expenses and this magazine are covered by separate foundation grants.*

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Over Two Decades, 90 BBRF Grants  
Helped Build a Scientific Foundation  
for the First Rapid-Acting  
Antidepressants







## **I**N THE SPRING OF 2019, THE

Food and Drug Administration granted approval for two breakthrough medicines that act rapidly to alleviate symptoms of major depression. Esketamine, a drug administered via a nasal spray, was approved for use in treatment-resistant major depression. Weeks later, brexanolone, administered intravenously, was approved for use in postpartum depression.

Both events are milestones.

*Brexanolone* is the first medicine ever approved specifically to treat depression that begins just before or in the months following childbirth. Its beneficial effects are usually felt within about 2 days of administration.

*Esketamine* is the first antidepressant with a novel mechanism of action to be approved since the FDA's 1959 approval of imipramine. Esketamine's beneficial effects—most notably, in patients who have not been helped by multiple existing antidepressant treatments—have been described as profound and astonishing, often beginning within an hour or two after administration. (Widely prescribed SSRI antidepressants typically take weeks or months to provide relief.)

Ninety grants awarded by BBRF over more than two decades and totaling over \$6.5 million have

substantially contributed to the development of these first two rapid-acting antidepressants. This record of productive grant-making can be traced back to two initial grants. One was a 1997 BBRF Independent Investigator award to **John H. Krystal, M.D.**, of Yale University, which supported the study of brain circuit mechanisms underlying the effects of ketamine. The other was a 1995 BBRF Young Investigator award to **Cynthia Neill Epperson, M.D.**, then also at Yale, for her early study of conventional antidepressant treatments in postpartum depression.

## **BASIC SCIENCE LEADING TO BREXANOLONE**

Dr. Epperson's grant marked the beginning of a multiyear quest that led from analyzing the effects of conventional antidepressants in women with postpartum depression to the search for more effective therapeutic options. In addition to the severe pain and suffering postpartum depression causes new mothers—about 10%–15% are affected—it is also associated with elevated suicide risk and is known to have profound effects on mothers' ability to care properly for their newborns. As historic longitudinal research led by BBRF Scientific Council member, prizewinner, and multiple grant recipient **Myrna Weissman, Ph.D.**,

has shown, children of mothers with untreated depression have elevated risk of longer-term behavioral and psychiatric disorders as they move through childhood and adolescence.

The research performed by Dr. Epperson, who received three BBRF grants from 1995 to 2005, and others, ultimately revealed the possible role of the inhibitory neurotransmitter GABA in postpartum depression. Working with Dr. Krystal and colleagues in the Yale Magnetic Resonance Center, Dr. Epperson was able to map changes in cortical GABA levels across the menstrual cycle and in postpartum women. Brexanolone enhances the activity of one of the cellular receptors of GABA, which is repressed due to hormonal action following childbirth. This may be part of the mechanism responsible for symptoms in postpartum depression.

Another member of the team that performed clinical tests of brexanolone, **Steven Paul, M.D.**, a member of the BBRF Scientific Council, is a pioneer in the study of the GABA receptors and their modulators. **Handan Gunduz-Bruce, M.D.**, a 2003, 2005, and 2007 BBRF Young Investigator, of Yale University, was also part of the research team that tested brexanolone.





Postpartum depression is associated with increased suicide risk and can profoundly affect a mother's ability to care for her newborn.

### **BOLD EARLY RESEARCH ON KETAMINE**

The Foundation this year awarded its Colvin Prize for Outstanding Achievement in Mood Disorders Research to Dr. Krystal, a three-time BBRF grantee and member of the BBRF Scientific Council, and his mentor and collaborator, **Dennis S. Charney, M.D.**, an emeritus Scientific Council member. Each of Dr. Krystal's BBRF grants has supported work pertinent to the search for rapid-acting antidepressants, while Dr. Charney's 2007 Distinguished Investigator grant supported the first clinical test of intranasally delivered ketamine for treatment of resistant major depression.

At this fall's BBRF Mental Health Symposium, Drs. Krystal and Charney recounted the circumstances that led them, together, to initially test ketamine in a small group patients with major depression. Dr. Charney had long been studying the two neurotransmitter systems—serotonin and norepinephrine—whose function was thought to be affected by so-called monoamine antidepressants. (These include SSRIs such as Prozac, Paxil, and Zoloft and SNRIs such as Cymbalta and Effexor. These medicines, respectively, elevate levels of serotonin and norepinephrine in the brain, thought to generate therapeutic effects.)

Looking closely at the mechanisms of action of SSRIs and SNRIs, Dr. Charney began to realize that “we had arrived at a kind of conceptual crisis.”

For example, their research revealed that depleting serotonin in healthy people did not lead those people to become depressed. It was the same when they depleted norepinephrine, and also dopamine, another neurotransmitter. So it was not a simple deficit in these brain chemicals that was causing depression. Something more complicated was going on.

Dr. Krystal, who trained with Dr. Charney, also had a lab at Yale in the late 1990s. He describes how “I used to go up to his office at the end of the day and we’d toss around ideas for research studies.” One day, they had a brainstorm. As Dr. Krystal tells it: “We said, what if the pathology of depression doesn’t lie in the norepinephrine and serotonin systems? What if these are systems that can be recruited to try to treat depression—but are not the *source* of the problem?”

This change of perspective led them to begin thinking about other neurotransmitter systems and their cellular receptors. Specifically, they thought about glutamate and GABA—which together mediate the bulk of signaling in the brain’s cortex and limbic systems. “We thought: what would be the best way to probe the role of glutamate in depression?” Glutamate is by far the most prevalent excitatory neurotransmitter. Excitation is what causes a neuron to fire, the essential action in cell-to-cell communication. GABA is an inhibitory neurotransmitter whose crucial function is to apply a braking action to excitation. If there is too much excitation, the brain can seize up, as it does in epilepsy.

Dr. Krystal, in his own lab, had been working on glutamate pharmacology, and was studying the drug ketamine, an anesthetic, as a tool for studying aspects of psychosis in schizophrenia. This was the subject of Dr. Krystal’s 1997 BBRF Independent Investigator grant.

Dr. Charney continues the story. “We wanted to push the envelope, and in one of our late-night meetings we had the thought that maybe NMDA receptors [which engage with glutamate] are involved in depression.” It so happened that the drug that Dr. Krystal was studying, ketamine, was thought to inhibit the activity of NMDA receptors.

Drs. Charney and Krystal decided to test ketamine at a very low “sub-anesthetic” dose in a small group of depressed patients. The dose was critical, since ketamine at high dosages was known to cause dissociative symptoms—“out-of-body” experiences that are similar to those sometimes experienced by people with psychosis. Ketamine was also known to be addictive. Although Dr. Krystal became interested in the drug as a way of experimentally probing the biology of psychosis and schizophrenia, he and Dr. Charney would now try to harness it at very low doses as a therapeutic.

The dose they agreed upon for the pilot study was quite low—but as they would learn, not low enough to prevent ketamine from having an impact on seven severely depressed patients in their initial double-blinded, placebo-controlled trial, conducted at the VA Connecticut Healthcare System in West Haven, CT. Most of the participants responded, and with a minimum of side effects. “The antidepressant response was apparent within 72 hours,” Dr. Charney remembers, “and in some cases, within just a few hours. We were smart enough to know that maybe we were on to something—but with only seven patients we weren’t positive.”



John H. Krystal, M.D.



Cynthia Neill Epperson, M.D.



Dennis S. Charney, M.D.



Carlos Zarate, M.D.



Husseini K. Manji, M.D.

**“I am struck by how BBRF grants played a part in the development of science in this area, across generations of scientists. Dennis Charney was my mentor. I mentored Neill Epperson, Handan Gunduz-Bruce, and Gerard Sanacora. BBRF grants were ways that we could help our mentees get a start in science and they went on to make major contributions in the field.”**

**—John H. Krystal, M.D.**

In 2000, Drs. Charney, Krystal and colleagues published a paper in *Biological Psychiatry* announcing their results. In the meantime, they continued to study ketamine’s antidepressant potential. “While ketamine is a short-acting drug, we were showing that at 3 days, 4 days, even 7 days in some, a response was still there,” Dr. Charney says. “We believed it—but almost nobody else did. So when we published the paper, it kind of sat there. Other groups didn’t replicate the findings.”

#### **‘PEOPLE REALLY STARTED BELIEVING IN KETAMINE’**

In 2000, Dr. Charney left Yale to lead the Mood Disorders and Anxiety Program at the National Institute of Mental Health. “I had a great group there,” he recalls, “and I suggested to [Drs.] **Carlos Zarate** and **Husseini Manji** that we needed to try to replicate that initial ketamine finding. That led to the second study, published in 2006.”

In 2005, Dr. Zarate was awarded a BBRF Independent Investigator grant to perform this work. His NIMH collaborator, Dr. Manji, had been awarded the Foundation’s Falcone Prize in 1999—the predecessor of the Colvin Prize for mood disorders research. He was a member of BBRF’s Scientific Council, as, by this time, were Drs. Charney and Krystal. As Dr. Zarate explains, the 2006 study with Drs. Charney and Manji went

beyond the 2000 Charney-Krystal paper in that it tested ketamine in treatment-resistant patients with major depression—participants who had in fact tried six or more other antidepressant treatments but had not been helped. The onset of response for these patients was within two hours, Dr. Zarate says. “Ever since, the field has moved rapidly forward.”

With continued BBRF grant support, Dr. Zarate, who was awarded BBRF’s Colvin Prize for his work on rapid-acting antidepressants in 2011, was able to push the line of research further. He was able to demonstrate for the first time that patients with treatment-resistant bipolar depression can respond to ketamine within one hour. Subsequently, his team was able to replicate this finding. “The Brain & Behavior Research Foundation has had an important impact on my career and permitted me to pursue a line of research that will hopefully help the field in developing next-generation treatments for our patients that are more efficacious and work more rapidly than existing treatments,” he says.

Dr. Zarate and his colleagues believed that if ketamine was given under carefully controlled hospital conditions, and to depressed people who had run out of treatment options, it might prove beneficial. “The key in generating interest in the study of ketamine was when we replicated the 2006 results some time later,



and then again in a third study,” he says. “People really started believing in ketamine’s rapid antidepressant efficacy.” Then, in early 2013, a larger NIMH-funded study with ketamine in treatment-resistant depression was completed and essentially confirmed the results of these earlier studies.

## MAKING A KETAMINE-BASED MEDICINE

There still was critical work to do. Following the lead of Dr. Charney’s team, which demonstrated the feasibility of intranasal delivery of ketamine, a team at Janssen Pharmaceuticals took up the work. Janssen was a subsidiary of Johnson & Johnson, where Dr. Manji had moved from NIMH to head global therapeutic neuroscience research. Now Dr. Manji and colleagues worked on a molecule called esketamine, a chemical derivative of ketamine, with the aim of bringing it to market for treatment of resistant depression.

In the spring of 2018, the Janssen-led team tested esketamine’s effects in 68 patients, aged 19–64, with severe depression and considered at imminent risk of suicide. All participants in the trial were voluntarily hospitalized and received standard-of-care medications for their depression. Importantly, all patients’ symptoms improved during the trial. But symptom reductions were greatest and most rapid among those who also received intranasal esketamine twice weekly, instead of a placebo. In addition to Dr. Manji, the team included **Wayne Drevets, M.D.**, and **Gerard Sancora, M.D., Ph.D.**, and the paper’s lead author, **Carla M. Canuso, M.D.**, a 1998 BBRF Young Investigator who was senior director of clinical development at J&J. Dr. Drevets, a 1999 Independent Investigator and 1996 Young Investigator, was awarded the Colvin Prize in 2014. Dr. Sancora, a professor at Yale, is a 2014 BBRF Distinguished Investigator, 2007 Independent Investigator, and 2001 and 1999 Young Investigator.

When the FDA’s advisory panel met to assess intranasal ketamine in early 2019, it considered this and nine other clinical studies, including five Phase 3 randomized, placebo-controlled studies in patients with treatment-resistant depression. The esketamine product recommended for approval was marketed under the name Spravato and took the form of a nasal spray, packaged in a delivery device that would contain two doses of 14 mg each.

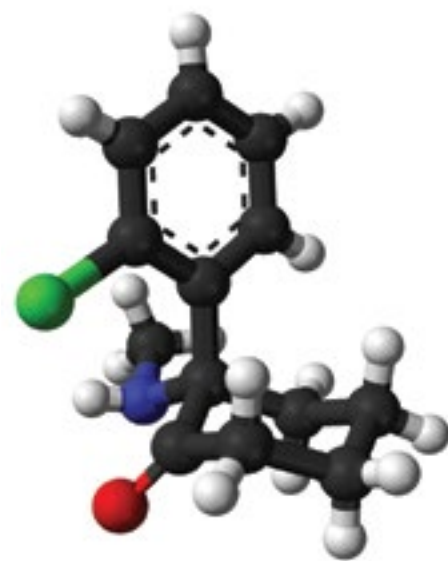
All the while, BBRF grants continued to support researchers investigating esketamine’s mechanism of action as well as other potential applications, not only in bipolar disorder but possibly in PTSD and other mood disorders as well.

A study by Dr. Zarate and colleagues including **Todd Gould, M.D.**, a three-time BBRF grantee, suggested in 2018 that another receptor in addition to the NMDA receptor—another glutamate receptor called the AMPA receptor—might also be involved in ketamine’s therapeutic mechanism. They also found evidence that a metabolite of ketamine called HNK might be the key to its antidepressant effects. This work remains under study, as is research by a Stanford University team that included BBRF Scientific Council member and 2005 Falcone Prizewinner **Alan Schatzberg, M.D.**, 2014 and 2009 BBRF Young Investigator **Carolyn Rodriguez, M.D., Ph.D.**, and **Nolan Williams, M.D.**,

which suggested in 2019 that ketamine cannot exert an antidepressant effect without engaging the body’s internal opioid system. This study was supported by Dr. Williams’ 2016 BBRF Young Investigator award.

The secret to ketamine’s remarkable antidepressant effects—which are experienced by about 70% of patients with treatment-resistant major depression—remains to be discovered. So too whether it will prove effective as a preventive in patients at very high risk of suicide, and separately, whether it can be used as a treatment for depressed patients who have not proven resistant to other treatments, as well as for patients with other disorders including PTSD.

BBRF grants continue to support this research, which will likely inform still other efforts to discover additional rapid-acting agents for depression and other disorders. A new stage in the battle against depression and other disorders has surely begun. ❖ **PETER TARR**



The ketamine molecule.

## EVENTS

# Celebrating the Power of Neuroscience, Research, and Humanitarian Efforts to Transform the Lives of People Living with Mental Illness



**CLOCKWISE FROM TOP LEFT:**

**1.** Dr. Robert Hirschfeld, Dr. Alan Brown, Dr. John Krystal, Dr. René Hen, Dr. John McGrath, Dr. Dennis Charney, Dr. James Kesby, Dr. Stephen Hinshaw, Dr. William Carpenter, Dr. Sophia Frangou, and Dr. Herbert Pardes. **2.** Dr. William Carpenter, Dr. Herbert Pardes, Cynthia Germanotta, and Dr. Jeffrey Borenstein. **3.** Standing L to R: Janet Susin, Maria Ceraulo, Mary Rossell, Jeffrey Peterson, and Dr. Rob Laitman; Seated L to R: Rob Elliott, Dr. Beth Elliott, Will Socolov, Sheila Scharfman and Dr. Ann Laitman.



## THE DAY BEGAN AT THE KAUFMAN MUSIC CENTER IN NEW YORK CITY

where the BBRF 2019 Outstanding Achievement Prizewinners presented updates on their research discoveries. The Prizewinners are selected by special committees of the BBRF Scientific Council. The symposium was moderated by Dr. Robert Hirschfeld, a BBRF Scientific Council Member who is a Professor of Psychiatry and is the DeWitt Wallace Senior Scholar in the Department of Psychiatry at Weill Cornell Medical College.

Dr. Alan Brown kicked off the symposium with his presentation *Early-Life Determinants of Schizophrenia & Other Psychiatric Disorders*. Dr. Brown's principal area of research is the epidemiology of prenatal risk factors for schizophrenia and other psychiatric disorders. In his presentation he discussed his current efforts to better understand how various risk factors might be involved in causing schizophrenia and other psychiatric disorders, estimate the degree to which they contribute to the illness, and to then apply this knowledge to generate interventions for prevention and treatment.

The second presentation, *Thalamo-Cortical Interactions in Cognition*, was given by Dr. Christoph Kellendonk. Dr. Kellendonk presented data from his mouse studies that establish a causal relationship between thalamic function and working memory, a key cognitive deficit in patients with schizophrenia. His mechanistic studies suggest that the thalamus interacts with the prefrontal cortex to sustain cortical activity necessary for working memory.

Dr. John McGrath spoke about *Preventing Schizophrenia—'Thinking the Unthinkable.'* In the last two decades, substantial progress has been made in understanding the epidemiology of schizophrenia. With respect to risk-factor epidemiology, several potentially modifiable factors have been linked to the risk of schizophrenia (like early cannabis use, trauma exposure, paternal age, low vitamin D levels, prenatal infection, and obstetric complications). Dr. McGrath suggested that it is now time to sharpen our hypotheses and design the next generation of studies to refine our understanding of the modifiable risk factors for schizophrenia. He stated his conviction that the primary prevention of schizophrenia is a tractable research question of great public health importance.

Next, Dr. James Kesby discussed *Decision Making & Neuropsychiatry: What Can We Learn from the Decisions We Make?* In schizophrenia, increased dopamine activity in the associative striatum is present prior to diagnosis and is central to the expression of psychotic symptoms. However, the associative striatum also integrates cortical inputs that are critical for the decision-making impairments in schizophrenia. According to Dr. Kesby, this makes the associative striatum an interface between psychotic and cognitive symptoms, providing a tantalizing opportunity for interventions that improve a broader spectrum of symptoms.

## 2019 PRIZEWINNERS

### PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH

Honoree: William T. Carpenter, Jr., M.D.  
Honorary Tribute: Cynthia Germanotta and Born This Way Foundation

### LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Alan S. Brown, M.D., M.P.H.  
Columbia University Irving Medical Center  
New York State Psychiatric Institute

John J. McGrath, M.D., Ph.D.  
The University of Queensland / Queensland Centre for Mental Health Research

### MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Christoph Kellendonk, Ph.D.  
Columbia University Irving Medical Center  
New York State Psychiatric Institute

James P. Kesby, Ph.D.  
The University of Queensland

### COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Dennis S. Charney, M.D.  
Icahn School of Medicine at Mount Sinai

Sophia Frangou, M.D., Ph.D.,  
F.R.C.Psych  
Icahn School of Medicine at Mount Sinai

John H. Krystal, M.D.  
Yale University

### RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

Stephen P. Hinshaw, Ph.D.  
University of California, Berkeley  
University of California, San Francisco

### GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE

René Hen, Ph.D.  
Columbia University / New York State Psychiatric Institute



Dr. Dennis Charney's presentation, *The Shape of Discovery: Ketamine for Treatment-Resistant Depression*, focused on a few questions about the process of discovery which included: What types of environment facilitate discovery? What is the optimal size of research groups? How did the science come together that led to the initial trials? What opposition existed? And finally: What was the initial reaction?

Following a lunch break a keynote presentation entitled *New Thoughts About Mental Illness: Implications for Discovery & Treatment* was given by Dr. William T. Carpenter, Jr., the winner of the 2019 Pardes Humanitarian Prize in Mental Health. The Pardes Humanitarian Prize in Mental Health recognizes an individual or organization whose extraordinary contribution has made a profound and lasting impact by improving the lives of people suffering from mental illness and by advancing the understanding of mental health. In his presentation Dr. Carpenter discussed how deconstructing psychiatric syndromes provides opportunity for further discovery.

The next presentation was *Resilient Brains: Adaptive Brain Mechanisms in Bipolar Disorder*, given by Dr. Sophia Frangou, in which she discussed the many factors that may contribute to resilience in relatives of people with bipolar disorder. These can be psychological (e.g., good coping skills), social (e.g., supportive relationships), and biological. She has focused on identifying the biological "signature" of resilience by studying differences in brain anatomy and function between patients and their well relatives. Her research suggests that it is possible to find biomarkers of disease and resilience to bipolar disorder, paving the way for the development of interventions that may mitigate the risk of this disorder.

Dr. John Krystal's presentation *Ketamine: Imagining New Ways to Treat Depression* highlighted the rationale for the initial ketamine study, the initial findings in depressed patients, and the subsequent clinical studies that have shaped our understanding of the role of ketamine in the management of treatment-resistant symptoms of depression and potentially other indications (suicide risk, PTSD). Dr. Krystal suggested that ketamine may be the prototype for a new class of rapidly acting antidepressant medications that build from what the field is learning about ketamine.

Dr. Stephen Hinshaw spoke about *Developmental Psychopathology & Stigma Reduction: A Synthesis* in which he highlighted the rising rates of suicide, mood disorders, ADHD, and functional impairments in children and adolescents. He discussed his work with neurodevelopmental disorders and disruptive behavior disorders, emphasizing the strong neurobiological risk for such conditions while calling attention to the role of peer relationships and optimal parenting strategies in predicting resilient outcomes. In terms of treatment, he discussed the need for combinations of pharmacologic and psychosocial interventions to address those at highest risk.





**CLOCKWISE FROM RIGHT:**

- 4.** Dr. John Krystal and Dr. Jeffrey Borenstein.  
**5.** Standing L to R: Faith Rothblatt, Léa Dartevelle, Marc Rappaport, Marilyn Waldman, Amy Tisler, Jason Stipanov, and Dr. Eric Nestler. Seated L to R: Anne Abramson, Cara Altimus, Louisa Benton.  
**6.** Standing L to R: Harold Pincus, Tim Bigdeli, Judy Harris, and Pamela Harris. Seated L to R: Dr. Nina Schooler, Tony Boeckh, Raymonde Boeckh, Norm Ornstein, Ellyn Pincus.  
**7.** Standing L to R: Janet Boardman, Lisa Beth Savitz, Michael Ross, Barbara Toll, Dr. Adam Savitz; Seated L to R: Donald Boardman, Louis Innamorato, Miriam Katowitz, Barbara Streicker, and Leslie Ross.





The day's final presentation, *Harnessing Hippocampal Neurogenesis to Improve Cognition and Mood*, was given by Dr. René Hen. Dr. Hen explained how his lab has approached the problem of determining the mechanism through which antidepressant medications work. The Hen lab's discovery that antidepressants increase neurogenesis in the dentate gyrus area of the brain's hippocampus, and that manipulations that countered this increase caused a partial loss of antidepressant effect, set the stage for two lines of research: one mechanistic, the other therapeutic. Dr. Hen discussed how, with collaborators in the New York State Psychiatric Institute, he is attempting to translate these discoveries to a clinical setting.

Following the symposium, more than 200 people gathered to celebrate the winners of the Pardes Humanitarian Prize in Mental Health as well as the Outstanding Achievement Prizewinners at the BBRF International Awards Dinner which was held at The Pierre hotel.

Bestowed annually since 2014, the Pardes Prize recognizes a person(s) or organization whose humanitarian work is transformative and of great magnitude, changing the lives and bringing the joy of living to those facing challenges to mental health. The Prize focuses public attention on the burden of mental illness on individuals and on society, and the urgent need to expand and enhance mental health services both in the developed world and in developing countries.

The Pardes Prize was presented to Dr. William Carpenter by Dr. Herbert Pardes, who leads the BBRF Scientific Council and for whom the prize is named.

**CLOCKWISE FROM LOWER LEFT:**

- 8. Dr. Sophia Frangou and Dr. Jeffrey Borenstein.
- 9. Standing L to R: Dr. Jeffrey Borenstein, Lisa Borenstein, Richard Hallack, Geoffrey Simon; Seated L to R: Michael Sperling, Jenna Borenstein, Giulia Suro, Mary Davis Clausen, Mark Clausen, and Andrea Graham Simon.
- 10. Dr. René Hen.
- 11. Standing L to R: Dr. Bruce Schwartz, Gerry Modell, Dr. Max Gomez, and Andrea Weiss; Seated L to R: Mary Woolley, Dr. Herbert Pardes, Stephen Lieber, and Virginia Clark.
- 12. Dr. Christoph Kellendonk.



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Dr. Carpenter has been a transformative force in psychiatry for more than 40 years and has dramatically changed how we treat schizophrenia, reduce stigma, and enhance the ethics of treatment and research.

Throughout his career, Dr. Carpenter has taken a person-centered, rather than an illness-centered, view of schizophrenia, which has led to more compassionate care for people with this illness. He has played a critical role in shifting the focus of treatment to the earliest stages of the illness, when interventions may have their most profound impact and maximize the likelihood of recovery. Dr. Carpenter chairs the BBRF Scientific Program Committee on the Scientific Council. He is also the recipient of 2008, 2001, and 1996 BBRF Distinguished Investigator grants and the winner of the 2000 BBRF Lieber Prize.

In presenting the award, Dr. Pardes noted that “Will is a man of absolutely exquisite integrity and uniquely admirable characteristics. He is the most modest, best informed, most dedicated, most friendly and most understanding person. He has been a tower of strength in mental health and medical research and also an outstanding member of the leadership of the BBRF. He is one of the most respected authorities on mental health throughout the world, having accomplished endless achievements both in research and in clinical care. In a word, he is an absolute champion.”

The Pardes Humanitarian Prize in Mental Health is sponsored in part by Janssen Research & Development, LLC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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The Honorary Pardes Prize was awarded to Cynthia Germanotta and Born This Way Foundation for their extraordinary accomplishments and commitment to supporting the wellness of young people, empowering them to create a kinder and braver world. Dr. Pardes said, “As believers in research as a powerful tool to help solve the problems facing today’s youth, they work to encourage and build communities that understand and prioritize mental and emotional wellness and that celebrate the individuality of those they serve. They inspire us all to look forward, toward a future that supports the wellness of young people and we thank them for their vast accomplishments and ongoing commitment to promoting mental health across the globe.”

The 2019 Prizewinners were then recognized for their extraordinary achievements in research on depression, ADHD, bipolar disorder, and schizophrenia.

In presenting the Outstanding Achievement Awards, Dr. Jeffrey Borenstein said, “These exceptional scientists are distinguished by their use of cutting-edge technology and devotion to finding innovative new therapies that will improve care for those living with mental illness and hold the key to preventive and diagnostic tools for the future.” He added, “We celebrate the progress being made in brain and behavior research and the scientific advancements that are paving the way for more people to live full, happy, and productive lives.” ❖ **LAUREN DURAN**

# Restoring a Delicate Balance

Seeking ways to therapeutically address subtle brain changes that imaging has revealed in mood disorders

Hilary P. Blumberg, M.D.

Director, Mood Disorders Research Program;  
John and Hope Furth Professor of Psychiatric Neuroscience and Professor of Psychiatry,  
of Radiology and Biomedical Imaging, and in the Child Study Center  
*Yale School of Medicine*

BBRF Scientific Council member  
2017 Colvin Prize for Outstanding Mood Disorders Research  
2006 Klerman Prize for Exceptional Clinical Research  
2006 BBRF Independent Investigator  
2002 BBRF Young Investigator



"I love the science of it!" says Dr. Hilary Blumberg, a research pioneer who has used advanced imaging to figure out how the brain subtly changes in bipolar disorder, major depression, and other mood disorders.

"But what really drives me," she stresses, "is bringing this work to the point where it is helping people—helping to relieve their suffering, improving their prognosis, and decreasing early mortality due to suicide. That's what guides me first every morning. I have a feeling of not being able to go fast enough, because so many people are suffering and people are losing their lives every day. I feel an urgency in this work."

Dr. Blumberg, a psychiatrist and clinical researcher, has been on the faculty of the Yale School of Medicine for more than 21 years, for the last 15 years serving as director of the Mood Disorders Research Program. She has been driven to reveal the inner workings of human emotions since she was 16 years old. That was when, as a precocious Hunter College High School student growing up in New York City, she was given her first chance to do research—at Cornell-New York Hospital (now Weill Cornell Medicine).

Dr. Blumberg was editor of a recent special issue of the *Journal of Affective Disorders* devoted to new research on suicide. In her introductory essay she noted that while it is "a preventable cause of death," suicide occurs somewhere in the world every 40 seconds, resulting in 800,000 deaths annually. Recently it has been estimated that people suffering from mood disorders have a lifetime risk of suicide 20 times greater than average (in the U.S., the average is 1.4 suicides per 10,000 people). As many as one person in two diagnosed with bipolar disorder makes a suicide attempt during their lifetime.





**“I have a feeling of not being able to go fast enough, because so many people are suffering and people are losing their lives every day. I feel an urgency in this work.”**

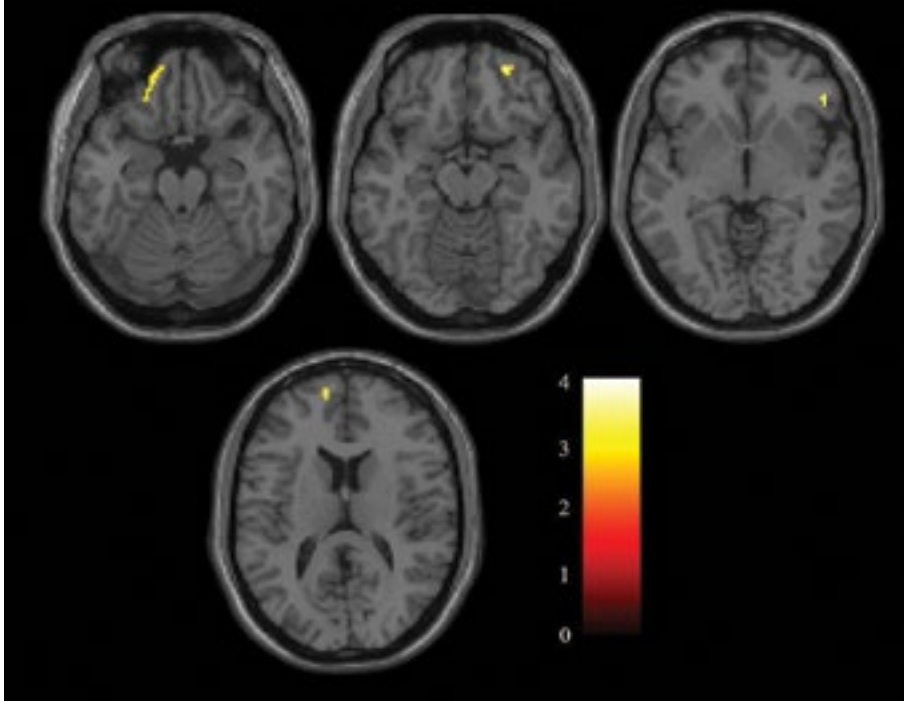
#### **DECIDING WHAT TO FOCUS ON**

There is no shortage of urgent causes in medicine. Dr. Blumberg relates that during her medical training at New York Hospital, she found herself reflecting on the “terrible things I was seeing as an intern at the Memorial-Sloan Kettering Cancer Center. It was devastating—you could see people losing their lives prematurely, every day.” But then, as she gazed out of her apartment window, her eyes focused on the Payne Whitney Clinic, the psychiatric hospital across the street. “I thought: the young people with psychiatric disorders in that facility actually may have a higher rate of mortality—and those illnesses could potentially be *preventable*. That realization fueled my motivation to focus on trying to help relieve the suffering of mental illness and prevent suicide.”

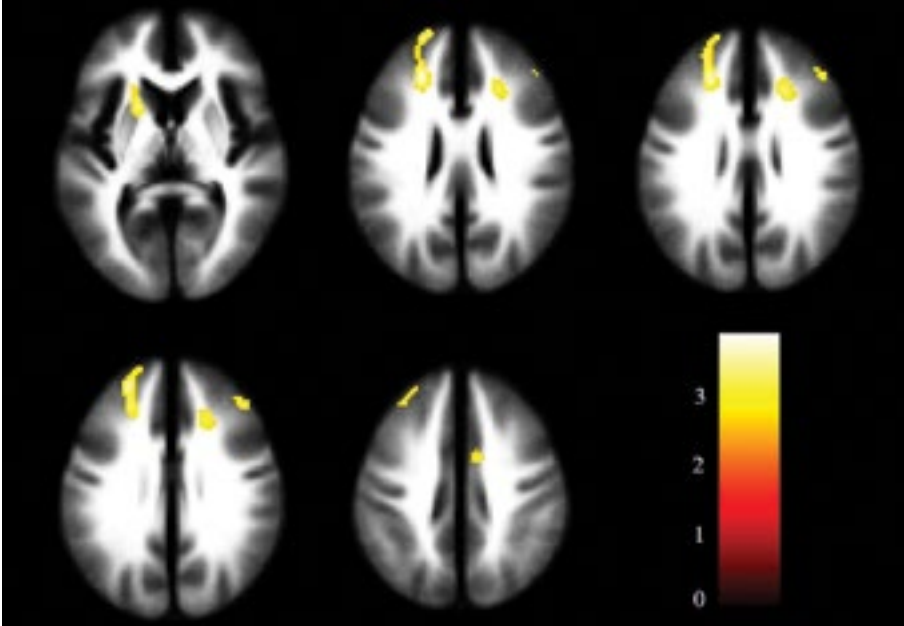
She did her medical residency in psychiatry and became “really immersed in the clinical side—the art of taking care of patients.” At the same time, “in the back of my mind, I had so many questions about the biology”—how changes in the brain are related to behaviors and symptoms seen in mental illness.

During her post-training fellowship, also at New York Hospital, Dr. Blumberg learned how to use a positron emission tomography (PET) scanner to look at the brain in people diagnosed with bipolar disorder. A research paper that emerged, published in 1999, helped establish her reputation. It was the first time brain scanning research showed decreases in functioning in the right prefrontal cortex in individuals who were experiencing manic symptoms of bipolar I disorder.

## Future-SA < NonFuture-SA



## Future-SA < NonFuture-SA



These brain images suggest it may be feasible to identify *in advance* individuals who are at high risk of making a future suicide attempt. Dr. Blumberg's team performed brain scans at the beginning of a multi-year study in 46 adolescents and young adults with mood disorders. During the next 3 years, 17 of these participants (37%) attempted suicide. These scans show areas in the brain that were different *in the initial scans* in these "future attempters" (yellow highlighted areas) compared with the rest of the group. This result, while suggestive, needs to be replicated with many more patients.

What exactly is going on inside the brain while individuals experience various symptoms of psychiatric illnesses? While doctors diagnose mental illnesses on the basis of behavioral symptoms—visible "on the outside"—the causes have remained stubbornly obscure. Research seeks to get to the level of mechanisms—changes in the biology of the brain across different subsets of patients, and between affected and unaffected individuals.

Findings in adults with bipolar disorder have focused attention on parts of the brain which regulate emotions. These include areas that span from emotional processing regions below the cortex, such as the amygdala, to the frontal regions of the cortex, the seat of higher thinking that provides executive control over emotions and impulses.

### WHY GREY AND WHITE MATTER MATTERS

It is remarkable how much the brain changes even after the end of adolescence. This is evident, for example, in imaging studies of the brain's grey and white matter. As Dr. Blumberg explains, "The grey matter is where the cell bodies are." She refers to the billions of neurons that populate the brain and comprise its complex circuits. "You can think of grey matter structures as 'nodes' in the circuitry." Gray matter, especially in prefrontal cortex, continues to change and mature through early adulthood. "It remains plastic during adulthood, but it is especially plastic during childhood and adolescence, so these are important times to minimize risk factors and build resilience," she says.

White matter is the brain's wiring, and specifically the insulation around the wiring, made of the whitish-yellow fatty substance called myelin. Bundles of white matter carry the connections between brain cells and between different brain regions. "Since white matter

continues to change, into a person's mid-adult decades, this suggests there are important windows in this period, as well, to prevent the progression of adverse brain changes that increase risk of mood disorders and suicide."

Differences in the brain between people who have bipolar disorder and those who do not, as well as between those in each group who have suicidal thoughts or make a suicide attempt and those who do not "are quite subtle," Dr. Blumberg points out. "We are not talking about differences that can be detected by holding up two scans using current technology to tell who does and who does not have bipolar disorder. These are subtle differences that are in brain areas that show plasticity. We are learning ways to help reverse some of these changes. New therapeutic strategies are being intensively researched, and new brain imaging technologies will be coming that will help guide us in developing them."

### STUDYING BIPOLAR DISORDER ACROSS THE LIFESPAN

Dr. Blumberg has devoted considerable effort in recent years to the study of adolescents with bipolar disorder. "Since symptoms are often first recognized during adolescence, it could be an age period that holds clues about the development of the illness," she says, "and its study could provide targets for early interventions to prevent the progression of symptoms."

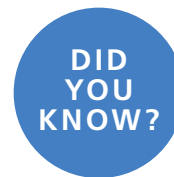
She achieved important firsts in the field, showing brain differences in adolescents with bipolar disorder, and particularly in the emotion centers below the cortex. Her findings in the amygdala in adolescents are especially important. She explains that "the deeper you go in the brain, the more primitive the structures and their functions." She's referring to the limbic centers that include the amygdala, which are central in emotional processing. These tend to

mature earlier than frontal "executive" regions of the brain.

Over the past decade, Dr. Blumberg and her team have delved into the circuitry that contributes to the risk for suicide in individuals with mood disorders. In a paper appearing in the *American Journal of Psychiatry* in 2017, for example, her team used various imaging types to study adolescents and young adults with bipolar disorder—and found differences in the structure and the functioning of prefrontal regions that were more pronounced in those who had made suicide attempts.

Most recently, her group has provided preliminary evidence that there are similar brain differences in adolescents and young adults with major depression and bipolar disorder who have attempted suicide. In another longitudinal study, Dr. Blumberg and her group provided preliminary evidence that prefrontal differences may be a predictor of future suicide. This is important, since "right now no one knows in advance which individuals will attempt suicide." Thus, the focus in Dr. Blumberg's current research is on the longitudinal approach—following people over time.

Among her many current projects, Dr. Blumberg is the U.S. lead investigator of a new international consortium that is looking for brain biomarkers of suicidal ideation in adolescents and young adults. Her team is focusing on individuals followed over the years, as they mature, and also in the periods before and after pharmacological and talk therapies. She is also attentive to the problems of older adults with mood disorders. "This is an area that has received less study but is critical," she points out, "since it is the group at highest risk for suicide." [for more on this subject, see page 27]



**GREY MATTER** consists mainly of the cell bodies of the billions upon billions of neurons that comprise the brain. The cerebrum, brain stem and cerebellum are especially rich in grey matter. The surface of the cerebral cortex and cerebellum, which are often seen in conventional pictures of the whole brain, are rich in grey matter.

**WHITE MATTER** refers to bundles of axons that extend between cell bodies in the brain, often over long distances. Axons are coated with an insulating material called myelin, which lend to the bundles, or "tracts," a characteristic whitish-yellow color. The structural integrity of white matter can be measured with a type of scanning called diffusion tensor imaging (DTI).

**BE-SMART (BRAIN EMOTION CIRCUITRY-TARGETED SELF-MONITORING AND REGULATION THERAPY)** is a non-drug therapy being developed by Dr. Blumberg and colleagues to help people with mood disorders learn how to better control their behavioral responses to emotions, as well as regularize biorhythms such as sleep that are often disrupted in mood disorders.

## TEACHING EMOTIONAL SELF-REGULATION

At Yale, Dr. Blumberg and colleagues are recruiting individuals for clinical trials testing a non-drug therapy, called BE-SMART, which stands for Brain Emotion Circuitry-Targeted Self-Monitoring and Regulation Therapy. Its goal is to help people who have mood disorders or who are at risk for them to better regulate their emotions. It targets prefrontal brain circuitry that regulates emotions, reflecting what Dr. Blumberg and colleagues have learned from brain imaging. It seeks to unlock the potential value in teaching people healthy strategies for modifying their behavioral responses to emotions as well as regularizing sleep and other daily activities.

“If someone’s got a mood disorder, they could be really sensitive to disruptions in the timing and amount of their sleep and other activity patterns, which in turn disrupt the alignment of other bodily rhythms,” Dr. Blumberg explains. “I’ve long had the dream that you could strengthen the brain to reduce acute symptoms and potentially prevent progression and improve prognosis while reducing suicide, by teaching healthy habits and ways for individuals to better self-regulate.”

Preliminary findings, she says, show that over 12 weeks of the intervention, with the majority of sessions provided by therapists via computer or smartphone videoconferencing apps, “emotional control and mood symptoms are improving, as reflected in improved functioning of prefrontal circuitry observed with functional MRI.”

The current BE-SMART program in bipolar disorder involves young people aged 16 to 24, as well as some younger participants at risk for bipolar disorder. Dr. Blumberg hopes to test it in other age groups and disorders. She is also incorporating wearable devices and smartphone technology to learn more about real-time changes in study participants. She plans to eventually incorporate feedback during therapy for patients and therapists, to optimize results.

Dr. Blumberg emphasized that there are many paths to mood disorders and many

potential ways to address them therapeutically. “Drug therapies, new targeted biological non-pharmacological treatments, talk therapies to improve ‘top-down’ emotion regulation, and behavioral therapies that enhance healthy habits, each has potential to provide benefits,” she says.

“And there are many new therapies on the horizon. The future is very hopeful—I believe we will continue to make progress on reducing the suffering and the risk of suicide in mental illnesses.”

❖ PETER TARR

## Dr. Blumberg Talks About BBRF



*“I absolutely believe that BBRF has been instrumental in my career. The Young Investigator award [in 2002] was so important for me to be able to do the multi-modal imaging work in bipolar disorder. Then I got an Independent Investigator award [in 2006] which enabled me to look at individuals at risk and pursue that work. Since then, many of my trainees have been awarded BBRF grants. So you start with my early award and see all these branches, opening into different aspects of my work over my career and that of people I’ve helped train. And as people in my lab get opportunities from awards of their own, the whole ‘tree’ just exponentially grows. It means a great deal to me to sit with my trainees and know that there are Young Investigator awards still out there to be won—this gives me tremendous hope that they’re going to be able to successfully launch their own programs, which is really crucial to the future of brain research.”*



# PLAN YOUR FUTURE, SHAPE YOUR LEGACY

There are many ways to support the Brain & Behavior Research Foundation during your lifetime and one particularly meaningful way is through planned giving.

When you include BBRF as part of your legacy plan, you help ensure that our groundbreaking research continues.

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



“Marla and I donate to the Brain & Behavior Research Foundation in support of science and the hope of finding better treatments for mental illness.

“Better treatments came too late for my brother, Stewart, who lost his battle with schizophrenia, and too late for my father, Ken, who suffered from depression. But we believe that with ongoing research, it will not be too late for millions of other people thanks to BBRF. We know this because we have seen the scientific breakthroughs and results that have come from funding scientists. Marla and I are dedicated to helping people who live with mental illness and doing what we can to be a part of the solution by our continued giving to BBRF.”

—Ken Harrison, Board Member

To learn more, please contact us at **646-681-4889** or [plannedgiving@bbrfoundation.org](mailto:plannedgiving@bbrfoundation.org)



## THE RESEARCH PARTNERS PROGRAM

# Supporting Science through Your Alma Mater Can Make All the Difference in Advancing Mental Health Research

**M**ANY BBRF DONORS HAVE A VERY PERSONAL interest in brain and behavior research. They know from often difficult, first-hand experience the devastation mental illness can bring upon family and friends, and they know that research will ultimately bring about better understanding and treatments.

Our Research Partners Program offers donors the opportunity to personally select and support scientists based on various criteria, including, but not limited to, illness specialty area or specific institutions, or a combination of these. Researchers are selected by the donor (our Research Partner) after members of our all-volunteer Scientific Council have conducted an independent peer review of the submitted applications and have made their recommendations for grant awards.

The Research Partners Program enables donors to choose among the best and brightest scientists and the most promising, cutting-edge proposals in mental illness research.

The results from these studies often provide the pilot data needed to apply for much larger federally funded grants (from the National Institute of Mental Health and the N.I.H., for example).

To date the BBRF Research Partner's program has funded more than 1,500 research grants.

Donors who are university alumni often decide to underwrite the work of a faculty member of their alma mater who has been chosen to receive a BBRF grant. The biggest advantage of supporting researchers through BBRF rather than directly through a university is the fact that 100 percent of any donation to BBRF goes directly to the researcher. None of the money goes to administrative costs.

To give an example of the power of this idea, over these past 32 years one anonymous donor, an alumnus of Yale University, has given BBRF approximately \$1,575,000 which has funded 19 researchers in our Research Partners Program. Investigators funded include 12 Young Investigators, five Independent Investigators and two Distinguished Investigators.

Each of the scientists on this list was at Yale University when they received their grant. They have gone on to receive additional funding for their research—many, for work that was based on the initial research ideas that were supported by BBRF grants.



The work of these investigators has accelerated the path forward to discovery and cures for mental illness. Here are some examples of the impact they have made:

## YOUNG INVESTIGATORS



**Gustavo Adolfo Angarita, M.D.**

*Yale University — 2016*

Dr. Angarita, whose BBRF grant enables him to test a potential treatment for ADHD, has now obtained a Federal grant to fund a placebo-controlled clinical proof-of-concept test in 24 people of exenatide, a peptide that stimulates

GLP-1, a gut hormone. It is a potential treatment for blocking cocaine euphoria and self-administration. At Yale he is currently Associate Research Scientist in Psychiatry; Inpatient Chief of the Clinical Neuroscience Research Unit, Psychiatry; and Medical Director, Forensic Drug Diversion Clinic.



**Chadi Abdallah, M.D.**

*Yale University — 2014*

Dr. Abdallah's BBRF grant enabled him to receive a career R-01 grant from the NIMH to use advanced imaging technology to examine glial and synaptic functions in major depression and to establish the potential utility of three biomarkers.

At Yale, he is currently Associate Professor of Psychiatry; Deputy Director for Research; and Director of Neuroimaging, Clinical Neuroscience Division, VA National Center for PTSD.



**Marcelo O. Dietrich, M.D., Ph.D.**

*Yale University — 2014*

Dr. Dietrich's BBRF grant enabled the study of biological processes that trigger anorexia nervosa. He now has a career R-01 award from NIH to study the same neuronal type, AGRP neurons, in a number of metabolic conditions. At Yale, he is Assistant

Professor of Comparative Medicine and of Neuroscience.



**Gianfilippo Coppola, Ph.D.**

*Yale University — 2013*

Dr. Coppola's BBRF grant supported the study of gene regulatory networks underlying the pathophysiology of autism spectrum disorders. This past year he obtained NIH funding to develop organoid technology with applications in

the study of autism, schizophrenia and Alzheimer's and Parkinson's diseases. In the Katz lab at Yale he currently works in the program in Neurodevelopment and Regeneration.



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

*Yale University — 2010*

Dr. Jou's BBRF grant enabled him to use structural and diffusion magnetic resonance imaging to investigate brain connectivity in individuals with autism relative to healthy controls.

This past October he was senior author on a paper examining altered

neural connectivity in females, but not males, with autism, proposing a female protective effect based on DTI imaging evidence. At Yale, he is currently Instructor of Clinical Child Psychiatry.



**Megan V. Smith, Dr.PH., M.P.H.**

*Yale University — 2010*

Dr. Smith's BBRF-funded research, on maternal depression, has led to two NIH grants, both involving innovative uses of technology as supports for treatment: a smartphone app to promote mental health in new mothers and a

career R-01 grant for an app to help curb postpartum smoking. At Yale, she is currently Associate Professor of Psychiatry, and in the Child Study Center; Director, Mental health Outreach for MotherS (MOMS) Partnership; and Director, Yale Child Study Center Parent and Family Development Program.



**Matthew M. Kurtz, Ph.D.**

*Institute of Living, Hartford Hospital — 2006*

Dr. Kurtz's BBRF grant enabled a randomized study of the effects of cognitive remediation alone vs. cognitive remediation plus social skills training in schizophrenia. Since 2010 he has been supported by a

number of Federal grants supporting a variety of projects in the same field. Currently he is Professor, Neuroscience and Behavior, at Wesleyan University.



**Handan Gunduz-Bruce, M.D.**  
*VA CT Healthcare System — 2005*  
 Dr. Gunduz-Bruce's BBRF award enabled the study of GABA-glutamate interactions and psychosis, which included work with the drug ketamine. She has recently been on the team that clinically demonstrated the effectiveness of brexanolone for

postpartum depression, paving the way for its FDA approval. She is currently affiliated with the Office of Cooperative Research at Yale.



**Vince D. Calhoun, Ph.D.**  
*Institute of Living, Hartford Hospital — 2004*

Dr. Calhoun used his BBRF grant to employ fMRI brain imaging to distinguish between people with schizophrenia and bipolar disorder, to help differentiate the conditions. The recipient of numerous Federal

grants, he currently has an NIH R-01 career award to develop a family of data-driven approaches to integrate fMRI, ERP, genetic, and behavioral data and enable the incorporation of available information in the context of a variety of psychiatric disorders. Currently he is Adjunct Professor of Translational Neuroscience, The Mind Research Network.



**Min Wang, Ph.D.**  
*Yale University — 2004*  
 Dr. Wang used her BBRF grant to study, in monkeys, the role of dopamine receptors in the prefrontal cortex that are involved in working memory, which is impaired in schizophrenia. The recipient of many Federal grants since then, her career

R-01 award examines how acetylcholine stimulation of the muscarinic M1 and alpha-7 receptors influence higher cognitive functioning. At Yale she is currently Senior Research Scientist in Neuroscience.



**Julio Licinio, M.D.**  
*National Institute of Mental Health — 1992*

Dr. Licinio's BBRF grant enabled a study of neuroendocrine-neuroimmune regulation in major depression and PTSD. His most recent NIH R-01 career award supported the study of depression

and metabolic syndrome in Mexican-American women. He is currently Professor of Psychiatry and Behavioral Sciences, and Dean of the College of Medicine at SUNY Upstate Medical University.

## INDEPENDENT INVESTIGATORS



**Jane R. Taylor, Ph.D.**  
*Yale University — 2008*

Dr. Taylor's 2008 BBRF award enabled her to model cognitive dysfunction in the prefrontal cortex. She focuses her research on dysfunction of cortico-limbic-striatal circuits involved in dysfunctional cognitive control, impulsivity,

and alterations in reward-related learning with relevance to drug addiction, depression, schizophrenia, and Tourette Syndrome. At Yale, she is currently Murphy Professor of Psychiatry, of Psychology and of Neuroscience.



**Daniel H. Mathalon, M.D., Ph.D.**  
*University of California, San Francisco — 2007*

Now Professor of Psychiatry at UCSF's Weill Institute for Neurosciences and a member of BBRF's Scientific Council, Dr. Mathalon's 2007 BBRF grant enabled him to track via fMRI the

effects of treatments for cognitive deficits in schizophrenia. Some of his recent NIH grants support his work on emotional regulation in PTSD, sexual dimorphism in PTSD, and identifying predictors of conversion to psychosis.

For donors who wish to support scientists at their alma mater or another university, we can provide you with a list of grantees from the university of your choice.





**Gerard Sanacora, M.D., Ph.D.**

*Yale University — 2007*

Now the Gross Professor of Psychiatry; Director, Yale Depression Research Program; and Co-Director, Yale New Haven Hospital Interventional Psychiatry Service, Dr. Sanacora's 2007 BBRF grant supported research on

effects of stress and antidepressants on neurotransmission and glial cell function. His current focus is contributions of the amino-acid neurotransmitter systems (GABA and glutamate) to the neurobiology of mood disorders and the mechanism of antidepressant action. He is among the BBRF grantees who have played an important part in the development of the first rapid-acting antidepressants.



**Samuel A. Ball, Ph.D.,**

*Yale University — 2005*

Dr. Ball's 2007 BBRF grant enabled him to assess the prevalence of severe personality disorders and their relationship to other psychiatric diagnoses in the homeless. Currently Professor of Psychiatry and Assistant Chair for Education and Career

Development at Yale, he focuses on the evaluation of personality dimensions and disorders as important constructs for subtyping addicted individuals for the purpose of predicting treatment outcome and developing interventions.



**Marina R. Picciotto, Ph.D.**

*Yale University — 2004*

In her 2004 BBRF grant, Dr. Picciotto studied the potential antidepressant effect of blocking nAChR, the nicotinic acetylcholine receptor. Now Murphy Professor of Psychiatry and Professor in the Child Study Center, of Neuroscience

and of Pharmacology; Deputy Chair for Basic Science Research, Dept. of Psychiatry at Yale; and Deputy Director, Kavli Institute for Neuroscience, Dr. Picciotto is a BBRF Scientific Council member and editor-in-chief of the *Journal of Neuroscience*. Her research focuses on understanding the role of single molecules in complex behaviors related to addiction, depression, feeding, and learning. She is a member of the National Academy of Medicine.

## DISTINGUISHED INVESTIGATORS



**Nenad Sestan, M.D., Ph.D.**

*Yale University — 2012*

Dr. Sestan received his first BBRF Young Investigator grant, supported by a Research Partner, to study schizophrenia genetics in 2006. In his Distinguished Investigator grant 6 years later he turned to the relationship of regulation and brain

development. This presaged his involvement as a charter member of the PsychENCODE project. Dr. Sestan has been supported by a succession of overlapping Federal grants as his work has matured. He is currently Cushing Professor of Neuroscience, and Professor of Comparative Medicine, of Genetics and of Psychiatry; and Executive Director, Genome Editing Center, at Yale.



**Flora M. Vaccarino, M.D., Ph.D.**

*Yale University — 2011*

Dr. Vaccarino's early BBRF awards clearly suggested the important career she has had. Now Harris Professor at Yale's Child Study Center and Professor of Neuroscience, and a member of the BBRF

Scientific Council, she is a leading innovator in iPSC stem-cell technology, in which human skin cells are reprogrammed back to a state in which they can redevelop as neurons and other brain cells. This has led to important discoveries about the developmental origins of pathologies in psychiatric illness. Dr. Vaccarino has received numerous Federal career grants, and continues to study Tourette Syndrome among other conditions—one subject of study in her 2011 BBRF grant. Like Dr. Sestan, she is a leading member of the PsychENCODE Consortium.

**Please consider becoming a Research Partner and supporting scientists who are poised to make their mark, leading us toward preventions and cures.**

**To learn more about the Research Partners Program, please call 646.681.4889 or email [researchpartner@bbrfoundation.org](mailto:researchpartner@bbrfoundation.org).**

*While many donors are public about the reasons why they support BBRF, others prefer to remain anonymous in their giving. We appreciate each and every BBRF donor and honor and respect each individual's wishes.*

❖ **LAUREN DURAN AND PETER TARR**

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### Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia

Tuesday, January 14, 2020 2:00pm–3:00pm EST

**Gregory A. Light, Ph.D.**

*University of California, San Diego*



### How Drug Dependence Impacts Decision Making

Tuesday, February 11, 2020 2:00pm–3:00pm EST

**Christina Gremel, Ph.D.**

*University of California, San Diego*



### Brain and Behavior-Based Strategies in the Treatment of OCD

Tuesday, March 10, 2020 2:00pm–3:00pm EST

**Christopher Pittenger, M.D., Ph.D.**

*Yale School of Medicine*



### Can Traumatic Memories Be Erased?

Tuesday, April 14, 2020 2:00pm–3:00pm EST

**Stephen Maren, Ph.D.**

*Texas A&M University*



### Using Neuroscience to Evaluate and Guide Treatment for Pediatric Mood Disorders

Tuesday, May 12, 2020 2:00pm–3:00pm EST

**Manpreet Kaur Singh, M.D. M.S.**

*Stanford University School of Medicine*



### MODERATOR

**Jeffrey Borenstein, M.D.**

*Brain & Behavior Research Foundation  
President and CEO*



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# Understanding and Preventing Suicidal Behavior

## Q&A with David A. Brent, M.D.

Distinguished Professor of Psychiatry, Pediatrics, Epidemiology, and Clinical and Translational Science and Endowed Chair in Suicide Studies  
*The University of Pittsburgh*

2006 Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research  
2001 BBRF Distinguished Investigator Grant



**In 2017, suicide was the tenth-leading cause of death in the United States, claiming the lives of over 47,000 people. Dr. Brent, you have treated and counseled numerous patients over the years who have engaged in suicidal behavior.**

**Before we discuss some of the warning signs and strategies that loved ones and friends can pursue in such cases, allow us to ask a basic question about risk. Could you explain to us about how the suicide rate changes with age? People often don't understand the relation between suicide attempts, on the one hand, and deaths from suicide, on the other.**

While young people *attempt* suicide more, the *rate* of suicide (deaths) goes up with age. There's a paper that Dr. Ronald Kessler [a leading American epidemiologist] published in 1999 that shows that the incidence of suicidal *behavior* peaks in late adolescence and early adulthood. The first attempt occurs around then, typically, but then the number of suicide attempts declines relative to suicide deaths, over time with age. In people over 60, one out of every eight suicide attempts may be fatal. In a young person that might be one in 200.

### **What is going on developmentally in young people that may explain this?**

Nobody knows for sure, but it parallels an increase in risky behavior in general such as substance misuse and unprotected sex, as well as the beginning of various psychiatric disorders and mood disorders. As kids go into adolescence, the limbic area (the "subcortical" part of the brain) that's involved in emotions and reward develops first. Whereas the prefrontal cortex (higher-level processes—the braking mechanism) develops later.

This fits with the fact that a lot of suicidal behavior in adolescents is very impulsive, and why the ratio of attempts vs. deaths declines with age. It's because suicide attempts become much more planned. A second developmental issue to consider is that adolescents have a shift in their circadian (24-hour

## **“Kids don’t come with an operating manual, and most parents aren’t equipped to deal with suicidal crises. Don’t get caught up in apportioning blame. Instead, try to figure out solutions.”**

day/night) rhythm, where they get tired later and go to bed later—but they have to get up early for school. A substantial proportion of adolescents are sleep-deprived. And we know that sleep problems are an imminent predictor of suicidal behavior and in fact magnify the issue of the imbalance between the prefrontal cortex and the subcortical part of the brain.

### **What signs could indicate that your loved one is contemplating suicide?**

The most obvious sign is that they are talking about suicide. There used to be a myth that people who talked about suicide didn’t do it. But it turns out that people who talk about it are the most likely to engage in suicidal behavior. So that type of communication, or even more vague statements like “People would be better off without me” or “I wish I was dead” should be very concerning. Another thing to watch out for is if somebody engages in any kind of preparatory behavior such as stocking up medication or practicing tying hang nooses.

### **Apart from the obvious signs of talking and preparatory behavior, what are some more subtle indications?**

Kids who engage in frequent non-suicidal self-injury such as self-cutting. An isolated self-cutting episode is very common, but repetitive self-cutting is unusual and is a strong predictor of suicidal behavior. I would also look out for kids with sleep problems and kids who show signs of moodiness, irritability, withdrawal, and difficulty regulating their emotions. If somebody has changed the way that they relate to their family, their friends, or how they’re doing in school, that’s a sign that something is amiss. Kids engaging in other kinds of risky behavior are also more likely to engage in suicidal behavior. Post-traumatic stress and any psychiatric disorder can also increase somebody’s risk for suicide.

### **Could you recommend some resources if we suspect somebody is at imminent risk?**

I think it’s reasonable to ask somebody directly if they are thinking about wanting to die. And if they say yes, you could say, “Would you like to get some help? There are things we can do to make you feel better. Do you want me to help you try and access that?” And in the rare instance when the person refuses and you feel that the situation is imminent, there is the national suicide hotline (1-800-273-8255). For kids, particularly, since a lot of them don’t like to talk on the phone, there is Crisis Text Line, where they can text HELLO to 741741 and get texting support. There may also be a local mental health crisis line. In our region (Pittsburgh and western Pennsylvania) we have “Resolve,” which provides mobile crisis services. They’ll send somebody to your house to do an assessment. Other localities may have similar services—it is worth checking. And finally, the police are also a resource.

### **What if there’s more of a subtle underlying concern—not necessarily regarding an imminent situation—that my loved one is potentially thinking about this?**

You can arrange for an assessment either with their primary-care doctor, or a mental health professional if you know of one or have access to one. And the way you would do that is you say to the person you’re worried about, “Look, I’m concerned about you. Things seem different, and not in a good way. And I think it would be helpful to get a better idea about what’s going on and what might be bothering you, because there are ways to make it better.”



**In terms of people who are actually in the care system, should the family be brought in to be part of the individual's treatment?**

I would say in general the family is very important. Sometimes a patient may say to the doctors or others involved in their care, "I don't want you to have any contact with my spouse or my family." But as a professional, a mental health professional also can say to them, "I won't really be able to effectively treat you if that's your stance. Let's talk about that." Because people don't make suicide attempts in isolation. There often are interpersonal motivations. They feel isolated, they feel like nobody cares. They feel they're a burden on people. And so being able to mobilize that family support is really critical.

It's true that sometimes families are toxic, and then you have to use your clinical judgment. But most families are more helpful than harmful and are well intended. I think that should be the starting assumption of the clinician in reaching out to relatives.

**After a suicide attempt, what can you do to support a friend in their recovery?**

You could ask them, "How can I be most helpful to you? Do you want me to ask you how you're doing? Are there things I can do, or we can do together, that would be helpful?" Ask them because some people don't want to be treated with kid gloves and don't want to feel like a victim. Be supportive and in touch with them and let them know that if they feel despondent, they can reach out to you.

**And if you're a parent and have a presumably closer relationship, is there something additional you should do?**

I think it's similar, but there are more ground rules. Kids want to be treated the way they were before the attempt happened. And parents are freaked out because this happened and maybe they didn't even see it coming. So now they're hovering. And so, you want to achieve a negotiation in which the kid wants to know from the parent, "What do I need to do to for you to trust that I'm doing okay?" For their part, the parents need to be able to tell their kid what they need from them to be able to feel confident that the kid is doing all right.

It's a negotiation. Sometimes as a therapist you have to say to the parent not to err on the side of caution to the point that they're actually making something worse. Or you have a scenario where a kid is relatively early in their recovery but they're doing well and now they have an opportunity to study abroad. This is something that could be really life-affirming for this kid, something they were looking forward to and you don't want to punish them for what happened before. The whole point of trying to keep them alive is so they can have these kinds of experiences and grow and develop.

Therefore you acknowledge the dilemma by saying something like, "What could we do to make this situation safer? Because we want you to be able to grow and have life-affirming experiences." And you see where the conversation goes. On the other hand, some kids are doing poorly and then it's a different conversation. But for other kids, I think

that you can err too much on the side of caution. And kids might become unwilling to disclose that they're in trouble because they feel that it's going to eventuate in restriction. It's much better to have the conversation about the dilemma than it is to try to immediately drill down and come to a decision.

**That's tremendously helpful, Dr. Brent. Any other advice for parents as they move forward?**

A lot of times parents feel that it's their fault. And maybe there are things they could've done better. But kids don't come with an operating manual, and most parents aren't equipped to deal with suicidal crises. So just realize that you're doing the best that you can. You could probably do better. You need specific advice in these cases that you wouldn't have needed for a kid who didn't have these issues. These things happen without it being anybody's fault. Don't get caught up in apportioning blame. Instead, try to figure out solutions that will make your family more harmonious, safer, and more fulfilling for everyone. ❖

## Recent Research Discoveries

### Important Advances by Foundation Grantees That Are Moving the Field Forward

#### MAJOR GENETIC STUDIES OF ADHD AND ANOREXIA NERVOSA BREAK NEW GROUND



Sarah Medland, Ph.D.

#### ***The first 12 genome “risk locations” are identified for ADHD***

After years of trying, researchers say they have now succeeded in discovering specific areas of the human genome that contain commonly occurring variations in DNA sequence that are robustly associated with risk for ADHD (attention-deficit hyperactivity disorder).

A large international team that included 10 BBRF grantees and

prizewinners identified, mapped, and analyzed the potential biological significance of 12 “significant risk loci” associated with ADHD. The findings appeared in *Nature Genetics*.

Nine years ago, a major effort to identify common DNA variations—single-DNA “letter” variations, called SNPs—found many variations that differed between people with ADHD and unaffected individuals. The problem was that none of these rose to a mathematical threshold called “genome-wide significance.” This standard is vitally important, for each of us harbors many SNPs, and while most have no impact on our health, some do affect health.

ADHD affects 5 children in every 100 and about 2 adults per 100, and many researchers believe that a significant portion of risk traces to the collection of SNPs that an individual happens to be born with. It takes several or many such common SNPs

to put an individual at significant risk, in combination with a range of environmental factors.

In contrast with earlier studies, the new assessment was massive, involving a total of 20,183 individuals diagnosed with ADHD and 35,191 controls. These were assembled from 12 different cohorts from Europe, North America, and China. The study was a meta-analysis, a study of previously collected data that adds statistical power to the analysis.

In all, over 8 million SNPs were included in the meta-analysis. Of these, 304 SNPs concentrated in 12 “loci”—locations on 11 of the 23 human chromosomes—rose to genome-wide significance for ADHD. Risk areas on chromosomes 2, 7, and 10 converged on single genes. These genes have roles in development of the brain, and are active when synapses between neurons are being formed, in neuronal development, and in neural mechanisms involved in the development of speech and learning.

By correlating their results with other large genetic studies, the researchers showed that the set of SNPs that increase risk for ADHD are correlated with the sets of SNPs that put people at risk for depression, learning difficulties, obesity, and other conditions that had been associated with ADHD in prior clinical, family, and twin studies.

The research team included: **Stephan Ripke, M.D., Ph.D.**, 2015 BBRF Young Investigator and 2014 Baer Prizewinner; **Daniel Geschwind, M.D., Ph.D.**, 1999 BBRF Young Investigator, 2012 Ruane Prizewinner and 2015 Distinguished Investigator; **Patrick Sullivan, M.D., FRANZP**, 2014 Lieber Prizewinner and 2010 BBRF Distinguished Investigator; the late **Pamela Sklar, M.D., Ph.D.**, 2016 Colvin Prizewinner, 2006 BBRF Independent Investigator and 1995 and 1998 Young Investigator; **Anita Thapar, Ph.D., MBBCh**, 2014 Ruane Prizewinner; **Sarah Medland, Ph.D.**, 2017 BBRF Independent Investigator; **Panos Roussos, M.D., Ph.D.**, 2013 BBRF Young Investigator; **Dorret Boomsma, Ph.D.**, 2011 BBRF Distinguished Investigator; **Hyejung Wong, Ph.D.**, 2018 BBRF Young Investigator; and **Elise Robinson, ScD, MPH**, 2014 BBRF Young Investigator.



Cynthia M. Bulik, Ph.D.

### **Genome analysis suggests anorexia nervosa is also a metabolic illness**

By far the largest genetic study to date of anorexia nervosa has identified eight areas in the human genome in which DNA variations are likely to contribute to risk for the illness. Even more important, potentially: the new

research extends our understanding of this psychiatric illness by showing that genetic factors that influence metabolism also contribute to its origins. "Our results encourage a reconceptualization of anorexia as a metabo-psychiatric disorder," the researchers wrote.

The leader of the large multinational team that performed the genomic study, **Cynthia M. Bulik, Ph.D.**, a 2017 BBRF Distinguished Investigator at the University of North Carolina (UNC) at Chapel Hill and Karolinska Institutet, commented on the new findings for the *Wall Street Journal* in July, after the study appeared in the journal *Nature Genetics*. "Many of us have wondered for a long time if there is more to anorexia nervosa than the psychological component," she said. Those afflicted seem to "override normal biology, override hunger signals. We've often wondered what it is that permits them to lose so much weight. This new research might help explain why they get metabolically out of control."

Anorexia nervosa affects up to 4% of women and less than 1% of men. People with anorexia nervosa may see themselves as overweight, even when they are dangerously underweight. They typically weigh themselves repeatedly, severely restrict the amount of food they eat, often exercise excessively, and/or may force themselves to vomit or use laxatives to lose weight. Anorexia nervosa has the highest mortality rate of any mental illness.

Dr. Bulik, along with **Patrick Sullivan, M.D., FRANZCP**, a 2014 BBRF Lieber Prizewinner, of UNC and Karolinska Institutet, and their large team of colleagues assembled a sample of sufficient size to make headway on the genetics of anorexia nervosa. By combining 33 samples they were able to compare the genomes of 16,992 people with anorexia nervosa with 55,525 controls.

At the eight risk "loci" identified—which together contain many genes—it is possible so far to say four genes in particular are likely involved in anorexia nervosa pathology. These genes tend to be active in the brain, in neuronal cell types that are linked to feeding behaviors, including food motivation and reward.

The study revealed significant correlation between the genetics of anorexia nervosa and metabolic traits. One such component is the body mass index, or BMI. Although low BMI in patients with anorexia nervosa is a result of restricting caloric intake and increasing energy expenditure, the new results open the possibility that a tendency to have low BMI may itself be a potential cause or contributing factor to developing anorexia nervosa. To put this another way, the processes in the body that normally regulate metabolism, including weight regulation, may be malfunctioning in anorexia nervosa patients, underlying some of the weight and feeding symptoms that have previously been explained as purely psychological.

The new study also revealed that anorexia nervosa shares genetic factors with other psychiatric disorders including obsessive-compulsive disorder, anxiety, major depressive disorder, and schizophrenia.

The new results place the problem of severe stigma and misunderstanding, which often attaches to anorexia nervosa, in a new light. Dr. Bulik states, "Anorexia nervosa has been misunderstood for decades. Patients often say they want to eat and desperately want to get well, but they find it enormously difficult to do so." The new results can help explain on a metabolic level why, even after hospital-based weight restoration, patients with anorexia nervosa rapidly lose weight again after discharge, often despite aftercare. These findings can help parents and loved ones understand that it is not just a matter of "deciding" to eat more. "Recovery from anorexia nervosa is fighting an uphill battle against their biology and patients need our support in doing so," says Dr. Bulik.

## EARLY REDUCTIONS IN IRRITABILITY PREDICTED TREATMENT RESULTS IN SOME PATIENTS WITH MAJOR DEPRESSION



Madhukar Trivedi, M.D.

Results of a clinical trial published in the *American Journal of Psychiatry* indicate that patients with major depression who become less irritable within 4 weeks of initiating treatment with an antidepressant medicine are much more likely to have a full remission of depression symptoms by the end of their 8th week of treatment.

Those whose irritability was reduced in the first month of treatment were found to be about twice as likely as patients taking the same medicines who didn't report significant reductions in irritability in the same interval.

The finding is relevant for an estimated 40% to 50% of all patients with major depression—those who say at the beginning of treatment that they have been irritable for at least half the time during their current depressive episode. The antidepressants prescribed in the study included medicines like Prozac and Effexor, which affect levels of the neurotransmitters serotonin and norepinephrine.

Curiously, irritability is not one of the nine “core” symptoms currently listed in the *Diagnostic and Statistical Manual* (the “DSM 5”) used by doctors to diagnose major depression—although it is included among the core symptoms in major depression affecting children and adolescents.

Noting the omission of irritability as a “core” adult major depression symptom in the DSM, the research team, led by **Madhukar Trivedi, M.D.**, a 2002 BBRF Independent Investigator and 1992 Young Investigator at UT Southwestern Medical Center, set out to discover whether it had any predictive power to help doctors better direct their patient's care. The team also included **John Rush, M.D.**, a 2000 Falcone Prizewinner and 1991 BBRF Distinguished Investigator.

The team assessed their idea in two patient samples drawn from six primary care hospitals and nine psychiatric care sites. Results in the first sample, which included 664 patients with major depression, were then tested on the second and independent cohort, numbering 163 patients. A majority of

the patients in the trial, aged 18 to 75, were white, female and non-Hispanic. Participants were assessed after their first 4 weeks of treatment, and again after 8 weeks.

Those whose irritability declined by 25% or more in the first 4 weeks with antidepressant treatment were about twice as likely to have a remission by the end of the 8th week. This fact was independent of whether their depression symptoms also diminished during those first weeks of treatment. Importantly, when both factors—irritability and severity of depression symptoms—were combined, the researchers found they could determine “with high accuracy” individual patient outcomes after 8 weeks in the independent, “second” patient sample.

To increase the chances of their findings being “clinically actionable,” the team developed a calculator based in part on a five-item irritability self-report for patients to use in coordination with their doctor. Changes in irritability, combined with evidence of response in “core” depression symptoms, enable doctors to predict which patients should continue on their current medications and which—those unlikely to have a remission based on the early evidence—should have their medications adjusted. It is not yet known if the irritability “predictor” applies to other kinds of antidepressant treatments. The team advises that further studies are needed, among other things, to test the validity of their calculator with other measures of depression severity. ❖



## Therapy Update

### Recent News on Treatments for Psychiatric and Related Brain and Behavior Conditions

#### DEEP-BRAIN STIMULATION SHOWED MULTI-YEAR EFFECTIVENESS IN SEVERELY DEPRESSED, TREATMENT-RESISTANT PATIENTS

A new long-term follow-up study of 28 people whose serious, treatment-resistant major depression was treated surgically with deep-brain stimulation (DBS) has found that “most of the patients experienced a robust and sustained antidepressant response.” The follow-up period ranged from 4 to 8 years. The results were published in the *American Journal of Psychiatry*.

Each participant in the study failed to respond to at least four prior antidepressant treatments, including electroconvulsive therapy (ECT) at least once. An estimated one-third of patients with major depression do not respond to standard therapies, which include psychotherapy, antidepressant medications, and various forms of brain stimulation.

DBS requires an invasive procedure involving the implantation of a battery-powered device often compared with a cardiac pacemaker. Via precisely positioned electrodes, it delivers continuous stimulation to a small area in the brain called Area 25 and the surrounding subcallosal cingulate white matter, which is implicated in depression. Multiple published studies by different teams over the years have been inconsistent in assessing the short-term impact of DBS.

DBS for treatment-resistant patients with severe major depression was pioneered in 2005 by a team co-led by **Helen S. Mayberg, M.D.** and colleagues at the University of Toronto, work that was supported by Dr. Mayberg’s 2002 BBRF Distinguished Investigator award. She is the senior author of the new study. A three-time BBRF grantee, winner of the Falcone Prize in 2007 and a BBRF Scientific Council member, she has continued to study DBS over the years, currently at the Icahn School of Medicine at Mount Sinai, where she is Professor and Director of the Center of Advanced Circuit Therapeutics.

The efficacy of DBS for severe, refractory major depression was called into question several years ago, when a multi-center clinical trial was halted by its industry sponsors

after only 6 months, a cut-off point chosen in advance. At that point, statistical evidence of the procedure’s advantage over placebo had not yet been demonstrated.

“Despite the fact that larger trials were halted early,” Dr. Mayberg comments, “what my colleagues and I were seeing as we continued to follow patients from our initial trials was that over time, they were getting better, and not only that, they were staying better. So we stayed the course.”

The new study reports on results in Dr. Mayberg’s patients who received DBS surgery between 2007 and 2013 at the Emory University School of Medicine—all performed by the same surgeon and using the same implanted device. The study found that 21 of the 28 participants met the treatment-response criterion of at least 50% for more than half of their duration of participation in the study. These results were associated with decreased overall symptom severity and increased ability to function. The team charted 56 serious adverse events related to DBS over a total of 178 patient-years, a medical complication rate they said was comparable to that seen when DBS is used in FDA-approved indications, including Parkinson’s Disease and obsessive-compulsive disorder. There were no suicides among the patients involved in the trial.

“Given that patients with treatment-resistant depression are highly susceptible to recurrent depressive episodes, the ability of DBS to support long-term maintenance of an antidepressant response and prevention of relapse is an advance that can mean the difference between getting on with your life or always looking over your shoulder for your next debilitating depressive episode,” Dr. Mayberg commented.

**Paul Holtzheimer, M.D.**, a 2016 BBRF Independent Investigator and 2007 Young Investigator; and **Steven Garlow, M.D., Ph.D.**, a 1997 BBRF Young Investigator, were also members of the team.

## STUDY FINDS LITHIUM HAS ADVANTAGES OVER OTHER MOOD STABILIZERS IN YOUTHS WITH BIPOLAR DISORDER

For years, the drug lithium has been widely regarded as a first-line treatment for adults with bipolar disorder, but the question of whether lithium should be used for the management of mood symptoms in youths with bipolar disorder has remained open. This is due to the lack of studies regarding its effects on suicidal attempts or ideation in youths—symptoms frequently experienced in bipolar disorder. This gap has now been addressed by a team whose members include **Boris Birmaher, M.D.**, a 2013 BBRF Colvin Prizewinner, and first author Danella Hafeman, M.D., Ph.D., both at the University of Pittsburgh.

The team took advantage of the ongoing Course and Outcome of Bipolar Youth (COBY) study that has been following 413 youths recruited in Pennsylvania, California, and Rhode Island for over 15 years. The participants had a diagnosis of bipolar disorder and were aged 7 to 17 when the study began. The study is longitudinal, meaning that researchers have been following the young people over a period of years, with assessments made on average every 8 months.

Data from 340 of the participants was analyzed, including 2,638 follow-ups for periods up to 10 years. Of these follow-ups, 886 were in participants who were being maintained on lithium, and 1,752 in participants who were taking other medications, including second-generation antipsychotics, stimulants, and to a lesser extent, valproate, lamotrigine, and antidepressants. The team only counted assessments in which participants were still under 18 years of age and were adhering to their mood-stabilizing prescription three-fourths of the time or more since the prior assessment.

The results were encouraging to the team: “We found that lithium use was associated with fewer suicide attempts, fewer depression symptoms, better psychosocial function, and less parent-reported aggression,” they said, as compared with other mood stabilizing medicines.

The new Pittsburgh study was not a randomized control trial, the gold standard for shorter-term trials, since participants and those who assessed them were not “blind” to which mood stabilizer they were taking. Still, the sample used did provide a good opportunity to assess medication effects in a large sample of young people, and to follow them over a long period of time under “real-world conditions,” the team said.

The large research team also included **Martin Keller, M.D.**, a member of the BBRF Scientific Council and winner of the 1998

Selo Prize; and **Benjamin Goldstein, M.D., Ph.D.**, 2014 BBRF Independent Investigator, 2007 Young Investigator and 2018 Colvin Prizewinner.

## EARLY-MORNING BRIGHT-LIGHT THERAPY HELPED PATIENTS WITH PTSD SYMPTOMS

In a small pilot study, researchers have obtained encouraging results in using bright-light therapy to treat people with symptoms of post-traumatic stress disorder (PTSD).

In addition to trauma-related symptoms such as flashbacks, people with PTSD often report depressed mood and reduced quantity and quality of sleep. The partial overlap in symptoms with those of depression led **Alyson K. Zalta, Ph.D.**, a 2016 BBRF Young Investigator now at the University of California, Irvine, and colleagues, to test whether bright-light exposure early in the day might help in PTSD, as it sometimes can in depression and seasonal mood disorder. Helen Burgess, Ph.D., of the University of Michigan, co-led the study.

Past tests of bright-light therapy indicate that its effectiveness has much to do with the time of day in which it is delivered and the frequency and duration of treatments. There is evidence that people with the most intense PTSD symptoms have what scientists call “an evening chronotype.” This means the body’s natural 24-hour circadian rhythm is shifted later in the day, resulting in sleep disturbances.

Dr. Zalta and colleagues used a commercially available, wearable bright-light device to see whether one hour of bright-light exposure in the morning might shift patients’ circadian cycle back “toward morningness.” The device used in the trial, called Re-timer, looks like a pair of oversized goggles with built-in LED lighting elements surrounding the eyes. The team also devised a “placebo” version of the same device. In a group of 15 volunteers who self-reported PTSD symptoms, nine received the “active” device and six the placebo version.

The results after 4 weeks of self-administered early-morning treatments led the team to conclude that bright-light treatment “was acceptable and feasible for patients,” and despite the small size of the study, appeared to help those in the “active” group, with improvements over baseline symptoms.

The team hopes to test the concept on a larger scale, and will explore ways of enhancing patient compliance within the range they regard most likely to produce therapeutic results. The team also included **Mark Pollack, M.D.**, a 2003 BBRF Independent Investigator. ❖

# GLOSSARY

**FRONTAL OR PREFRONTAL AREAS:** These terms usually refer to the cerebral cortex, the seat of higher brain functions located at the front of the frontal lobe of the brain. This is the most evolved part of the brain, responsible for cognition and the integration of other brain inputs that inform complex behaviors. Limbic areas feed into the cortex, which performs higher processing on the inputs.

**GABA:** A neurotransmitter, or message-carrying chemical, in the brain that inhibits the strength of signals traveling between excitatory neurons, notably those activated by glutamate.

**LIMBIC AREAS:** The term refers to parts of the brain that perform lower-order emotional processing based on input from the senses. Sometimes referred to as “subcortical,” the limbic system is located beneath the cortex in the midbrain and includes the amygdala.

**MANIA:** A state of elevated arousal that is the “flip side” of depression in bipolar disorder (BD) and experienced at least once, helping to distinguish BD from unipolar depression. It is characterized by high energy, rapid speech, decreased need for sleep, often unrealistic optimism or enthusiasm, irritability, distorted judgment, and excessive risk-taking.

**METABOLIC DISORDER:** Metabolism refers to multitude of chemical reactions that drive life-processes and sustain living things. Among many other things, it involves the conversion of food into energy and the molecules that form cells and organs. Diabetes is a well-known disorder of metabolism—but anorexia nervosa may also be, new research suggests, reflecting its connection with the biological underpinnings of feeding behaviors.

**MONOAMINE NEUROTRANSMITTERS:** A large class of message-carrying neurotransmitters that share certain structural and biochemical features. Examples include serotonin and norepinephrine, whose systems are the targets of some antidepressant drugs. Early work on the anesthetic ketamine, which has proved to have rapid-acting antidepressant properties, began with the decision to explore beyond the “monoamine hypothesis” of depression. Ketamine and esketamine engage with the glutamate neurotransmitter system.

**PLASTICITY:** refers to the brain’s ability to change, typically in response to experience. Plasticity is the basis of learning and depends upon the ability of synapses—the points of connection between communicating neurons—to change in strength. Learning involves a strengthening of synapses. Erasure of memory, which is part of normal short-term memory management, involves the weakening of synaptic connections. The ability to recover from depression and other psychiatric illnesses is thought to depend, in part, on plasticity.

**POSTPARTUM DEPRESSION:** The most common complication of childbirth, affecting about 10%–15% of new mothers. It can begin in the weeks before childbirth or in the days, weeks and months following it. In addition to its link with elevated suicide risk, it can seriously impair the ability of a new mother to care properly for her newborn, in turn raising the child’s risk for developing psychiatric disorders in subsequent years.



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