Brain&Behavior MAGAZINE
JULY 2017

New Approach for Treatment-Resistant Depression

Developing Neuroscience Tools That Can Improve Treatments

Diagnosing Depression In Young Children

INVESTING IN BREAKTHROUGHS TO FIND A CURE

100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover our Foundation's operating expenses.

OUR MISSION:

The Brain & Behavior Research Foundation is committed to alleviating the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research.

HOW WE DO IT:

The Foundation funds the most innovative ideas in neuroscience and psychiatry to better understand the causes and develop new ways to treat brain and behavior disorders. These disorders include depression, bipolar disorder, schizophrenia, autism, attention-deficit hyperactivity disorder, anxiety, borderline personality disorder, chemical dependency, obsessive-compulsive disorder and post-traumatic stress disorders.

OUR CREDENTIALS:

Since 1987, we have awarded more than $365 million to fund more than 5,000 grants to more than 4,000 scientists around the world.

OUR VISION:

To bring the joy of living to those affected by mental illness-those who are ill and their loved ones.

Contents

Board of Directors

PUBLICATION CREDITS

Writers
Fatima Bhojani
Bahar Gholipour
Becky Ham
Jennifer Michalowski
Peter Tarr, Ph.D.

Editors
Lauren Duran
Becky Ham

Designer
Jenny Reed

168 Members (4 Emeritus)
2 Nobel Prize Winners
4 Former Directors of the National Institute of Mental Health as well as the current Director
4 Recipients of the National Medal of Science
13 Members of the National Academy of Sciences
26 Chairs of Psychiatry & Neuroscience Departments at Leading Medical Institutions
55 Members of the National Academy of Medicine

SCIENTIFIC COUNCIL

PRESIDENT
Herbert Pardes, M.D.

VICE PRESIDENT EMERITUS
Floyd E. Bloom, M.D.

Ted Abel, Ph.D.
Anissa Abi-Dargham, M.D.
Schahram Akbarian, M.D., Ph.D.
Huda Akil, Ph.D.
Susan G. Amara, Ph.D.
Stewart A. Anderson, M.D.
Nancy C. Andreasen, M.D., Ph.D.
Amy F.T. Arnsten, Ph.D.
Gary S. Aston-Jones, Ph.D.
Jay M. Baraban, M.D., Ph.D.
Deanna Barch, Ph.D.
Jack D. Barchas, M.D.
Samuel H. Barondes, M.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.
Pierre Blier, M.D., Ph.D.
Hilary Blumberg, M.D.
Robert W. Buchanan, M.D.
Peter F. Buckley, M.D.
William E. Bunney, Jr., M.D.
Joseph D. Buxbaum, Ph.D.
William Byerley, M.D.
William Carlezon, Ph.D.
Marc G. Caron, Ph.D.
William T. Carpenter, Jr., M.D.
Cameron S. Carter, M.D.
BJ Casey, Ph.D.
Bruce M. Cohen, M.D., Ph.D.
Jonathan D. Cohen, M.D., Ph.D.
Peter Jeffrey Conn, Ph.D.
Edwin Cook, M.D.
Richard Coppola, DSc
Rui Costa, Ph.D., HHMI
Joseph T. Coyle, M.D.
Jacqueline N. Crawley, Ph.D.
John G. Csernansky, M.D.
Karl Deisseroth, M.D., Ph.D.
J. Raymond DePaulo, Jr., M.D.
Ariel Y. Deutch, Ph.D.
Wayne C. Drevets, M.D.
Ronald S. Duman, Ph.D.
Stan B. Floresco, Ph.D.
Judith M. Ford, Ph.D.
Alan Frazer, Ph.D.
Robert R. Freedman, M.D.
Fred H. Gage, Ph.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.
David Goldman, M.D.
Frederick K. Goodwin, M.D.
Joshua A. Gordon, M.D., Ph.D.
Elizabeth Gould, Ph.D.
Anthony A. Grace, Ph.D.
Paul Greengard, Ph.D.
Raquel Gur, M.D., Ph.D.
Suzanne N. Haber, Ph.D.
Philip D. Harvey, Ph.D.
Stephan Heckers, M.D.
René Hen, Ph.D.
Fritz A. Henn, M.D., Ph.D.
Takao Hensch, Ph.D.
Robert M.A. Hirschfeld, M.D.
L. Elliot Hong, M.D.
Steven E. Hyman, M.D.
Robert B. Innis, M.D., Ph.D.
Jonathan A. Javitch, M.D., Ph.D.
Daniel C. Javitt, M.D., Ph.D.
Dilip Jeste, M.D.
Lewis L. Judd, M.D.
Ned Kalin, M.D.
Peter W. Kalivas, Ph.D.
Eric R. Kandel, M.D.
Richard S.E. Keefe, Ph.D.
Samuel J. Keith, M.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.
Kenneth K. Kidd, Ph.D.
Mary-Claire King, Ph.D.
Rachel G. Klein, Ph.D.
John H. Krystal, M.D.
Amanda Law, Ph.D.
James F. Leckman, M.D.
Francis S. Lee, M.D., Ph.D.
Ellen Leibenluft, M.D.
Robert H. Lenox, M.D.
Pat Levitt, Ph.D.
David A. Lewis, M.D.
Jeffrey A. Lieberman, M.D.
Irwin Lucki, Ph.D.
Gary Lynch, Ph.D.
Robert C. Malenka, M.D., Ph.D.
Anil K. Malhotra, M.D.
Husseini K. Manji, M.D., FRCPC
J. John Mann, M.D.
John S. March, M.D., M.P.H.
Daniel Mathalon, Ph.D., M.D.
Helen S. Mayberg, M.D.
Robert W. McCarley, M.D.
Bruce S. McEwen, Ph.D.
Ronald D.G. McKay, Ph.D.
James H. Meador-Woodruff, M.D.
Herbert Y. Meltzer, M.D.
Kathleen Merikangas, Ph.D.
Richard J. Miller, Ph.D.
Karoly Mirnics, M.D., Ph.D.
Bita Moghaddam, Ph.D.
Dennis L. Murphy, M.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.
Steven M. Paul, M.D.
Godfrey D. Pearlson, MBBS, M.D.
Mary L. Phillips, M.D.
Marina Piciotto, Ph.D.
Daniel S. Pine, M.D.
Robert M. Post, M.D.
James B. Potash, M.D., M.P.H.
Steven G. Potkin, M.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.
Carolyn B. Robinowitz, M.D.
Bryan L. Roth, M.D., Ph.D.
John L.R. Rubenstein, M.D., Ph.D.
Bernardo Sabatini, M.D., 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.
Philip Seeman, M.D., Ph.D.
Yvette I. Sheline, M.D.
Pamela Sklar, M.D., Ph.D.
Solomon H. Snyder, M.D., DSc, D.Phil. (Hon. Causa)
Matthew State, M.D.
Murray Stein, M.D., M.P.H.
John S. Strauss, M.D.
J. David Sweatt, Ph.D.
John A. Talbott, M.D.
Carol A. Tamminga, M.D.
Laurence H. Tecott, M.D., Ph.D.
Ming T. Tsuang, M.D., Ph.D., DSc
Kay M.Tye, Ph.D.
Leslie G. Ungerleider, Ph.D.
Rita J. Valentino, Ph.D.
Jim van Os, M.D., Ph.D., MRCPsych
Susan Voglmaier, M.D., Ph.D.
Nora D. Volkow, M.D.
Mark von Zastrow, M.D., Ph.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Marina Wolf, Ph.D.
Jared W. Young, Ph.D.
L. Trevor Young, M.D., Ph.D.
Jon-Kar Zubieta, M.D., Ph.D.

MEMBERS EMERITUS
George K. Aghajanian, M.D.
Dennis S. Charney, M.D.
Jan A. Fawcett, M.D.

JEFFREY BORENSTEIN, M.D.
President & CEO
Brain & Behavior Research Foundation

As the Brain & Behavior Research Foundation enters its 30th year of grant-making, it's tempting to look back on the advancements and breakthroughs in mental health that we have supported with your generous help. From research discoveries like the use of clozapine as an antipsychotic medication in patients with treatment-resistant schizophrenia, deep brain stimulation as a treatment for depression, optogenetics to provide precise control over brain circuitry in awake, behaving animals, to increasing public awareness and destigmatization around mental illness, the Foundation has been at the front lines of so many advances in treating the ones we love.

But our 30th year has us looking forward, not back. The goal of our Foundation has always been to move forward toward a better future, and the accomplishments of the past three decades only spur us to do more. We draw our inspiration from you, our donors, who work with us to try and make sure that mental illness does not rob one more person of their unique potential, or lead one more family through years of despair.

In this issue you will also find the moving story of Patsy Hollister and her family, (p. 38) who have been champions of this Foundation since its beginning. We get a glimpse into the fascinating research being conducted by Dr. Lisa Pan on treatment-resistant depression and its connection to metabolic abnormalities (p. 13). Our Parenting story features a conversation with Dr. Joan Luby about the early emergence of depression in children and understanding key risk factors and treatments (p. 28).

Dr. Daniel Pine, a Foundation Scientific Council Member and the Chief of Child and Adolescent Research in the Mood and Anxiety Disorders Program at the National Institute of Mental Health, shares his thoughts (p. 9) about the great challenge the field of neuropsychiatry now faces: integrating decades of careful observations of brain disorders made by doctors with deep knowledge about circuits in the brain that give rise to our behaviors, including circuits that are malfunctioning. Among other things, he's deeply interested in using knowledge of brain circuits to understand what makes people react differently to the same things. Such knowledge promises to enable brain researchers to design treatments specific to individual patients.

The future of research for mental illness will propel forward and we will continue to lead the way. With your sustained commitment, we will accelerate breakthroughs that will lead to better treatment and ultimately cures and methods of prevention. This is our mission and our commitment. Thank you for taking the journey with us.

Sincerely,

Jeffrey Borenstein
President & CEO

Women Breaking the Silence about Mental Illness

Luncheon Highlights Depression and Schizophrenia Research

Dr. Jeffrey Borenstein, Barbara Streicker, Dr. Myrna Weissman, Ellen Levine, Carol Mallement, Dr. Dolores Malaspina and Suzanne Golden

Dr. Herbert Pardes, Dr. Jeffrey Borenstein and Suzanne Golden

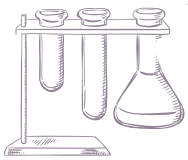
Stephen Lieber and Dr. Barbara Van Dahlen

Dr. Dolores Malaspina, Dr. Myrna Weissman and Ellen Levine

On April 25, 2017 Ellen Levine, a longtime Hearst editor and innovator, led a wide-ranging conversation with pioneering mental health researchers Dolores Malaspina, M.D. and Myrna Weissman, Ph.D. before a sold-out audience of 300 at the Brain & Behavior Research Foundation's third "Women Breaking the Silence about Mental Illness" luncheon at the Metropolitan Club in Manhattan.

The event, co-chaired by BBRF board members Suzanne Golden, Carole Mallement and Barbara Streicker, raised more than $250,000 to help the Foundation support its Young Investigator Research program and accomplish its mission to alleviate the suffering caused by mental illness by funding research that will lead to better diagnosis and treatments.

"Our luncheon, which featured a conversation between Ellen Levine, who has done so much to help the public understand mental illness, and Drs. Malaspina and Weissman, pioneering researchers in mental health, showcases the vital collaboration between generous donors and scientists that has enabled the Foundation to fund the most innovative research in neuroscience and psychiatry," says Jeffrey Borenstein, M.D., President & CEO of the Foundation, who notes that 100 percent of every dollar raised for research—all from private donations—goes to support research grants.



"One of the challenges we're seeing is the decrease in government funding for research, especially for young scientists," Dr. Borenstein added. "The proposed cuts to the NIH put us at risk of losing an entire generation of young scientists, so support from the private sector is more important than ever before."

The two world-renowned researchers discussed why they chose to study and look for cures for schizophrenia and depression. For Dr. Malaspina, her reasons were very personal. For Dr. Weissman, her reasons touched her both as a woman and as a mother. In addition, the topic of stigma and how to deal with mental illness in a family member or other loved one without fear of judgment complemented the Foundation's standard programs about science and research.

Dr. Malaspina is the Anita & Joseph Steckler Professor of Psychiatry and Child Psychiatry, former Chairman of the Department of Psychiatry at *NYU Langone Medical Center*, and a co-host of a weekly radio show on Psychiatry for the Sirius/XM satellite radio channel for "Doctor Radio." Dr. Malaspina has spent her career working to understand schizophrenia, which afflicts her younger sister. Her groundbreaking work found that a quarter of all people living with schizophrenia may owe their symptoms to spontaneous mutations in paternal sperm, which are more likely to occur in older fathers. Still a practicing clinician, Dr. Malaspina has received two Young Investigator Grants, as well as Independent and Distinguished Investigator Grants from the Foundation.

Dr. Weissman, the Diane Goldman Kemper Family Professor of Epidemiology at *Columbia University's Mailman School of Public Health*, and Chief of the Division of Epidemiology at *New York State Psychiatric Institute (NYSPI)*, specializes in understanding rates and risks of mood and anxiety disorders, and is working to bring psychiatric epidemiology closer to translational studies in neuroscience and genetics. For more than 30 years, she has directed a three-generation study of families at risk for depression. She also directs a study to determine the impact of maternal remission from depression on children and was one of the developers of Interpersonal Psychotherapy, an evidence-based treatment for depression. Dr. Weissman is a member of the Foundation's Scientific Council, a four-time Foundation Distinguished Investigator Grantee, and a member of the National Academy of Sciences.

Ellen Levine made publishing history in October 1994 as the first woman to be named editor-in-chief of *Good Housekeeping* since the magazine was founded in 1885. She was instrumental in launching new titles at Hearst Magazines, including *O, The Oprah Magazine*, the most successful magazine launch ever. In May 2006, Levine was appointed editorial director at Hearst Magazines and she is now working across several divisions of the corporation. In addition to many other awards, Levine received the first annual Media Award by the American College of Neuropsychopharmacology for the numerous articles on mental illness she published in *Good Housekeeping*.

Adelaide Farah and Lillian Clagett

Donna Stillman and Ornella Morrow

Photo Credit: Chad David Krauss Photography

In 2015 as participants in the Foundation's major donor Research Partners Program, the New York Women's Committee selected four Young Investigators from a pool of hundreds of early career researchers. The Research Partners Program offers donors the opportunity to personally select and support scientists based on various criteria, including, but not limited to, illness specialty area or specific institutions, or a combination thereof. The Women's Committee chose to fund four scientists with diverse areas of expertise. These scientists are: Lynette Astrid Averill, Ph.D. of *Yale University* who is researching PTSD, Estefania Pilar Bello, Ph.D. of the *University of Buenos Aires*, Argentina who is studying schizophrenia, Laura K. Fonken, Ph.D. of the *University of Colorado Denver* who is looking at late-life depression, and James J. Prisciandaro, Ph.D. of the *Medical University of South Carolina* who is researching substance misuse and bipolar disorder.

Bonnie Hammerschlag and Elaine Novick

At the Foundation's first women's luncheon in November of 2013, Swanee Hunt, former Ambassador to Austria and Harvard University's Eleanor Roosevelt Lecturer in Public Policy, discussed her struggles to get her daughter help for bipolar disorder. In 2015, at the second luncheon, philanthropist and activist Lee Woodruff discussed how her life changed dramatically in a single moment after her husband, ABC News journalist Bob Woodruff, was injured in a roadside bomb while reporting from Iraq and how she experienced firsthand the feelings of depression, anxiety, and despair.

The Women's Luncheon series is designed to pay tribute to the brave women who are willing to speak candidly and personally about mental illness and use them as an inspiration to galvanize all of the necessary resources needed to speak out, remove stigma, and break the silence about brain and behavior disorders.

Cullen Stanley and Anne D'Innocenzio

Lisa Wilens and Virginia Silver

THE NEW YORK WOMEN'S COMMITTEE

Co-Chairs

Suzanne Golden*
Carole Mallement*
Barbara Streicker*

Committee Members

Jan Abrams
Anne Abramson*
Carol Atkinson*
Amy Rose Beresin
Lillian Clagett
Judy Cohn
Judy Daniels
Anne D'Innocenzio
Beth Elliott
Luisa Francoeur
Bonnie Hammerschlag*
Ellie Hurwitz
Lynn Jeffrey
Judy Iovino
Fran Kittredge
Ann Laitman
Ornella Morrow
Jacqueline Rofé
Sheila Scharfman
Helen Tsanos Sheinman
Lilian Sicular
Virginia Silver*
Randi Silverman
Dorothy Sprague
Jill Sirulnick
Ellen Sosnow
Patricia Specter
Cullen Stanley
Andrea Stark
Reneé Steinberg
Barbara Toll*
Fran Weisman*

*Foundation Board Member

INTERVIEW WITH A RESEARCHER

DEVELOPING NEUROSCIENCE TOOLS TO IMPROVE TREATMENTS

DANIEL S. PINE, M.D.
Chief, Emotion and Development Branch and Section on Development and Affective Neuroscience
National Institute of Mental Health

Scientific Council Member
2011 Ruane Prizewinner
2000 Independent Investigator

By Peter Tarr, Ph.D.

Psychiatry, says Dr. Daniel Pine, is at a crossroads. The two crossing paths can be labeled "clinically-focused diagnosis" and "patient-oriented biological understanding" of mental illness. Beginning in the 1970s, psychiatrists embraced the important goal of achieving greater consistency in making diagnoses. They achieved this through a massive multi-year effort to base patient evaluations on what could be observed consistently in each of the many brain and behavior disorders, in the clinical setting of doctors' offices and hospital inpatient units.

It was vitally important that a person diagnosed with major depression by a psychiatrist in, say, Detroit, would be likely to receive the same diagnosis, made according to the same set of agreed-upon criteria, in Los Angeles or New York or Peoria, Illinois. The famous "DSM" manual (Diagnostic and Statistical Manual, now in its 5th edition) is the product of this effort by mental health professionals to achieve greater consistency and precision in their diagnoses.

"The current crossroads," says Dr. Pine, has been reached after a sobering realization: "The major advances in diagnosis and treatment that we all want are going to be difficult to achieve as long as we remain solely focused on what can be observed in the clinic." His own career, which spans some 25 years and over 500 published research papers, exemplifies a transition that is under way. It involves taking the great insights generated in recent years by neuroscience "and making them clinically relevant," Dr. Pine says. In his view, we have come about as far as we can by simply observing—albeit very accurately and consistently—the range of behaviors exhibited by patients.

Dr. Pine is among the world's leading experts in childhood disorders. He spent the first decade of his career, the 1990s,

performing what he calls "bread-and-butter" research on pediatric mood and anxiety disorders, hoping to learn three things. One was "what happens to kids with these disorders as they grow up? Which kids will overcome it, and which will not? Who will go on later in life to develop mood or other psychiatric disorders?" A second question concerned families with a parent suffering from a mood or anxiety disorder: was it possible to understand why one child would be affected and another would not? A third objective was to determine what treatments were most effective for these disorders. When he began his research around 1990, very little was known about treatments in young patients.

In the last years of the 1990s Dr. Pine and colleagues conducted a clinical trial that resulted in a 2001 paper in the *New England Journal of Medicine*. It had broad impact in the world of patient care. While anxiety disorders were well known to be "extremely common" in childhood, in Dr. Pine's words—they are the most prevalent of the childhood psychiatric disorders—very little of the research on popular SSRI antidepressants had considered whether they were safe or effective in children, particularly anxious children; most of the work had been based only in adults. His team and other collaborating teams worked together to demonstrate that the SSRI medicine fluvoxamine (Luvox) was an effective treatment for children and adolescents with social phobia, separation anxiety disorder, or generalized anxiety disorder, and caused few side effects.

The following year, Dr. Pine's interest shifted to a related question: "for how long is SSRI treatment appropriate" in a young patient? His review of published data led to valuable suggestions for clinicians. He recommended they consider trying a period off the medication in young patients who had been helped by them in a first round of treatment.

While proud of this research, Dr. Pine says he has long yearned to go beyond it. For the truth remains that we still know relatively little about the precise biological causes of mental illnesses, including those on which he focuses. He says he had a "life-changing" realization around the year 2000—when his very successful work on SSRIs in young patients was progressing quite well.

"Scientists like me are trained to look at behaviors, whether in people or in mouse models of human illness. But let's consider the anxious child who refuses to raise their hand in class. That's a 'behavior.' What we've learned from neuroscience is that when you look in the brain, there can be many different changes that can give rise to that very same behavior. As a result of this complexity, one would expect that different treatments might have different effects in children with problems classified based only on their behavior."

"I was spending a lot of time with neuroscientists around then and was so impressed by the level of detail and experimental control that they had in their research, compared to what we [behavioral researchers] had. But something else really shook me up. I started to learn about unpublished evidence from large scale clinical trials, discussed in regulatory committees beginning around 2002, which suggested that the efficacy data on pediatric conditions including depression and anxiety really wasn't as strong as we had initially thought."

What was the problem? Dr. Pine explains that the problem has many components. One facet is particularly important. "Scientists like me are trained to look at behaviors, whether in people or in mouse models of human illness. But let's consider the anxious child who refuses to raise their hand in class. That's a 'behavior.' What we've learned from neuroscience is that when you look in the brain, there can be many different changes that can give rise to that very same behavior. As a result of this complexity, one would expect that different treatments might have different effects in children with problems classified based only on their behavior."

That was one issue. A related issue, Dr. Pine says, was that "neuroscience experiments teach us that we can manipulate the brain in two different animals, and with the same manipulation we can induce the animals to express their behaviors in different ways!"

This is not to minimize the value of these experiments. They help teach scientists about how the brain works. What they cannot do, at least with our current level of knowledge, is tell us definitively why certain constellations of behavior occur in any one particular patient, even in two different patients with the same diagnosis.

Realizing these things was "humbling," Dr. Pine says, but it was also a powerful motivation to move forward in new ways. He modestly describes much of his research in the last 17 years as a "retooling," by which he means an extended

period in which he and colleagues have worked to develop powerful new tools grounded in neuroscience and sought to begin to use them in ways that may eventually influence clinical practice.

What happens in the clinic, when doctor meets patient, has motivated him from the beginning of his career. "When I went into medicine," he recalls, "it was almost entirely because I wanted to help people. That's why I did it. I love science, and I'm really interested in it. But it has always been about helping people, most of all."

Some examples of Dr. Pine's recent work show how his love of science intersects with this strong desire to have an impact on patient care. In a November 2016 "Commentary" published in *Biological Psychiatry*, he proposed how "computational approaches" could hasten our journey toward advances in the clinic. "Some patients with anxiety disorders benefit from cognitive behavioral therapy, others benefit from medication, and still others require both," he noted. How might doctors, then, "better tailor available treatments" to specific patients, and how might scientists go about discovering new therapies with similar specificity?

The image on the next page depicts how a computer-based approach might enable researchers to understand particular sets of defensive behaviors in children asked to perform a fear-conditioning task. In this task, children learn about aversive events that might happen after the child sees one or another face. The goal in this research is to "understand particular sets of defensive behaviors, which researchers can then use to elucidate mechanisms" underlying complex, hard-to-pin-down clinical features, such as the various ways anxious children report what they are feeling as they are learning. "We want to quantify factors that tightly link behaviors to brain function," Dr. Pine says—which takes researchers an important step beyond simply observing and grouping those behaviors.

The idea behind the experiment shown is to get behind that baffling complexity that led Dr. Pine to "retool." Different patients will report different responses to a sequence of faces displayed on a computer monitor. Some of the faces are neutral in expression; others show faces of people who are surprised, horrified, afraid. Some of the faces might predict an aversive event, and others will not. During this stream of events, the experiment can measure bodily responses of the participants as they respond to the faces, their skin response ("skin conductance") registered with electrodes slipped over two fingers. At an entirely different level, the activity of key brain areas involved in the fear response also can be recorded via functional magnetic resonance (fMRI) imaging scans.

The various streams of hard data generated in such a computer-directed experiment "address the fundamental challenge made so difficult by the complex nature of brain-behavior relationships," Dr. Pine says. The data offer views at different levels about what is happening as fear conditioning proceeds. Responses to both conditioned and intentionally ambiguous stimuli presented to research subjects via the computer reveal their startle responses, their tendency toward avoidance of danger, and at the same time, makes possible cross referencing these to specific responses within the circuitry in the brain's amygdala as all of these "behaviors" are being manifested.

There is much to be learned when data is compared from young people without anxiety disorders and those who have been diagnosed with them. Hard data—beyond mere surface observation of behavior—helps elucidate mechanisms in the brain "that allow healthy people to adapt to aversive events." This becomes a basis for understanding what is going on in the brains of different people suffering from anxiety—people, for example, who have a too-strong reaction to potential ambiguity or even actual danger. Fear is useful to us, but excessive fear is problematic—it can lead to excessive inhibition, which can impair a child's social relationships, for example, or prevent him or her from raising their hand in class.

CONTINUING THE CONVERSATION WITH DR. PINE

BIOMARKERS THAT CAN MAKE A DIFFERENCE

Psychiatry, says Dr. Daniel S. Pine, "might achieve a needed paradigm shift" by adopting a research approach used in other branches of medicine, an approach called "experimental medicine." It involves not just finding biological markers that correlate with illness—for example, high blood pressure or high cholesterol suggesting elevated risk of heart disease. Rather, explains Dr. Pine, the approach "identifies manipulations that affect biomarkers while substantially changing the course of an illness in patients. An example might be a statin drug that reduces cholesterol levels or a beta-blocker that reduces blood pressure, which in turn can be shown to improve patient outcomes which would lead to reductions in heart attacks.

From data in the "computational psychiatry" experiment described in the main story, it is possible to discover biomarkers—biological patterns of activity in the brain, as discerned by brain imaging—that can help clarify why certain anxiety patients respond better to some treatments than others, or to none of the available treatments. This is the stated goal of a "Viewpoint" article written by Dr. Pine and published in *JAMA Psychiatry* in July 2015. There, he argues for the

importance of finding biomarkers "with a mechanistic focus."

Biomarkers that reveal mechanisms underlying major depression or anxiety can be contrasted, he says, with biomarkers that are more simply "predictive" of having these diagnoses or symptoms associated with them. It is not that predictive markers are not needed. They are, he stresses. "But in terms of how we use our research funds and our time, we must recognize a need to support both kinds of studies. Nevertheless, I myself prefer pursuing markers that reveal what is causing these disorders. This kind of research is slower to show results and is much harder to perform, because it deals with the incredible complexity of the brain and how changes in different circuits affect behavior."

Brain imaging could be used to extend insights from neuroscience on mechanisms of healthy brain-behavior relationships, Dr. Pine suggests. "For example, basic research charts how exquisitely orchestrated rapid shifts in the function of circuits connecting the amygdala and prefrontal cortex influence attention when rodents and primates confront threats. Imaging can extend this work by linking individual differences in human anxiety and attention to disturbances in those same circuits." By refining these techniques, researchers might "generate tools analogous to those used in cardiology, helping psychiatrists of the future identify subgroups of anxious patients—whose circuit patterns could predict unique outcomes and suggest specific treatments."

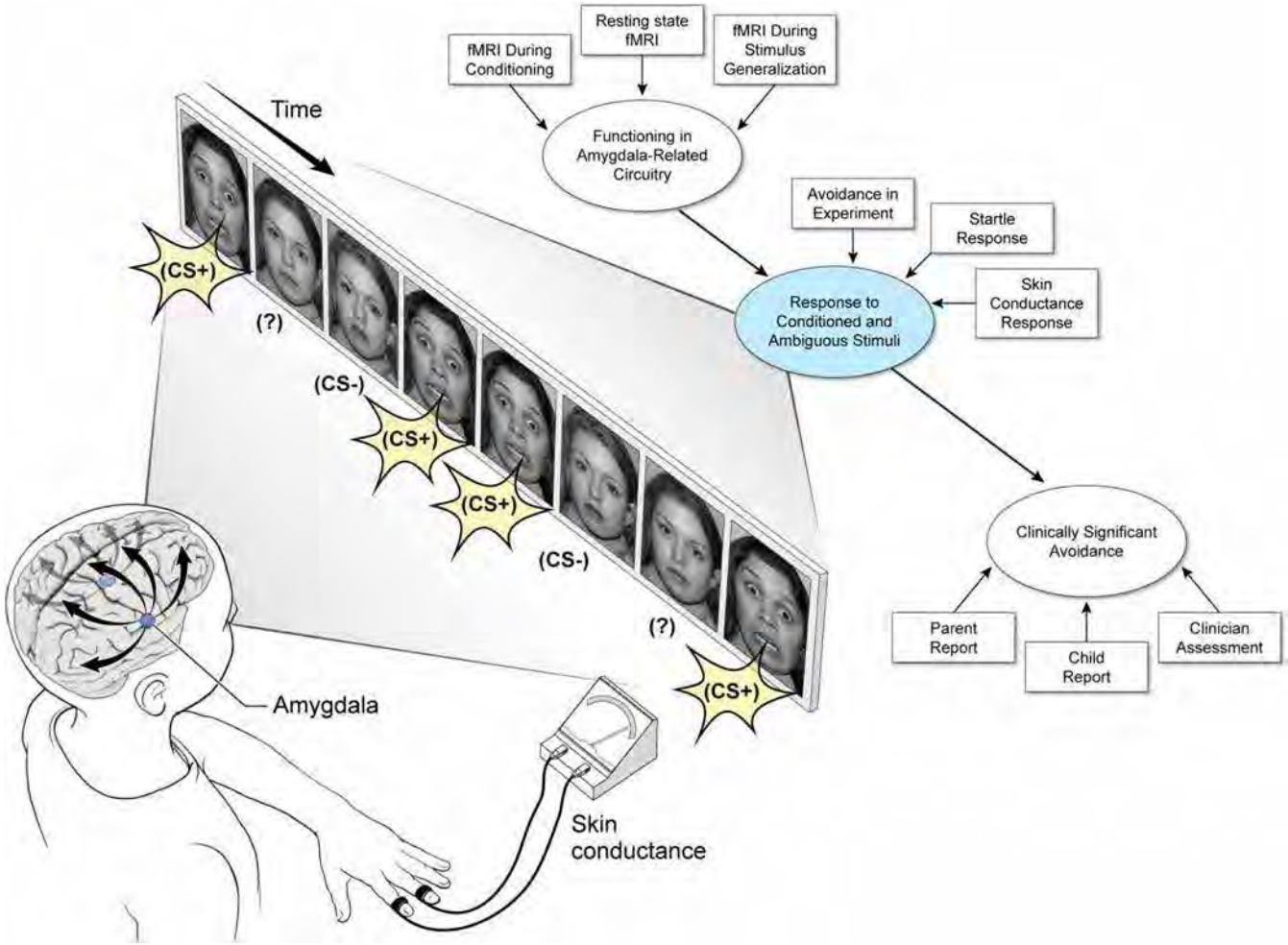


Photo courtesy of Dr. Daniel Pine. *Biological Psychiatry* DOI: (10.1016/j.biopsych.2016.09.020)

If we know more about why different people respond differently to the same situations, it should be possible to design better treatments for those whose responses are not normal. In this computer-enabled example of fear conditioning, a young person is shown a succession of faces—some fearful, some neutral, others ambiguous—while his or her responses are measured at different levels: in circuits within the brain's amygdala; in expressions of emotions, revealed in associated changes in the body's autonomic responses, measured via the skin; and in clinically observable measures. The idea is to bridge these three levels to arrive at a deeper understanding of the response to danger that can be translated into effective patient-specific treatments.

RELIEVING TREATMENT–RESISTANT DEPRESSION BY TREATING METABOLIC DEFICIENCIES

LISA A. PAN, M.D.
Assistant Professor, Psychiatry, Clinical and Translational Science, and Human Genetics
University of Pittsburgh
2012 Young Investigator

by Peter Tarr, Ph.D.

RELIEVING TREATMENT-RESISTANT DEPRESSION BY TREATING METABOLIC DEFICIENCIES

An important discovery has been made at the University of Pittsburgh. It raises the prospect that there may be an entirely new way of relieving major depression in people who repeatedly have failed to respond to existing treatments—people at elevated risk for suicide whose lives are often unrelentingly dark and full of anguish.

There are 15 million Americans suffering from major depression, and 15 percent of these (that is, 2,250,000 people in the U.S. alone) do not respond to treatment.

Last August, 2012 Young Investigator Grantee Lisa A. Pan, M.D., in collaboration with a team that includes 2001 Distinguished Investigator and 2006 Ruane Prizewinner David A. Brent, M.D., at the *University of Pittsburgh*, reported in the *American Journal of Psychiatry* that they had successfully tested—so far on a small scale—an approach to treating patients with longstanding, treatment-resistant depression.

The team's new approach is based on the theory that in at least some people, resistance to treatment in depression is caused by abnormalities in metabolism—abnormalities that can be corrected. "Metabolism" refers to the myriad processes inside our bodies in which chemical reactions generate all of the compounds that we rely upon to function as living beings.

That covers a lot of ground. Drs. Pan, Brent and colleagues had something more specific in mind. A portion of our metabolism is involved in the manufacturing of the message-carrying chemicals called neurotransmitters that have long been implicated in many brain disorders, including depression.

"Not enough serotonin in the brain." That vitally important observation, made three decades ago in people with depression who were at elevated risk of suicide, helped spur the development of Prozac and other drugs of the same class, called SSRIs (selective serotonin reuptake inhibitors), for depression and other disorders, (notably anxiety, which often occurs along with depression). Prozac (fluoxetine) came on the market in 1987. It and other SSRI drugs have been prescribed tens of millions of times since then, for depressed people in the U.S. and around the world.

SSRIs prevent serotonin from being soaked up by cells that make and release it. This allows it to remain longer in the tiny gaps between nerve cells, called synapses, and presumably enhances the ability of adjacent cells to communicate. This, in turn, is thought to reduce symptoms of depression, for reasons that even today are not clear.

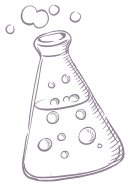
SSRI drugs address the problem of what scientists call serotonin "re-uptake." But what about the chain of chemical processes through which serotonin is created within cells? This involves metabolic processes. As Dr. Pan has pointed out, strategies that address "reuptake may not be effective if there is an inability to make serotonin."

She became acutely interested in the possible role of metabolism in depression after attempting over a period of years to help a young man with treatment-resistant major depression. Dr. Pan had been caring for adolescents and young adults at risk for suicide since 2002. In the lab, some of her research involved using brain imaging to look for markers of such risk.

At the STAR Center (Services for Teens At Risk) at the *University of Pittsburgh Medical Center's Western Psychiatric Institute,* Dr. Pan tried to solve the mystery of the young man's persistent deep depression, which involved suicidal thinking and several suicide attempts and resisted all forms of treatment they tried.

In 2011, in what she later called a "case of necessity," Dr. Pan brought others in to consult. Facing the alternative of committing this young person to a psychiatric institution for long-term care, she engaged Jerry Vockley, M.D., Ph.D., chair of genetics at Pittsburgh, who had helped to train her years earlier. Another consultant was David Finegold, M.D., a professor of human genetics.

The team conducted tests that ordinarily would not be given to people with depression. Among them was a detailed analysis of the cerebrospinal fluid, or CSF. It is a colorless fluid that circulates around the spinal cord and throughout the brain, and bears evidence of the many metabolites—the chemical reactants—engaged in the synthesis of the many proteins, including hormones and neurotransmitters, that help the cells in the brain function.



Analysis of his CSF revealed the 19-year old had abnormally low levels of "intermediates"—chemical precursors—of tetrahydrobiopterin, or BH4. It has many roles, among them in the synthesis of neurotransmitters including dopamine, norepinephrine and serotonin. The doctors knew of a replacement for BH4 called sapropterin. After a few weeks of receiving it, the young man's depression began to melt away. Rather than a psychiatric hospital, he went to college, graduating at age 24.

His dramatic result encouraged Dr. Pan and colleagues to examine the CSF of five more adolescent patients in the same clinic, all suffering from treatment-resistant major depression. Three of the five had low CSF levels of 5-MTHF. This is a chemical breakdown product of folic acid, an essential metabolite throughout the body, including in the brain.

During pregnancy, mothers must have sufficient dietary intake of folic acid to assure proper development of the fetus's brain. Deficiency can result in neural tube defects and brain damage to the newborn. Folic acid supplementation, ideally begun before conception and continued through the perinatal period, especially in women with poor diets, is accepted practice worldwide.

That is only one of many functions of folic acid, however. Deficiency of 5-MTHF in the brain—a condition called cerebral folate deficiency (CFD)—was seen in three of the five additional adolescents studied by Dr. Pan and colleagues. This, too, could be addressed, via treatment with folinic acid over a period of weeks. The patients improved.

This provided the rationale for the more rigorous "case-control" study funded by Dr. Pan's 2012 Young Investigator Grant and reported in the *American Journal of Psychiatry* in August 2016. Dr. Pan and colleagues recruited 33 young people with treatment-resistant depression and 16 healthy comparison subjects. The results were impressive and full of hope. First, none of the healthy participants had metabolite deficiencies in their CSF. In contrast, 21 of the 33 refractory depressed patients (63 percent) were found to have abnormal metabolite levels in the CSF, with 12 of the 21 (36 percent of the total group) suffering specifically from cerebral folate deficiency. Ten of these 12 made it through the treatment and a follow-up period. All 10 had reductions in depression symptoms, and four had remissions. A number of those treated also had significant reductions in suicidal thinking.

"We're looking at the end product of multiple complicated metabolic pathways and [in patients we studied] we're finding something missing, and we're working backwards to replace it," Dr. Pan told the *Pittsburgh Post-Gazette*.

In reporting their results, the team stressed that blood tests alone would not have identified the metabolic deficiencies that showed up in the CSF. It is not easy to obtain CSF—a lumbar (lower back) puncture with a needle is required, a procedure that is uncomfortable and involves more than nominal risk. Yet it was crucial to obtain the fluid, for in cerebral folate deficiency, folate levels in the blood are normal. The lack of folate is in the brain, where the chemical is involved in neurotransmitter synthesis. They hope to devise a blood test that will identify what the CSF tests reveal.

In addition to its known role in brain development, folate in one of its several forms (L-methylfolate) has previously been used as adjunctive treatment to improve depression symptoms. L-methylfolate is involved in neurotransmitter metabolism. But, say Dr. Pan and her colleagues "this is different from our findings" in cerebrospinal fluid. In fact, L-methylfolate addresses a different part of the metabolic pathway involving folic acid, and may not help the patients with cerebral folate deficiency, the researchers say.

At the same time, while folinic acid treatment "seems appealing," they add, it may take several years to show its full effect due to the very slow turnover of neurons in the brain. They want to know more about the precise role of metabolite abnormalities in depression as well as in treatment resistance. They move forward on two fronts: expanding the size of their study to include more treatment-resistant patients, and trying to learn more about them by sequencing their full genomes. To date, only small portions of patient genomes have been sequenced. With the entire genomes in view, it is expected that new knowledge will be gleaned that can help to resolve the age-old mystery about depression's root causes.

2017 Independent Investigator Grants

Forty mid-career neuroscience researchers from 36 institutions in 10 countries have been chosen to receive a total of $3.9 million in funding from the Brain & Behavior Research Foundation.

Since 1987 we have given out 828 Independent Investigator Grants, totaling–more than $82 million.

21 NATIONAL GRANTS & 19 INTERNATIONAL GRANTS

These grants fund research on brain and behavior disorders in the following four areas:

BASIC RESEARCH
To understand what happens in the brain to cause mental illness.

EARLY INTERVENTION/ DIAGNOSTIC TOOLS
To recognize early signs of mental illness and treat as early as possible.

NEXT GENERATION THERAPIES
To reduce symptoms of mental illness and retrain the brain.

NEW TECHNOLOGIES
To advance or create new ways of studying and understanding the brain.

The Foundation's Independent Investigator Grants provide each scientist with $50,000 per year for up to two years to support their work during the critical period between the start of their research and the receipt of sustained funding. Every year, applications are reviewed by members of our Scientific Council, led by Dr. Robert Post.

The Council is composed of 168 active leading experts across disciplines in brain and behavior research who volunteer their time to select the most promising research ideas to fund. We are very grateful to them and to all of our donors whose contributions make the awarding of these grants possible.

This year's 40 Independent Investigator grantees represent an exciting group of basic and clinical proposals which should make major contributions to the better understanding and treatment of serious psychiatric illness. **304 grants were reviewed by 50 members of the Scientific Council.**

We are delighted to support these researchers' work and are pleased to introduce them to you in the pages that follow.

"This set of grant recommendations offers the exploration of many new and exciting potential approaches to the therapeutics of serious mental disorders and a better understanding of their molecular and neurobiological underpinnings, thus providing additional new targets for treatment."

–Robert M. Post, M.D.
Professor of Psychiatry
George Washington University School of Medicine
Bipolar Collaborative Network
Chair of the Independent Investigator Grant Selection Committee
Foundation Scientific Council Member

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

Sarah Elizabeth Medland, Ph.D.
QIMR Berghofer Medical Research Institute, Australia

Dr. Medland will study the ways in which genetic variants contribute to ADHD. Her team will use an Australian database of families affected by ADHD to collect in-depth phenotypic data provided by the parents and combine the data with electronic medical records and pharmaceutical treatment details. The team plans to collect DNA samples from those with ADHD in this cohort to examine the genetic variants that have been previously linked to ADHD and map their effects.

Basic Research

AUTISM SPECTRUM DISORDER

Christina Gross, Ph.D.
Cincinnati Children's Hospital Medical Center,
University of Cincinnati

Dr. Gross will work on connecting gene defects already associated with autism and schizophrenia to molecules that can be targeted by drugs. The work aims to bridge the gap between discovery of large number of gene defects underlying mental illnesses and the development of treatments tailored to target those defects, which will ultimately pave the way toward developing precision-medicine treatments for autism and schizophrenia.

Basic Research

Grainne M. McAlonan, M.B.B.S., Ph.D.
Institute of Psychiatry/King's College London, UK-England

Dr. McAlonan will study the interplay between excitatory and inhibitory brain system in people with autism. The balance between these two systems influences the communication between brain networks controlling behavior and cognition. In people with autism, this balance seems to be altered, leading to a different brain communication pattern from that of controls. Dr. McAlonan's team will explore the brain responses of people with autism to pharmacological activation of the inhibitory neurotransmitter GABA. Their aim is to determine whether shifting the balance through medication will restores brain communication pattern abnormalities in autism.

Next Generation Therapies

Terunaga Nakagawa, M.D., Ph.D.
Vanderbilt University

Dr. Nakagawa aims to understand the molecular mechanisms behind abnormal communication between neurons and how this leads to mental illnesses, such as autism and depression. He and his team will look at the AMPA receptor, which regulates the majority of excitatory synaptic transmission in our brain. The team will focus on a component of AMPA receptor, a membrane protein called GSG1La, the amount of which is linked to autism. Deciphering the basic biology of GSG1L may help develop novel drugs to treat abnormal neuronal communication in mental illnesses.

Basic Research

BIPOLAR DISORDER

Cynthia V. Calkin, M.D.
Dalhousie University, Canada

Dr. Calkin will study the relationship between the progression of bipolar disorder and declining health of the blood-brain barrier, a thin web of small vessels that protect the brain from foreign molecules. Using their new method for assessing the functioning of blood-brain barrier, Dr. Calkin's team plans to compare healthy controls and people with bipolar disorder, and also measure the corresponding brain electrical activity in both groups, while gauging the severity of individuals' bipolar disorder.

Basic Research

Koko Ishizuka, M.D., Ph.D.
Johns Hopkins University

Dr. Ishizuka will use olfactory neurons obtained from the nasal cavity (the brain's olfactory bulb) to study bipolar disorder. Access to living human tissue will further the exploration of molecular changes in people with bipolar disorder. Dr. Ishizuka's team has developed a novel, quick and non-invasive method to capture neurons from nasal tissue of participants who are given a local anesthetic spray. The team plans to study the link between neuronal markers and mood symptom severity in patients with bipolar disorder.

Basic Research

Po-Hsiu Kuo, Ph.D.
National Taiwan University, Taiwan

Dr. Kuo aims to understand the mechanisms behind varying response to treatment for bipolar disorder. Lithium medication is often the first treatment option for bipolar disorder but many patients do not fully respond to this treatment. Genetic markers that may be at play will be identified. Dr. Kuo's team will explore the functional properties of identified genetic variants to uncover the underlying mechanisms of lithium response.

Basic Research

Bradley John MacIntosh, Ph.D.
Sunnybrook Health Sciences Centre
University of Toronto, Canada

Dr. MacIntosh will examine the link between cardiovascular health and bipolar disorder and test whether problems with small blood vessels relate to cognitive problems in people with bipolar disorder, who have a high rate of cardiovascular disease. The team will use non-invasive imaging-based biomarkers, such as stiffness of the arteries, and test for differences between adolescents with and without bipolar disorder.

Early Intervention/ Diagnostic Tools

Christian Georg Schuetz, M.D., Ph.D., M.P.H.
University of British Columbia, Canada

Dr. Schuetz is seeking to translate findings from brain imaging studies of bipolar disorder into a clinical intervention. He will use Theta Burst Stimulation (TBS) to activate and to modulate specific brain regions. The team will evaluate whether stimulating the brain can augment cognitive control and help individuals with bipolar disorder to stop urges, an ability that's impaired in this disorder.

Next Generation Therapies

Gloria Choi, Ph.D.
Massachusetts Institute of Technology

Dr. Choi will explore the pathways through which inflammation can cause depression. She and her team will study how inflammatory responses, as reflected in the increased blood concentrations of pro-inflammatory cytokines—signaling cells of the immune system—lead to depressive-like behaviors. The team plans to identify key immune cell types and molecules that result in depressive-like symptoms upon inflammation and potentially help provide additional biomarkers and treatment for depression caused by problems in the immune system.

Basic Research

DEPRESSION

Alexandre Bonnin, Ph.D.
University of Southern California

Dr. Bonnin will investigate the risks of using antidepressants by women during pregnancy, specifically in regard to increasing the risk of autism for children. His team plans to characterize \a new molecular pathway by which SSRIs antidepressants, such as citalopram, could reach the brain of the fetus brain and directly impact fetal brain development. By altering serotonin signaling, SSRI antidepressants could affect brain areas involved in social cognition and lead to life-long problems. Building on their previous research, Dr. Bonnin's team plans to measure the molecular effects of exposure to citalopram before and after birth using pharmacological methods as well as 3D imaging techniques.

Basic Research

Gabriel S. Dichter, Ph.D.
University of North Carolina at Chapel Hill

Dr. Dichter plans to study the role of inflammation in developing deficits in motivation and pleasure, together known as anhedonia, which is seen in a number of psychiatric illnesses, including mood and anxiety disorders, substance-use disorders, schizophrenia, and attention-deficit/hyperactivity disorder. The team will evaluate relations between treatment-related changes in symptoms of anhedonia, inflammatory markers in the body, and brain functioning over time. The team will use several methods including individualized psychotherapy and functional magnetic resonance imaging (fMRI) scans.

Basic Research

Kristen C. Jacobson, Ph.D.
University of Chicago

Dr. Jacobson will study how common, adverse daily experiences impact the developing brain of children and their risk of developing depression later on. The team will focus on investigating the effects of witnessing and experiencing community violence, which is a strong environmental risk factor for depression. Using brain imaging, the team will probe the link between exposure to violence and heightened sensitivity to threat and deficits in reward processing in the brain.

Basic Research

Pilyoung Kim, Ph.D.
University of Denver

Dr. Kim aims to identify the neural signatures that precede the onset of postpartum depression, in order to elucidate what happens in the brain before mental illness becomes evident. The team will track neural responses to emotional stimuli in pregnant women and compare them in mothers who will go on to develop depression and mothers who will not. The study will also assess environmental, psychosocial, and hormonal measures. The findings could inform efforts to identify women who may be at high risk for developing depression.

Basic Research

Matthew S. Milak, M.D.
Columbia University

Dr. Milak will investigate the mechanisms by which the anesthetic drug ketamine treats depression. Unlike commonly prescribed "SSRI" antidepressants which take weeks to show effect, ketamine has been shown to quickly lift depression, often in a matter of hours, even in patients with treatment-resistant depression. However, ketamine at high doses also has serious side effects. Dr. Milak's team will study the role of ketamine's metabolites—molecules into which it breaks down once in the body—with the goal of zeroing in on those that produce an antidepressant effect. This could pave the way for developing rapid-acting antidepressants that lack the undesirable side effects of ketamine.

Next Generation Therapies

Jose A. Moron-Concepcion, Ph.D.
Washington University

Dr. Moron-Concepcion will examine the emotional component of pain and study the role of Kappa opioid receptors in comorbid (co-occurring) pain and depression. Some opioid receptors modulate both the sensory component of pain and the negative emotions associated with it. The team will determine whether pain reduces the activity of the same neural circuits that process motivation and reward, and whether manipulation of opioid receptors prevents pain from leading to depression.

Basic Research

Thomas M. Olino, Ph.D.
Temple University

Dr. Olino studies the mechanisms that contribute to the onset of depression during adolescence. His team examines the heightened risk in children from depressed parents. The team will also study how a stressful life alters the development of reward responsiveness, ultimately leading to the emergence of depressive symptoms in youth. To do so, Dr. Olino and his team will collect blood samples from young participants to measure markers of inflammation.

Basic Research

Thomas L. Rodebaugh, Ph.D.
Washington University

Dr. Rodebaugh will examine the biological mechanism through which loneliness can lead to poor health and increased mortality, particularly among older adults. Social support reduces loneliness and shields against mood consequences of stress. The hormone oxytocin may play a role in the protective effects of social support. Dr. Rodebaugh's team will measure circulating oxytocin levels in the biological samples of an ongoing longitudinal study of older adults to examine associations between this hormone and indices of social function and experience. The findings will also reveal whether oxytocin level can act as a potential biomarker for future vulnerability to loneliness and mental health symptoms.

Early Intervention/ Diagnostic Tools

MENTAL ILLNESS – GENERAL

Andrea Mele, Ph.D.
Universita' di Roma La Sapienza, Italy

Dr. Mele will investigate the neurobiological basis of a brain training technique aimed at slowing cognitive decline. The technique is based on the spacing effect, a phenomenon whereby information that's spread out over time is easier to learn and remember than information presented over and over in a short time. Spaced training can help with memory deficit and alter molecular process in mice. Dr. Mele's team plans to study the cellular basis of distributed learning and identify the neural bases of the spacing effect. Understanding the mechanisms that underlay this effect could help identify new pharmacological approaches for memory enhancement.

Basic Research

Eric Matthew Morrow, M.D., Ph.D.
Brown University

Dr. Morrow will investigate the role of mitochondrial metabolism in brain development of newborns. Mutations in a mitochondrial enzyme are found to be linked to a novel childhood disorder that involves intellectual disability and reduced brain growth after birth. Given the role of mitochondria in producing energy and regulating the metabolism of cells, including neurons, Dr. Morrow's team will examine the metabolic pathways in the brain and their relationship to cognition and learning.

Basic Research

Irving Michael Reti, M.B.B.S.
Johns Hopkins University

Dr. Reti plans to explore new treatments for reducing self-harm behaviors in people with intellectual and developmental disabilities. Such behaviors, which include self-directed slapping, punching and biting, can be extreme in some patients, leading to devastating consequences for the patient and their family. Currently, treatments include medications, behavioral therapy, and electroconvulsive therapy. In search of a better treatment for severe cases, Dr. Reti's team will evaluate the feasibility of deep brain stimulation, using mouse models.

Next Generation Therapies

POST-TRAUMATIC STRESS DISORDER (PTSD)

Timothy William Bredy, Ph.D.
University of Queensland, Australia

Dr. Bredy will turn to the "dark matter" of the genome, which encode RNAs and not proteins, to elucidate their role in fear-related anxiety disorders such as PTSD. To understand how fear-related memories are made permanent, the team will study the gene-environment interactions and determine the mechanisms by which certain non-protein encoding RNAs regulate gene expression and influence fear-related learning. This will allow scientists to better understand how the brain changes across the lifespan and may lead to better therapies for phobia and PTSD.

Basic Research

SCHIZOPHRENIA

Clare L. Beasley, Ph.D.
University of British Columbia, Canada

Dr. Beasley aims to uncover the role of microglial cells in altering the communications between neurons in bipolar disorder and schizophrenia. Her recent postmortem studies have uncovered changes in the shape and density of microglial cells in the brains of people with bipolar disorder and schizophrenia. Dr. Beasley's team plans to focus on the signaling protein fractalkine, which is produced by neurons and plays a major role in communication between neurons and microglial cells. The team will quantify fractalkine in postmortem brain tissue and measure its blood levels in the same subjects, in order to examine the potential of this protein as a biomarker of microglial function.

Early Intervention/ Diagnostic Tools

James Andrew Bourne, Ph.D.
Monash University, Australia

Dr. Bourne will study the role of a subcortical brain area known as the medial pulvinar, which connects strongly with the dorsolateral prefrontal cortex, a brain area implicated in schizophrenia. The medial pulvinar is thought to 'gate' the transfer of information across the brain. Therefore, it could be responsible for symptoms of sensory information overload, which is a frequent complaint of people with schizophrenia. Dr. Bourne's team hopes to better understand the role of the medial pulvinar by defining the connectivity of this region from early life to adulthood in the marmoset monkey. The team will then also inactivate the medial pulvinar and its connectivity in early life, to see what consequence this has on the neurons of the DLPFC and behavior of the animal once it reaches adulthood.

Basic Research

Alessandro Gozzi, Ph.D.
Italian Institute of Technology, Italy

Dr. Gozzi will study how imbalances in regional excitatory and inhibitory functions may lead to abnormal communication between brain regions in schizophrenia or autism. The team will genetically alter inhibitory and excitatory cells in the mouse brain, and measure the ensuing brainwide network activity using functional magnetic resonance imaging (fMRI), to detect any connectivity alterations.

Basic Research

Christopher Martin Hammell, Ph.D.
Cold Spring Harbor Laboratory

Dr. Hammell will study the function of hundreds of genes that are considered to be likely involved in schizophrenia. The team has developed a rapid and cost-effective strategy to ascribe and test putative functions to individual genes. The team plans to use the roundworm, *C. elegans*, as a model organism to explore the role of all known schizophrenia-risk genes in controlling the specification and shape of developing neurons.

Basic Research

Simon McCarthy-Jones, Ph.D.
Trinity College, Dublin, Ireland

Dr. McCarthy-Jones will study the potential of neurofeedback training for diminishing auditory hallucination in schizophrenia. Hearing voices is a common symptom experienced by the people with schizophrenia, which causes major distress and is hard to treat. McCarthy-Jones and his team will employ a brain-computer interface to present participants' neural activity to them in real time, and help them alter this activity through reinforcement learning. Brain activity readings will be based on EEG, which is an inexpensive and accessible method to use in outpatient clinics.

Next Generation Therapies

Oded Meiron, Ph.D.
Sarah Herzog Memorial Hospital,
Hebrew University, Israel

Dr. Meiron plans to examine whether executive functioning can be improved in people with schizophrenia by using a noninvasive method to electrically stimulate the brain, known as Transcranial Direct Current Stimulation or tDCS. Schizophrenia patients suffer from impaired brain communication across widely dispersed brain regions. Building on promising early results, Dr. Meiron's team plans to use tDCS to stimulate the frontal regions of the brain to enhance working memory in people with schizophrenia, and determine the right amount of stimulation and duration for optimal results.

Next Generation Therapies

Vijay Anand Mittal, Ph.D.
Northwestern University

Dr. Mittal will probe the effects of brain stimulation for improving verbal working memory in people with psychosis. The ability to hold verbal information in mind is central to achieving everyday goals but can be impaired in psychosis. Dr. Mittal's team will use transcranial direct current stimulation or tDCS, a noninvasive method, to temporarily stimulate parts of the brain, to determine if cerebellar tDCS can improve verbal working memory in psychosis, while keeping track of brain responses via fMRI scans.

Next Generation Therapies

Derek William Morris, Ph.D.
National University of Ireland, Galway, Ireland

Dr. Morris aims to uncover the role of epigenetics in schizophrenia and cognitive ability. More specifically, he will focus on a group of newly identified genes that regulate the functions of other genes and are shown to both increase the risk for schizophrenia and affect cognitive function. Dr. Morris hopes to extend the list of known schizophrenia risk genes, and study their effects on educational attainment and direct measures of different cognitive functions.

Basic Research

Sergiu P. Pasca, M.D.
Stanford University

Dr. Pasca studies the mechanisms causing brain abnormalities in people with 22q11.2 deletion syndrome. In this syndrome, the deletion of a small piece of chromosome 22 leads to abnormalities in the brain's white matter and oligodendrocytes, and puts people at higher risk for developing mental illnesses such as schizophrenia, depression, anxiety, and bipolar disorder. Dr. Pasca and his team have developed a novel 3D model that allows them to investigate the development of oligodendrocytes in cultures derived from patients with 22q11.2 deletion syndrome.

Basic Research

Rebecca Ann Piskorowski, Ph.D.
French National Institute of Health and Medical Research, INSERM, France

Dr. Piskorowski will take an integrative approach to decipher the complex relationships between environmental, genetic and epigenetic factors in numerous psychiatric diseases, including schizophrenia. She and her team focus on problems in social cognition, a core symptom of schizophrenia. The team will study how environmental factors alter social memory formation by affecting certain neurons in the hippocampus, which appear critical for social memory.

Basic Research

Laura M. Rowland, Ph.D.
University of Maryland School of Medicine

Dr. Rowland studies the underlying neurobiological mechanisms responsible for learning and memory deficits in schizophrenia. An important element of learning is the brain's ability to alter the strength of connections between neurons, known as plasticity. Research has suggested plasticity is impaired in schizophrenia. Dr. Rowland's team will test whether repetitive transcranial magnetic stimulation (rTMS) will enhance plasticity in the brain's visual areas in people with schizophrenia.

Next Generation Therapies

Amar Sahay, Ph.D.
Massachusetts General Hospital

Dr. Sahay will study the neurobiology of a group of hippocampal neurons and their role in schizophrenia. Through communication with the dentate gyrus, CA3 neurons play a critical role in how the hippocampus faithfully stores and retrieves memories. A problem in this network may not only contribute to episodic memory impairments but also underlie negative bias perception in depression and psychosis in schizophrenia. Dr. Sahay and his team will use their optimized method to rapidly generate CA3 neurons from human fibroblasts to study how physiological properties and connectivity of CA3 neurons are altered in schizophrenia.

Basic Research

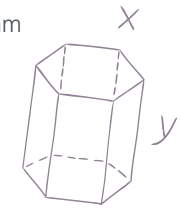
Patrick David Skosnik, Ph.D.
Yale University

Dr. Skosnik will examine the interaction between cannabinoid and glutamatergic receptors and their role in psychosis. Drugs acting on these receptors can bring about a disruption in the activity of neurons and lead to psychotic symptoms. Dr. Skosnik and his team will administer ketamine and THC, two drugs that act on cannabinoid and glutamatergic systems, in order to evaluate the interactive contributions of these two systems to psychosis in people using both EEG and behavioral measures.

Basic Research

Deepak Prakash Srivastava, Ph.D.
Institute of Psychiatry/King's College London, UK-England

Dr. Srivastava plans to study the molecular mechanisms underlying the beneficial effects of estrogen-based treatments in schizophrenia. The team will grow neurons from patients' own samples to test whether estrogen-based compounds can increase the number of synapses in the brain, which are thought to be reduced in schizophrenia. The team will also determine the molecular changes that estrogenic compounds induce in these cells, which will inform attempt to develop new medications with fewer side effects.



Basic Research

Bryan Andrew Strange, M.B.B.S., Ph.D.
Technical University of Madrid, Spain

Dr. Strange will use deep-brain stimulation (DBS) to investigate abnormal activity in the dopamine system in schizophrenia. The team will collect electrophysiological recordings through DBS in a patient to study the firing pattern of dopaminergic neurons, which is thought to be impaired in schizophrenia. Secondly, the team will test patients in behavioral tasks such as working memory, in order to determine the cognitive effects of DBS treatment.

Next Generation Therapies

Duje Tadin, Ph.D.
University of Rochester

Dr. Tadin will explore whether sensory noise underlies working-memory problems, a core feature of schizophrenia. Although working memory abilities are linked to the frontal regions of the brain, it is possible that abnormalities in sensory processing also contribute to working memory deficits. Dr. Tadin's team will focus on neural noise, a fundamental limitation in neural processing. The team will use electrical brain stimulation to manipulate the level of internal noise and test the effects on working memory performance.

Basic Research

Elisabet Vilella, Ph.D.
Institute Pre Mata (IISPV -HPU), Spain

Dr. Vilella will investigate the role of gene variants affecting the integrity of myelin, the protective sheath around the axons that connect neurons. Myelin alterations, in addition to causing multiple sclerosis, have been shown in psychiatric diseases such as schizophrenia and bipolar disorder. Dr. Vilella and her team have identified a receptor, DDR1, present in the cells that produce brain myelin. The team aims to study the impact of DDR1 variants on processing speed and myelin volume in patients with schizophrenia and bipolar disorder.

Basic Research

James T.R. Walters, M.D., Ph.D.
Cardiff University, United Kingdom

Dr. Walters will investigate why some people who are at high genetic risk for schizophrenia do not develop the condition. Numerous genetic variants have been found to increase risk of schizophrenia. However, many healthy individuals carry these variants with minimal detrimental effects. Dr. Walters and his team seek to identify factors that lead to resistance to developing schizophrenia. They will compare people at the highest genetic risk to those without such genetic risk factors to determine whether the high-risk individuals also have protective genetic factors or lower levels of environmental risk such as cannabis use, social deprivation and adverse childhood events.

Basic Research

PARENTING

DIAGNOSING EARLY–ONSET DEPRESSION IN YOUNG CHILDREN

by Fatima Bhojani

Joan Luby, M.D.

Joan Luby, M.D. is the Samuel and Mae S. Ludwig Professor of Child Psychiatry and Director of the Early Emotional Development Program at the *Washington University in St. Louis*. She is also the Co-Principal Investigator of the university's National Institute of Mental Health Post-doctoral training program in developmental affective neuroscience. Dr. Luby received a Young Investigator Grant in 1999 and Independent Investigator Grants in 2004 and 2008.

What's the earliest age at which symptoms of early-onset childhood depression seem to appear?
The available data suggests that age three is the lowest threshold at which childhood depression appears, but that doesn't mean it can't be identified earlier or that there aren't risk signs earlier.

Is there something about being three years old that somehow makes it possible to diagnose or measure depression reliably?
We know how to distinguish extreme behavior from the norm in that age group. Children at age three start to have enough social, interactive and emotional behavior by that time that it is possible to more easily make a diagnosis.

How was early-onset childhood depression formerly viewed in the literature? People were very skeptical, right? To what extent was its existence acknowledged?
There was a longstanding belief that pre-pubescent children were too developmentally and cognitively immature to experience the core aspects of depression. In the mid-1980s research studies disputed those claims. By the late '80s, it was widely accepted that children ages six and older could experience clinical depression. Subsequently, treatment studies looked at various forms of psychotherapy and psychopharmacology for that age group. Recent studies, including ours at Washington University, have extended that story down to age three.

Why do you think it took so long to acknowledge the existence of childhood depression?
One reason is that people don't want to consider that possibility, just like you don't want to think about children having cancer. But while cancer makes itself clear in the body, depression can be ignored or overlooked. The other problem is that we were looking for adult-style manifestations of depression, and not thinking about how symptoms appear in the context of a child's life. For example, anhedonia (the inability to experience pleasure in normally pleasurable activities) in adults is often identified by decreased sexual drive and motivation. In young children anhedonia would equate to decreased enjoyment in play. Nobody had designed an interview that captured age-adjusted manifestations until the mid-1990s.

Do children have any of the same symptoms seen in depressed adults?

It was speculated that pre-pubescent children would have masked symptoms of depression such as stomach aches or acting out, rather than the classic symptoms. Studies that validated depression in pre-pubescent children refuted that claim, showing that these children more frequently have the core symptoms like adolescents and adults do, such as sad or irritable mood, and disturbances in sleep and appetite.

What are the telltale signs for a concerned parent?
Look to see if the child has a preponderance of sadness and irritability, that is, one who spends more than two hours a day in a sad or irritable state, even if they have periods of brightening. Children who have experienced loss or trauma may have a more transient sad or irritable mood, which resolves relatively quickly. Depressed children stay in negative mood states for sustained periods of time; they are easily tipped into these states, and don't extract pleasure from normal activities or play as they once did.

Another important sign is excessive guilt and taking responsibility for things that aren't their fault. Also look at self-concept: Does the child have a negative, pessimistic view of himself?

Where does a concerned parent begin if they suspect symptoms?
I would recommend probably starting with a pediatrician, with the hope that they are well informed. If you are seriously concerned about your child, it can't hurt to go see a psychologist or psychiatrist with an expertise in early childhood.

And they can point you to the next level of care or provide therapy themselves?
Exactly. It's important not to take the attitude of "Don't worry, they'll grow out of it." Our longitudinal neuroimaging study—one in which we followed kids from preschool into adolescence—showed that repeated experiences of depression in early childhood alter the way the brain develops and functions over time. So it's not something either parents or we as a society should continue to ignore.

Where does early childhood depression come from? Is there a play between genetic predisposition and environmental factors?
It was once thought that only abused or neglected children were vulnerable to depression. That's a major misconception. Children who grow up in nurturing, supportive and well-resourced families can have depression. It's a disorder with genetic roots, although the genetic element of it has not been clarified. And there is an interaction between genetic vulnerability and stressful life events: you can have a genetic vulnerability and experience a stressful event, and that could spur a child's plunge into depression.

How do you make a diagnosis in a very young child?
We start by with looking at symptom manifestations and taking a detailed history from caregivers. Teacher reports are also useful. Additionally, we consider family history because this is a disorder that runs in families. We also look at general development because we have to rule out developmental problems. We primarily focus on parenting because it can either exacerbate or alleviate depressive proclivities in a child: we observe the child in two different interactive play sessions with a primary caregiver and a secondary caregiver. One of the play sessions has a mildly stressful event that is designed to put pressure on the child and the caregiver.

Usually with those three pieces of information—a mental status exam, an observation at two occasions, and a detailed parent report, we're able to come up with a diagnosis.

How do you treat a young child with depression?
That's where our current state of knowledge needs more help. We are in our last year of a large, randomized controlled trial we designed to test a form of psychotherapy for preschool depression. The treatment involves working closely with the primary caregiver and the child together, and it views depression as a disorder of emotional development. That's the only form of treatment specific to preschoolers that has any testing to date. The other potential treatment modality is psychopharmacology [drug treatments], but that's not been looked at in children under six.

Tell us about the form of psychotherapy that you favor, and how you came up with it.
We call it Parent Child Interaction Therapy Emotion Development (PCIT-ED), and we based it on an empirically tested form of psychotherapy called Parent Child Interaction therapy (PCIT). PCIT was developed in the 1970s by the psychologist Sheila Eyberg and is designed to target the parent-child relationship: to teach the parent how to interact with the child like a play therapist, and how to set loving, yet firm limits.

There were several things that made PCIT compelling. It has a great deal of empirical backing, has been very well tested, and as we scientists say, it has an effect size of over 1.0, which is huge for psychotherapy. This means that it has a powerful impact on reducing symptoms.

Why do you think PCIT is so successful?
One reason is that it targets children when they're young. Another is that it uses a completely different psychotherapeutic approach. The parent and child are seen together. The parent is wearing a "bug" in their ear and they're coached by a therapist standing behind a one-way mirror, helping the parent interact with the child in a new way. So for example, we

would be coaching the parent on how to play with the child in a way that follows the child's interests, gives positive feedback, and isn't critical. Parents come to us with all different levels of skills in this domain, but pretty much everybody could use a little help.

The nature of the bond between the primary caregiver and the child, especially at this phase of life—and arguably from infancy—seems absolutely critical.

Absolutely. We know from case studies, and studies on institutionalized children, that in the absence of a caregiver and the nurturing and psychological stimulation they provide, children do not develop normally. This is true even if there is appropriate food and shelter.

So that's why you are particularly optimistic about this therapy?

Exactly. We're optimistic because a) we're focusing on a fundamental, foundational issue; b) we're focusing on early childhood, when the brain is more plastic; and c) we're targeting a caregiver who is then part of the child's life for the next 20 years. It's like cleaning the air you're breathing and then you keep breathing it.

The availability of any type of psychiatric care in this country is difficult. You have written that the availability of these interventions is a pretty big problem?

Yes. Accessing psychotherapy is especially hard. The standard PCIT is somewhat more available. You could get PCIT probably in most major cities, although it wouldn't be that easy. But at no place other than St. Louis (*Washington University*) could you get PCIT-ED at this time.

So this really is a frontier, and you're a pioneer in this field?

Exactly. Our therapy takes fundamentally a developmental approach to the treatment of early-onset depression. It looks at emerging depression in a young child in terms of the child not experiencing normative or optimal emotion development. In other words, the child is not learning to regulate his or her emotions in an optimal way, is not experiencing sustained positive affect, and does not have a successful way of resolving transgressions. If we target really early in childhood when the brain is rapidly developing—if we can alter the foundation—it may result in a better lifelong trajectory.

So you're optimistic that early interventions are particularly effective?

We see very large effect sizes in a number of treatments implemented in early childhood. This is clearly true for treatment of speech disorders, motor disorders and autism. We speculate it's because you're treating a brain-behavior dimension when the brain is rapidly developing. Another thing to note is that brain development is not just genetically driven, but also very responsive to environmental inputs, which have a much bigger impact earlier in development.

> It's important not to take the attitude of "Don't worry, they'll grow out of it." Our longitudinal neuroimaging study – one in which we followed kids from preschool into adolescence – showed that repeated experiences of depression in early childhood alter the way the brain develops and functions over time. So it's not something either parents or we as a society should continue to ignore.

Tell us about the biological correlates of these behaviors.

Depressed people tend to be focused more on negative affect, are more reactive to negative affect, and are ruminative. Some of those things have also been found in depressed preschoolers using functional magnetic resonance imaging (fMRI) and other methods like electroencephalography (EEG), which records electrical waves in the brain. So all of this information really helps us target our treatment, for example by helping children regulate negative emotions, and helping their parents serve as coaches in those domains. In our current study, we are measuring brain activity at the beginning, middle and end of treatment to see, in addition to behavioral changes, if there is a change in neural activity in the expected direction.

INSIGHTS FROM THE DIRECTOR OF NIMH

Joshua Gordon, M.D., Ph.D.
Director, *National Institute of Mental Health* (NIMH)

Scientific Council Member
2003 & 2001 Young Investigator

Are there other types of genetic differences found in people with schizophrenia that you think might be related to the brain "synchrony" problem—beyond the 22q11 deletion syndrome that you mentioned in your interview last month?

Yes, there are other genes that have been associated with risk for schizophrenia and might be related to brain synchrony. These synchrony changes can be complex, sometimes selectively affecting fast versus slow cell activity or affecting synchrony differently for nearby versus remotely located cells. For example, certain subtypes of the Neuregulin-1 gene increase the degree of synchrony among neurons that are close to each other and decreases synchrony among cells that are located further away. These changes appear to be related to disruptions in working memory.

Are there any plans for human trials of the drug that you tested in mice with 22q11 deletion syndrome?

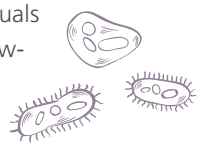
The compound used in our research with mice is helping us understand the neurobiology of the brain and how a genetic variation associated with schizophrenia can cause disruptions in brain function that lead to symptoms. While animal models are invaluable in exploring these questions, compounds that have beneficial effects in animals often don't work the same in humans; we need to know much more before starting the process of testing a potential medication in human patients. We are currently examining the effects of more specific pharmacological agents as one step in this process. We also need to know when during development the drug exerts its effects.

Does it seem more likely that scientists will find a way to prevent synchrony problems from developing in the first place, or that they will develop a drug that patients can take to ease those problems?

Intervening early to prevent the symptoms of schizophrenia, including cognitive deficits, is one of the goals of research. A first step is to be able to identify those at risk, a high priority area of NIMH-supported research. Future therapies might include medications, but could also encompass cognitive remediation therapies or brain stimulation methods that address the function of brain circuits involved in symptoms.

My daughter has schizophrenia, and I've noticed that many people don't consider memory and attention problems to be part of her disorder. Can you recommend an easy way to describe the cognitive problems that affect some schizophrenia patients?

Although people tend to think of the symptoms of schizophrenia as mostly involving delusions and hallucinations, most individuals experience cognitive deficits which can be disabling, even if the delusions and hallucinations are successfully treated. There is some evidence that these difficulties are present in childhood and, in some studies, cognitive impairment is as strongly related to everyday functioning as the symptoms of psychosis. Cognitive deficits seen in schizophrenia include difficulties with executive functioning—the ability to understand information and use it to make decisions and to carry out tasks; trouble focusing or maintaining attention; and problems with memory, both with remembering facts and information and with working memory, the short-term memory that helps us carry out everyday tasks. Also, some individuals with schizophrenia experience a general slowing of their ability to process information.



JUDGE FACES THE CHALLENGE OF THE CRIMINALIZATION OF MENTAL ILLNESS

by Fatima Bhojani and Peter Tarr, Ph.D.

Miami, Florida is famous for its sun, sand and sea. Less commonly known is the fact that it hosts the highest percentage of people with a mental illness of any urban area in the U.S.—three times the national average, to be exact. While 9.1 percent of Miami-Dade county's general population has a serious mental illness (disabling disorders that prevent a person from consistently holding a job or caring for themselves without assistance), antiquated procedures that favor arrest over re-integration of people into society often exacerbate the situation, giving rise to a full-blown crisis. In effect, and entirely by default, the criminal justice system has become greater Miami's mental health system.

When Steven Leifman became a county court judge in 1995, he inherited this legacy—one, remarkably, that made him gatekeeper to the largest psychiatric facility in the state of Florida: the Miami-Dade County Jail. The same can be said for the largest jails in Los Angeles, Chicago and New York: each houses more mentally ill people—relatively few of whom are receiving care—than any other institution in their respective states. In the past 10 years, this segment of the prison population has risen by over 170 percent.

"Judges tend to see people with more psychiatric illness than psychiatrists do these days," Judge Leifman said on a recent episode of the Public Television series *Healthy Minds*, hosted by BBRF President Dr. Jeffrey Borenstein.

Judge Leifman explains that many are brought to court by police because of so-called quality-of-life offenses (e.g., urinating in public, disorderly intoxication) or low-level felonies. The problem in Miami and in other large urban centers in America is that in the wake of de-institutionalization—the push that began in the 1970s to shutter state-run mental institutions—hundreds of thousands of people who once would have been taken in to such custodial facilities have been on their own. To the extent they are unable to care for themselves, these people, particularly those who are severely mentally ill, have become involved in the criminal justice system that was not designed to handle them.

It has been estimated that on any given day in this country some 550,000 of the 2.2 million inmates in our jails and prisons are suffering from a diagnosable mental illness. That number is almost precisely the number of people housed in state-run psychiatric hospitals in the U.S. in the years just before de-institutionalization began.

After being shaken by the experiences of some of the mentally ill defendants in his court, and coming to appreciate the lack of understanding and training among those who staff the criminal justice system, Judge Leifman set out to spur reforms.

About 15 years ago, he organized a Technical Assistance Summit where he invited various stakeholders, including law enforcement personnel and judges, to map out how criminal justice intersected with community mental health. Realizing that the current procedures in place were making the problem worse, the group decided to design a criminal justice model that made jail the last resort, and not a point of entry into mental health care.

Judge Leifman envisioned a reform program that would help people re-integrate into society by helping them with housing, relationships, and health care—especially mental health care. The program was so successful that the number of mentally ill people in jail in Miami-Dade dropped by half, with very low recidivism rates. Over the past five years, the program has expanded into non-violent felony cases, with a recidivism rate of only six percent.

Another initiative Judge Leifman helped to develop was a police training program, which has so far trained over 4,600 officers in Miami-Dade in how to identify someone with a mental illness, how to de-escalate situations involving public disturbances by mentally ill individuals, and where to take them instead of putting them in jail. The program also helps officers understand themselves and their own emotions, including traumas and other difficulties that may have occurred in their own families. According to Judge Leifman, this training has drastically reduced police injuries and police shootings of people with mental illness.

Judge Leifman's model is simple: instead of sending people with low-level felony offenses (such as cocaine possession) to a prison cell or a hospital, send them instead to a facility which emphasizes treatment, restoration and reintegration into the society's mainstream. It's about one-third cheaper, one-third quicker, and has a near-zero recidivism rate, he says. Tested in Miami Dade, the model approach has been such a phenomenal success that the state of Florida is looking to expand it on a state-wide basis.

Judge Leifman's latest project is a $22 million, first-of-its kind "forensic diversion facility," set to open in two years. The 180,000-square-foot building will consist of a crisis unit, a short-term residential unit, a courtroom, a day activity program, a primary health care unit, and a kitchen with a culinary supportive employment program. The building is designed to gently reintegrate individuals into their communities.

With the support of the American Psychiatric Association Foundation, the National Association of Counties and the Council of State Governments, Judge Leifman is trying to bring Miami-Dade's humanitarian approach to the rest of the nation—to make it a model for how society should respond to the very real problem of seriously mentally ill individuals getting in trouble with the law.

In 2012 Judge Leifman received the Foundation's Productive Lives Award. This Award was established to acknowledge the challenges, hope and the capacity for families and individuals to persevere and live productive lives with the help of science, family, friends and compassionate efforts of responsible civic and corporate leadership.

Judge Steven Leifman and Dr. Herbert Pardes

THE POWER OF A

Research Partnership

UNITING DONORS WITH RESEARCHERS

Virginia and Mark Silver

Eleonore Beurel, Ph.D.

Virginia Silver, a member of the Foundation's Board of Directors, and her husband, Mark Silver, M.D., have a research partnership with 2013 NARSAD Young Investigator Grantee Eleonore Beurel, Ph.D., of the University of Miami. Dr. Beurel is working to help usher in a new generation of better, more effective medications for the treatment of mood disorders.

Partner with a NARSAD Grantee:

- Select a scientist in your area of interest, an institution or geographic area.
- Learn more about their work through personal communications and events.
- Receive progress reports that outline their research findings.
- Be recognized in published work resulting from the research.

"Our daughter was diagnosed five years ago with clinical depression and severe anxiety disorder. Although now stabilized and living a happy, productive life, I came to realize that if it weren't for research, she would not have had the medications that have worked for her. We were drawn to support the Brain & Behavior Research Foundation because we believe so strongly that research has to be supported for the sake of our children's children–and for all the generations down the road."

—Virginia Silver

For information on becoming a Research Partner or to support research in other ways, please call 800-829-8289 or visit our website at bbrfoundation.org/research-partner.

Recent Research Discoveries

DECLINES IN MEMORY AND ATTENTION PRECEDE ONSET OF PSYCHOSIS

TAKEAWAY: In the largest analysis to date of cognitive function in individuals at clinical high risk of psychosis, researchers found that memory and attention were most significantly impaired among those who later developed a psychotic disorder.

In people who develop schizophrenia and other psychotic disorders, mild cognitive impairments begin before the onset of other symptoms and get worse as patients progress toward full psychosis. A detailed new analysis has found that within this general cognitive decline, certain attention and memory problems may be warning signs to help identify which high-risk individuals are most likely to develop a psychotic disorder.

The study, published November 2 in the journal *JAMA Psychiatry*, was led by *Harvard Medical School* psychologist Larry J. Seidman, Ph.D., a 1998 and 2004 Independent Investigator. It is the largest analysis to date of cognitive function in people who, because they have experienced certain disruptions in their thoughts, beliefs, and perceptions, are considered at high-risk for schizophrenia and other disorders involving psychosis. It was conducted at eight institutions in the United States and Canada as part of the ongoing North American Prodrome Longitudinal Study.

Dr. Seidman and his colleagues wanted to understand which aspects of cognition decline most dramatically affected an individual's progress toward psychosis. In particular, they wondered if monitoring certain cognitive functions might help clinicians predict which at-risk individuals are most likely to develop psychotic disorders.

Nearly 1,000 people participated in the study, including 689 in the clinical high-risk group. At the outset of the study, participants took 19 different neurocognitive tests to assess a wide range of cognitive functions, including attention, memory, verbal abilities, visual-spatial skills, and executive functions. As a group, the high-risk individuals performed worse than the healthy controls, showing slight deficits in most areas. Although many individuals in the high-risk group were taking antidepressants, stimulants, or antipsychotics, the researchers found no evidence that these medications were responsible for impairments in cognitive function.

Of the high-risk individuals in the study, 13 percent progressed to full psychosis within two years. The researchers found that these individuals had exhibited greater cognitive deficits during the original testing than individuals in the high-risk group who did not develop psychosis during the study period. Those who eventually progressed to psychosis performed worse on all of the neurocognitive tests, with deficits in attention, working memory (the temporary storage of information while it is being processed), and declarative memory (memories of facts or experiences) being the most significant.

Cognitive symptoms are difficult to treat and can have a major impact on quality of life. Based on the team's findings, early interventions that aim to enhance memory and attention should be priorities in the treatment of high-risk individuals, the study authors say. The findings will also be valuable as researchers work to develop better ways to identify people who are at the greatest risk of developing psychosis.

The research team included William S. Stone, Ph.D., a 1997 and 2000 Young Investigator at *Harvard Medical School*; Carrie E. Bearden, Ph.D., a 2003 and 2005 Young Investigator at the *University of California, Los Angeles*; Kristin S. Cadenhead, M.D., a 1992 and 1999 Young Investigator at the *University of California, San Diego*; Tyrone D. Cannon, Ph.D., a 1997 Independent Investigator and 2006 Distinguished Investigator at *Yale University*; Daniel H. Mathalon, M.D., Ph.D., a 2001 Young Investigator, 2007 Independent Investigator, and BBRF Scientific Council member at the *University of California, San Francisco*; Thomas H. McGlashan, M.D., a 1997 Distinguished Investigator at *Yale School of Medicine*; Ming T. Tsuang, M.D., Ph.D., D.Sc., a 1998 Distinguished Investigator and BBRF Scientific Council member at the *University of California, San Diego*; Elaine F. Walker, Ph.D., a 1989 Distinguished Investigator at *Emory University*; and Scott W. Woods, M.D., a 1998 Independent Investigator and 2005 Distinguished Investigator at *Yale University.*

Larry J. Seidman, Ph.D.
2004, 1998 Independent Investigator

MISREGULATED EMOTION-PROCESSING CIRCUITS MAY CONTRIBUTE TO SUICIDAL BEHAVIOR IN YOUNG PEOPLE WITH BIPOLAR DISORDER

TAKEAWAY: Parts of the brain involved in emotional processing are smaller and less active in young people with bipolar disorder who have attempted suicide, than they are in people in the same age group who have been diagnosed with the disorder but have not attempted suicide.

About half of people with bipolar disorder make a suicide attempt in their lifetimes, and identifying those who are at the greatest risk is a high priority for those scientists who study and treat the illness. Findings published January 31 in the *American Journal of Psychiatry* may help.

For people who experience the intense emotions and mood shifts of bipolar disorder, thoughts of suicide often begin in adolescence or young adulthood, when the brain's emotion-regulating circuits are maturing. Few studies to date have investigated the neural circuits involved in suicidal behavior at this age.

In the new study, researchers led by Hilary P. Blumberg, M.D., a Scientific Council Member, 2006 Klerman Prizewinner and Independent Investigator, and 2002 Young Investigator at *Yale University*, used magnetic resonance imaging (MRI) to study the brains of young people with bipolar disorder, and found structural and functional differences between those who had attempted suicide and those who had not. The differences they observed mainly affect parts of the brain involved in emotional processing and impulse control.

The study included 68 people between the ages of 14 and 25 who had been diagnosed with bipolar disorder. Of these, 26 had made a suicide attempt. Forty-five healthy adolescents and young adults with no history or mental illness or suicide attempts were also included. Study participants received three types of MRI scans, each of which revealed a different feature of their brain's structure and activity. The researchers used the imaging to examine the volumes of specific brain regions and the connections between them. They also monitored activity as subjects were shown faces with happy, fearful, or neutral expressions and their brains responded to the emotional stimuli.

The research team, which included *Yale* scientists 2012 and 2008 Young Investigator Fei Wang, Ph.D. and 2016 Young Investigator Jie Liu, Ph.D., found that parts of the brain that regulate emotion and control impulses were smaller in size and less active in those who had attempted suicide than they were in the other study participants—both healthy controls and individuals with bipolar disorder who had not attempted suicide. The structural and functional connections between brain regions involved in emotion were also diminished, and were weakest among those whose past suicide attempts were considered the most serious.

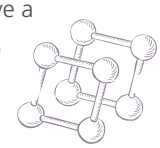
Based on their findings, the researchers suggest that the diminished activity of emotion-regulating circuits may cause some people with bipolar disorder to experience particularly intense emotions and make them more likely to act on suicidal impulses. Abnormalities in these brain regions have also been observed in adults with psychiatric disorders who have attempted suicide. Zeroing in on these circuits could help researchers identify patients with the greatest need for intervention and develop new strategies for suicide prevention.

Hilary P. Blumberg, M.D.
Scientific Council Member
2006 Klerman Prizewinner
2006 Independent Investigator
2002 Young Investigator

COCAINE'S EFFECTS ARE MOST POTENT WHEN ESTROGEN LEVELS ARE HIGH

TAKEAWAY: Animal research demonstrates how hormones can make females more vulnerable to addiction than males.

New animal research suggests that female sex hormones make cocaine use more pleasurable—and therefore more addictive. According to a study reported January 10 in the journal *Nature Communications*, female mice are particularly susceptible to the drug's addictive effects when their estrogen levels are high. The findings may help explain why girls and women who try cocaine become addicted more quickly and have a harder time overcoming their addiction than males who use the drug.



Understanding gender differences in drug-related behavior is vital for effectively preventing and treating substance use disorders. Males tend to have more opportunities than females to try cocaine, but researchers have found that once females start using the drug, they consume more and become addicted more quickly than males. During recovery, they are more susceptible to relapse.

Many of these gender-specific patterns have also been observed in animals, suggesting they are caused by biological differences rather than social or cultural factors. To investigate how hormones might contribute to these differences, a research team led by Eric J. Nestler, M.D., Ph.D., and Ming-Hu Han, Ph.D., at the *Icahn School of Medicine at Mount Sinai*, studied how female mice respond to cocaine, tracking their behavior and neuronal activity at different stages of the estrous cycle, a hormone-driven cycle similar to the menstrual cycle in women. Some studies in people have found that women report stronger cravings and a more intense response to cocaine at specific times during their menstrual cycles.

Dr. Nestler is a 1996 Distinguished Investigator, BBRF Scientific Council member, and winner of the 2008 Goldman-Rakic Prize and 2009 Falcone Prize. Dr. Ming-Hu Han is a 2007 Young Investigator and 2015 Independent Investigator. The research team also included 2016 Young Investigator Erin S. Calipari, Ph.D., and 2015 Young Investigator Michael Edward Cahill, Ph.D., at the *Icahn School of Medicine* and 2005 and 2008 Young Investigator, BBRF Scientific Council member, and 2013 Goldman-Rakic Prizewinner Karl Deisseroth, M.D., Ph.D., at *Stanford University*.

Cocaine causes its pleasurable effects by blocking the brain's ability to clear the neurotransmitter dopamine from the junctions between neurons. The resulting accumulation of dopamine in the neurotransmitter activates the brain's reward pathways. When mice in the study were given cocaine, they quickly learned to associate the pleasurable feelings triggered by this dopamine accumulation with the place where they were given the drug, favoring this location in their cage even after the drug was removed.

This preference was strongest in female mice that consumed cocaine when their estrogen levels were high, indicating the drug had more strongly activated their brains' reward pathways than it had in males or in females that consumed the drug while their estrogen levels were low.

The researchers determined that estrogen makes a protein that transports dopamine more vulnerable to inhibition by cocaine, thus enhancing the drug's pleasurable effects.

Eric J. Nestler, M.D.
Scientific Council Member
2009 Falcone Prizewinner
2008 Goldman-Rakic Prizewinner
1996 Distinguished Investigator

Sunshine from Darkness– The Hollister Family Story

By Fatima Bhojani

Until the day she passed away, Patsy Hollister and her husband, Hal, left home every morning at 7:30 a.m., and drove the ten miles to their beloved NARSAD Artworks office in Brea, California.

The inspiration for Artworks was their middle child, Annick, who has been creating art since she was three, and who was diagnosed with schizophrenia at age 15. Soon after Annick's diagnosis, the Hollisters got involved with their local chapter of the National Alliance on Mental Illness (NAMI). They then joined the founding members of the Brain & Behavior Research Foundation, formerly known as NARSAD ("a cause we believed in from the word 'go,'" says Hal). They were instrumental in helping create its mission, and for more than two decades have remained involved with the Foundation. But, the Hollisters wanted to do more.

Even during their daughter's darkest moments, art was the one thing that gave her hope and meaning. Patsy had wondered if it would be possible to use art as a kind of therapy for Annick, and for anyone living with mental illness, on the hope that art could provide meaning and purpose for them.

In 1989 the Hollisters founded a nonprofit which empowered mentally ill artists. NARSAD Artworks, named after NARSAD, reproduced and sold their creations, distributing millions of note cards, posters, T-shirts and calendars nationwide. From the more than $1.5 million raised, Artworks paid the artists commercial rates, and donated the proceeds from product sales to the Brain and Behavior Research Foundation for research.

"Mom was always so positive, and forward-looking, and Artworks was about positivity and helping the artists feel good about themselves," says Meggin, Patsy's youngest daughter, a Ph.D. and the winner of a Foundation Young Investigator grant in 1996 for her innovative work on schizophrenia.

What began with local exhibits in California moved to displays at annual NAMI conventions and then to exhibits in various art hubs such as New York City. To give recognition to the talented artists, in 1997 Hal and Patsy took the "Sunshine from Darkness" series on the road. The show included over 140 works by mentally ill artists, and was displayed in galleries and museums across the country. They also published a book under the same name which featured the best pieces, ensuring that the work of these unrecognized artists would far outlast their lives. Through their years of dedication, the Hollisters did much to destigmatize those with mental illness, demonstrating the valuable, and beautiful, contributions that they can make, if supported in the right way.

Hal and Patsy worked at Artworks as full-time volunteers, every single day, until Patsy passed away this February from natural causes. The entire Hollister family: Patsy, her husband Hal, and her three children, Annick, Meggin and John have in their own unique ways all contributed to a greater understanding of mental illness.

Athletic, with long blond hair, and Mediterranean skin, Annick was a straight-A student, and the "fastest girl to ever step on the high school track freshman year," her elder brother John recalls. What initially exhibited itself as rebellious teenage behavior (smoking pot, hanging out with the wrong crowd) culminated into her first psychotic break at a Halloween party.

Back then, in 1977, little was known about schizophrenia, and no adequate treatment existed. Some doctors still believed that the cause was rooted in upbringing and family dynamics.

John remembers those early meetings with psychiatrists: "They were searching for who to blame, who to pin the responsibility on—looking to see what mom and dad did to cause this behavior." Once, the Hollisters visited a family counselor, who asked them to make a crayon drawing. After watching John's attempt, the counselor called him the "controlling factor in this household." To which Hal replied, "No, you're a quack, we're out of here."

Even back then, Hal and Patsy had a very progressive view of schizophrenia as a brain disorder, and not something that was the fault of the family of origin, as was the prevailing idea. In this way, "they were ahead of their time by 20 years," says Meggin, "they were so amazing, and so open. Even today, people hide, or are embarrassed by mental illness."

Since then science has caught up with the Hollisters' progressive views, and Meggin's research, motivated by her sister's illness, has contributed to a better understanding of the genesis of this brain disorder.

As a graduate student in the Department of Psychology at University of Southern California, Meggin used data and statistical analysis to explore her suspicion that incompatibility in blood types between her mom and her sister could have something to do with Annick's schizophrenia. While Meggin, John, and Patsy all had a blood type of Rh negative, Annick was Rh positive, which, it was theorized, may have triggered an immune response while Patsy was pregnant. Meggin's Ph.D. dissertation was published in 1996 in the *Archives of General Psychiatry*, and hailed by the journal as a "landmark study." Her breakthrough has sparked subsequent research looking at the significant role that genes and obstetrical and immune system complications can play in causing this illness.

Meggin was 12 when Annick became sick, and growing up she saw first-hand the suffering her sister went through. She and John visited mental hospitals where Annick was held in padded solitary cells, "scared to death."

"Now that I have five kids, I can't even imagine the fear that must be inside somebody, who to begin with isn't thinking clearly, and then is locked up in solitary confinement," recalls John, who headed off to Stanford in the fall of 1979, and was thus more insulated from Annick's care than Meggin.

The whole family struggled through those tough 15 years, when Annick frequently ran away for weeks or even months, and was in and out of hospitals. Once she landed in jail after being robbed; another time she got hit by a car. "I think the worst part was that she would disappear for weeks at a time," says Hal. None of the drugs available at the time to treat schizophrenia worked for Annick.

For some time she was put on Haldol which was "torturous" to her. It bound her in mental and emotional handcuffs so that she couldn't feel anything, while creating vivid, violent images in her head. Then she was put on Prolixin, from which she may have developed neuroleptic malignant syndrome and suffered an associated coma.

Change came in 1989, when Annick became part of a clinical trial for a new antipsychotic drug called clozapine. After having her life upended for fifteen years, she was finally able to get it back on track. Since then, this second-generation antipsychotic drug and its successors have helped millions of people worldwide.

Today Annick, 55, lives an independent life, spending her days making art. For her parents' anniversary, she created a Noah's Ark out of raffia grass with hundreds of pairs of animals. The 6 foot-by-5-foot sculpture took her five years to complete.

Patsy & Hal Hollister

Patsy Hollister with John and Annick in Paris, France in April, 1962.

"She is the most thoughtful person on planet Earth," says John. A hallmark of schizophrenia is an inability to plan. With her art, that requires extensive planning and precise timing, and, he says, "Annick defies that."

Throughout all of this, "my mom and dad were doing all of the things that loving parents can do to support their daughter," John says. And their support extended beyond their daughter, to the larger cause of mental illness awareness and research.

When Patsy and Hal were not organizing events for BBRF on the West Coast, they were frequently seen at NAMI conventions, American Psychiatric Association gatherings, and American Psychological Association conferences. They received the Warren Williams Award from the American Psychiatric Association, and the Peterson Leadership Award from NARSAD for their outstanding contributions to the field of mental illness.

"My mom and dad had been eating, breathing and living, first NARSAD, and now BBRF, until they became too worn out to do much more. Some years ago they turned over the reins in terms of board membership and participation to me," says John, who serves as the Secretary of the Board. Hal, 85, has passed the operations of NARSAD Artworks to the San Mateo, CA chapter of NAMI.

While Patsy is no longer with us, her impact will be felt by countless people for many years, and decades, to come.

IN MEMORIAL

Patricia Grubbs Hollister

July 5, 1933 – February 17, 2017

From **Stephen A. Lieber**, Chairman of the Board of Directors, The Brain & Behavior Research Foundation

Patsy & Hal Hollister

The Brain & Behavior Research Foundation Officers and Directors mourn the passing of Patsy Hollister. Patsy, together with her husband Hal, provided exemplary leadership and service to the cause of brain and behavior research over a period of 30 years. Their contributions were uniquely creative and continually effective. They participated in the early development of NARSAD and sought to address the challenge of improving patients' lives. Their original focus was on the fact that many people, who had challenges of mental illness, also had artistic talent. This led them to create NARSAD Artworks.

NARSAD Artworks' aim was to give people who had mental disabilities and artistic talent a vehicle for expressing those talents and finding public recognition. Beginning in the late 1980s they provided invitational exhibits for people with artistic talents. They also offered the opportunity for these people to earn monies with sale of their artworks.

Patsy and Hal built a consistently growing vehicle for distribution and sale of these artworks, which in turn also provided contributions to the research of the Brain & Behavior Research Foundation. They moved from local exhibits in their native southern California region, to exhibits at annual conventions of NAMI (National Alliance of Mental Illness) and even to a special exhibit in the headquarters of Citibank in New York. Year after year, the range and the number of participants of NARSAD Artworks showed steady growth. All of this was made possible by the continuing work of the Hollisters. They created a separate office for NARSAD Artworks, and they worked there on a daily basis.

The Hollister involvement with NARSAD went well beyond their building and maintenance of NARSAD Artworks. They served on the Board of Directors. Hal was the Chairman of the Board. They brought in outstanding donors who were among their vast acquaintance, including the first estate amount in excess of $10 million. Beyond attending related events, such as the NAMI conventions, they also acted as hosts and supporters of major Foundation fundraising events.

From an elegant dinner at the Beverly Hills Hilton Hotel, to a symposium at a major movie studio in Hollywood, to a dinner and symposium in Pasadena, to a symposium at the University of California Los Angeles, the Hollisters were powerfully, and one might say almost perpetually, leading in the cause of mental illness research support.

The motivation which led Patsy and Hal, and subsequently their son John, to such consistent and important activity was found in the challenged mental condition of one of the Hollister children. That daughter was the inspiration of much of what they did, since she had the challenges of a mental disorder and the talents of a skillful artist. They saw the opportunity to help and they achieved the results of that opportunity in a unique and remarkable way.

Few can have had the dedication over so many years, and even decades, to a cause which they understood, interpreted for others and supported so brilliantly.

Discovery to Recovery: Therapy Update

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

MEDITERRANEAN-STYLE DIET BOOSTS DEPRESSION REMISSION

A Mediterranean-style diet may enhance the benefits of conventional treatments for people with depression, according to the first randomized controlled study of dietary intervention for depression, called Supporting the Modification of Lifestyle In Lowered Emotional States (SMILES).

The Mediterranean-style diet is typically high in fiber, lean protein and healthy fats, and has been associated with reduced risk of depression in previous research.

The new study, published January 30 in *BMC Medicine*, included 67 people with moderate to severe depression. Most of the participants were being treated for depression, either with psychotherapy or medications, or both. Importantly, at the start of the study, all of the participants reported having an unhealthy diet with high intake of sweets, processed meats, and salty snacks.

The participants were randomly assigned to two groups. The first group regularly met with a dietitian and received advice to follow a Mediterranean-style diet composed of fruits, vegetables, whole grains, legumes, lean red meats, fish, low-fat dairy products, eggs, nuts, and olive oil. They were also encouraged to reduce their intake of sweets, fried foods, processed meats, and limit their alcohol consumption. The control group didn't received nutritional guidance but still had regular meetings with a research assistant for social support.

Those who followed a Mediterranean-style diet for three months showed a greater improvement of symptoms than patients who didn't follow a specific diet. About one-third of the group on the Mediterranean diet achieved remission of depression symptoms, compared with only 8 percent of those in the control group.

The findings need to be followed up with larger studies. But the preliminary results suggest that doctors should consider discussing the benefits of healthy eating with patients being treated for depression.

The study was led by 2010 Young Investigator Felice Jacka, Ph.D., 2012 Young Investigator Olivia May Dean, Ph.D., and 2015 Colvin Prizewinner Michael Berk, Ph.D., MBBCH, MMED, FF(Psych)SA, FRANCZP, all at *Deakin University* in Australia, and their colleagues.

Full text: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-017-0791-y

SINGLE-DRUG THERAPY FOR BIPOLAR II DISORDER MAY BE BETTER THAN COMBINATION THERAPY

People with bipolar II disorder respond similarly to antidepressants alone, or mood stabilizers alone, but may have a harder time sticking to a combination of the two, according to a new study published in the *American Journal of Psychiatry* in March.

Patients with bipolar II disorder typically have long depressive episodes occasionally punctuated with a condition called hypomania, which is a less intense form of mania. (Mania is characterized by a state of very high arousal and often risk-taking behaviors.) Many patients with bipolar II are prescribed a mood stabilizer, as is standard in bipolar I disorder, but this is often supplemented with an antidepressant. There's a concern, however, that using antidepressants might increase the risk of the patient "switching over" from a depressed to a hypomanic state.

In the new study, researchers examined patients' response to three forms of treatment over 16 weeks. The study included 142 patients who were randomized into three groups: one group received the SSRI antidepressant sertraline, while another group received the mood stabilizer lithium, and a third group received a combination of the two.

The risk of "switching over" to hypomania did not differ among the three treatment groups. This suggested that, unlike in bipolar I patients, antidepressant treatment in bipolar II disorder may be safe.

The response rate to treatment was high and similar across all of the groups in the study. However, those participants who received the combination treatment had a higher rate of dropping out than those who received only one medication. This suggests combination therapy, which is the most commonly recommended treatment in clinical practice, may in fact be the least desirable option for some patients, the researchers said.

The research team was led by Trisha Suppes, M.D., Ph.D. (two-time Young Investigator Grantee), Lori Altshuler, M.D., and Susan McElroy, M.D. The late Dr. Lori Altshuler, who was the first author of this paper, died in November 2015. Dr. Altshuler was a three-time Foundation Grantee, as well as the 2006 Colvin Prizewinner for Outstanding Achievement in Mood Disorders Research.

Full Text: http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2016.15040558

BRAIN STIMULATION COULD HELP TREAT BIPOLAR DEPRESSION

Stimulating the brain with a non-invasive method called deep transcranial magnetic stimulation, or dTMS, may boost the effects of medication treatment for bipolar depression, according to a February 1 study published in the journal *Neuropsychopharmacology*.

The treatment uses magnetic fields to stimulate brain cells and is delivered by a helmet worn by the patient. For the study, the medical device company Brainsway provided the dTMS devices and financial support.

Fifty people with bipolar depression, who were being treated with medication, took part in the study. Half of the participants received dTMS in 20 sessions over four weeks. The other half received a "sham" treatment with a similar looking but non-functional helmet.

After four weeks, patients who received dTMS showed a significant improvement in overall functioning after four weeks, compared with those who received the sham treatment. The dTMS treatment was associated with an average increase of 4.88 points on a survey measuring depression symptoms. Other than scalp pain, there were no significant side effects, and none of the patients "switched over" to manic episodes after the treatment.

The results suggest that magnetic stimulation of the brain could be a useful add-on treatment for bipolar depression. The differences between groups disappeared by eight weeks after the start of treatment (four weeks after treatments ended), suggesting that longer dTMS treatment programs should be tested.

The study was led by Dr. André R. Brunoni, of the *University of São Paulo*, Brazil, a 2013 Young Investigator, and included Z. Jeff Daskalakis, M.D., Ph.D., of the Centre for Addiction and Mental Health, *University of Toronto*, a recipient of 2004 and 2006 Young Investigator Grants and a 2008 Independent Investigator Grant.

Full text: http://www.nature.com/npp/journal/vaop/naam/abs/npp201726a.html

Women and Mental Illness

Q A

ARE WOMEN MORE LIKELY THAN MEN TO BE DIAGNOSED WITH A MENTAL ILLNESS?

Yes. The Substance Abuse and Mental Health Services Administration (SAMHSA) has estimated that 23.8 percent of women have had a diagnosable mental illness within the past year, compared to 15.6 percent of men.[1] Several studies show that women are about twice as likely as men to be diagnosed with major depression, twice as likely to develop post-traumatic stress disorder after a traumatic event, and more likely to have higher rates of depressive symptoms in bipolar disorder.[2] A recent study also concluded that women are also twice as likely as men to be diagnosed with an anxiety disorder.[3] Rates of schizophrenia and bipolar disorder, however, appear to be similar among men and women worldwide.[4]

Q A

ARE THERE ANY TYPES OF DEPRESSION OR OTHER MENTAL ILLNESSES THAT ARE UNIQUE TO WOMEN?

Yes. There are a few types of depression that are only diagnosed in women, which are related to the female reproductive cycle and birthing. These can include the severe form of premenstrual syndrome called premenstrual dysphoric disorder (PMDD); perinatal and postpartum depression, which can occur during or after pregnancy; and perimenopausal depression, experienced during the transition into menopause.[5]

ARE THERE DIFFERENCES BETWEEN MEN AND WOMEN AT RISK FOR SUICIDE?

Yes. Women are more likely than men to attempt suicide, but they die less often by suicide than men.[6] Foundation Young Investigator Alexander Bogdan Niculescu, M.D., Ph.D., at *Indiana University School of Medicine*, who has studied molecular markers related to the risk of suicide in people with mental illnesses, also has found that men and women have a different set of risk markers in their blood.[7]

Q
A

WHY DO WOMEN AND MEN DIFFER IN THEIR PREVALENCE OF MENTAL ILLNESSES LIKE DEPRESSION?

Researchers suggest that there could be a number of reasons behind this difference. Higher lifetime levels of trauma and stress among women, hormonal differences between men and women, and higher levels of reporting and diagnosis of mental illnesses among women may all contribute to differences in prevalence.[8] Foundation grant-supported scientists have also uncovered some differences between women and men in how the brain develops during puberty[9] and in how different parts of the brain are interconnected[10] that could affect differences in mental health.

Q
A

DO ANTIDEPRESSANTS AFFECT WOMEN AND MEN DIFFERENTLY?

Yes. Several studies have shown that women and men differ in how their brains process certain types of antidepressants, and how well their symptoms respond to the medications. In general, women are more likely to respond to selective serotonin reuptake inhibitors (SSRIs) than to tricyclic antidepressants.[11]

1. SAMHSA, "Results from the 2009 National Survey on Drug Use and Health (NSDUH): Mental Health Findings," http://store.samhsa.gov/product/SMA10-4609.
2. Harvard Mental Health Letter, "Women and depression," http://www.health.harvard.edu/womens-health/women-and-depression.
3. O. Remes et al. "A systematic review of reviews on the prevalence of anxiety disorders in adult populations," Brain & Behavior, Volume 6, Pages 1-33, July 2016.
4. World Health Organization, Department of Mental Health and Substance Dependence, "Gender Disparities in Mental Health," http://www.who.int/mental_health/media/en/242.pdf?ua=1.
5. National Institute of Mental Health, "Depression in Women: 5 Things You Should Know," https://www.nimh.nih.gov/health/publications/depression-in-women/index.shtml.
6. American Foundation for Suicide Prevention, "Suicide Statistics," https://afsp.org/about-suicide/suicide-statistics.
7. DF Levey et al. "Towards understanding and predicting suicidality in women: biomarkers and clinical risk assessment," Molecular Psychiatry, Volume 21, Pages 768-785, June 2016.
8. JH Young, "Women and Mental Illness," Psychology Today, https://www.psychologytoday.com/blog/when-your-adult-child-breaks-your-heart/201504/women-and-mental-illness.
9. SD Satterthwaite et al., "Sex Differences in the Effect of Puberty on Hippocampal Morphology," Journal of the American Academy of Child & Adolescent Psychiatry, Volume 53, Pages 341-350, March 2014.
10. M Ingalhalikar et al., "Sex differences in the structural connectome of the human brain," Proceedings of the National Academy of Sciences, Volume 111, Pages 823-828, 2013.
11. WK Marsh and KM Deligiannidis, "Sex-related differences in antidepressant response: When to adjust treatment," Current Psychiatry, Volume 9. Pages 25-30, May 2010.

AMYGDALA: an almond-shaped structure located deep within the brain's medial temporal lobe (one in each hemisphere of the brain). The amygdala is part of the limbic system and is known to play a key role in the processing of emotions. Mental illnesses, including anxiety, autism, depression, post-traumatic stress disorder, and phobias are suspected of being linked to abnormal functioning of the amygdala.

DEEP TRANSCRANIAL MAGNETIC STIMULATION (DTMS): a magnetic method used to stimulate small regions of the brain, increasing or decreasing the excitability of the neurons there. The procedure uses a small magnetic field generator or coil that produces small electric currents under the coil. It is being tested in a variety of mental disorders, but most notably in treatment-resistant depression.

ELECTROENCEPHALOGRAPHY (EEG): a method for recording electrical activity in the brain.

FMRI: a variant of magnetic resonance imaging, which enables researchers to make key measurements of activity and function in the resting brain.

NEUROLEPTIC MALIGNANT SYNDROME: a rare, but life-threatening disorder caused by an adverse reaction to anti-psychotic medications used to treat conditions such as schizophrenia. It is characterized by fever, muscular rigidity, delirium and dysfunction of the autonomic nervous system.

PRODROME/PRODROMAL PERIOD: Refers to the early stage of a brain and behavior disorder, a period just before an illness fully manifests. Researchers are particularly interested in studying the prodromal period of psychosis with the hopes of developing early intervention techniques that can prevent the damage of a psychotic break and greatly improve the chances for recovery.

What Will Your Legacy Be?

Support Cutting Edge Mental Health Research and Advancements

Name the **Brain & Behavior Research Foundation as a beneficiary** of your:

- Will or Trust
- IRA or other retirement plan
- Life Insurance policy
- Charitable Gift Annuity, Remainder Trust, or Lead Trust

Bequests and other planned gifts have a profound and lasting impact on the field of research. Your support enables scientists to pursue new, pioneering ideas to answer important questions or help identify new potentially game-changing targets for treatment in brain and behavior research.

100% of donor contributions for research are invested in our grants leading to advances and breakthroughs in brain and behavior research. This is made possible by the generous support of two family foundations which cover all of the Foundation's operating expenses.

For more information **bbrfoundation.org/plannedgiving** | plannedgiving@bbrfoundation.org | Call **800-829-8289**

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

90 Park Avenue, 16th floor
New York, NY 10016—1301
646.681.4888 | 800.829.8289
bbrfoundation.org

Overcoming Mental Illness with Science

- For the past *30 years* the Brain & Behavior Research Foundation has fostered new research pathways and transformative breakthroughs.
- Our *60,000 donors* have joined together in the great challenge of modern medical science–overcoming mental illness.
- Our *168 member volunteer Scientific Council* has selected the best research strategies and scientists to pioneer in ending the suffering from brain and behavior disorders.
- Our *4,000 research grantees* have dedicated their outstanding talents and training to develop improved treatments and methods of prevention for mental illness.

Join us in finding cures for mental illness. **Make a gift today.**
Learn more at **bbrfoundation.org**