Helping Children With Emotional Problems — a Q&A

Ten New BBRF Distinguished Investigators

Brain&Behavior MAGAZINE

SUMMER 2024

A Tribute to the late Herbert Pardes, M.D., BBRF Co-Founder and Scientific Council President

PRESIDENT'S LETTER

This issue of *Brain & Behavior Magazine* is dedicated to Herbert Pardes, M.D., a co-founder of the Brain & Behavior Research Foundation and the founding president of the BBRF Scientific Council. Dr. Pardes passed away at his home in New York City on April 30, 2024.

Dr. Pardes was an internationally renowned advocate for mental health, academic medicine, medical research, education, children, access to care, and humanism and empathy in care delivery. Trained as a psychiatrist, he was Chairman of three academic psychiatry departments and for nearly 12 years led the largest hospital in New York City, NewYork-Presbyterian, as its President and CEO.

During the presidential administrations of Jimmy Carter and Ronald Reagan, Dr. Pardes was Director of the National Institute of Mental Health (NIMH). Among his many legacies at the NIMH was his enthusiastic support for basic and clinical research in a dawning era of biological psychiatry deeply informed by neuroscience.

Our **TRIBUTE TO DR. HERBERT PARDES** in this issue features a biographical **IN REMEMBRANCE** article, followed by **CELEBRATIONS** of his life and achievements contributed by 13 members of our Scientific Council. The tribute concludes with an excerpt from Dr. Pardes' autobiography, published just prior to his passing, in which he describes how BBRF was founded and explains its importance in advancing research and reducing stigma.

Scientific Council member Helen S. Mayberg, M.D., speaks for many in offering these words about Dr. Pardes: "Herb did so many things that changed the way we think about mental health: catalyzing research, fighting stigma, mentoring, collaboration, scientific philanthropy, building integrated models of care, recognizing humanitarian deeds beyond science." The close relationships Dr. Pardes forged with members of the Council were among the highlights of his career. He wrote: "One of the thrills of my career has been to know some of the research and clinical innovators who have helped to change the game. They and those they now train to carry the work forward have inspired and motivated me." Of course, Dr. Pardes inspired and motivated all of us. We shall miss him.

This past May, BBRF's Board of Directors announced that Dr. Judith Ford was appointed President of the BBRF Scientific Council, and that Dr. John Krystal would continue to serve as BBRF's Scientific Council Vice President.

This issue also features news of the 10 senior-level investigators who were selected by the Council to receive **BBRF DISTINGUISHED INVESTIGATOR GRANTS** for 2024. We thank the WoodNext Foundation for making these grants possible. Our **ADVICE ON MENTAL HEALTH** story captures a conversation I had with Scientific Council member Daniel S. Pine, M.D. of the NIMH about how parents and teachers can help children and adolescents with emotional problems. As always, we also report recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and on important scientific advances moving the field forward in **RECENT RESEARCH DISCOVERIES.**

I thank you for being an important part of the BBRF community. Together, we will continue to fund innovative and impactful research that will pave the way forward for scientific advancements that are making a difference in the lives of those living with mental illness.

Sincerely,

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.

CONTENTS

President & CEO
Jeffrey Borenstein, M.D.

President, Scientific Council
Judith M. Ford, Ph.D.

Vice President, Scientific Council
John H. Krystal, M.D.

OFFICERS

Chairman
Geoffrey A. Simon

Vice President
John Osterhaus

Secretary
Judy Genshaft, Ph.D.

Treasurer
Miriam E. Katowitz

DIRECTORS
Carol A. Atkinson
Donald M. Boardman
J. Anthony Boeckh
Martin H. Borell
John Kennedy Harrison II
John B. Hollister
Carole H. Mallement
Milton Maltz
Jeffrey R. Peterson
Marc R. Rappaport
Mary Rubin
Virginia M. Silver
Ken Sonnenfeld, Ph.D., J.D.
Barbara K. Streicker
Barbara Toll
Robert Weisman, Esq.

PUBLICATION CREDITS

Writers
Peter Tarr, Ph.D.
Lauren Duran

Editors
Lauren Duran
Peter Tarr, Ph.D.

Designer
Gene Smith

IN REMEMBRANCE

HERBERT PARDES, M.D.
July 7, 1934—April 30, 2024

Herbert Pardes, M.D., president of the BBRF Scientific Council since its inception, died on April 30, 2024 at his home in New York City. He was 89. In 1987, Dr. Pardes was among the small group of patient advocates and physicians who founded the National Alliance for Research on Schizophrenia and Depression (NARSAD), renamed the Brain & Behavior Research Foundation in 2011.

Trained as a psychiatrist, Dr. Pardes served as President and Chief Executive Officer of NewYork-Presbyterian Hospital and the NewYork-Presbyterian Healthcare System from 2000 through 2011. Subsequently he was Executive Vice Chairman of the Board of Trustees of the hospital. Under his leadership, NewYork-Presbyterian became one of the premier hospitals and comprehensive healthcare institutions in the United States.

Dr. Pardes was an outspoken advocate for mental health, academic medicine, medical research, education, children, access to care, humanism and empathy in care delivery, and information and genomic technology in medicine. He chaired psychiatry departments at three institutions: Downstate (New York) Medical Center, the University of Colorado School of Medicine, and Columbia University College of Physicians and Surgeons.

Between 1978 and 1984, during the presidential administrations of Jimmy Carter and Ronald Reagan, Dr. Pardes was Director of the National Institute of Mental Health (NIMH) and the United States Assistant Surgeon General. He had the opportunity to head the nation's mental health agency at a time when it was vital to define for the first time the true prevalence of mental illnesses in society; to understand the extent and impact of mental and physical comorbidities; and to respond to the looming crisis of those with severe and often untreated serious mental illness. He was also an enthusiastic supporter of research in a dawning era of biological psychiatry deeply informed by neuroscience.

In 1989-90 Dr. Pardes was President of the American Psychiatric Association (APA). He served on some fifteen editorial boards and as board member and consultant to many not-for-profit organizations and committees. He served on commissions related to health policy appointed by Presidents George Bush and Bill Clinton, including the Presidential Advisory Commission on Consumer Protection and Quality in the Healthcare Industry and the Commission on Systemic Interoperability. He also served as Chairman of the Greater New York Hospital Association, the Hospital Association of New York, the Association of American Medical Colleges, and the New York Association of Medical Schools.

RAPID ASCENT

Dr. Pardes received his undergraduate degree from Rutgers University, where he graduated *summa cum laude* and was elected to Phi Beta Kappa. He attended medical school at the Downstate Medical Center, where he graduated Alpha Omega Alpha. This was followed by a year of psychiatry residency training before he was drafted into the Army and appointed head of the Mental Health Center at Fort Meyer in Arlington, Virginia. He returned for the completion of his residency and undertook a fellowship in the Doctor of Medical Science program at the State University Center. From there he started a career in academic medicine at Downstate Medical Center as Assistant Professor. He rapidly rose to Chairman of that department and served in that role until 1975, when he moved to the University of Colorado to chair its psychiatry department.

Following his years of leadership at the NIMH, from 1989 to 2000 Dr. Pardes served he served as the Dean of the Faculty of Medicine at Columbia University College of Physicians and Surgeons and Vice President for Health Sciences at Columbia University. As Vice President, he oversaw the School of Dentistry, the School of Nursing, and the Mailman School of Public Health, in addition to leading the medical school. During Dr. Pardes' tenure, dramatic improvements were made in the medical center's facilities, with the construction of new buildings focusing on technology, diabetes, and research, and development of a plan to build a new center dedicated to cancer research. In addition, he led efforts to build a new Psychiatric Institute Research Building (which was named for him), secure the naming and relocation of the Mailman School of Public Health, and oversaw the acquisition of space by the medical school in Health Sciences for dramatic expansion of educational and research space.

At Columbia, Dr. Pardes ushered in a new era of academic innovation. He established one of the first academic departments of informatics at a medical school in the country, and launched a fundraising effort for the Health Sciences

Dr. Pardes with First Lady Rosalynn Carter.

which totaled approximately $1 billion during his 11-year term. He revised the curriculum to introduce clinical medicine earlier and to diversify the curriculum offerings to include a greater focus on the social and related aspects of medicine for medical students. He also played a central role in developing the Dementia Center and the Berrie Diabetes Center, and recruited some of the top minds in medicine and health science from around the country to the university.

After serving as Dean and Vice President at Columbia, he was asked to assume the leadership of the newly integrated NewYork-Presbyterian Healthcare System, one of the largest hospital systems in the world. Serving as President of NewYork-Presbyterian from 2000 to 2011, he led the recruitment of a vast number of top-notch hospital staff, clinicians and clinical scientists. These recruitments, along with close to $2 billion in philanthropic contributions over 11 years, enabled the hospital to dramatically increase the quality and variety of its programs, continue to recruit highly talented clinical and academic physicians, and change the tenor of the hospital to a far more patient-centered and personally responsive enterprise.

In his memoir, published earlier this year, Dr. Padres explained the immense challenge of bringing together two distinguished hospital systems (New York Hospital and Columbia-Presbyterian Hospital) and their 20,000 employees to work toward common goals. "We began in each instance by making a major commitment to excellence—improving not one thing or a few things, but many things. Big things. The more we improved, the more we found we were able to do. Excellence was institutionalized. It became contagious."

Dr. Pardes stressed how hospital employees are always exposed to high risk and danger when on the job, and how, fundamentally, those who choose this line of work do so, nearly always, because they care about other people. Healthcare jobs carry immense responsibility, and perfection is the standard

against which one is judged. Yet, he noted, "we live in a time when trust in hospitals and healthcare personnel, including the most accomplished doctors and nurses, is appallingly low." In this sense, he said, his memoir was "offered as a corrective—a reminder of what is right about medicine, and about how its excellence helps define what is best about our society."

CONTRIBUTIONS TO PSYCHIATRY AND MENTAL HEALTH

Dr. Pardes played a major role in many aspects of psychiatric care, education, and research. He served as Chair of the American Association of Chairs of Departments of Psychiatry, and worked to advance collaboration between citizen's advocacy groups and providers, activity that led to the formation of the National Alliance on Mental Illness (NAMI) in 1979 and NARSAD in 1987. (Dr. Pardes tells of the founding of NARSAD/BBRF in an excerpt of his memoir, which follows on page 14.) He also served as head of the Scientific Review Committee of Autism Speaks; was Vice Chair of the Human Genome Center in New York City; and Chair of the Lieber Institute for psychiatric research, affiliated with Johns Hopkins University.

His involvement with the founding of the Lieber Institute was one of many endeavors in which Dr. Pardes joined hands with the Lieber family. BBRF was their original and perhaps most endearing collaboration. Steve Lieber, BBRF's late Board Chairman, and the late Connie Lieber, who led NARSAD and BBRF for over 20 years, were among his closest friends and confidantes. He spoke effusively about them and often remarked on how his life was deeply affected following their loss. "Connie and Steve, whom I miss terribly, were the most selfless, wise, and generous leaders I encountered in all my years in mental health," he wrote.

Dr. Pardes was a member of the Institute of Medicine and the American Academy of Arts and Sciences, and received the United States Army Commendation Medal. He is also a recipient of the Sarnat International Prize for leadership in the field of mental health, and is the first recipient of the annual prize awarded by BBRF in his name, The Pardes Humanitarian Prize in Mental Health. The Pardes Prize recognizes a physician, scientist, public citizen or organization whose extraordinary contribution has made a profound impact on advancing the understanding of mental health and providing hope and healing for people who are living with mental illness.

In his memoir, Dr. Pardes above all stressed the compassion and humanitarian concern that he said were always, for him, at the heart of medicine. These were values that he traced back to his experience of serious illness, as a child of 7. Diagnosed with Perthes disease, he was placed in a nearly full-body cast for the better part of a year. He remembered being treated competently but coldly by doctors and nurses, and feeling great fear while alone at night in the hospital ward. Empathy for the patient and the patient's family informed his

Dr. Pardes with sons Lawrence (left) and James.

approach as a psychiatrist and physician, but also as a leader of large healthcare institutions.

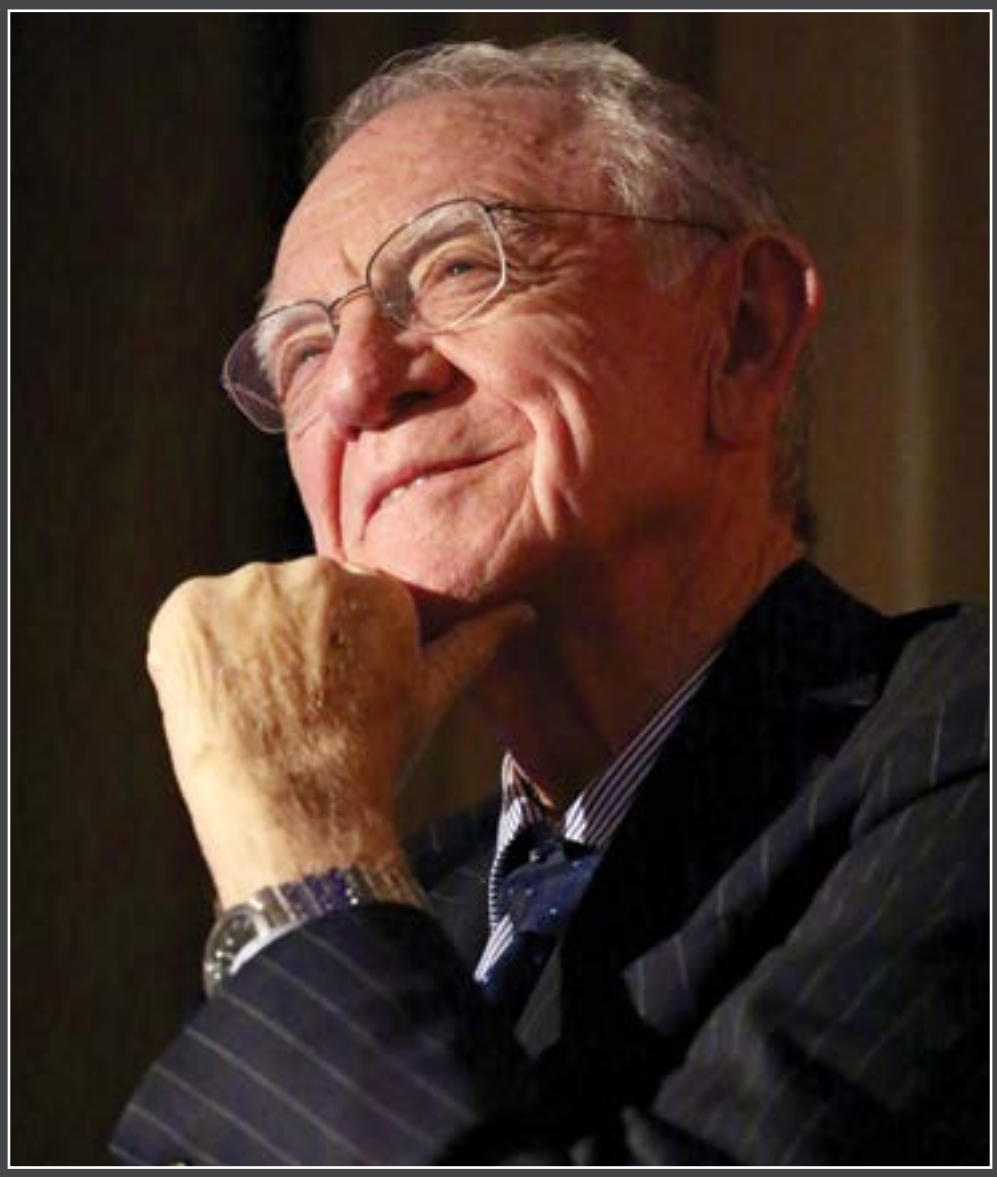
In a recent essay on how to improve healthcare in America, Dr. Pardes placed stress on integrating the care of "bodily" and "mental" illnesses, in this way "fully mainstreaming" the care of psychiatric disorders. He urged devoting particular attention to preventive care, especially for new mothers and their children. Citing decades of research performed by BBRF Scientific Council member Dr. Myrna Weissman and colleagues, he noted the immense benefit to be gained in treating new mothers with depression and other psychiatric problems, a practice that Dr. Weissman and others have shown to prevent or significantly reduce the occurrence of behavioral problems in their children. Dr. Pardes also devoted considerable attention to a problem he and colleagues worked hard to address during his tenure at the NIMH: how to compassionately and much more effectively treat individuals with serious, disabling mental illnesses including chronic schizophrenia, bipolar disorder, and major depression. He took pride in the Mental Health Systems Act, legislation passed at the end of the Carter presidency designed to provide more and better care for the seriously mentally ill, among others. The law was repealed early in the administration of President Reagan, one of several reversals in mental health policy whose deleterious impacts Dr. Pardes worked vigorously and effectively to lessen. Tragically, he noted, his team was not able to secure restoration of federal support for community mental health, which he suggests is one of the roots of the crisis we have faced ever since in caring for people with serious mental illnesses.

The plight of those with chronic, serious mental illness is informed by another historic phenomenon in which Dr. Pardes was both witness and participant: the response of medical and political institutions to the emptying of the state asylums—"deinstitutionalization"—as it gained momentum in the 1960s and 1970s. During these years he was both a deeply committed participant and caregiver, who helped to found a community mental health center in the underserved community of Bedford-Stuyvesant, Brooklyn. Offering thoughts on how to "navigate out of the crisis" today facing those disabled by serious mental illness—especially the 100,000 or more who are not receiving sufficient care and not likely for a variety of reasons to be rehabilitated—Dr. Pardes wrote: "Is it possible that we as a nation—mighty and rich beyond the imagination of our Founders—lack the *means* to properly care for the most vulnerable among us?" He rejected that notion. "What has been missing over these last 40 years is the will to act. This means, really, the will to pay for better outcomes. If we believe that it is important to treat the most vulnerable mentally ill, particularly those who need special help staying on medications and finding stability in society, as well as those who are so sick that institutional care is required for the sake of their own safety and the public's, then we have to be willing to pay the price." He felt that good and decent societies are those whose members are willing to address the problems faced by the least fortunate.

Herb Pardes and Nancy Wexler.

Dr. Pardes and his late wife, Judith, had three sons, Lawrence, Stephen, and James, who, with their wives, survive him along with six grandchildren. Also surviving him is his partner of many years, Dr. Nancy Wexler. She is an Albert Lasker Public Service Award winner, Columbia University professor, and a leader of research efforts that culminated in the identification of the variant gene that gives rise to Huntington's Disease (HD), as well as the genetic test and specialized genetic counseling that have been the result of Huntington's research. ❖ **PETER TARR**

13 Leaders in Psychiatric Research Celebrate the Contributions of Dr. Herbert Pardes, Founding President of BBRF's Scientific Council



We asked several members of BBRF's Scientific Council to reflect upon Dr. Pardes' remarkable life, his dedication to psychiatry and mental health, his vigorous support for research, and his role in helping to make BBRF possible.

William E. Bunney, M.D.

University of California Irvine School of Medicine

BBRF Scientific Council

2001 BBRF Falcone Prize

1997 BBRF Distinguished Investigator

Herb Pardes was a unique and outstanding individual who made remarkable contributions to the field of mental health. I had multiple interactions with him over many years. During my 19 years in the Intramural Program at the NIMH, Herb appointed me Acting Director of the entire Basic and Clinical Intramural Program.

Another important area of interaction with Herb involved BBRF, where he asked me to serve on the Committee that selected a scientist to receive the Colvin Prize for Outstanding Achievement in Mood Disorders Research. He also asked me to chair the Committee that selected the international winner of the Lieber Prize for Outstanding Achievement in Schizophrenia Research.

My ongoing interactions with Herb over the years were always positive and I greatly appreciated his support. Herb's dedication and contributions were absolutely critical to the success of the Brain and Behavior Research Foundation. He was nationally and internationally recognized for his leadership in many aspects of mental health. He will be greatly missed.

William T. Carpenter, M.D.

University of Maryland School of Medicine

BBRF Scientific Council

2019 BBRF Pardes Humanitarian Prize

2000 BBRF Lieber Prize

2008, 2001, 1996 BBRF Distinguished Investigator

We have now lost the physical presence of this wonderful man. But his effect on so many of us changed our ability to advance knowledge and understanding regarding mental illness. Herb Pardes has brought together persons with mental illness, persons eager to find solutions to treat or prevent illness, persons committed to advancing knowledge, to enable prevention or cure, and persons willing to invest in supporting these objectives.

Herb has led the BBRF from a feeble start to incredible success as a research provider built with personal donations that are used to advance knowledge from scientists across the world. Those of us who have the privilege of working closely with him know the incredible gift he has made to advancing science in support of curing and preventing mental illness. While we have now lost this wonderful person, we live better lives with what we have learned and experienced. He was always with us, and with so many others. He stays in our hearts and minds.

Judith Ford, Ph.D.

University of California, San Francisco

President, BBRF Scientific Council

2003 BBRF Independent Investigator

I first met Herb Pardes 15 years ago, over the phone, when he called to tell me that I had been elected to the Scientific Council of NARSAD, as it was then known. I was touched that he made this call personally—he did not relegate it to his staff or email. He approached the Scientific Council as family, a family that he started and maintained. I loved the summer meetings of the Council when I had a chance to see how the best of the best runs meetings—he was efficient, effective, and fair. He presided over long discussions managing different points of view, summarizing what was said, and nimbly moving us forward. I wish I had had a chance to ask him how he does it, and I am hoping that his leadership secrets will be revealed in his autobiography.

When I was asked to join the leadership of the Young Investigator grants committee, I was honored and excited to play a more vital role in BBRF's mission. It was then that I got the opportunity to work more closely with Herb, and in recent years, stepped in for him when he needed a bit of help. It is daunting to step into his shoes now, but I am a BBRF zealot and want to do whatever I can to keep Herb's vision alive and move the Scientific Council forward through this transition.

Robert Freedman, M.D.

University of Colorado School of Medicine

BBRF Scientific Council

2015 BBRF Lieber Prize

2006, 1999 BBRF Distinguished Investigator

Herbert Pardes M.D. uniquely excelled at seeing connections between people—connections past, present, and future. He excelled at making full use of existing connections, in strengthening connections that were dormant, and in creating new connections among people who had been unaware of each other. He brought many of us, including myself, out of the isolated nooks of our research laboratories. He connected us with people who could help us and whom we could help, not only other scientists, but clinicians and community leaders as well. Herb was not hesitant to add his imprimatur to a new connection, so that each party would take it seriously and work to make it worthwhile.

I was his last recruitment when he was Chair of the Department at the University of Colorado. I saw my career as an investigator of the detailed electrophysiological actions of antipsychotic drugs at the single neuron level in animal models. Herb saw much more—he introduced me to clinicians and scientists at my own medical school and beyond. The connections he made helped me to see that that my neuroscience could and should be used to improve clinical treatment and ultimately to prevent mental illness.

He also asked much of me. He foresaw that I could lead the department that he left behind at Colorado and contribute my expertise to the national organizations that he saw as important to psychiatry—first and foremost the Brain and Behavior Research Foundation.

So many of us valued Herb's help and cajoling because it was always clear to us that he had a higher purpose—the betterment of all of us and the conquering of mental illness, just as other diseases are being conquered. If there is a monument that he would value most, I think it would be the Brain and Behavior Research Foundation, his forging of a unique, enduring bond between the community and the scientists whom he foresaw fulfilling that purpose.

Dilip V. Jeste, M.D.

Social Determinants of Health Network

BBRF Scientific Council

2002 BBRF Distinguished Investigator

I knew Herb from the time I was a research fellow at NIMH. He was a wonderful mentor, leader, friend, and advocate. I was always touched by his genuine kindness and compassion. He was a role model for countless people. It is really difficult to imagine how one person can have all the skills and talents he had. He was unquestionably one of the most important psychiatrists in the world of all times.

One of Herb's singular accomplishments as the NIMH Director was managing to fund $228 million in research during two fiscal years after President Reagan and his budget advisor David Stockman drained NIH funding in 1980-81. This would have been impossible for any other leader in medical and especially mental health research. I was also taken by his acceptance of the offer to be the CEO/President of NewYork-Presbyterian. What distinguished Herb from others is how he made the most difficult jobs in the world seem so easy! Indeed, it was his ability to be positive and to be perceived as positive that makes the impossible possible.

I don't know of anyone else who combines compassion and empathy with integrity in the large field of healthcare as well as Herb did. He never moved away from his forever motto: *The patient comes first.* One of my areas of research is wisdom. To me, Herb was the ultimate personification of wisdom.

John H. Krystal, M.D.

Yale University School of Medicine

Vice President, BBRF Scientific Council

2019 BBRF Colvin Prize

2006, 2000 BBRF Distinguished Investigator

1997 BBRF Independent Investigator

My first memory of Dr. Pardes dates to 1987 and served as a master class in scientific leadership. I was a third-year psychiatry resident who wrangled a liaison role to the American Psychiatric Association Research Council, then chaired by Dr. Pardes and facilitated by Dr. Harold Pincus.

I watched with awe as Dr. Pardes kept this group on track, despite numerous efforts by some to derail discussion, in order to achieve a number of important objectives. What I learned by watching him was that you could bring people who fundamentally disagreed to consensus through clarity of vision, openness to differing opinions, the judicious use of humor, and to frame discussions in a way that moved discussions toward resolution.

I never forgot that master class and I was thrilled to continue that class when I joined the Scientific Council and other groups in which he was active. He was a singular individual whose loss is deeply felt.

Francis S. Lee, M.D., Ph.D.
Weill Cornell Medicine
Cornell University
BBRF Scientific Council
2010 BBRF Independent Investigator
2005, 2002 Young Investigator

I have had the privilege of working with Herb Pardes for more than 10 years at the Center for Youth Mental Health (formerly Youth Anxiety Center). One of my fondest professional experiences was serving as research co-director (along with Dr. Blair Simpson) as the Center was first launched. Herb convened weekly meetings with the Center faculty, and I observed his formidable talents as a leader with a vision to create a new type of Center that spanned basic research to clinical care of youth. He was a master at bringing together and inspiring a variety of faculty and stakeholders to work collectively on a common goal.

Over the years, Herb and I continued to meet regularly as he took an interest in my academic career. In our meetings, I would update him, and he would impart his typically sage advice. He would share stories about his own experiences in various leadership positions. I learned firsthand how one lives a life in the service of a greater good. I did not realize it at the time, but these meetings were a rare and generous gift imparted to me by a remarkable person—they had a profound influence on me at an inflection point in my career. To this day, I still reflect on his advice and am deeply grateful for his mentorship and friendship.

Helen S. Mayberg, M.D.
Icahn School of Medicine at Mount Sinai
BBRF Scientific Council
2007 BBRF Falcone Prize
2002 BBRF Distinguished Investigator
1995 Independent Investigator
1991 Young Investigator

My interactions with Herb spanned nearly 30 years, all as part of the NARSAD/BBRF family. Herb always seemed the perfect paradox--both a leader and an everyman; and he often seemed to assume both roles simultaneously. It was one of his many superpowers.

Herb did so many things that changed the way we think about mental health: catalyzing research, fighting stigma, mentoring, collaboration, scientific philanthropy, building integrated models of care, recognizing humanitarian deeds beyond science—that to make any list understates his deep and sustained impact on our collective culture.

Herb was a visionary thought leader, but he didn't live in abstractions. He was both an optimist and pragmatist who saw his ideas through with deliberate and dogged persistence, always aware that it took a clear and well-thought-out plan with all hands on deck to achieve big goals. To be in a meeting with Herb as chair was a masterclass in how to listen deeply to all sides, while also ensuring an actionable plan by meeting's end.

Similarly, a phone call from Herb with an ask for help was never ambiguous or frivolous. He always made you feel that your participation would make a difference. He inspired by example, and we are all better for learning to follow his lead. I know I am.

Herbert Y. Meltzer, M.D.

Northwestern University Feinberg School of Medicine

BBRF Scientific Council

1992 BBRF Lieber Prize

2007, 2000, 1994, 1988 BBRF Distinguished Investigator

As one of the small group of mental health researchers interested in starting what was to become the NARSAD Scientific Council, I worked closely with Herb Pardes on all aspects of the effort to shape the policies that guided his efforts to get it right from the start.

Great credit is due to Herb and his expert leadership for the success of our policies, evident in the amazing growth of the Scientific Council, whose members have contributed their expertise, and for the ability of NARSAD and later BBRF to work with the families to secure funding for research. All of this makes BBRF one of the premier organizations dedicated to research and education in mental health to have emerged worldwide over the last several decades. Herb Pardes's unselfish advice, good humor, and wisdom provided the leadership which led to our success.

Eric J. Nestler, M.D., Ph.D.

Icahn School of Medicine at Mount Sinai

BBRF Scientific Council

2009 BBRF Falcone Prize

2008 BBRF Goldman-Rakic Prize

1996 BBRF Distinguished Investigator

Herb Pardes made extraordinary contributions to the field of psychiatry. As director of the NIMH from 1978-1984, Herb strengthened the scientific mission of NIMH and reinforced the importance of fundamental biology in driving our nation's efforts to better understand and treat mental illness. Herb later built Columbia Psychiatry into a powerhouse Department—one of the best in the country—by establishing key research groups across the spectrum of basic and clinical science.

He also uniquely engaged patient advocacy groups and earned their support for this renewed focus on the central importance of research. He was instrumental in founding NARSAD in 1987. As founding president of the Scientific Council, Herb garnered a spectacular level of philanthropic support from the Lieber family and many others to establish and sustain a new paradigm to provide research support for young investigators in mental health research. This was a crucial advance for our field which, unlike many others, lacked this type of investment. Since 1987, NARSAD/BBRF has awarded close to half a billion dollars to more than 5,000 scientists globally, arguably having a greater impact in building and nurturing our psychiatry research workforce than any other organization in the world other than NIH. This impact is testimony to Herb's creative vision, commitment, and perseverance and defines his extraordinary legacy. He will be missed.

Alan F. Schatzberg, M.D.

Stanford University School of Medicine

BBRF Scientific Council

2005 Falcone Prize

Herb Pardes was a giant in our field and succeeded at the highest levels of mental health academia, professional associations, and government. He was a successful Chairman at the University of Colorado and Columbia University because he had a great ability to select faculty whom he could nurture to become "winners" as well as his own interpersonal charm and warmth. Those traits were beacons for me personally on how to succeed as a Chair of Psychiatry and Behavioral Sciences, in my case at Stanford University.

My own personal interactions with Herb were largely around the American Psychiatric Association and the Brain and Behavior Research Foundation. He was a great president of the APA in 1989–1990 and a model for me during my presidency 20 years later. He remained involved over the ensuing years and was available for giving helpful advice. I remember three interactions with Herb at the APA. We were both on a small committee to select the next Medical Director and CEO. Herb was a diligent member who had a keen eye for evaluating leadership talent. Another involved a passion of his as chair of a session at the Annual Meeting which featured up-and-coming scientists' work. I was honored to present at one of those and Herb was gracious in his hospitality and made incisive comments about the science presented. A few years back, Herb was unable to chair the symposium, and he called me and asked if I could stand in for him. I was honored to do so, and I was struck by how important he thought the session was for the Annual Meeting and how sorry he was not to be able to come to San Francisco.

His support for the up-and-coming young mental health scientist was a love that fueled his co-founding BBRF and chairing the Scientific Council for years. I have so many memories of his work at the BBRF. One day he called me to indicate I had been elected to the Council and then less than an hour later called again to congratulate me on winning the Falcone Award. (I didn't tell him that he could have save some money in combining these into one call.) I was always impressed by his great stewardship of the annual meetings of the Scientific Council, his emceeing the Scientific Council and the annual awards dinners, etc. All of this was done with warmth and a dedication to the mission of the BBRF, its Board and its Scientific Council, and the importance of ultimately helping those who suffer from mental illness. He will be missed by all of us.

Daniel Weinberger, M.D.

Johns Hopkins University; Lieber Institute for Brain Development

BBRF Scientific Council

1993 Lieber Prize

2000, 1990 BBRF Distinguished Investigator

Dr. Pardes was a dear friend over many years, a colleague and an inspiring leader. I have been blessed by having had the opportunity to work with, learn from, and follow in his footsteps since I began as a medical staff fellow at the NIMH where he was director.

He helped me in ways that go far beyond any specific event. My earliest memories of Herb echo his prescient insight about moving psychiatry research into the mainstream of neuroscience, including his passionate support for launching PET imaging research at the NIMH in Bethesda.

Dr. Pardes had a unique combination of wisdom, humor and compassion. He was a leader's leader, as Director of NIMH, then as Chair of Psychiatry at Columbia, eventually as President of the NewYork-Presbyterian Hospital system. During all these years, he sustained the BBRF Scientific Council with his singular skills and leadership. His indelible footprints are responsible for the unprecedented successes that mark all of his endeavors. He epitomized being a good listener, not just waiting for his chance to talk, but asking illuminating questions and translating information into constructive action. Anyone who has attended years of his leading Scientific Council meetings for BBRF can testify to his unique skill in navigating the egos of prominent scientists wanting to be heard.

Dr. Pardes devoted his life to mental health research. He mentored gifted scientists to ensure a bright future for the field. He fostered growth in neuropsychiatric research to pave the way for new treatments to benefit patients and their families. His legacy will live on in the work of all those who benefit from BBRF, from its staff, its scientific advisory Board members, from the many scientists and trainees who were supported by BBRF, and the patients whose lives were touched by the science that he embraced. I extend my deepest condolences to his beloved family as we grieve alongside them.

Myrna Weissman, Ph.D.

Vagelos College of Physicians and Surgeons, Columbia University

BBRF Scientific Council

2020 BBRF Pardes Humanitarian Prize

1994 BBRF Selo Prize

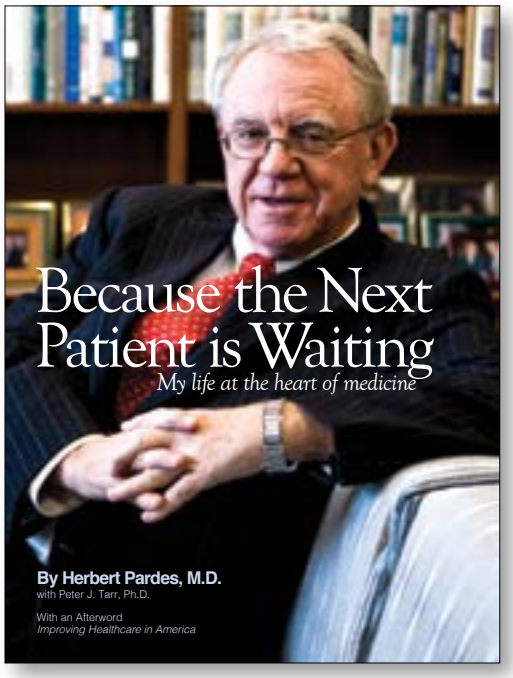
2005, 2000, 1991 BBRF Distinguished Investigator

Herbert Pardes knew the importance of science in dealing with illness. He knew how compassion would accelerate its impact. He knew the structure upon which to build. He was a giant and an approachable friend.

He decided that I should join the faculty at Columbia, even though I really didn't want to move to New York and was happy at Yale. He came to our home on a Saturday morning. I was convinced he would not leave until I agreed. He subsequently told me that I was a great negotiator, ignoring the power of his persuasion.

He will be missed. His person, his ideas, his brilliance and his humor are in so much of what we do here every day.

Dr. Pardes on how BBRF was founded and its importance in advancing psychiatric research



In his recently published memoir Because the Next Patient is Waiting, *Dr. Pardes told the story of his remarkable career, stressing the compassion and humanitarian concern that were always, for him, "at the heart of medicine." In an Afterword, he left us with concrete ideas about how to improve healthcare in America, with a stress on integrating the care of mental health with general medical care, more compassionately treating serious mental illness, and devoting special attention to preventive care, including mental health care, especially for new mothers and their children. In the book (written with Peter Tarr, BBRF's chief science writer), he also made a vigorous case for investing generously in research. In one chapter, excerpted here, Dr. Pardes explains how through the formation of BBRF, citizen philanthropy was directed to the cause of advancing research on the brain and psychiatric illness—a cause that was close to his heart and which played a central role in his life.*

After leaving my post as Director of the National Institute of Mental Health (NIMH) in 1985, having served for 5 years under presidents Carter and Reagan, I wanted to find new ways to make clinical psychiatry more effective for people who needed it most. I also wished to follow up on projects in which I had been involved while still at the NIMH. One favorite of mine had to do with developing collaborations with citizens, to secure more vigorous advocacy and also more patient-inspired philanthropy for psychiatric patients and programs.

In 1979 I had been invited to a meeting in Madison, Wisconsin held by a group of parents of people with schizophrenia. "What if we had a family advocacy group that worked for mental illness causes?" they asked. I thought it was a great idea. Other such advisory groups had been working for some time on behalf of the victims of other illnesses, including cancer, diabetes, muscular dystrophy, and heart disease. There was no substantial advocacy group for people with mental illness. For obvious reasons: most patients were not able to advocate, either because of incapacity, few resources, or a fear of being stigmatized. Also, most people without experience with mental illness often figure they will never suffer from one—though they do fear developing cancer, heart disease, or Alzheimer's.

I felt the time was ripe for a partnership between people in my profession of psychiatry and the public. I thought it would be important in the years ahead to have in place another source of funds to complement the essential role played by government. Research on mental illness was funded almost entirely by the government at this time. There was little private or philanthropic role. As for the funding by government, mental illness was certainly not receiving its fair share. For every American with cancer, $300 was spent annually on research in 1986. The comparable figure for people with schizophrenia was a mere $7.

I thought we could make a serious dent in stigma by bringing families into the picture on a national scale. The group that emerged from that 1979 gathering in Madison did just that. It was called the National Alliance for the Mentally Ill, or NAMI. With satisfaction, I observed its impact increase over time, energized by effective leaders such as Laurie Flynn, who guided the organization through the end of the 20th century, and augmented by the important support of Dr. Fuller Torrey.

After NAMI had been functioning for a while, they raised the question: "Shouldn't we launch a private organization that would be dedicated to the support of research, to complement the citizen's advocacy group?" I agreed. At the beginning of this effort, the core group consisted of several leaders from NAMI and a group from Kentucky including Phil Ardery and Boz Todd called the Schizophrenia Foundation. Together, NAMI and the Schizophrenia Foundation formed NARSAD, the National Alliance for Research on Schizophrenia and Depression. It was led initially by Gwill Newman, a wonderful advocate and leader whose life had been jarred by the tragic death of her son who had been afflicted with mental illness.

With help from Katharine Graham, the owner of the *Washington Post,* a first-rate scientific advisory panel for NARSAD was formed, naming me its president 1986. Little did I know then that the Scientific Council's work would be one of the great professional and personal experiences of my life. Over more than 36 years, NARSAD, which in its first year debated launching a grant-giving function with the $50,000 it then had in hand, built itself by recruiting to the Scientific Council top leaders in all aspects of neurobiology, neuroscience, clinical research, psychology, psychiatry, and other allied fields. The Council now has some 190 members. The Foundation, renamed the Brain & Behavior Research Foundation (BBRF) in 2011, to date has awarded some 6,500 grants worth over $450 million to the very best scientists all over the world working on mental illness. Many of them are just starting out and in greatest need of external support. From early days, "having a NARSAD"

Dr. Pardes (6th from right, top row) and Connie Lieber ((3rd from right, bottom) with members of BBRF's Scientific Council in the early years of the Foundation.

grant became a mark of distinction, something academic researchers boasted about, in part because the grants are thoughtfully awarded by experts in the field.

THE MULTIPLIER EFFECT

The institutional history of BBRF teaches some important lessons. One of the advantages is the multiplier impact of effective grant giving. Over 80% of BBRF's 6,500 grants awarded to date have had the unique purpose of jump-starting careers of young researchers demonstrating unusual promise. Although a proportionately smaller number of the grants sought to sustain proven mid-career scientists and to provide senior, distinguished scientists with funds to pursue highly novel or risky research (often marking a departure from the work they've already accomplished), the over 5,100 grants so far awarded to Young Investigators have probably had the greatest impact. Although the dollar amounts are modest (now $70,000 over 2 years), these early-career grants have been the equivalent of seed funding. They have enabled the best and brightest entrants to the field to perform research which, when successful, facilitates their scientific career, in part by providing a basis for multi-year, career-sustaining federal grants.

Federal granting agencies do not take the same risks as an organization like BBRF in the current funding environment. This is one of the key lessons of private philanthropy, pursued intelligently. The general scarcity of research funds has resulted in increased competition for a steady or sometimes shrinking pot of money. This, in turn, has encouraged federal grant administrators and review committees to select projects that are comparatively safe. BBRF expects positive results, but accepts projects that are riskier. Seeding such projects has often led to disproportionately high rewards—"breakthrough science."

To cite one of many examples: the Scientific Council issued a Young Investigator award in 2005 to a young man from California named Karl Deisseroth. A practicing clinical psychiatrist with an M.D., Karl is also a brilliant Ph.D. neuroscientist in a faculty position at Stanford. With BBRF's seed money, he was instrumental in spawning an entirely new technology, called optogenetics, which enables researchers to use beams of colored laser light to switch individual neurons on and off—painlessly and reversibly—in living, "behaving" mice. This, in turn, has enabled his team and hundreds of others across the world to make new discoveries about the neural circuitry involved in schizophrenia, depression, epilepsy, and other brain disorders. Karl was co-winner of the Lasker Basic Medical Research award in 2021 for his part in the development of optogenetics.

Karl began to innovate on BBRF's dime, and while most of his discoveries have since had the benefit of being backed by much more abundant federal aid, we can't be certain he would have had the chance to secure that aid as rapidly as he did if he had applied for a federal grant when his ideas were still untested. Dr. Deisseroth is a prime example of a scientist awarded small grants with potentially powerful multiplier effects. He himself now mentors other brilliant young people in his Stanford lab, a number of whom have independently and on their own merits won their own BBRF seed funding. Karl was barely 40 years old when he was elected a member of the BBRF Scientific Council. In recent years, one of the BBRF-supported researchers in Karl's Stanford lab, Vikaas S. Sohal, M.D., Ph.D., has himself achieved success that has enabled him to launch a very successful lab of his own and merited his election, at an even earlier age than Karl, to BBRF's Scientific Council.

Holding annual Mental Health Symposia, free and open to the public, is an important tool in fighting stigma, Dr. Pardes strongly believed.

REDUCING STIGMA

What impresses me about BBRF's private philanthropy is how well it enables donors and scientists to interact for maximum mutual benefit. When the Foundation began issuing grants in 1987, I was in the second year of my first post-NIMH position at Columbia University, as chair of the University's psychiatry department. In concert with BBRF (then still "NARSAD"), we decided to hold public conferences—all-day seminars—on mental illness, and invite the public to attend. We found it important for non-professional people to better understand what was going on in the field. It would put us in a better position to raise funds and to perform what we regarded as a desperately needed public service. The more people knew and understood about the biological basis of mental illness, the more "mainstream" the illnesses would become. Our biggest hope was that such enlightenment would lessen stigma, and equally important, lead more people to get treatment.

All this sounded wonderful. The day arrived for our first "mental health symposium," in Manhattan. It was a rainy Saturday morning. I worried attendance would be disappointing. But 700 people showed up. It was a spectacular success, and marked the beginning of a series that has continued and is stronger than ever today, decades later. Those of us who gave talks that first day could feel the hunger in the audience to hear us. They wanted to learn more about a subject that occupied so much of their lives and yet was rarely spoken about in public. Speakers and audiences alike understood we were doing something important that rainy Saturday.

Dr. Pardes with Steve and Connie Lieber.

CONNIE AND STEVE LIEBER'S INDISPENSABLE CONTRIBUTION

It proved to be an important day for BBRF's future, too. After the symposium ended, a couple came over to me and said simply, "We'd like to do something for mental illness." I sensed that their interest in research went beyond just one institution, but was for the whole field. These volunteers, Steve and Connie Lieber, had a daughter with a psychiatric disorder and wanted to get involved. It was a stroke of extraordinary good fortune. Subsequently, Connie for 20 years served as president of the Foundation. After her retirement in 2007, Steve carried on in her place, and was Board Chairman of BBRF at the time of his passing in 2020. Connie, who passed away in 2016, was a giant in mental health and a woman of great intelligence and compassion as well as extraordinary modesty. The Liebers helped us award those first 10 NARSAD Young Investigator grants in 1987. Our existing financial assets of only $50,000 were obviously insufficient, but our Board, stimulated by Steve and Connie, urged us to issue the grants at the levels we intended, assuring us that they, the Liebers, would make up the difference. After Connie Lieber became

the organization's head, she meticulously built the organization that administered the grants, and kept at it with the vigor of a 25-year-old for two decades.

The success of the organization is largely due to this extraordinary couple. They wisely let the Scientific Council handle the science decisions while they directed the Board of Directors and made BBRF one of the most friendly and supportive private research institutions active anywhere. Their family, and others, agreed to cover the administrative costs, so that all the funds raised from the public could be devoted exclusively to research grants. We on the Scientific Council all agreed to fund high quality research around the world from any scientific discipline with the primary criterion being the quality of the research and its pertinence to mental illness. Connie and Steve, whom I miss terribly, were the most selfless, wise, and generous leaders I encountered in all my years in mental health. And we now know that their gifts run in the family. Geoff Simon, Steve's nephew, immediately demonstrated, upon assuming the role of Board Chairman after Steve's passing, both his aunt and uncle's dedication to the cause and talent for inspirational leadership. Geoff cares deeply about the mission, and his ability to connect with people and to make the case for the Foundation has delighted all who care about BBRF.

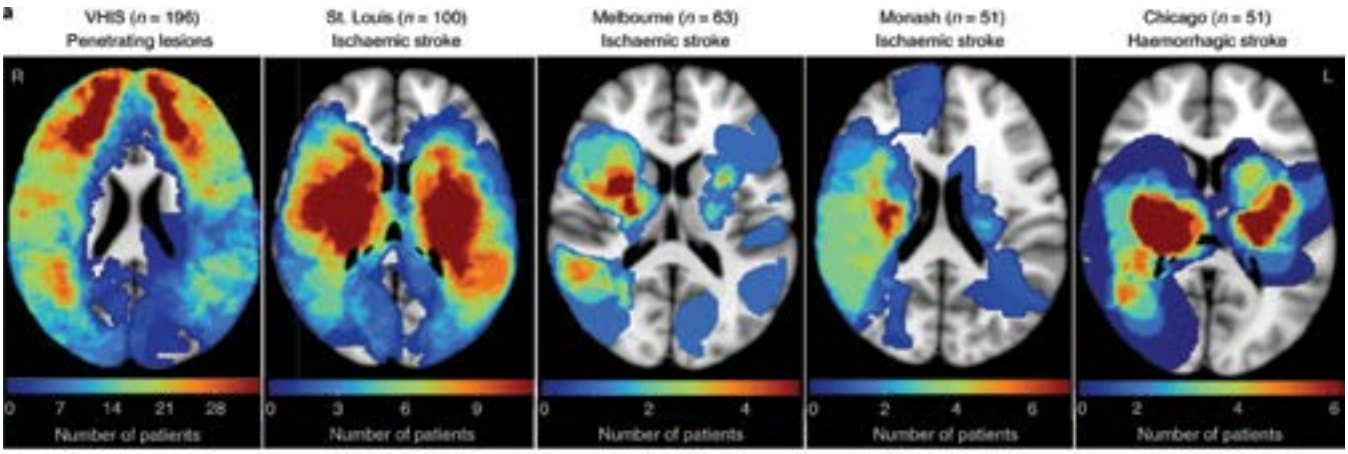
Dr. Pardes with Dr. Eric Kandel, who has credited BBRF with "seeding the field" with researchers devoted to unlocking the mysteries of the brain and finding new treatments for psychiatric illnesses.

My central point in discussing BBRF's philanthropy is that from the beginning, the Liebers and other major donors understood that scientific competence in the organization resided in the Scientific Council. They consistently deferred to our judgment regarding grant-making. Members of the Council assess the annual applications. No additional politics comes into the process, and everything is done on a volunteer basis. I removed myself from any involvement in the review and awarding of grants. The BBRF Board and the professional staff under the Liebers brought in money. We were able to fund the best research. This in my experience is the only the way to go in disbursing funds for scientific work. Between fund-raising and grant-making there should be a wall as inviolate as that between church and state.

A FEW OF THE PEOPLE ON BBRF'S SCIENTIFIC COUNCIL WHO HAVE MADE A DIFFERENCE

During the more than 36 years I've had the honor of leading BBRF's Scientific Council, I have had the opportunity to observe and know intimately many of the hundreds who have served this body as volunteers—as I have said, leaders in their fields and subfields. I think it is true that the Foundation has, as my Columbia colleague Eric Kandel has suggested, "seeded the field" with investigators who have helped to chart a course for contemporary brain research. I'd be remiss if I did not mention here just a few of the people I have known well through my association with the Foundation. More people should know about them.

Dr. William T. Carpenter, a pioneering psychiatrist and researcher whose work on schizophrenia and on symptomatology—classifying symptoms in ways that help us treat patients—was present at the creation of the original NARSAD organization. I have turned to Will innumerable times for advice and counsel that I have found, consistently, to be indispensable.



Robust funding for new brain imaging technologies and other brain research was a lifelong passion and commitment for Dr. Pardes.

Dr. Frederick T. Goodwin, also a founding Council member, who, beginning in 1981, was Scientific Director and Chief of Intramural Research at the NIMH, made an especially important contribution when he led a study showing that lithium was significantly more effective than other widely used mood stabilizers in protecting against suicide in those with bipolar disorder. My dear friend Dr. Jack Barchus was there from the beginning—a brilliant leader of academic psychiatry departments, and an important researcher who has made vital discoveries regarding neurotransmitters such as serotonin, melatonin, epinephrine, norepinephrine, and dopamine, among others. Jack for many years spectacularly led the BBRF Scientific Council committee charged with selecting Distinguished Investigators. Another marvelous friend of longstanding is Dr. William E. Bunney, Jr. "Biff" Bunney was the very first of the BBRF Lieber Prize winners—investigators recognized for their important work in schizophrenia research. Dr. David Shaffer was for many years the Irving Philips Professor of Child Psychiatry & Professor of Psychiatry and Pediatrics and Chief of the Division of Child and Adolescent Psychiatry at Columbia. A BBRF Distinguished Investigator, David was awarded BBRF's Ruane Prize for Outstanding Achievement in Child & Adolescent Psychiatric Research. This was well-deserved: he was a pioneer in the study of suicide and was lead investigator in developing the Children's Global Assessment Scale (C-GAS). He led a team of colleagues in developing and modifying the Diagnostic Interview Schedule for Children (DISC) and the Columbia Teen Screen, standard diagnostic tools used the world over to identify and assess young people at risk for suicide. Dr. Francis S. Lee has approached the problem of youth mental health from another angle. Francis, a Council member who now chairs the psychiatry department at Weill Cornell, has applied his skills as a neurobiologist and psychiatrist to learn more about the molecular basis of mood and anxiety disorders, with the goal of understanding why many of these disorders emerge during the transition from childhood to adolescence.

Dr. Judith L. Rapoport is a notable winner of BBRF's Ruane Prize, a BBRF Distinguished Investigator and a member of the Scientific Council. As chief of the Child Psychiatry Branch at the NIMH, Judy has been a pioneer in studying and treating childhood-onset schizophrenia, ADHD, and OCD. It is relevant to note that years ago it was felt by most experts that such illnesses (as well as depression) did not occur in childhood. We know better now. Additionally, Judy harnessed the tools of genetics and genomics, following completion of the Human Genome Project, to unlock the mysteries of

pathology and causation in a number of psychiatric illnesses.

Another pathbreaker is Dr. Dilip V. Jeste, who brought to our attention the special issues of aging for those with psychiatric problems, notably including schizophrenia and depression. A past president of the American Psychiatric Association and a BBRF Distinguished Investigator and Scientific Council member, Dilip has helped the public understand the problem of what he has called "an epidemic of loneliness" in contemporary society. He has notably developed a body of work on the therapeutic concept of "wisdom," which he defines as pro-social behavior (i.e., empathy or compassion); emotional regulation; self-reflection; acceptance of uncertainty and diversity of perspectives; the ability to be decisive; the ability to give appropriate advice and support to others; and spirituality.

Two long-serving members of the BBRF Scientific Council immediately come to my mind when I think of research on therapeutics. Dr. Herbert Meltzer, a founding member of the Council, performed vital research demonstrating that clozapine, the first of the "second-generation" antipsychotic medicines, was both effective in reducing psychotic symptoms, and, importantly, in reducing suicidality in patients. This was a signal contribution—and here I do not even mention Herb's dedication for years in helping the Scientific Council to identify the best young researchers worthy of receiving the organization's Young Investigator grants. Dr. Robert Freedman, who was a distinguished chair of Psychiatry at the University of Colorado, is one of the few researchers who has developed a preventive measure for serious psychiatric illness. Bob and his team, after conducting basic research for many years supported in part by BBRF grants, discovered that the nutrient choline, deficient in the diets of many pregnant women, if supplemented during pregnancy, can reduce the risk of serious mental disorders in the child. The work is still ongoing. This is a very hopeful discovery which can be implemented readily and cost-effectively. The possible benefits are reductions in risk for psychosis and schizophrenia, and possibly other illnesses.

Dr. Pardes with Dr. Jeffrey Borenstein.

A special expression of my gratitude is due Dr. Jeffrey Borenstein, who for the last decade has expertly led BBRF as its president and CEO. Jeff has brought great credibility to BBRF and its mission by virtue of his long experience as a practicing psychiatrist who is also a leader in the profession. He has proven to be a wonderful communicator, making the case for philanthropy's essential role in keeping research moving forward. Jeff developed and hosts the television series *Healthy Minds,* which for nearly a decade has been seen on PBS stations across the United States. I know of no other regular television series in America that has chosen mental illness and mental health as its prime subject, and Jeff has used the opportunity to explain illness, convey the promise of ongoing research, and, perhaps most important of all, transmit the message of hope. BBRF has been fortunate to have a person with Jeff's gifts and great empathy and kindness at the helm of the Foundation.

The peril is obvious in recognizing the importance of individuals such as the several I have mentioned in the paragraphs above: I have only scratched the surface. The list and the appreciations could go on for many more pages. Elsewhere in my memoirs I have written of the contributions of others: Dr. Aaron Beck, who developed cognitive behavioral therapy which has helped millions; Dr. Daniel X. Freedman, my excellent friend in academic medicine who provided so much sage advice; Dr. Gerald Klerman, a brilliant administrator in the federal government and a superb researcher and dear friend; Dr. Myrna Weissman, who has made a great contribution to epidemiology and our knowledge about the special risks that depression poses for women and their children…. There are so many others I want to tell you about. One of the thrills of my career has been to know some of the people who have taken psychiatry and our understanding of the brain and mental illness from what it was when I was trained to what it is today. These research and clinical innovators have helped to change the game. They and those they now train to carry the work forward have inspired and motivated me.

❖ **HERBERT PARDES**

"The Quest for Healthy Minds"

TOP RIGHT: Dr. Jeffrey Borenstein with Dr. Laura Berner.

IMMEDIATELY ABOVE: Dr. Judy Genshaft and Geoffrey Simon.

On Thursday, January 11, 2024, Dr. Judy Genshaft, President Emerita of the University of South Florida and a BBRF Board Director, hosted a private event at the Judy Genshaft Honors College where attendees learned about BBRF's unique model for advancing the frontiers of brain science.

The evening's program, *The Quest for Healthy Minds,* featured a tour of the honors college, dinner, an introduction by Dr. Genshaft, followed by remarks from BBRF Chairman of the Board Geoffrey Simon, a video presentation, and culminated in a conversation about eating disorders between Dr. Jeffrey Borenstein, BBRF President & CEO, and Dr. Laura Berner. Dr. Berner is a recipient of a 2020 BBRF Young Investigator grant and is an Assistant Professor of Psychiatry at the Icahn School of Medicine at Mount Sinai in New York City and a Principal Investigator in the Center for Computational Psychiatry & Center of Excellence in Eating & Weight Disorders.

The evening premiered the new BBRF video, also entitled *The Quest for Healthy Minds*, which highlights how BBRF's support for brain research is paving the way to new treatments and and methods of prevention.

BBRF has funded more than 5,400 scientists over the past 37 years. The Young Investigator Grant Program allows these researchers to explore out-of-the-box ideas that are often difficult to fund. This funding mechanism has led to discoveries that continue to advance the frontiers of brain science.

The Quest for Healthy Minds features four groundbreaking scientists who were supported by BBRF during their early research when they were struggling for funding and now are world leaders in mental health research. The video can be viewed here: https://www.youtube.com/watch?v=qh0QWi2zTBs ❖ **LAUREN DURAN**

Helping Children and Adolescents With Emotional Problems

A Q&A for parents, teachers, and families by Dr. Jeffrey Borenstein with Dr. Daniel Pine, based on a recent BBRF Webinar

Daniel S. Pine, M.D., is the Chief of Child and Adolescent Research in the Mood and Anxiety Disorder Program at the National Institute of Mental Health. He is a longstanding member of the BBRF Scientific Council, 2011 winner of the BBRF Ruane Prize for Outstanding Achievement in Child and Adolescent Psychiatric Research, and recipient of a BBRF Independent Investigator grant in 2000.

Jeffrey Borenstein, M.D.
is a psychiatrist, President & CEO of BBRF, and host of the PBS television series *Healthy Minds*

IN BRIEF
It's often hard for a parent or teacher to determine if a child has a problem with anxiety that needs to be referred to a doctor. Dr. Pine suggests when and how they should proceed, while explaining the range of possible symptoms and behaviors, and a variety of treatment types that are often recommended. He deals with the question of medication, advising an open yet conservative approach. He also talks about issues that can arise when parents and teachers meet to discuss a child's problems.

What does anxiety look like in children and adolescents?

Anxiety is a common part of life. We all have anxiety. Children in particular, as they develop, have anxiety, which can present in many different ways. Mental health professionals really have a concern when a child has an anxiety disorder. Anxiety disorders are probably the most common mental health problem in childhood with at least 10% of children being affected at any moment in time.

One of the tricky things for parents, teachers, and even children is to tell the difference between normal anxiety that is an expected part of growing up and an anxiety disorder. The simplest rule is to notice when anxiety prevents a child from doing things that other children can do. If a child can't give a presentation in school because they're too nervous to speak, that's a suggestion of an anxiety disorder. Other signs to watch out for include if a child can't go on overnight visits to friends or can't spend time alone in their room or can’t take part in a sporting event because they are too worried about performing well.

If it's affecting their functioning, that's when you cross the line into a disorder as opposed to the normal anxiety that any child will feel.

That's exactly right. The usual way we see that effect on functioning is through avoidance, meaning that children don't want to do things that make them afraid.

Often as a parent or an educator, we may want to help that child. But it may not be helpful to assist them if it means helping them to avoid the activity that we may think brings on the anxiety. What should we do?

That is an excellent question and an excellent thing to think about. We do a lot of research on children who show mild or not quite clinical signs of anxiety, and we follow those children over time as they grow up. We've found there are a lot of things that predict what's going to lead to persistent anxiety.

When we follow children who have minor problems with anxiety whose parents encourage them to face their fears and attend the kind of events that make them afraid, we find that those children actually do better over the years. They have lower rates of anxiety compared to the children who are not pushed to do the things that make them afraid.

Now, it's a difficult call for many parents about how much to push their child, and if you're a parent or an educator who is unsure, a mental health professional can be particularly helpful. A good place to start is with your pediatrician. Pediatricians are quite familiar with the full range of behaviors, and they're also able to help a parent find access to mental health professionals who can work with them to push their kids the appropriate amount.

How young can a child be when these kinds of symptoms get in the way of their functioning?

We see the signs of anxiety even during preschool, but it's quite rare for anxiety to interfere with a preschooler's ability to function. It really becomes much more common in the early school years, and in those years, anxiety tends to present itself as worry about specific objects or specific situations like being alone or being separated from parents.

As kids approach adolescence, we see that anxiety tends to shift and focuses on social issues. For kids in the 9-14 range, we see social anxiety as the most common form of anxiety. Then a few years later, we see general worries about competence—how well you're going to do in school, how you're doing in sports, how you're doing with peers—"do they like me?" Anxiety happens all throughout childhood once school begins, and we see different flavors in children of different ages.

Tell us a little bit about the treatment. You go to the pediatrician; the pediatrician may suggest going to a psychiatrist, a psychologist, or some other mental health professional. What is a mental health professional going to do?

The first thing we want to do is help children learn how to use constructive thoughts to control their anxiety. There is

a whole range of techniques children can learn with a therapist. The second thing we want to do is make a list of all the things that worry the child. You want to work with a therapist who's going to help the child and their family do what we call "exposure." That means facing your fears. You're going to want to start with something that's slightly anxiety-provoking, and have the child use those new skills that they've developed with their therapist to control their anxiety. Then as they learn how to navigate a mildly fearful situation, you want to gradually increase the exposures. We call this form of therapy cognitive behavioral therapy (CBT) or exposure therapy. That's usually the first-line treatment that most people recommend.

Now, that's not an easy thing to do. Partly because the therapist has to have some skill and experience in helping children learn how to face the feared thing or situation. For some children, it's simply too difficult. For those children, the other treatment we consider is to prescribe an SSRI [one of a group of similar medications like Prozac or Lexapro that are often prescribed for depression and anxiety in adults].

There's some debate about whether or not we should consider those as first-line treatments. If an experienced therapist is available and a child is willing to engage in cognitive behavioral therapy, most people recommend starting with that. Yet, there are not enough experienced therapists who can do this, and not all children will comply. If therapist who can administer CBT to a child cannot be found, I think it's perfectly reasonable for the child to be treated with one of the SSRI medications.

What advice do you give to parents who are—appropriately—concerned about giving their child medicine, especially on an ongoing basis.

We have a lot of information about the safety of SSRI medications in the short term, meaning for one to two years, and this information suggests that the benefits far outweigh the risks. It is important to consider that there are considerable risks to the child when they have serious anxiety that is left untreated. The benefits of overcoming their anxiety in the short-term are greater than the risks of not treating, in my view.

We could debate if it makes sense to start with cognitive therapy first. It probably does, but again, parents can be reassured of the safety of medication over one to two years. Where things get trickier is if you use medication beyond two years, and different physicians, therapists, and scientists feel differently about this. Anxiety has a very good prognosis. Most children can overcome their anxiety, and it might come and go, but most children can get to the point where their anxiety is substantially better. For children who have responded to a medicine and are doing well, after a year, I like the idea of beginning a trial period in which the child is not taking the medication. It's not that we know with certainty that there's something bad about taking the medication over the long term, but we have less information.

Not everybody agrees with this. Some think that anxiety can be chronic, and if you get a child well, they recommend that the child remain on the medication for a number of years. They point to the fact that there is no evidence that the medicine is harmful if taken over many years. I tend to be more cautious, mostly speaking to concerns that I hear from many parents, and also because many children come off the medicine and they do fine. Some experts feel otherwise. My view is that you can always put that child back on the medicine for another year if symptoms

recur after stopping the medication. I feel more comfortable, and many of the parents who I talk to feel more comfortable, with that strategy.

I should add: this is why organizations like BBRF are so important. It's very important that we continue to do more research, particularly on the long-term safety of these medicines so that we can be more definitive.

I want our readers to understand: you've dedicated your career to research. With what we currently know, we can help a lot of people, but we still need to learn more.

Yes. One other really important thing to note is that there's a very strong relation between having anxiety in childhood and developing depression in adolescence and adulthood.

Although it is the most prevalent psychiatric condition, we are quite effective in treating anxiety. We have a much harder time treating major depressive disorder in adolescence or in adulthood. A lot of people, including me, think that it is appropriate to treat childhood anxiety (and use medicine when CBT is not available) because not only do you help children in the short-term, but you might reduce the chance that they're going to develop major depressive disorder years down the road, which will be harder to treat. With major depressive disorder, the options are much fewer and the duration of the remission once we achieve it is not as robust.

It's a very important point you're making. We in the field of psychiatry haven't in the past focused as much on prevention as other fields in medicine. That's a reflection of where we are with the science. If somebody has high blood pressure or high cholesterol, which we can easily measure, then we treat that to decrease the risk of a heart attack down the road.

You're saying that a benefit of treating anxiety with talk therapy, or medicine, or both, is not only helping the child in the here and now, but it also potentially decreases the risk of developing depression down the road.

That's exactly right. Your point about prevention is absolutely right. By treating anxiety not only are you potentially inoculating that child against later risk for depression, but you are also making a big difference in the immediate life of that child.

You mentioned at the beginning that anxiety is very common. One out of 10 kids has anxiety in any given moment in time.

If we follow kids over time, I think it's probably double that, at least.

Has the rate increased over time?

That's a tough question to answer because a lot of things can change the rate. For example, efforts from BBRF

and other organizations have helped the public fear psychiatric problems less, thus reducing stigma—so people are more willing to talk about problems, including anxiety. That could in some ways artificially inflate the rates of anxiety disorders. There was concern that some subtle upticks we saw maybe 15 or 20 years ago might have been related to that. The data that we have now, though, suggests that there probably has been a genuine increase in anxiety in the years immediately before the pandemic, and quite clearly during the pandemic. It's pretty clear even among relatively conservative scientists, like me, that the problem is worse now than it was definitely 10, but probably even 5 years ago.

I don't know that I would go as far as to call it an "epidemic," because the rate of increase hasn't been that profound. But some experts do say that. People like the Surgeon General or other important, prominent spokespeople for the health of the nation do talk about anxiety in that way, and I think that reflects agreement among many people who follow the research on this that the problem has gotten worse.

Obviously, COVID would be a clear-cut reason for the increase in kids having anxiety. Are there other potential causes for the problem becoming worse? To what extent does social media play into this?

Pretty much all mental illnesses are caused by many things, all interacting in complicated webs. That's clearly the case with anxiety.

Some problems like attention deficit disorder (ADD), ADHD, schizophrenia, and autism have a more prominent genetic component, even though they have an environmental component as well. We know this from research. Other problems like anxiety have a more prominent environmental component than a genetic component. The most potent thing we see in the environment is stress. Anxiety can manifest in children who are exposed to stress from just about anything. Stress that involves social things is particularly harmful, such as being bullied or absorbing the stress of family members. We think when parents are struggling or dealing with their own mental health issues, that stress contributes to a child's anxiety.

Hard economic times also creates stress for the child.

The issue of social media is a very interesting one. It's pretty clear that there is an association "cross-sectionally," meaning that if we look at kids who are struggling the most, they tend to use social media the most. However, longitudinal research—research that tracks people over longer periods of time—suggests that not much of that is likely causative.

It's more likely that kids who are suffering seek out certain kinds of social media as opposed to kids who use social media and don't have problems. Some of those kids may get worse, but that's probably relatively rare. Still: social media is becoming such a ubiquitous part of life for children that it has become a major conduit for stress. Without question, the availability of social media has made it possible for children to be bullied in unique ways. We know that bullying is a big factor and risk for anxiety and mood disorders. I don't think it's social media per se, as much as all the things going on in society right now that are contributing to different kinds of stress.

Years ago, if we were bullied, it would be in the schoolyard and then you'd go home and you'd be safe and sound, whereas now if you're bullied, it continues when you get home on social media.

Absolutely.

If a teacher is aware that bullying is taking place, that would be a reason to think that the child who's been bullied might be at a higher risk of anxiety.

Absolutely. Teachers are in a difficult position because on the one hand, they're on the front lines, so they see a lot of things that other people don't. On the other hand, teachers really need to involve the parents. I work a lot with schools, and not all parents necessarily think that mental health issues are the purview of the school. There arises the question of how to handle that in a delicate way, where, on the one hand, you are entirely working through the parents, and on the other hand, you're handling it when parents might not want to hear about it. That can be a difficult situation, and it's a place where I think having mental health experts within the school who understand mental health concerns can be really helpful.

What's the best approach for a teacher to engage the family in helping their child?

A place to start is to describe the behaviors that you're seeing and to see if you can get parents to the point where they can acknowledge that it's a problem and they want to get involved. That's usually the best first thing to do. The second thing you want to do is adjust your discussions based on the comfort level of the parent. Some parents will immediately want to hear about what can be done. Usually the pediatrician is the first place to go, and it's particularly helpful when there's some understanding of pediatricians one can take such problems to.

But not every parent can hear that, so in that situation, teachers can guide parents to someone within the school to speak with. Ideally that would be the guidance counselor. Wonderful guidance counselors are able to have those conversations with teachers and parents, and sometimes they have a little more experience with these situations. A teacher has to keep trying all different kinds of things, working with the principal and other resources at the school to try to get a parent to at least have an open ear. Eventually where you want to get to is the pediatrician.

What advice do you have for parents who have been approached by a teacher? What should they be listening for?

One big thing is to think about impairment. Ask the teacher about the signs of impairment and the activities that their child can't do. Secondly, you should figure out if this is a change. When a child has been having a problem for a while, it's more likely to be an indicator of a significant mental health issue. If it's a new problem, that's less likely. In that instance, something has typically changed in the child's environment. Teachers often have a sense of this. Has the friendship dynamic changed? Is the academic material more difficult? Is there something else about the activities in which a child is engaging? As a parent, you want to look for those clues, and you want to get to a place where you can discuss them with your child. A child just knowing that somebody's paying attention and removing some of those immediate stressors can significantly reduce anxiety.

The child knows people are aware of their problem, care about them, and are intervening. I think that in itself makes a very big difference for the child. They're not alone anymore. Having that conversation is helpful in its own right.

Absolutely. That's why I personally think, and not all schools agree with this, having conversations about mental health within schools can be a good thing because it shows that this is a common problem that many people face at different times in their life, and it's good to talk about it. But not everybody feels that way, and we need to recognize that. ❖

BBRF Names Ten Distinguished Investigators for 2024

In April, BBRF announced the award of Distinguished Investigator grants valued at $1 million to 10 senior-level scientists who are conducting innovative projects in neurobiological and behavioral research. Recipients of the $100,000, one-year grants are exploring new frontiers in understanding a wide range of neuropsychiatric disorders, including autism, anxiety, bipolar disorder, schizophrenia and the potential connection between mental illness and cannabis use.

"The grants will fund new approaches that might otherwise go unfunded," said Jeffrey Borenstein, M.D., BBRF's President and CEO. "We thank the WoodNext Foundation for the extraordinary philanthropic support that makes it possible for us to award the 2024 Distinguished Investigator Grants to these leading mental health scientists."

"WoodNext is very proud to support innovative research via the Brain & Behavior Research Foundation Distinguished Investigator Grants with a total commitment of $5 million across five years," said Nancy Chan, Executive Director of the WoodNext Foundation, a component fund administered by Greater Houston Community Foundation. "We recognize that scientific research is the key to discovering new pathways to understanding and treating psychiatric illnesses. The ground-breaking work of the Distinguished Investigator Grant recipients will bring hope and healing to people and families impacted by mental illness. We applaud these scientists for their extraordinary dedication, innovation, and leadership."

Recipients of the Distinguished Investigator Grants are full professors at research institutions in the United States and abroad. They were selected by a committee of the BBRF Scientific Council, which is comprised of 192 experts across disciplines in brain and behavior research who review grant applications and recommend the most promising ideas to fund.

Eric J. Nestler, M.D., Ph.D., Chair of the BBRF Distinguished Investigator Grant Committee and member of the Scientific Council, said "it is wonderful to see the relaunching of this very important component of BBRF's research portfolio." The Distinguished Investigator Award Program, he noted "serves a unique niche by supporting established investigators to explore high-risk but also high-yield ideas. We are delighted with the slate of award winners this year. The new awards were selected from a large group of highly competitive applications and will support exciting and innovative lines of research consistent with BBRF's mission to better understand and ultimately treat severe mental illness."

Here are the recipients of the 2024 BBRF Distinguished Investigator grants:

Dorit Ben-Shachar, Ph.D., Dsc

Head, Laboratory of Psychobiology
Department of Neuroscience
The Ruth and Bruce Rappaport Faculty of Medicine

Technion — Israel Institute of Technology

"Receiving this grant will enable me to extend my mechanistic studies in schizophrenia patient-derived lymphocyte cell lines to a translational study. The results can advance our understanding of the role of mitochondrial dysfunction in schizophrenia and constitute an important step toward identifying a potential therapeutic target for this devastating disease."

Dorit Ben-Shachar, Ph.D., DSc, seeks a mitochondria-related target that therapeutically impacts schizophrenia-related molecular and behavioral pathologies. If successful, the study will provide mechanistic insight into the role of mitochondria in schizophrenia and identify a potential novel therapeutic target.

Basic Research: **Schizophrenia**

Laura L. Colgin, Ph.D.

Professor, Department of Neuroscience
Director, Center for Learning and Memory

The University of Texas at Austin

"My lab is very grateful to receive this grant. Because of it, we can begin implementing new techniques that will allow us to test our most innovative ideas about why social behaviors are abnormal in many individuals with Fragile X syndrome."

Laura Lee Colgin, Ph.D., seeks to enhance our understanding of how neurophysiological disturbances in the hippocampus contribute to abnormal social behaviors in individuals with autism that are associated with Fragile X syndrome.

Basic Research: **Autism Spectrum Disorders**

Sanjay J. Mathew, M.D.

Professor & Vice Chair for Research

Baylor College of Medicine

"This grant will allow our team to pursue a novel brain imaging technique to understand the role of a key receptor system in patients with PTSD. More broadly, we hope this work will yield new directions for therapeutic innovations for common and disabling stress-related psychiatric disorders."

Sanjay J. Mathew, M.D., will evaluate a novel radioligand for positron emission tomography (PET) imaging in individuals with PTSD. The goal of this work is to understand the role of a key glutamate receptor (AMPA) in the brain and its relationship to post-traumatic psychopathology.

Diagnostic Tools/Early Intervention, Basic Research: **PTSD**

Peter Penzes, Ph.D.

Director, Center for Autism and Neurodevelopment
Ruth and Evelyn Dunbar Professor of Psychiatry and Behavioral Sciences
Professor of Physiology and Psychiatry and Behavioral Sciences

Northwestern University

"This award enables us to explore a new research direction, a path considered too uncertain for standard NIH funding. It will help us gather important preliminary data for an NIH application. We're excited about the opportunity to expand our research horizons and make progress in areas that might lead to significant advancements in our field."

Peter Penzes, Ph.D., will continue with research in which his team has detected synaptic ectodomains in cerebrospinal fluid, a discovery with potential breakthrough implications for biomarkers and novel therapeutics in schizophrenia.

Diagnostic Tools/Early Intervention: **Schizophrenia**

Elizabeth A. Phelps, Ph.D.

Pershing Square Professor of Human Neuroscience

Harvard University

"This project represents a new approach for my lab of merging basic research advances with clinical techniques to specifically target the subjective symptoms of anxiety. New approaches like this are hard to fund through traditional means, and I am so grateful BBRF took a chance on us. I hope our project demonstrates, once again, that innovations happen when we push beyond the status quo of our science."

Elizabeth A. Phelps, Ph.D., is exploring novel ways of treating subjective clinical symptoms of anxiety. She will assess the clinical technique of cognitive restructuring during a period of memory vulnerability. The aim is to discover whether it will more persistently and effectively diminish the negative and distressing feelings evoked by intrusive, symptom-relevant autobiographical memories in socially anxious adults, compared with current first-line therapies for anxiety disorders.

Next-Generation Therapies: **Anxiety**

Noah S. Philip M.D., DFAPA

Professor of Psychiatry and Human Behavior, Alpert Medical School

Brown University

Director, Psychiatric Neuromodulation Lead, Mental Health Research, Center for Neurorestoration and Neurotechnology, VA Providence Healthcare System, Providence RI

Baylor College of Medicine

"Receiving this award is a personal and professional honor. It also underscores our team's collective achievements and the impact of our work on the intersection of neuroscience and patient care. It serves as a reminder of the boundless possibilities that await when passion, innovation, and perseverance converge in pursuit of scientific excellence."

Noah Stephen Philip, M.D., will study low-intensity focused ultrasound (LIFU) to the amygdala in depressed patients. The goal is to examine whether changes in brain perfusion are associated with clinical improvements, and to use individual-level findings as a ground truth to evaluate the accuracy of the acoustic modeling used to target the ultrasound.

Next-Generation Therapies: **Depression**

Mary L. Phillips M.D., M.D. (Cantab)

Distinguished Professor in Psychiatry and Clinical and Translational Science; Emmerling Endowed Chair in Psychotic Disorders; Director, Center for Research in Translational and Developmental Affective Neuroscience

University of Pittsburgh

"I am delighted and humbled to be receiving this award. It will allow my lab to take a new direction by providing a unique opportunity to determine the extent to which abnormalities in mitochondria, the source of energy production in cells, and specifically in mitochondrial Complex I, are associated with neural circuit abnormalities. This will be an important step forward in linking the changes in energy production that characterize people with Bipolar Disorder."

Mary L. Phillips, M.D., M.D. (Cantab), will examine mitochondrial Complex I (MC-I) in the brain in individuals with bipolar disorder (BD), and determine relationships among MC-I and indices of neural activity and neurotransmission known to be aberrant in BD. The study will guide future, larger-scale studies examining MC-I in BD to aid in risk detection and the development of new, mitochondrial dysfunction-informed treatments.

Basic Research: **Bipolar Disorder**

Carmen Sandi, Ph.D.

Laboratory of Behavioral Genetics

Brain Mind Institute, Ecole Polytechnique Federale de Lausanne (EPFL), Switzerland

"I am deeply grateful to the BBRF Foundation for their support of our work on the neurometabolic underpinnings of anxiety and depression. This award will enable us to expand our research into how mitochondria influence brain circuits related to anxiety and motivation and assess the effectiveness of targeting mitochondrial functions as potential treatments for anxiety disorders."

Carmen Sandi, Ph.D., investigates anxiety and its co-morbidity with depression, using rodent models. This project will evaluate a promising nutritional intervention that targets mitochondrial dysfunction called mitophagy. The project aims to elucidate the mechanisms of action of this intervention, assess its feasibility, and investigate its long-term safety. It could lay the groundwork for human nutritional studies aimed at alleviating anxiety symptoms.

Next-Generation Therapies: **Anxiety, Depression**

Karin Verweij, Ph.D.

Department of Psychiatry

Amsterdam University Medical Centers, The Netherlands

"This grant not only boosts our current project (where we use genetic approaches to examine causal relationships between cannabis use and mental health), but also opens up new opportunities for discovery and understanding. I am truly grateful for this recognition and the chance it gives us to further our exploration in psychiatric genetics."

Karin Johanna Hendrika Verweij, Ph.D., seeks to unravel the causal relationship between cannabis use and mental illness. Does cannabis use increase the risk or severity of mental illness, or can a mental illness lead individuals to increase their use of cannabis, for example as self-medication? The team will use novel, genetically informed methods to investigate this question.

Basic Research: **Substance Use Disorders, Addiction**

Kate M. Wassum, Ph.D.

Professor Jeffrey/Wenzell Term Chair in Behavioral Neuroscience

UCLA Department of Psychology

Integrative Center for Learning & Memory, Integrative Center for Addictive Disorders

Brain Research Institute

"This grant will enable our lab to go in a new, bold direction to discover how the brain represents potential reward options and determines their value on the fly to make good decisions. I've been excited about these ideas for some time, and I'm very grateful for the opportunity to pursue them."

Kate M. Wassum, Ph.D., seeks to reveal how value judgements for food reward options are constructed in the brain and used to guide adaptive decision making. The work has the potential to transform how we view the neuronal computations that support decision making and will enable subsequent investigation of the biological architecture of value construction and decision making, facilitating a deeper understanding of maladaptive cognition and decision making that can characterize psychiatric illnesses.

Basic Research: **Eating Disorders, Biology of the Brain**

Recent Research Discoveries

Important advances by Foundation grantees, Scientific Council members and Prize winners that are moving the field forward

A Connectivity Signature Predicting Antipsychotic Response is Identified in First-Episode Psychosis Patients

In people who experience a first psychotic episode—often the prelude to schizophrenia and related disorders—the response to antipsychotic medicines can be crucial, and often varies considerably from patient to patient.

It is widely considered that how well a first-episode patient responds to antipsychotic medications often affects how the patient fares over the long-haul—both in terms of psychosis symptoms and how well they can function in society. "Identification of predictors of response at an early stage of illness would help physicians make optimal individualized treatment plans and benefit long-term quality of life for patients," note a team of researchers in a newly published paper in the *American Journal of Psychiatry*.

The team reports encouraging news in its search for robust biomarkers that might predict treatment response to antipsychotics. They were led by **Anil K. Malhotra, M.D.**, of the Feinstein Institutes for Medical Research and Zucker Hillside Hospital. Dr. Malhotra is a member of BBRF's Scientific Council, a 2006 and 2001 BBRF Independent Investigator and a 1999 Young Investigator. The new paper's first author is **Hengyi Cao, Ph.D.**, a 2018 BBRF Young Investigator whose grant was devoted to using functional imaging to understand behaviors in psychotic disorders. Four other BBRF grantees were among the co-authors.

MRI-based functional brain imaging has been a key tool in attempts to understand how connectivity in the brain changes in people with psychosis. The knowledge gained to date has not, however, yielded reliable biomarkers. Drs. Malhotra, Cao and colleagues developed a method combining several distinct modalities in which fMRI is used to observe connectivity in the brain. It's possible, for example, to look at network connections in the brain when the brain is in a "resting state"; as well as in various active states that can be induced in test subjects by asking them, during the scan, to perform various kinds of tasks.

The team combined multiple fMRI paradigms with the hope of identifying neural traits most predictive of response to antipsychotic treatment—across the entire brain, not just in one specific region of interest.

Two groups of patients were recruited in the early stages of psychotic illness. Each had cumulatively taken antipsychotics for less than 2 weeks since their initial psychotic episode. One group comprised 49 patients with first-episode psychosis (30 were male, average age about 24). A second group of 24 similar patients (20 males, average age 22) was used as a "validation sample," to test whether any connectivity biomarkers identified in the main sample could be replicated in their predictive accuracy. Patients were randomly assigned to begin treatment on either risperidone or aripiprazole for 12 weeks. The severity of psychosis symptoms was assessed multiple times. Computer-based modeling was used to "train" a model that might enable identification of a connectivity-based biomarker based on the fMRI scans made before treatments began that would predict how well each patient then responded to the 12 weeks of antipsychotic treatment.

The researchers succeeded in identifying "a functional connectome-based neural signature for the prediction of individualized treatment outcome in patients with first-episode psychosis." There were both "positive" and "negative"

predictors of treatment response. Positive predictors were mainly connections between the cerebellum and the cerebral cortex, where lower connectivity at baseline predicted better response to antipsychotics. The researchers noted that this finding was consistent with their past findings that *increased connectivity* between cerebellum and cortex was consistently present, and abnormal, in people with psychotic disorders; also, that higher connectivity between cerebellum and cortex tended to predict worse clinical outcome after 2 years of continuous antipsychotic treatment.

"These lines of evidence converge," the team said, "to show that cerebellar-cortical hyper-connectivity is a highly robust pathological finding in psychosis," and "has the potential to be clinically used as a predictor of illness development and prognosis." The stronger connectivity may result from the dysregulation of dopamine in cortical cognitive systems, the team said. Dopamine receptors are the target of antipsychotic medicines, but they are located in abundance throughout the brain. The new evidence helps identify where at least some of the pathology underlying psychosis resides.

The predictions generated by the modeling predicted results with considerable accuracy. The difference, on average, between the psychotic symptom score predicted by the model and the actual score in each patient after 12 weeks of treatment was about 1.6 (the actual scores, on average, were about 18-20 at baseline and about 8-9 following 12 weeks of therapy). This relatively small variance between prediction and actual post-treatment score suggested to the team the potential of the connectivity signal to "assist clinical judgment for individual patients."

In addition to calling for replication of their results in larger and more diverse groups of patients, the team suggested that their method might be used to investigate possible signatures of outcomes and responses to treatment in different kinds of symptoms, for instance negative symptoms (affecting cognition and social functioning) in schizophrenia.

The team also included: **Todd Lencz, Ph.D.**, 2013 BBRF Independent Investigator and 2001 Young Investigator; **Juan A. Gallego, M.D.**, 2013 BBRF Young Investigator; **Anita D. Barber, Ph.D.**, 2009 BBRF Young Investigator; and **Delbert G. Robinson, M.D.**, 2005 BBRF Independent Investigator. ❖

PTSD Trauma Memories Are Not Represented in the Brain Like Other Memories, Study Suggests

Researchers studying the stories that people with PTSD tell about their traumatic experiences and then analyzing them in terms of the way they are represented in the brain (by measuring patterns of firing neurons) have found evidence that trauma memories are "an alternative cognitive entity" quite distinct from other representations of memory, including sad memories. The findings recently appeared in the journal *Nature Neuroscience*.

The question that drove the study, which was co-led by 2015 BBRF independent Investigator **Ilan Harpaz-Rotem, Ph.D.**, of Yale University and Daniela Schiller, Ph.D., of the Icahn School of Medicine at Mount Sinai, was whether traumatic memory is "an exceptionally strong kind of sad autobiographical memory—or a different kind of neural representation altogether." **John H. Krystal, M.D.**, of Yale, Vice President of BBRF's Scientific Council, 2019 BBRF Colvin Prize winner and 3-time BBRF grantee, was a co-author of the paper.

Previous research has established the role of the hippocampus in the formation of episodic memories—memories of events as they unfolded in space and time that enable a person to relate a sequence of events. Not only does the hippocampus enable us to construct narratives from discrete events; it is also involved in our ability to retrieve such memories. In PTSD, these capabilities of the hippocampus are thought to be impaired. PTSD also has been linked with structural changes in the brain, including a shrinking of the volume of the hippocampus and a loss of functional connectivity between the hippocampus and other brain areas.

One aim of the new study was to observe neural activation patterns in the hippocampus (among other brain areas) in PTSD patients while they were exposed to spoken accounts of their own memories.

The team used functional MRI (fMRI) imaging to examine neural activity in 28 patients with PTSD while they were listening to narratives based on their own accounts of their trauma, as well as two other types of their own memories. The patients, 11 of whom were female, were on average 38 years old. After being recruited, each was asked to elaborate on three types of autobiographical memories: one was the traumatic event associated with their PTSD; a second was a "sad" but meaningful experience that did not traumatize them (e.g., the death of a family member); a third was a neutral event, called the "calm" condition by the researchers (e.g., memory of a place one visited on vacation). Each of these memories was converted by the team to a 2-minute text which participants heard for the first time when they were read aloud by a member of the team while an fMRI scan was made.

Before the scans were analyzed, a separate "semantic content" analysis was performed of each participant's three narratives. One object of this analysis was to see if the memories of the two emotionally negative experiences—the trauma and the sad experience--could be distinguished in strictly linguistic and semantic terms from one another and from the "calm" experience. Word-clouds based on the pooled results enabled the team to see how the three types of memories "clustered," linguistically. Once this was established, it was then possible for the researchers to see if memories with similar linguistic structure and emotional content type could be correlated with patterns of neural activation revealed by the fMRI scans. For example, did linguistically similar accounts of negative memories ("sad" and "traumatic") in different participants correlate with similar neural activation patterns in their brains?

This question generated one of the study's most important results. Recounted memories of sad but non-traumatic memories—which were found to be linguistically similar—did indeed generate similar neural firing patterns in the hippocampus, across the participant group. In contrast, recounted traumatic memories were observed to generate different, highly idiosyncratic neural patterns in the hippocampus in each person.

Another brain area, the posterior cingulate cortex (PCC), which is involved in processing autobiographical memories, was also scrutinized in the fMRI scans. It too had a distinct way of responding to memories with similar emotional and linguistic content: the more severe the individual's PTSD symptoms, the stronger the correlation between the linguistic features of the recalled memory and the neural response pattern.

The team drew these conclusions: first, two major brain systems involved in processing autobiographical memory, the hippocampus and PCC, represent the emotional content of recalled memories differently. Second, the processing of trauma memories appears to be unique in the hippocampus, in that it generates neural firing patterns that do not correlate with the linguistic or emotional content of triggered memories. The latter observation moved the team to ask: if trauma memories differ from merely "sad" memories in the way in which they are processed and represented in the hippocampus, why is this the case, and what might account for this?

Here, the researchers drew on extensive clinical experience with people with PTSD. "A great deal of psychotherapy is geared toward reconstructing the traumatic event as a narrative," the team notes—"one that is embedded within life-long memories, in the attempt to distance a past trauma from the current 'safe' present."

This goal of "embedding" the trauma memory in personal history as prelude to establishing temporal and spatial distance from it is a way of enabling the patient to counter the intrusion that trauma memory often makes in everyday life—when no threat is present. The findings from the hippocampus in the new study may help explain the problem of intrusion at a biological and circuit level. It is possible, the researchers say, "that traumatic memory reactivation is not experienced as memory as such but is rather disconnected from time and space and from current surroundings." This enables the intrusion of trauma to be "experienced as an intrinsic mental event," in other words, not as other sad memories are

processed, but "as an alternative cognitive entity that deviates from memory per se."

One question raised by the study is how this perspective can help to inform and improve existing psychotherapies for PTSD. It will be interesting, for example, to investigate whether successful treatment for PTSD results in the hippocampal representation of the trauma becoming similar to representations of sad but non-traumatic memories in the same individual. ❖

A Food-Seeking Circuit in the Brain Can Override Hunger or "Fullness" Signals and May Shed Light on Eating Disorders

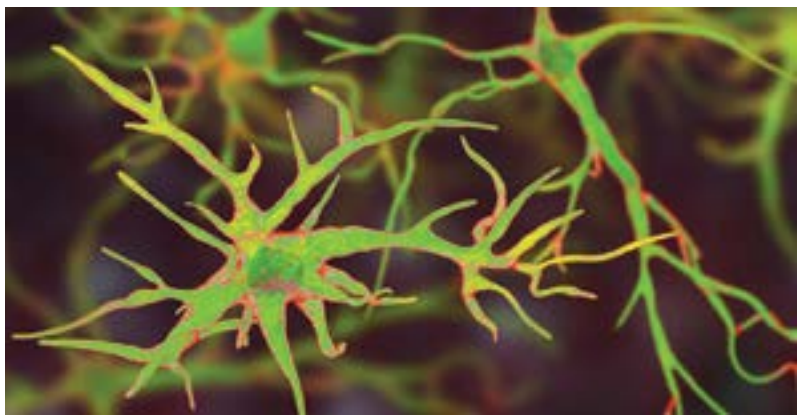
Research that was initially focused on fear, anxiety, and defensive behaviors has resulted in a series of unexpected discoveries that have shed new light on eating behaviors, and, possibly, on eating disorders involving both compulsive eating when already "full" as well as aversion to food even when hungry.

In a paper newly appearing in *Nature Communications,* a team led by 2014 BBRF Young Investigator **Avishek Adhikari, Ph.D.**, of UCLA, reports that it has identified a brain circuit in mice whose activation causes the animals to search for food even when they are not hungry. By manipulating the circuit, the researchers demonstrated they could increase or decrease food-seeking in mice, a discovery that might have translational potential in people with eating disorders since the circuit, or one very similar to it, likely also exists in the human brain.

The paper's first author, who designed and performed many of the experiments just reported, was **Fernando M. C. V. Reis, Ph.D.**, also of UCLA. His 2018 BBRF Young Investigator award helped support research that was originally focused on fear memory. A second Young Investigator grant in 2022 funded work that enabled Dr. Reis and colleagues to pursue unexpected discoveries pertaining not just to fear and defensive behaviors but to the brain's food-seeking circuitry as well.

The investigators were studying an area in the brain called the periaqueductal grey, or PAG. This region was known to have an important role in fear, but not in the pursuit of food. The team was initially investigating how cells in the PAG that release the neurotransmitter GABA (called VGAT-expressing neurons) affect fear. In the course of their experiments, the team was surprised to discover that these VGAT-expressing neurons can dramatically alter feeding—their activation led the animals to forage for food and to eat on a full stomach.

The PAG is located in the brainstem, notes Dr. Adhikari, "which is very old in evolutionary history, and because of that, it's functionally similar between humans and mice." While acknowledging the team's findings were a surprise, he said it did "make sense that foraging is rooted in such an ancient part of the brain, since foraging is something all animals must do."



Dr. Adhikari's studies initially focused on how fear and anxiety help animals assess risks and minimize exposure to threats. The PAG is particularly associated with the panic response, in rodents and people. "When we used optogenetics to selectively simulate only this specific group of VGAT-expressing

GABA neurons in the PAG, we found it did not affect the animals' fear responses; rather, it caused them to forage and eat," he notes.

The team further observed that when these cells were stimulated, mice that were not hungry started to specifically crave fatty food—so much that they were willing to endure mild electrical shocks to their feet in order to obtain this food. Conversely, when the researchers experimentally suppressed the activity of the same cells in the PAG, mice that were very hungry ate significantly less.

This suggests the potential relevance of the results to eating disorders in people. It is almost certain that humans also have VGAT cells in the PAG, as these neurons have been confirmed in a wide range of animals, including rodents, cats, and monkeys.

If additional research confirms that humans also have VGAT-expressing cells in the PAG, researchers can then try to determine if overactivity in the circuit is correlated with the feeling of reward and with craving high-calorie food even when an individual is not hungry. It is also conceivable that if underactive, the same circuit might also help explain reduced pleasure associated with eating, perhaps leading in some people to the avoidance of food. Compulsive eating when not hungry is a behavior seen in binge eating disorder. Avoiding nutrition even when deprived of calories is seen in anorexia nervosa.

In the near-term, there is more basic research to do. In their paper, the team suggests the need to investigate, for instance, how connections between the VGAT-expressing cells in the PAG and cells in a brain area called the zona incerta may regulate important aspects of the motivation to forage and eat.

The team also included **Jonathan C. Kao, Ph.D.**, a 2020 BBRF Young Investigator; and **Alcino J. Silva, Ph.D.**, a 1999 BBRF Independent Investigator. ❖

Therapy Update

Recent news on treatments for psychiatric conditions

NEW, POTENTIAL FIRST-IN-CLASS SCHIZOPHRENIA MEDICINE REDUCED POSITIVE AND NEGATIVE SYMPTOMS IN PHASE 3 TRIAL

Steven M. Paul, M.D.

Christoph U. Correll, M.D.

A new medicine for treating schizophrenia—one that appears to help reduce both positive and negative symptoms of the illness—has passed a first hurdle in phase 3 clinical testing. Phase 3 is often pivotal in deciding whether a medicine is effective and safe enough to obtain FDA approval.

The medicine, xanomeline-trospium, is called KarXT by Karuna Therapeutics, the company that is developing it and which paid for the initial phase 3 trial. The drug has a novel mechanism of action that distinguishes it from all previously approved antipsychotic medicines.

In December 2023, the pharmaceutical giant Bristol-Myers Squibb Co. entered into a deal valued at over $14 billion to purchase Boston-based Karuna. The announcement came just weeks after positive results of the first of two positive KarXT phase 3 trials were published in the journal *Lancet*. Senior author of the paper reporting the results was **Steven M. Paul, M.D.**, a BBRF Scientific Council emeritus member who is currently Chief Scientific Officer and President of R&D at Karuna. One of the paper's co-authors was 2007 BBRF Young Investigator **Christoph U. Correll, M.D.**, of Northwell/Zucker Hillside Hospital.

252 patients with acute psychosis requiring hospitalization were enrolled in the randomized, double-blinded, placebo-controlled trial. Half received KarXT for 5 weeks and half received placebo. KarXT was observed to significantly reduce both "positive" and "negative" symptoms of schizophrenia compared with placebo. In addition to reductions in both kinds of symptoms, patients receiving the new medicine in most cases were able to tolerate it well, reporting only moderate side effects. Larger and longer phase 3 clinical trials are now underway.

KarXT is the culmination of research begun decades ago to find a new way of treating symptoms of schizophrenia. Since the first antipsychotic medicine approved in the 1950s, every antipsychotic approved to date targets a cellular receptor for the neurotransmitter dopamine called the D2 receptor. Some "atypical" or second-generation antipsychotic medicines, including clozapine, also have important therapeutic effects related to their impact on receptors for serotonin. Both first- and second-generation antipsychotics are often very effective in reducing delusions and hallucinations that are the chief positive symptoms of the illness. But they have essentially no impact on negative symptoms such as blunted affect, anhedonia, lack of motivation and asociality, and no appreciable impact on cognitive symptoms that are also among the core symptoms of schizophrenia (reduced executive function, difficulty in sustaining attention, impaired long-term memory, among others).

An estimated 30%-40% of schizophrenia patients are resistant to the therapeutic benefits of current antipsychotic medicines; others derive only partial positive-symptom benefits. Short- and long-term side effects associated with approved antipsychotics are also an issue for many patients, and range from motor impacts, such as akathisia, Parkinsonism and tardive dyskinesia, to cardiometabolic effects including weight gain, lipid and glucose abnormalities, hyperprolactinemia and sexual dysfunction, as well as somnolence and sedation.

The idea that led to KarXT began with the aim of developing a drug with a novel mechanism of action—one that would not block D2 dopamine receptors but rather would stimulate

cellular receptors called the M1 and M4 muscarinic receptors. These receptors are part of the cholinergic (acetylcholine) neurotransmitter system. The theory was that agents targeting the muscarinic acetylcholine receptors might indirectly impact the balance in the brain between the dopamine and acetylcholine systems, including in the brain's striatum, which in turn might help therapeutically address pathology that gives rise to psychosis.

For many years, preliminary tests of medicines targeting the muscarinic M1 and M4 receptors suggested that they had excellent potential for reducing schizophrenia's positive, psychosis-related symptoms. The problem has always been side effects: the early candidate drugs had significant side effects in the body's gastrointestinal system, including nausea and vomiting. To potentially overcome this obstacle, developers of KarXT have tested the idea of combining a compound (xanomeline) that stimulates the M1 and M4 muscarinic receptors in the brain with a compound (trospium chloride) that blocks the M1 and M4 receptors in bodily tissue outside the brain, including the gastrointestinal tract. In phase 1 and 2 trials, KarXT appeared to demonstrate antipsychotic efficacy while reducing the frequency and severity of gastrointestinal side effects.

The 252 individuals recruited for the phase 3 trial just reported were drawn from 22 inpatient sites in the U.S.; all had experienced a recent worsening of psychosis warranting hospital admission. The average participant was about 46 years old. Participants were randomly assigned to receive KarXT or placebo twice a day for 5 weeks. Those receiving KarXT were started on a dose of 50mg of xanomeline and 20mg of trospium twice daily for 2 days, then 100mg and 20mg of the two drugs, respectively, from days 3-7. Beginning on the 8th day, dosing was flexible, and increased to 125mg/30mg twice daily if tolerated by the patient, otherwise the dose was reduced to the 100mg/20mg level. Nearly all participants were able to tolerate the maximum dose after day 8 for the duration of the trial.

After 5 weeks, those in the KarXT group had significant reductions in both positive and negative schizophrenia symptoms, as measured by the PANSS assessment tool. From an average total symptom score of about 98, the typical participant had a 21-point reduction after 5 weeks on KarXT, compared with an 11.6-point reduction in the placebo group. On separate "subscales" measuring positive or negative symptoms, KarXT was also superior to placebo. KarXT-treated patients had a reduction of nearly 7 points compared with about 4 points in the placebo group. Negative symptoms declined 3.4 points in the KarXT group vs. 1.6 points in the placebo group. In the KarXT group, 55% had an overall symptom reduction of 30% or greater, compared with 28% in the placebo group.

Side effects were present, as they are with virtually all medications, but were considered comparatively mild to moderate by the researchers. The most common were constipation, dyspepsia, headache, and nausea. Importantly, KarXT "was not associated with many of the adverse events typically associated with current antipsychotic treatments including motor symptoms, weight gain, changes in lipid and glucose parameters, prolactin elevation/sexual dysfunction and somnolence [drowsiness]."

Noting KarXT's apparent ability to significantly reduce both positive and negative schizophrenia symptoms as well as the reports on side effects, the researchers concluded that KarXT "has the potential to be the first of a new class of effective and well-tolerated antipsychotic medicines."

The team looked forward to results from additional clinical trials now in progress. These may help assess whether the observed decline in negative symptoms in the KarXT patients was a direct result of the medicine's mechanism of action or might be related in part to its ability to reduce positive symptoms. Also, trials in progress will explore over the longer-term the drug's impact as adjunctive treatment on patients with ongoing positive symptoms due to only a partial response to currently available antipsychotics.

Future trials may explore the new drug's impact in patients whose predominant symptoms are negative symptoms or cognitive dysfunction. Still other trials might pit KarXT against an active control group, to enable direct comparison with other antipsychotic medicines in patients with schizophrenia. Finally, trials are also ongoing to examine the efficacy and safety of KarXT for psychosis in patients with Alzheimer's dementia. ❖

PRELIMINARY TRIAL OF PSYCHOACTIVE DRUG IBOGAINE YIELDS 'INITIAL EVIDENCE' FOR THERAPEUTIC POTENTIAL IN TRAUMATIC BRAIN INJURY

Nolan R. Williams, M.D.

In an exploratory and preliminary clinical test, a team of researchers at Stanford University has obtained "initial evidence" suggesting that a psychoactive compound called ibogaine, when co-administered with magnesium, "could be a powerful therapeutic" to safely treat a variety of psychiatric symptoms, including PTSD, major depression and anxiety, and suicidality, all of which may emerge following traumatic brain injury (TBI).

Ibogaine, derived from the root bark of a shrub, has been used for traditional religious and healing purposes in Africa for centuries. Sometimes called an atypical psychedelic, the Stanford researchers prefer to classify it as an "oneirogen," based on a Greek word that describes its main psychotropic effect: therapeutic dosing leads to dreamlike states of consciousness that persist for several hours and sometimes even longer. Proponents of the compound say it facilitates self-reflection and self-evaluation.

Ibogaine is not thought to be addictive, although it does have powerful and potentially harmful effects on users. Until now little academic research has been conducted into its possible therapeutic value. The paucity of research is directly due to its illegality in the U.S., although the drug can be used legally in Mexico and Canada.

Ibogaine is a drug of interest to some researchers for several reasons, the chief of which is that those who suffer from traumatic injuries to the brain are often not helped, or helped only partly, by existing FDA-approved therapies. TBI is considered the "signature injury of U.S. military veterans from recent military conflicts, most often caused by blast exposure," note the authors of the paper reporting results of a small trial with ibogaine just published in the journal *Nature Medicine*. Lead author of the study was **Nolan R. Williams, M.D.**, of Stanford, a BBRF Young Investigator in 2018 and 2016, and 2019 winner of BBRF's Klerman Prize for Exceptional Clinical Research. **Jennifer Keller, Ph.D.**, a 2009 BBRF Young Investigator, was among the co-authors.

First-line therapies for conditions often arising following TBI—cognitive rehabilitation, psychotherapy, and medications that target specific symptoms—tend to be less effective for veterans compared with other populations, the Stanford team says, with remission rates ranging from 20% to 40% following treatment. "Most concerningly, veterans make up 20% of U.S. suicides," they note, although they account for only 6% of the population. Exposure to blasts can result in changes to the brain, including brain structure, functional connectivity, cerebral blood flow, and white matter damage. TBI is also linked with cognitive problems involving memory, attention, neural processing speed, and executive function. These can disable sufferers.

"No drug to date has been able to alleviate the functional and neuropsychiatric symptoms of traumatic brain injury," Dr. Williams notes. "There were a handful of veterans who had gone to a clinic in Mexico and were reporting anecdotally that they had great improvements in their lives after taking ibogaine. Our goal was to characterize those improvements with structured neurobiological assessments."

The Stanford researchers entered into a collaboration with a company called Ambio Life Sciences, which had received a grant from a nonprofit called Veterans Exploring Treatment Solutions (VETS), Inc. to test ibogaine in a group of 30 male volunteers who, independently of the university, had enrolled themselves in what is called an open-label trial to be conducted at a clinic in Tijuana, Mexico. In such trials, there is no "blinding"; participants know that they will be receiving a particular treatment. There is no placebo given for comparative purposes, and no control group. The Stanford team conducted pre-trial assessments and brain scans of the 30 volunteers before they traveled to Mexico for their treatments, and assessed them again within days after the treatments, once they had returned to the U.S., as well as one month following treatments. That data continues to be under review and will be the subject of subsequent papers.

All of the participants were males who had served in U.S. special forces and had suffered mild to moderate traumatic

brain injury which impaired their functioning. These injuries occurred an average of 8 years prior to the trial. Many participants had related disorders: 23 met the criteria for PTSD, 14 for an anxiety disorder, and 15 for alcohol use disorder. Over their lifetimes 19 had exhibited suicidal behavior and 7 had attempted to end their life.

Prior to treatment with ibogaine the 30 participants were found to have an average rating of 30 on a WHO disability scale, which translates into "mild to moderate" disability. "These men were incredibly intelligent, high-performing individuals who experienced life-altering functional disability from TBI during their time in combat," Dr. Williams said. "They were all willing to try most anything that they thought might help them get their lives back."

After being administered ibogaine along with concurrent injections of magnesium to reduce the potential impact on heart arrhythmia and other known potential cardiac side effects, "participants showed a remarkable reduction in symptoms" of disability, PTSD, depression and anxiety," the team reported. The benefits were sustained at the 1-month follow-up. In fact, disability measures "continued to improve and psychiatric symptom remission and response rates remained high" after 1 month, the team noted. "Neuropsychological testing revealed areas of improvement after treatment particularly in processing speed and executive function, without any detrimental changes observed. With regard to safety, no serious or unexpected adverse events occurred and management of adverse effects was uncomplicated." Such adverse effects included nausea, headache, and anxiety. Motor effects were uncommon and resolved within 24 hours.

The disability score of a typical participant declined from 30 to 19.9 in the assessment immediately following treatment; this further plunged to 5.1 after one month ("no disability"). Mean percentage reduction in PTSD, depression and anxiety symptoms was 81%; 93% were "responders" and the remission rate was 83%. Suicidal ideation, present in 47% pre-treatment, fell to 0% just after treatment and 7% after one month. The tests of neurocognitive functioning included a finding that reaction time slowed significantly post-treatment, which may translate into a reduction in impulsivity among those in whom this was a problem. Impulsivity is associated with relapse after substance-use treatment and also with suicidality.

Because the trial was not blinded and there was no control, it was impossible for the researchers to estimate the magnitude of the placebo effect—which is present in all trials. In this case, it might have been powerful, the researchers note, since the participants had elected to travel internationally to be treated and were not being helped sufficiently by any prior treatments (which they discontinued prior to the beginning of the trial). Thus, the factor of "expectancy," of wanting and expecting a positive result, was no doubt present. Researchers have long noted the special challenge of clinical research involving psychedelic compounds: those who ingest them know they have received a "treatment"—there is no known neutral, non-psychoactive agent that effectively mimics a psychedelic drug experience.

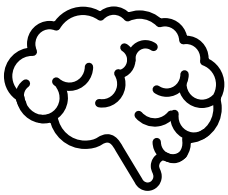
Another important factor in considering the strong results is the potential impact of "complementary therapies" which all participants received as part of the trial in Tijuana. Each participant was paired with a licensed therapist experienced in coaching patients undergoing ibogaine treatment. Each was coached prior to the administration of the treatment, during the treatment while the dream-like effects of ibogaine were being experienced, and following treatment—the next day, when coaches and patients discussed the processing of their emotions and how to interpret and "integrate" insights they may have gained from the treatment into their everyday lives.

Further study of the data from the brain scans made before and after the treatments will lead to additional papers by the team. Dr. Williams hopes that results of subsequent studies with more diverse patient populations, including those with more severe TBI, will reveal "a host of different brain areas" that may be involved in any therapeutic impact of ibogaine—data that might "help us to treat other forms of PTSD, anxiety, and depression that aren't necessarily linked to TBI." ❖

MONTHLY GIVING HELPS BBRF AND YOU!

What's the most effective and efficient way to impact brain science research at BBRF? By becoming a Monthly Donor.

Here's why:



IT FUELS ONGOING RESEARCH

You'll enable BBRF grantees to continue their vital work year round.

IT'S SAFE AND EASY

Your gift will be securely and automatically processed each month.

AND MOST IMPORTANTLY... IT'S EASIER FOR YOU.

If you're looking to have your financial support for brain research go as far as possible, then become a Monthly Donor.

You'll be a critical partner in helping support BBRF's research grantees working toward advancements that dramatically improve the lives of those living with mental illness and enabling people to live full, happy, and productive lives.

So please consider becoming a Monthly Donor today.

For more info, please email development@bbrfoundation.org

100% OF EVERY DOLLAR DONATED FOR RESEARCH GOES TO RESEARCH

BRAIN & BEHAVIOR RESEARCH FOUNDATION

Awarding **NARSAD** Grants

Now Airing: The 9th Season of *Healthy Minds with Dr. Jeffrey Borenstein*

Now Available on pbs.org
https://www.pbs.org/show/healthy-minds-with-dr-jeffrey-borenstein/episodes/season/9/

The ninth season of the Emmy®-nominated public television series *Healthy Minds with Dr. Jeffrey Borenstein* premiered nationally on PBS.org on May 1 for Mental Health Awareness Month. This season once again features top experts sharing the latest information about new approaches in the prevention, diagnosis, and treatment of mental illness and inspiring personal stories from families.

"Millions of individuals and families across the United States are facing mental health challenges, however stigma and misunderstanding still often keep people from seeking help," says Jeffrey Borenstein, M.D., who developed the series and serves as its host and executive producer. *Healthy Minds* provides understandable information and resources for viewers, inspires open discussions about mental illness and demonstrates that with help, there is hope."

The latest season includes 12 new half-hour episodes in which Dr. Borenstein speaks with leading experts about some of the most pressing mental health issues in the United States, including the nexus between mental health, obesity, and diabetes; COVID and mental health; post-traumatic stress in children and adolescents; how to recognize the differences between normal worry and anxiety in young people, and how to best bring mental health resources to people who are homeless.

Guests who speak from personal experience this season include the mother of a patient with bipolar disorder, who, along BBRF Scientific Council President Dr. Judith Ford of the University of California, San Francisco, discusses how a ketogenic diet focused on increased protein and decreased carbohydrates has shown positive results for patients with bipolar disorder, epilepsy, and schizophrenia. A psychiatrist, herself the sibling of a patient with early onset psychosis, explores advances in treating young people who experience symptoms of psychosis. And the chairman of the board of an academic program founded by parents of neurodiverse students discusses education and opportunities for people with neurodiversity.

In addition to viewing the series on PBS.org, the series can be viewed on many local public television stations; a link can be found on the BBRF website at www.bbrfoundation.org/healthy-minds-tv.

Healthy Minds is produced by the Brain & Behavior Research Foundation, presented by Connecticut Public Television (CPTV) and distributed by the National Education Telecommunications Association (NETA). Funding is provided by the American Psychiatric Association Foundation and the John & Polly Sparks Foundation.

❖ **LAUREN DURAN**

Season 9 Episode Details:

Jan Ellison Baszucki

METABOLIC PSYCHIATRY

A ketogenic diet focused on increased protein and decreased carbohydrates has shown positive results for patients with bipolar disorder, epilepsy, and schizophrenia.

Guests: Jan Ellison Baszucki, mother of bipolar patient, now funding research as President, Baszucki Group; Judith M. Ford, Ph.D., Professor of Psychiatry, University of California, San Franciso.

Maura Boldrini, M.D.

UPDATE ON COVID AND MENTAL HEALTH

A follow up to the 2022 season of "Healthy Minds" explores some potential long-term effects of COVID including depression, anxiety, psychosis, and brain fog, as well as treatments for these conditions.

Guest: Maura Boldrini, M.D., Associate Professor of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons and Director, Quantitative Brain Biology Institute (Brain QUANT).

Katherine Koh, M.D.

HELPING PEOPLE WHO ARE HOMELESS, PART 1

A model program in Boston offers a holistic approach to clinical care for the homeless built around a street team bringing mental health resources directly to those most in need, including case workers, psychiatrists, and a recovery coach who has experienced being homeless.

Guest: Katherine Koh, M.D., Assistant Professor of Psychiatry, Harvard Medical School and Street Psychiatrist, Boston Health Care for the Homeless Program.

HELPING PEOPLE WHO ARE HOMELESS, PART 2

Research to improve clinical care and positive outcomes for the homeless population includes understanding risk factors for homelessness, including the need for mental health support during transitions out of the military, jail, and foster care.

Guest: Katherine Koh, M.D., Assistant Professor of Psychiatry, Harvard Medical School and Street Psychiatrist, Boston Health Care for the Homeless Program.

Ryan Herringa, M.D., Ph.D.

POST-TRAUMATIC STRESS IN CHILDREN AND ADOLESCENTS

PTSD looks different in children and adolescents than in adults; what factors contribute to trauma's long-term effects?; unique treatments for youth including eye movement desensitization and reprocessing (EMDR); and the need for suicide prevention awareness after trauma in young people's lives.

Guest: Ryan Herringa, M.D., Ph.D., University of Wisconsin Health Professor in Children and Adolescent Psychiatry, University of Wisconsin School of Medicine and Public Health.

Robert Freedman, M.D.

PRENATAL CHOLINE AND BRAIN HEALTH

The nutrient choline has been shown to support fetal brain development, and supplements taken during pregnancy may lead to improved concentration and attention spans in childhood as well as a decreased risk of schizophrenia for these children later in life.

Guest: Robert Freedman, M.D., Department of Psychiatry, University of Colorado School of Medicine.

Conor Liston, M.D., Ph.D.

DIAGNOSIS AND TREATMENT FOR SUBTYPES OF DEPRESSION

New research using brain scans and biological markers has revealed areas of connectivity in the brain that can make diagnosis and treatment of the various types of depression more efficient and effective and identify the fundamental mechanisms that make moods change.

Guest: Conor Liston, M.D., Ph.D., Professor of Neuroscience and Psychiatry, Weill Cornell Medicine.

Lisa Dixon, M.D.

TREATMENT OF EARLY PSYCHOSIS

Coordinated care including early intervention, education, a team of medical experts, and a strong support system of family as well as peers with shared experience can increase positive outcomes for young people after a first psychotic episode. The leader of the "On Track New York" program, a doctor and sibling of an early onset patient herself, explores the advances in understanding and treating adolescents and young adults experiencing hallucinations and other symptoms.

Guest: Lisa Dixon, M.D., Professor of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons.


Roger McIntyre, M.D., FRCPC

MENTAL HEALTH, OBESITY AND DIABETES

Research that looks at mental health holistically has revealed that half of all patients with depression or bipolar disorder patients are diabetic or pre-diabetic, leading to a new perspective on symptoms and treatment regarding insulin and brain function.

Guest: Roger McIntyre, M.D., FRCPC, Professor of Psychiatry and Pharmacology, University of Toronto, Canada


Stephen P. Hinshaw, Ph.D.

ADHD: WHAT YOU NEED TO KNOW

Demystifying the symptoms of Attention-Deficit Hyperactivity Disorder and understanding the variety of ways ADHD presents in young people including differences in which aspect of the disorder is manifested, and best advice for caregivers to help young people lead successful lives after diagnosis.

Guest: Stephen P. Hinshaw, Ph.D., Distinguished Professor of Psychology, University of California, Berkeley, and Professor of Psychiatry and Behavioral Sciences, University of California, San Francisco.


Keli Mondello

EDUCATION AND OPPORTUNITIES FOR PEOPLE WITH NEURODIVERSITY

A model academic program in Florida addresses the needs of neurodiverse students, founded by parents looking for resources. LiFT (Learning Independence for Tomorrow) Academy serves kindergarten through 12th grade, and LiFT University Transition Program is a four-year post-secondary transition program for students who have completed high school for continued academics, career readiness, and life skill training.

Guest: Keli Mondello, co-founder and Chairman of the Board, Learning Institute for Tomorrow (LiFT).


Daniel Pine, M.D.

ANXIETY IN YOUTH

Diagnosing and treating anxiety in childhood and adolescence can decrease the risk of developing depression and other mental disorders later in life. Advice for parents to recognize the differences between normal worries and anxiety, and the impact of outside factors including bullying and social media.

Guest: Daniel Pine, M.D., National Institutes of Health Distinguished Investigator.

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**

OUR SCIENTIFIC COUNCIL

192 Scientific Council Members
46 Members of the National Academy of Medicine
43 Chairs of Psychiatry & Neuroscience Departments
14 National Institutes of Health Chiefs & Directors
7 Members of the National Academy of Sciences
3 Recipients of the National Medal of Science
1 Director of the National Institute of Mental Health
1 Nobel Prize Winner

PRESIDENT
Judith M. Ford, Ph.D.

VICE PRESIDENT
John H. Krystal, M.D.

Ted Abel, Ph.D.
Anissa Abi-Dargham, M.D.
Nii A. Addy, Ph.D.
Susanne E. Ahmari, M.D., Ph.D.
Olusola Ajilore, M.D., Ph.D.
Schahram Akbarian, M.D., Ph.D.
Susan G. Amara, Ph.D.
Stewart A. Anderson, M.D.
Nancy C. Andreasen, M.D., Ph.D.
Carmen Andreescu, M.D.
Victoria Arango, Ph.D.
Amy F.T. Arnsten, Ph.D.
Gary S. Aston-Jones, Ph.D.
Randy P. Auerbach, Ph.D.
Tracy L. Bale, Ph.D.
Debra A. Bangasser, Ph.D.
Tallie Z. Baram, M.D., Ph.D.
Deanna M. Barch, Ph.D.
Samuel H. Barondes, M.D.
Carrie E. Bearden, Ph.D.
Francine M. Benes, M.D., Ph.D.
Karen F. Berman, M.D.
Wade H. Berrettini, M.D., Ph.D.
Randy D. Blakely, Ph.D.
Julie A. Blendy, Ph.D.
Pierre Blier, M.D., Ph.D.
Hilary P. Blumberg, M.D.
Vadim Bolshakov, Ph.D.
Kathleen T. Brady, M.D., Ph.D.
Kristen J. Brennand, Ph.D.
Robert W. Buchanan, M.D.
Peter F. Buckley, M.D.
William E. Bunney, Jr., M.D.
Joseph D. Buxbaum, Ph.D.
Tyrone D. Cannon, Ph.D.
William Carlezon, Ph.D.
William T. Carpenter, Jr., M.D.
Cameron S. Carter, M.D.
Edwin H. Cook, Jr., M.D.
Richard Coppola, D.Sc.
Christopher W. Cowan, Ph.D.
Ronald L. Cowan, M.D., Ph.D.
Joseph T. Coyle, M.D.
Jacqueline N. Crawley, Ph.D.
Kathryn R. Cullen, M.D.
Z. Jeff Daskalakis, M.D., Ph.D.
Karl Deisseroth, M.D., Ph.D.
J. Raymond DePaulo, Jr., M.D.
Robert Desimone, Ph.D.
Ariel Y. Deutch, Ph.D.
Ralph DiLeone, Ph.D.
Lisa Beth Dixon, M.D., M.P.H.
Wayne C. Drevets, M.D.
Kafui Dzirasa, M.D., Ph.D.
Guoping Feng, M.D., Ph.D.
André Fenton, Ph.D.
Robert L. Findling, M.D., MBA
Stan B. Floresco, Ph.D.
Alan Frazer, Ph.D.
Robert Freedman, M.D.
Aurelio Galli, Ph.D.
Mark S. George, M.D.
Elliot S. Gershon, M.D.
Mark A. Geyer, Ph.D.
Jay N. Giedd, M.D.
Jay A. Gingrich, M.D., Ph.D.
James M. Gold, Ph.D.
David Goldman, M.D.
Andrea Beth Goldschmidt, Ph.D.
Rita Z. Goldstein, Ph.D.
Joshua A. Gordon, M.D., Ph.D.
Elizabeth Gould, Ph.D.
Anthony A. Grace, Ph.D.
Dorothy E. Grice, M.D.
Raquel E. Gur, M.D., Ph.D.
Suzanne N. Haber, Ph.D.
Philip D. Harvey, Ph.D.
Stephan Heckers, M.D.
René Hen, Ph.D.
Takao K. Hensch, Ph.D.
Elliot Hong, M.D.
Laura Marianne Huckins, Ph.D.
Yasmin L. Hurd, Ph.D.
Robert B. Innis, M.D., Ph.D.
Alicia Izquierdo, Ph.D.
Jonathan A. Javitch, M.D., Ph.D.
Daniel C. Javitt, M.D., Ph.D.
Dilip V. Jeste, M.D.
Shafali Spurling Jeste, M.D.
René S. Kahn, M.D., Ph.D.
Ned H. Kalin, M.D.
Peter W. Kalivas, Ph.D.
Eric R. Kandel, M.D.
Thomas L. Kash, Ph.D.
Ege T. Kavalali, Ph.D.
Richard S.E. Keefe, Ph.D.
Christoph Kellendonk, Ph.D.
Martin B. Keller, M.D.
John R. Kelsoe, M.D.
Kenneth S. Kendler, M.D.
James L. Kennedy, M.D.
Robert M. Kessler, M.D.
Mary-Claire King, Ph.D.
Arnold Kriegstein, M.D., Ph.D.
Cecile D. Ladouceur, Ph.D.
Amanda J. Law, Ph.D.
James F. Leckman, M.D., Ph.D.
Francis S. Lee, M.D., Ph.D.
Robert H. Lenox, M.D.
David A. Lewis, M.D.
Jeffrey A. Lieberman, M.D.
Gregory A. Light, Ph.D.
Kelvin O. Lim, M.D.
Sarah Hollingsworth Lisanby, M.D.
Joan L. Luby, M.D.
Irwin Lucki, Ph.D.
Beatriz Luna, Ph.D.
Gary Lynch, Ph.D.
Robert C. Malenka, M.D., Ph.D.
Anil K. Malhotra, M.D.
Husseini K. Manji, M.D., F.R.C.P.C.
J. John Mann, M.D.
John S. March, M.D., M.P.H.
Stephen Maren, Ph.D.
Keri Martinowich, Ph.D.
Daniel H. Mathalon, Ph.D., M.D.
Helen S. Mayberg, M.D.
Carla A. Mazefsky, Ph.D.
Colleen A. McClung, Ph.D.
Ronald McKay, Ph.D.
James H. Meador-Woodruff, M.D.
Herbert Y. Meltzer, M.D.
Kathleen R. Merikangas, Ph.D.
Richard J. Miller, Ph.D.
Guo-Li Ming, M.D., Ph.D.
Karoly Mirnics, M.D., Ph.D.
Bita Moghaddam, Ph.D.
Lisa M. Monteggia, Ph.D.
David A. Morilak, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
Andrew A. Nierenberg, M.D.
Patricio O'Donnell, M.D., Ph.D.
Dost Ongur, M.D., Ph.D.
Maria A. Oquendo, M.D., Ph.D.
Martin P. Paulus, M.D.
Godfrey D. Pearlson, M.D., Ph.D.
Peter Penzes, Ph.D.
Mary L. Phillips, M.D., M.D. (CANTAB)
Marina R. Picciotto, Ph.D.
Daniel S. Pine, M.D.
Robert M. Post, M.D.
James B. Potash, M.D., M.P.H.
Susan Powell, Ph.D.
Pasko Rakic, M.D., Ph.D.
Judith L. Rapoport, M.D.
Perry F. Renshaw, M.D., Ph.D., M.B.A.
Kerry J. Ressler, M.D., Ph.D.
Victoria B. Risbrough, Ph.D.
Carolyn Rodriguez, M.D., Ph.D.
Bryan L. Roth, M.D., Ph.D.
Laura M. Rowland, Ph.D.
Scott J. Russo, Ph.D.
Gerard Sanacora, M.D., Ph.D.
Akira Sawa, M.D., Ph.D.
Alan F. Schatzberg, M.D.
Nina R. Schooler, Ph.D.
Robert Schwarcz, Ph.D.
Yvette I. Sheline, M.D.
David A. Silbersweig, M.D.
Vikaas S. Sohal, M.D., Ph.D.
Matthew W. State, M.D., Ph.D.
Murray B. Stein, M.D., M.P.H., F.R.C.F.C.
Joanna C. Steinglass, M.D.
Stephen M. Strakowski, M.D.
Carol A. Tamminga, M.D.
Laurence H. Tecott, M.D., Ph.D.
Flora M. Vaccarino, M.D., Ph.D.
Rita J. Valentino, Ph.D.
Jeremy M. Veenstra-VanderWeele, M.D.
Susan M. Voglmaier, M.D., Ph.D.
Aristotle N. Voineskos, M.D., Ph.D.
Nora D. Volkow, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Jared W. Young, Ph.D.
L. Trevor Young, M.D., Ph.D., F.R.C.P.C., F.C.A.H.S.
Carlos A. Zarate, Jr., M.D.
Jon-Kar Zubieta, M.D., Ph.D.

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding **NARSAD** Grants

747 Third Avenue, 33rd Floor
New York, NY 10017

800.829.8289
info@bbrfoundation.org
bbrfoundation.org

RESEARCH FOR RECOVERY

For more than 35 years the Brain & Behavior Research Foundation has fostered new research pathways and transformative breakthroughs.

Our 70,000 donors have joined together in the great challenge of modern medical science–overcoming mental illness.

Since 1987 the Foundation has awarded more than $450 million to fund more than 6,500 grants.

Grants have been given to 5,400 leading scientists around the world.

100% OF EVERY DOLLAR DONATED FOR RESEARCH GOES TO RESEARCH

Sign up for eNews at **bbrfoundation.org/signup**.
Find BBRF on: