A Precision-Health Approach to Bipolar Disorder

Dr. Judith Ford on Leading BBRF's Scientific Council

Brain&Behavior

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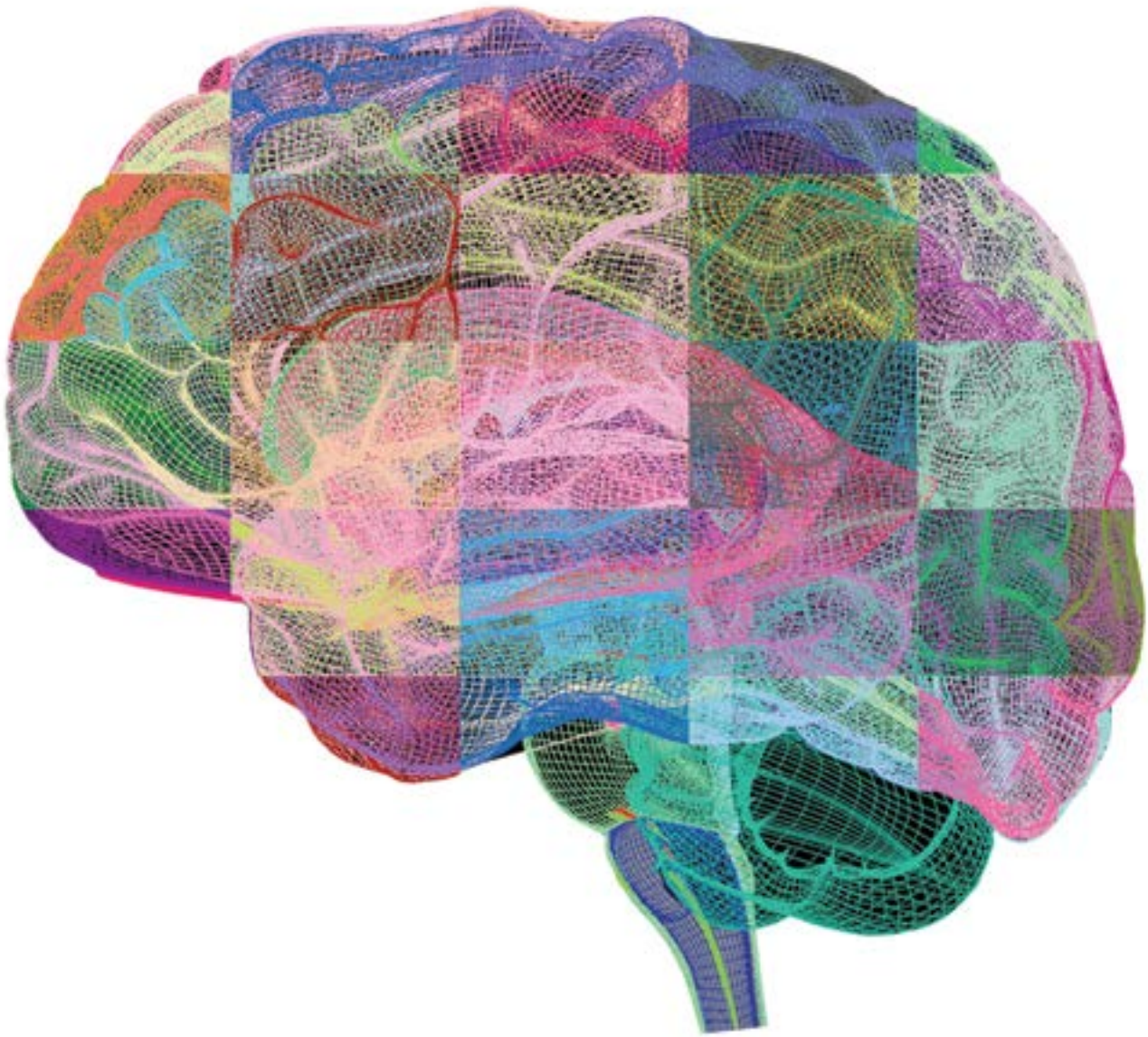

Establishing Causal Connections Between Stress, Inflammation, and Depression

PRESIDENT'S LETTER

Welcome to our Winter issue of *Brain & Behavior Magazine*.

In Spring 2024, following the passing of Dr. Herbert Pardes, the founding president of BBRF's Scientific Council, Dr. Judith Ford was chosen by the BBRF Board of Directors to lead the Council. Our **BBRF LEADERSHIP** story introduces you to Dr. Ford, a distinguished researcher who has made important contributions to our understanding of auditory hallucinations, a key symptom of psychotic disorders including schizophrenia. For years, Dr. Ford has co-led, with Dr. Suzanne Haber, the committee of the Scientific Council that administers BBRF's Young Investigator grant program. Stepping into Dr. Pardes' shoes is a daunting prospect, she acknowledges in our article. But it's a responsibility for which Dr. Ford is eminently prepared and eager to take on.

In our **PATHWAYS TO THE FUTURE** story, we describe important new research that offers evidence of causal connections between stress, activation of the body's immune system, and psychiatric disorders. Two-time BBRF grantee Dr. Scott Russo and colleagues have demonstrated how stress can cause pro-inflammatory immune cells that are manufactured outside the brain—in the body's "periphery"—to invade the brain and cause changes that (in mice) give rise to behaviors similar to some of those seen in human depression, notably social withdrawal.

In **A RESEARCHER'S PERSPECTIVE,** Dr. Sarah Sperry presents results of the research that her 2022 BBRF Young Investigator grant helped to support. She and colleagues have assembled data on over 700 individuals diagnosed with bipolar disorder. Evidence based on mood records from these patients encourages us to scrutinize the assumption that periods between low and high mood in bipolar disorder are ones of "normal" mood. Dr. Sperry's finding of considerable "mood instability" between major episodes of depression and mania/hypomania could lead to future efforts to treat such mood fluctuations in a subset of patients, and in so doing potentially improve their quality of life and ability to function in society.

This issue also features summaries of BBRF's 2024 Fall **EVENTS**—The International Mental Health Symposium, and our International Awards Dinner featuring winners of our Outstanding Achievement Prizes—the BBRF Leiber, Maltz, Colvin, Ruane, and Goldman-Rakic prizes. In **AWARDS**, we provide details of the 2024 winners of the Pardes Humanitarian Prize in Mental Health.

We also report recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and on important scientific advances moving the field forward in **RECENT RESEARCH DISCOVERIES**.

I am continually inspired by the extent of the discoveries being made by the scientists we fund together and appreciate your ongoing support to help find improved treatments, cures, and methods of prevention for people living with psychiatric illness.

Sincerely,

Jeffrey Borenstein, M.D.

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

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Lauren Duran

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Lauren Duran
Peter Tarr, Ph.D.

Designer
Gene Smith

‘A Responsibility That I Cherish’

Dr. Judith Ford on Leading BBRF’s Scientific Council

Judith M. Ford, Ph.D.

Co-Director, Brain Imaging and EEG Lab
Professor, Department of Psychiatry
University of California, San Francisco
Senior Research Career Awardee
San Francisco VA Health Care

President, BBRF Scientific Council
2003 BBRF Independent Investigator

IN BRIEF

In Spring 2024, following the passing of Dr. Herbert Pardes, Dr. Judith Ford was chosen by BBRF’s Board to lead BBRF’s Scientific Council. Stepping into Dr. Pardes’ shoes is a daunting prospect, Dr. Ford acknowledges, but a responsibility for which she is eminently prepared and eager to carry out. We discuss her career and her views on the Council’s—and BBRF’s—mission.

‘One day I got a call. It was Dr. Herbert Pardes, and he was calling to tell me that I had been elected to BBRF’s Scientific Council. It was a real shock! First of all, I’m not even sure I knew that I had been nominated. But more than that, I couldn’t believe that *he* called to deliver the news!”

This is Dr. Judith Ford remembering a day about 16 years ago, when seemingly out of the blue, one of the most eminent figures in American psychiatry took the time, personally, to let her know that she was now part of the body that he and a handful of other eminent doctors had established, decades earlier.

It was a message that conveyed congratulation, but also a sense of the stakes. Being appointed to the Council was not just an honorary gesture. It was an elevation to an active group with a critical mission. Accepting the position involved important work that one performed voluntarily, and for the most part, invisibly.

Dr. Pardes and a few colleagues had founded the Scientific Council in 1987 to guide the awarding of research grants to deserving investigators—an event coordinated with the establishment that same year of the non-profit foundation issuing the grants, the National Alliance for Research on Schizophrenia and Depression, or NARSAD. (In 2011, the name was changed to the Brain & Behavior Research Foundation.)

Anyone who knew Dr. Pardes well knew that the Council, and BBRF, were one of the most important commitments of his long and highly influential career in psychiatry and medicine, which included directorship of the National Institute of Mental Health under two U.S. presidents and serving for a dozen years as CEO of New York’s largest hospital, NewYork-Presbyterian.

The late Herbert Pardes, M.D., Founding President, BBRF Scientific Council

Beginning from a tiny core, BBRF's Scientific Council, which provides scientific guidance to the Foundation by independently selecting annual grant and prize recipients, now comprises over 190 members, drawn from all fields and subfields of psychiatry, neuroscience, and related disciplines.

Dr. Pardes thought of the Scientific Council as his baby. "I was touched that he made this call personally—he did not relegate it to his staff or email," Dr. Ford remembers. "I soon learned that he approached the Scientific Council as family, a family that he started and maintained. I loved the summer meetings of the Council when I had a chance to see how 'the best of the best' runs meetings—Herb was efficient, effective, and fair."

"Some years ago," Dr. Ford continues, "I was asked, along with Dr. Suzanne Haber, to lead the committee of the Scientific Council that directs the annual selection of the BBRF Young Investigator grantees. I was honored and excited to play a more vital role in BBRF's mission. And it was then that I got the opportunity to work more closely with Herb."

In late April 2024, Dr. Pardes passed away at the age of 89. Later that spring, Dr. Ford was the choice of the BBRF Board to carry forward the legacy.

"In recent years, I had stepped in for Herb when he needed a bit of help. Of course, it is daunting now to step into his shoes, but I am a BBRF zealot and want to do whatever I can to keep Herb's vision alive and move the Scientific Council forward in its mission."

BBRF's Scientifc Council with NARSAD President Connie Lieber (3rd from right, bottom row) in early days. The Council now has over 190 members.

As a young researcher, Dr. Ford was captivated by the possibilities of EEG (electroencephalography), which registers electrical activity in the brain. Here, a subject is fitted with a cap that places electrodes over the scalp to record EEG signals.

RESEARCH ON HALLUCINATIONS

Judith Ford is the daughter of a scientist who worked in Los Alamos, New Mexico, tracking radioactive fall-out from above- and below-ground tests of nuclear bombs. When the Second World War ended, her father got his Ph.D. in chemistry and in 1949 started working at the Los Alamos Scientific Laboratory, when nuclear testing was in its ascendency. Judith Ford spent her youth in Los Alamos, "a totally weird place to grow up," she concedes, because of its remarkable (and intentional) isolation. She got her B.A. in psychology at Stanford, after becoming interested in "attitudinal change," and went on to earn a Ph.D. in neuroscience at Stanford's Medical School. In her doctoral work, she began to focus on human attention—a subject that is related in an interesting way to the research that she is now known for, which involves problems of perception in people with schizophrenia and other psychotic disorders.

"The real pivot" in her early academic career came when she took a year off from grad school and worked in a laboratory in which EEG (electroencephalography) was used to probe the workings of the brain. In EEG, electrodes are placed on the scalp and recordings are made of electrical activity generated by the workings of the collectivity of neurons, billions of them. The waves are measured in several key wavelengths (among them, alpha, beta, theta, and delta) which have been found to correspond with particular mental operations. Young Dr. Ford found EEG to be a kind of wonder, "a window onto the brain."

She has used EEG and other tools to probe the mystery of auditory hallucinations in psychosis. This is a difficult subject to study, in part because of the powerful stigma associated with the phenomenon of hallucinations. Put simply: patients who experience hallucinations hear "voices" that do not correspond with objective reality. But how does one tell (or convince) another person that what they are experiencing is "not real"? If one cannot trust one's own senses, what can one trust? This goes to the core of personhood.

It may be tempting to say: the voices that patients hear "are not real," but for those who hear these sounds, they are absolutely real, and often, upsetting and terrifying, and sometimes, in Dr. Ford's words, "commanding"—seemingly urging an individual to take particular actions. For this reason, Dr. Ford has found, "many patients are guarded and are not inclined to tell you about what they're experiencing. You need to give a person time to trust you before they will tell you about their experiences."

"Talking to patients about their lives and trying to understand their symptoms is one of the most interesting things I do. You can learn a lot about what might be going on in the brain by listening to how patients describe these experiences."

Among her many published papers is one that notes that "the

phenomenology of inner experience is hard to describe." By this, Dr. Ford means that it is hard for anyone, and not only people with schizophrenia, to describe what is going on inside their thought process—to the extent we are even aware that we are "thinking." So much of what we do, while the result of brain operations, is not something we are consciously aware of.

When a person says, "I hear a voice saying such and such" when no one else can hear it, we ask a basic question: how do people process sensations and know whether or not they themselves were the source of that sensation? Another question might be: is our perception accurate? In other words, does it correspond with "objective reality?"

To sum up a great deal of thinking and careful research performed by Dr. Ford and colleagues over many years, she is working to flesh out the hypothesis that auditory hallucinations result from misperceptions of sensations—sensations and perceptions that originate within the self, but are attributed to external sources, outside the self.

Dr. Ford's hypothesis centers on mechanisms in the brain that are responsible for predicting how to act or what to think on the basis of sensations and perceptions. It's a fundamental operation of the brain that is bound up with basic survival at the most elemental level. If an individual (human or animal) is out in the environment and trying to process sensations, it is absolutely essential to be able to distinguish thoughts or sensory perceptions that are generated within (or by) the self from inputs that are coming "from the outside." In evolutionary terms, to know that a sound you made is yours (as opposed to coming from outside) may be the difference between safety and danger in an encounter with a predator.

Dr. Ford and others have closely studied a phenomenon called "corollary discharge." It's part of the process that "enables an individual to determine if what it is experiencing is coming from 'self' or not."

The corollary discharge research helps explain how we are able to accurately predict, and to have a realistic picture of the external environment, as a guide for action. Importantly: when there is a dysfunction in this mechanism, the research posits, and there is a problem making such predictions, someone may sense a thought as coming from the outside, whereas in fact it is really coming from inside. This may be what is happening in at least some cases when someone "hears voices" when no one is talking. The "voice" may not be "out there" in the environment; instead, it may be a misperception of one's own thoughts that are present in one's own mind.

BBRF's Scientific Council now comprises over 190 members, drawn from all fields and subfields of psychiatry, neuroscience, and related disciplines.

THE CARDINAL PRINCIPLES

Today, Dr. Ford is Co-Director of the Brain Imaging and EEG Lab and a professor in the Department of Psychiatry at the University of California, San Francisco and a Senior Research Career Awardee with the San Francisco VA. She has authored or co-authored over 220 scientific papers, but she is also the mother of two adult daughters and one teen-aged son. Her academic path from Stanford to Yale, and from Yale to UCSF, was energized by a deep commitment to research, but it was unconventional.

One remarkable fact about her career is that, despite her long list of publications and her success in obtaining major, career-sustaining NIH grants and in leading NIH-sponsored clinical trials, she did not work full-time as a research scientist until her younger daughter had left home for college. During the girls' early years, "at a certain point, I started taking the desktop computer in my office home in the back of my station wagon and would plug it in when I got home. I'd put the girls to bed at 7:30… and start working." This was before laptops. She admits: "My friends were amazed that I could put the girls to bed so early!"

"Selecting grantees involves considering how the project will contribute to the field, add to knowledge…and not least, how this will serve our ultimate concern, which is improving the lives of patients. This was Herb Pardes' vision, and it's what we're dedicated to keep going."

Like every other member of BBRF's Scientific Council, Dr. Ford volunteers her time to the task. Over the last decade, she and Dr. Haber have had one of the more labor-intensive tasks to perform each year, organizing the Scientific Council members in reviewing as many as 1,000 annual applications for the BBRF Young Investigator grant. In recent years, 150 grantees have been selected annually.

In this work, Drs. Ford and Haber have put into practice several of the cardinal organizing principles put in place by Dr. Pardes and colleagues when the Council was founded. The first principle is merit. Members of the selection committees, she explains, set their sights on finding the best grantees possible, which in the BBRF universe means: funding the very best science, projects deemed to have the greatest potential to move the field forward. It means considering applicants from anywhere in the world. It means looking at who the applicants have studied with and how they are supported by their current institutions.

In back of these considerations is one principle that Dr. Pardes often stressed. In his words, typically succinct: "no politics." As Dr. Ford with equal brevity explains this vital point which has helped NARSAD, and later BBRF, earn the admiration and credibility it has within the scientific world: "There is no place for favoritism. There are no thumbs on the scale." Her co-administration of the Young Investigator grants has schooled her and Dr. Haber in "taking the precautions to prevent conflicts of interest."

"We are very careful with institutional conflicts," she says. "If you have an applicant from Yale, then Scientific Council members who are on the Yale faculty must step aside and are assigned to another set of applications. Even if they have never heard of the applicant." This rigor, combined with the attention to the scientific merit of the proposed projects, is what gives the Young Investigator grants the reputation they have had since the early days of NARSAD.

Another cardinal principle concerns the functional separation of the Scientific Council from BBRF's Board of Directors and the professional staff that administers the grants and raises money to fund them. Between the staff's fund-raising activities and the Council's selection of grantees there always must be, Dr. Pardes liked to say, "a wall as inviolable as that between Church and State." Neither BBRF staff nor the BBRF Board has any role in deciding who should or will receive BBRF grants.

When Council members are assessing grant applications, they weigh the merits of the science, while being attentive to identifying "out-of-the-box" ideas that are relatively high-risk but with outsized potential rewards. They are also sensitive to how the award will serve the investigator and her/his career. Over the decades the grants have helped thousands of recipients build their careers, especially in the early days when seed funding is needed to get initial results that can serve as the basis for much larger career-sustaining federally funded grants. "But also, the process is about how the results of the grantee's project will contribute to the field, to knowledge…and not least, how this will serve our ultimate concern, which is improving the lives of people living with brain and behavioral disorders," Dr. Ford says. "This is Herb's vision, and it's what we're dedicated to keep going."

Dr. Ford with BBRF President and CEO Dr. Jeffrey Borenstein.

CALLING NEW MEMBERS

"I think we've been pretty successful. One of my favorite things right now is to talk to people who didn't know I have taken on the position that Herb left when he passed away. I cannot tell you how many say, 'Oh, I had one of those [BBRF] grants. It totally changed the direction of my career.' At the annual Symposium this past October, one of the BBRF outstanding achievement prize winners—one of the most accomplished people in psychiatric research today—told me a that if he hadn't gotten the BBRF grant he received early on, he would not be doing the work he's doing today, 30 years later! And you hear that over and over again. I think it's fair to say we're having a lot of success."

Dr. Ford helps direct the annual search for new Scientific Council members, as the Council's membership changes as the science advances and new areas of expertise need to be represented in order to most effectively assess the latest group of grant applicants. "We look for people who have breadth, because we try to match up an applicant with reviewers who know something about their field. People with breadth are those who are editors-in-chief of the various scientific journals. They are people who have proven themselves in terms of productivity, funding, visibility, expertise. They lead departments of psychiatry and neuroscience and related fields in academic institutions. In short, they are the people who are leaders in our profession, across the whole range of sub-fields that come under psychiatry and neuroscience—leaders in the field."

Thinking back 16 years to her first call with Dr. Pardes and her invitation to the Council, Dr. Ford says: "Needless to say, I was thrilled. And his phoning me directly has set for me a kind of standard. Now I am the one who calls people who have been elected to the Council. It's not only an honor to do this; it's fun. I can't tell you how often I run into people who say, 'Why can't I be on the Council? Why doesn't somebody nominate me?' So, I am taking this new responsibility very seriously. It is one that I cherish." ❖

PETER TARR

Scott J. Russo, Ph.D.
Leon Levy Director, Brain and Body Research Center,
Department of Neuroscience,
Icahn School of Medicine at Mount Sinai

BBRF Scientific Council Member
2008, 2006 BBRF Young Investigator

Research on Brain-Body Relationships Reveals How Stress-Related Immune Activation May Alter the Brain and Impair Behavior

IN BRIEF
Dr. Scott Russo and colleagues have demonstrated how stress can cause pro-inflammatory immune cells that are manufactured outside the brain—in the body's "periphery"—to invade the brain and cause changes that appear to have an adverse impact on behavior. Establishing causal linkages between brain and bodily systems holds promise for developing completely novel therapies for many illnesses, including depression and anxiety.

In the fall of 2021, BBRF Scientific Council member **Scott J. Russo, Ph.D.**, and colleagues at the Icahn School of Medicine at Mount Sinai launched the Brain and Body Research Center at that institution. It is composed of researchers and clinicians from diverse specialties, from neuroscience and neurology to cardiology, gastroenterology, dermatology, and immunology, who, says Dr. Russo, "are pioneering a holistic approach to revealing the intricate connections between the brain and body that drive health and disease."

Central in this effort, which Dr. Russo directs, is to "decode the brain's conversations" with other organ systems, including the heart, gut, and skin. "We are trying to understand how the brain and peripheral organ systems interact," he explains, "and, importantly, to understand why there are so many co-morbidities between mental illnesses, neurological conditions, and systemic organ diseases."

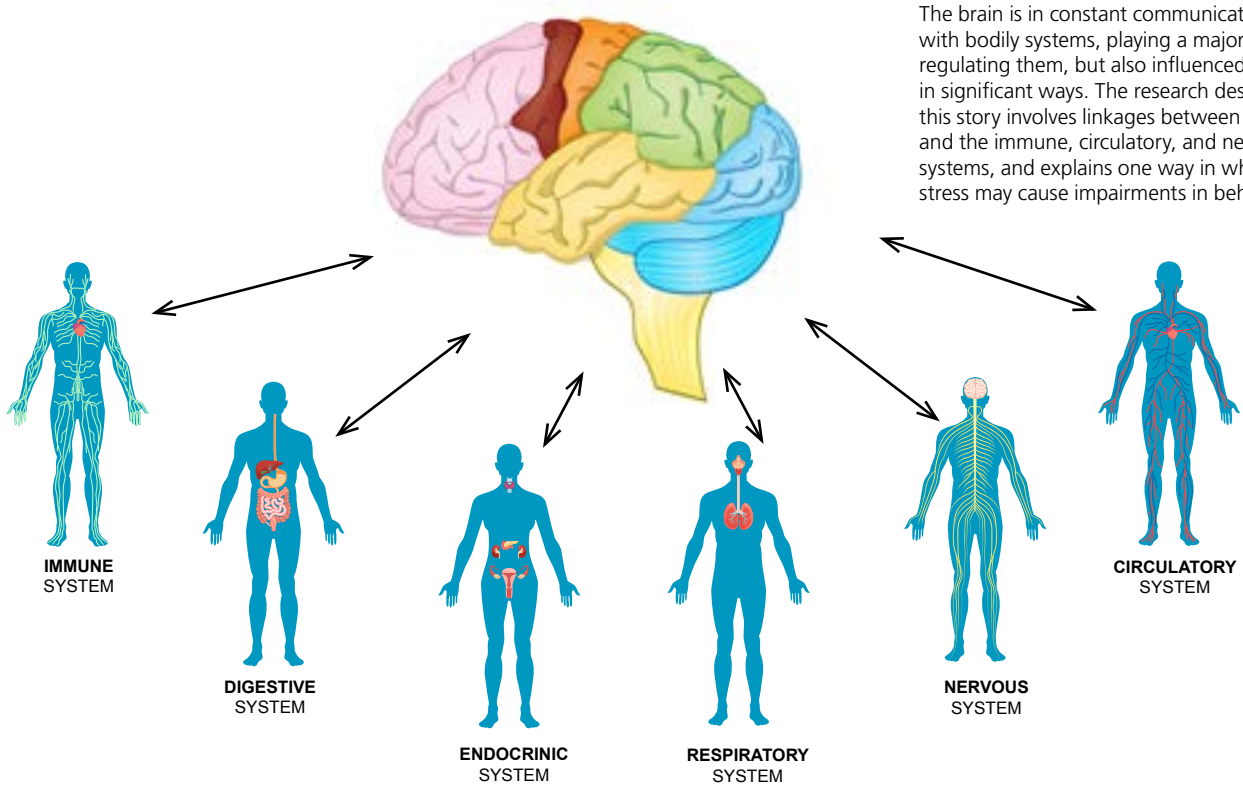
This past year, Dr. Russo, who received Young Investigator grants from BBRF in 2008 and 2006, joined with colleagues including **Flurin Cathomas, M.D.**, a 2020 BBRF Young Investigator; **Eric J. Nestler, M.D. Ph.D.**, BBRF Scientific Council member, prize-winner and past grantee; and six other BBRF grantees, to report in the journal *Nature* on one specific

way in which stress and activation of the immune system in the body may contribute to changes in social behavior—one of the symptoms of depression.

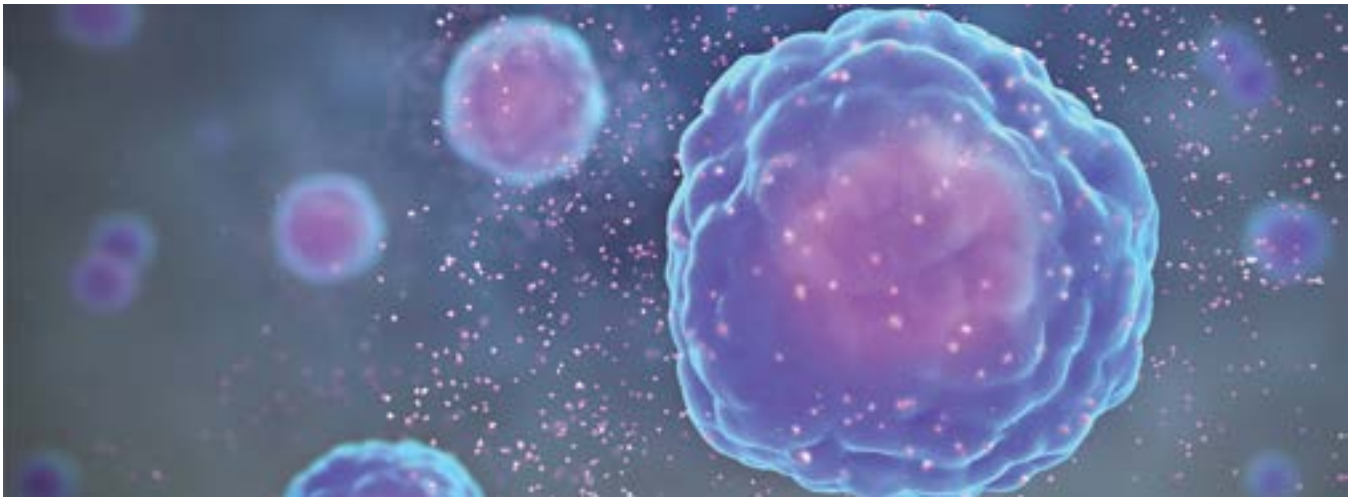
As will be explained later in this story, they demonstrated how stress can cause pro-inflammatory immune cells that are manufactured outside the brain—in the body's "periphery"—to invade the brain and cause changes that appear to have an adverse impact on behavior.

Tracing potentially causal relationships like this is at the heart of why Dr. Russo and colleagues have formed their new research center. It is virtually a matter of common sense, today, to assume that the brain and body are in various ways "connected." The critical questions have to do with explaining *how* they are connected, via which biological mechanisms, and how disturbances in either brain or body—or both—can be understood together ("holistically"). To put this another way: how can highly specific chains of causation be established through research—chains that illuminate potential targets for therapies to treat both brain and bodily illnesses that would not be possible to conceive absent sophisticated understanding of mutual brain-body interactions?

"We've known for quite some time that brain-body connections are *there*," Dr. Russo says, "and we hypothesized about what they were doing, but in the past we never really had the proper tools to test causality." But, he adds, "we do have the tools now." He cites optogenetics (a technology co-developed by BBRF Scientific Council member and past grantee **Karl Deisseroth, M.D., Ph.D.**, which enables researchers to experimentally control neuronal cell firing in animals with beams of colored laser light); imaging tools that enable researchers to map and observe the functioning of neural circuits throughout the brain and body; and tools of immunology, which are enabling them to see how immune cells and nerve cells interact at brain-body interfaces.



The brain is in constant communication with bodily systems, playing a major role in regulating them, but also influenced by them in significant ways. The research described in this story involves linkages between the brain and the immune, circulatory, and nervous systems, and explains one way in which stress may cause impairments in behavior.



When the immune system is activated in the body's periphery, white blood cells (among others) can send tiny proteins called cytokines into the bloodstream, stimulating the immune response.

STRESS, INFLAMMATION, DEPRESSION

For years there has been much discussion about the relationship of stress to major depression, and the relation of both to inflammation. This has led to some obvious questions: Is it possible that someone with major depression goes on to develop bodily inflammation—thus changing risk for other bodily diseases? What about the reverse: can inflammation in the body somehow cause changes in the brain that give rise to depression? In the same vein: If one is under acute or chronic stress, can that cause depression or raise risk for it? What mechanisms are involved?

As Dr. Russo points out, before proper investigative tools were developed, it had been assumed by neuroscientists and physicians who treat organs of the body other than the brain that having a serious non-brain illness, such as severe heart disease, can "make" a person depressed simply by changing the manner in which one goes about daily life. "Your life is negatively impacted by having heart disease, and it made sense to assume you get depressed because you have to deal with this chronic illness that makes life difficult," Dr. Russo says.

He and others began to think more deeply about this some years ago when a researcher injected an immune system molecule (which had potentially therapeutic pro-inflammatory effects) into patients with hepatitis C. About a third of them soon developed diagnosable depression. To Dr. Russo, this data was suggesting the possibility of causality—that an inflammatory molecule (normally generated by the immune system but in this experiment introduced artificially), when delivered throughout the system via the bloodstream, could help cause behavioral changes such as those seen in depression.

Many were unconvinced. It wasn't clear that the immune system molecule introduced into these patients was the direct cause of the depression that some reported. Perhaps more powerful was an objection based on biology. We have a protective layer in the brain called the blood-brain barrier that shields us from toxins, viruses, as well as the pro-inflammatory immune molecules that circulate in the blood. An inflammatory immune molecule introduced into the bloodstream, it was once assumed, should not be able to penetrate the blood-brain barrier. (The brain has its own defense system composed of cell types only seen in the brain—e.g., microglia and astrocytes.)

But what if this protective barrier was modified by stress or by other factors? "That's where my lab came into the picture," Dr. Russo explains. He and colleagues made good use of animal models—rodents (with brains very similar to the human brain due to commonalities in evolution) that can be the subjects of experiments in the lab in which, for example, inflammatory molecules are introduced during stress, while the brain is closely monitored.

"Our brain clearly senses stress," Dr. Russo notes, "and work that Flurin [Cathomas] in our lab was involved in, in collaboration with the lab of Dr. Fil Swirski, Director of the Cardiovascular Research Institute at Mount Sinai, showed that the brain areas that sense stress also send neuronal projections out to the periphery of the body. For example, to the bone marrow, where leukocytes (white blood cells) and inflammatory molecules are manufactured."

Dr. Swirski and others showed that in the presence of stress, activation of this pathway from the brain via the nervous system to the bone marrow causes

stem cells in the marrow to be activated and to generate a class of cells called inflammatory monocytes, which then get released into the bloodstream.

It is important before we trace what happens next, to understand that the operation of the body's innate immune system is being described here. Under conditions of stress, but also, a wide range of threats from bodily invaders like viruses, this first-line defense of the immune system is triggered. It happens many times every day of our lives, and helps keep most of us healthy most of the time. A challenge sets the immune system into action, and it responds by sending immune cells into the blood and thus to every point in the body's "periphery." Certain activated immune cells cause inflammation by design; that helps explain why they are able to kill invaders and other threats. It's why your finger gets hot and swells up when a bad cut gets infected. But what if such molecules were active in the brain?

PENETRATING THE BLOOD-BRAIN BARRIER

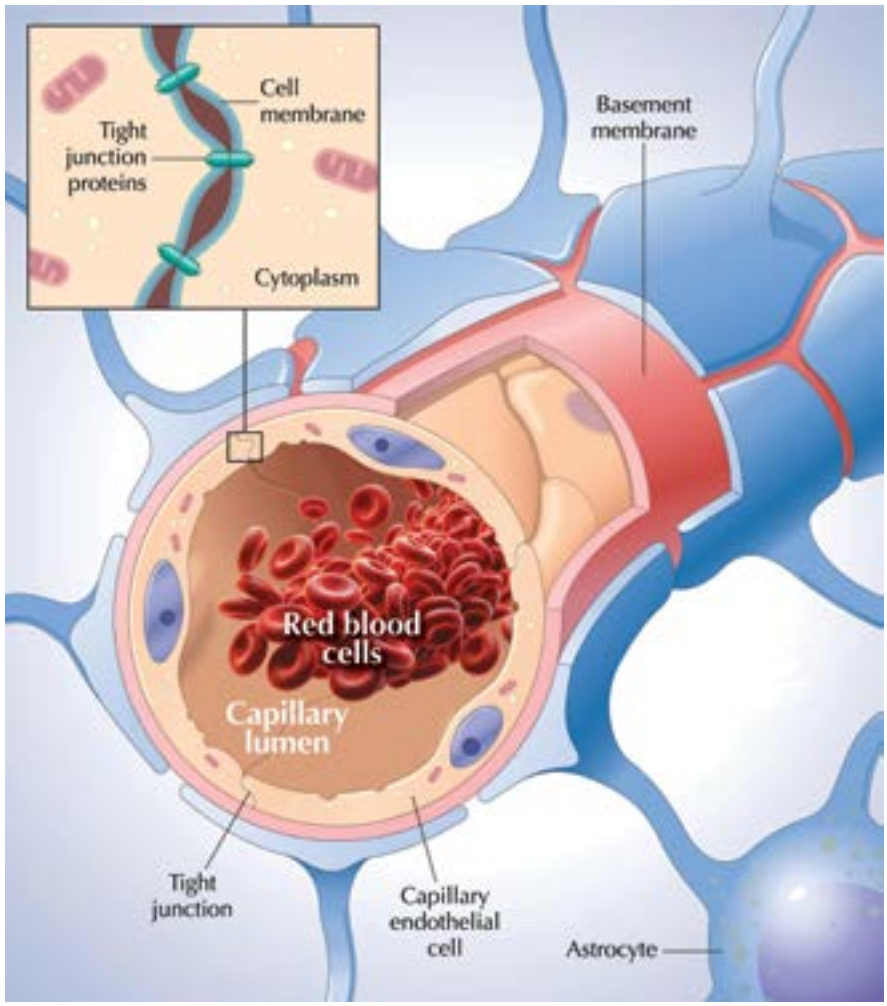
Inflammation has its place in health. But not only in health. In people experiencing chronic stress, past research has shown that the innate immune system is activated, resulting in the mobilization of immune cells including white blood cells in peripheral organs and blood, as well as the production of tiny proteins called cytokines, which, like pathfinders, are sent out into the body and can trigger inflammation by attracting immune cells to the site of a problem.

One intriguing discovery in psychiatry research has been that a subset of people with stress-related psychiatric disorders, including major depression, display a state of chronic low-grade inflammation. Two phenomena associated with such inflammation are an increase in the affected individual's pro-inflammatory cytokines in circulation throughout the body, as well as an increase in white blood cell numbers.

Some people appear to be at greater risk for inflammatory damage than others, due to genetics or to life experiences. A healthy child who becomes the target of abuse or is exposed to violence or other trauma may develop an overactive or over-zealous immune system. Might having an overactive immune system (for whatever reason) be a risk factor for illness, including mental illness?

In experiments in recent years by Drs. Russo, Cathomas and others in mice, evidence has been generated suggesting how **stress can induce changes to the blood-brain barrier**. When modified by stress, the barrier in mice leaks a bit, allowing the entry of circulating proteins into the brain that normally cannot pass through. One region in the brain particularly affected by such invasion following stress, in mice, is the nucleus accumbens (NAc), which is central in the processing of rewards and also in the response to aversive stimuli, and implicated in depression.

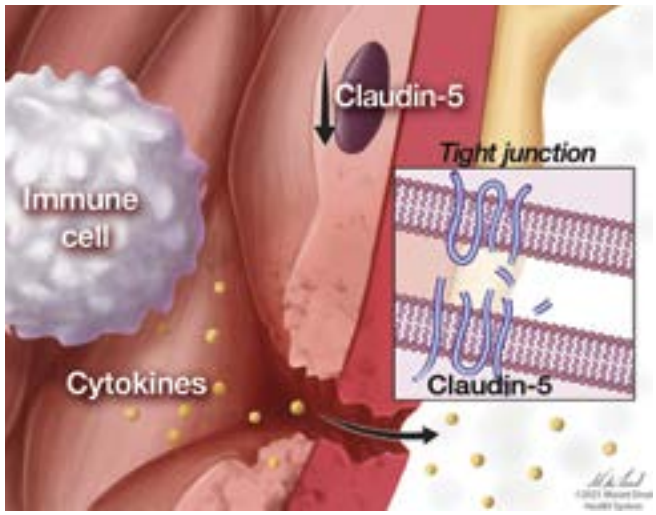
Why the NAc? What is distinctive about it that makes it vulnerable to stress-induced local disruption of the blood-brain barrier? "The short answer



Looking down the "tube" of a capillary ("lumen") in the brain in this cutaway view, we see elements of the blood-brain barrier, which protects the brain from toxins, viruses, and other potentially harmful elements circulating in the bloodstream. Endothelial cells make up the inside of the capillary wall that separates brain tissue from the bloodstream.Tight junction proteins form a complex at cell junctions that regulate what gets into the brain and what is kept out. Leaks at these zipper-like junctions may occur during stress (see illustration, next page).

is we don't know," says Dr. Cathomas, "but we do know that when you look at endothelial cells—those are the cells that line the blood-facing side of the barrier—there is a huge heterogeneity." The diversity of subtypes of cells that make up the barrier contributes to the emerging fact that in different organs, as well as in different regions in the brain, the cell types that make up the barrier often differ from one to the next and likely have different properties.

It's a mistake, say Drs. Cathomas and Russo, to think of the "barrier" as an impervious "Great Wall." The cells making up the barrier vary from region to region, each with potentially distinct relationships with cells circulating in the blood including immune cells. Thus, under certain conditions of stress, the barrier may behave differently in different bodily areas. The point, says Dr. Russo, is that the blood-brain barrier "is definitely not like a Great Wall. It's very plastic. Its shape and function undergo changes all the time." If you are acutely stressed, he suggests, the barrier might open up, transiently. It is possible that the particular configuration of the barrier in NAc renders it particularly plastic when we experience stress.



Research by Drs. Russo and Cathomas indicates how the blood-brain barrier may leak under conditions of stress. In this depiction, one of the barrier's "tight junctions" is breached (due to changes in a protein called claudin-5, a potential therapuetic target), allowing pro-inflammatory cytokines released by a circulating immune cell to enter brain tissue.

HOW STRESS CHANGES BIOLOGY—AND BEHAVIOR

In the new experiments Drs. Russo, Cathomas and team reported recently in *Nature*, they demonstrate a distinct way in which stress promotes interactions of immune cells in the periphery with the brain—an indirect way that they have succeeded in linking with adverse changes in social behavior.

The research uncovered the role in this process of enzymes called MMPs (matrix metalloproteinases) and, in particular, MMP8. This enzyme, like others in the MMP family, has roles in shaping and regulating the space between neurons, called extracellular space (ECS), as well as the extracellular matrix (ECM), which is a dense web-like material that individual neurons extend out into ECS.

"The extracellular matrix is a supporting structure and is really key in many physiological processes," Dr. Cathomas says. "It's also a really important structure for the blood-brain barrier," a key factor in giving structure to this membrane that separates the bloodstream from brain tissue. "It has so many functions and therefore it has to be plastic and is changing all the time."

Experiments by the team in mice and humans leads them to conclude that MMP8, which is released during chronic social stress by immune cells circulating in the body's periphery, can invade the brain perhaps due to damage to the blood-brain barrier, and alter the shape of ECS and ECM in the brain's NAc and possibly other brain areas.

In mouse experiments, such changes were causally linked by the team with changes in behavior—changes (social avoidance, for example) like to those observed when a person experiences chronic social stress.

One potential implication is that it may be possible to develop treatments that target not the brain directly (which is always difficult, in part because of the blood-brain barrier), but rather molecules such as MMP8 in the peripheral immune system that circulate in the bloodstream—a totally novel approach to potentially treat psychiatric illnesses including depression.

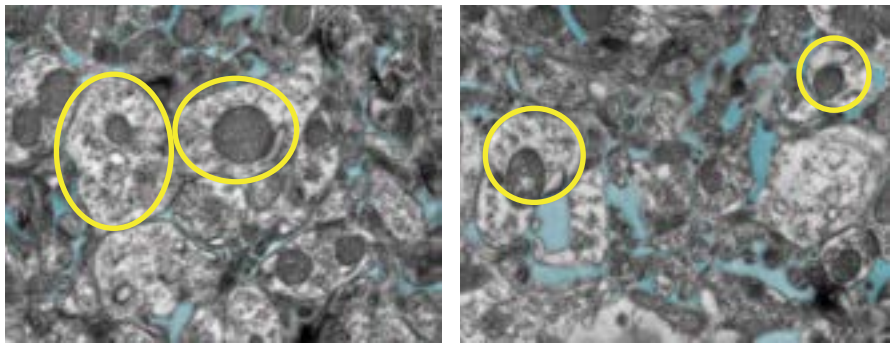
The irony, notes Dr. Ruusso, is that remodeling of the extracellular matrix—possibly the culprit in this story of how chronic stress leads to behavioral problems—is not the full picture. "There is another situation in which you definitely *want* remodeling of the ECS, for example in the hippocampus. You're trying to form a new memory, and to do so you need to strengthen synapses or add new synapses to change the properties of the cells that are holding those memories. In order for that to happen, the ECS [i.e., the space between neurons] has to open up. I think of this as our brain's way of opening up windows of plasticity throughout our lives. Unfortunately, in the NAc, when we are under stress this plasticity might just be a bad thing."

The complex behavior of MMP8 has important implications. Dr. Russo notes that pharmaceutical companies experimented some time back with drugs to target various members of the MMP enzyme family, but since the different members are so structurally similar, the drugs were not specific enough to warrant development. One MMP-targeting drug is being tested in heart

disease, but Dr. Russo thinks the better opportunity is to develop extremely specific agents like monoclonal antibodies, which are designed only to "hit" targets with a specific molecular structure.

Other approaches are also possible. But another reflection on the MMP8 discovery involves the realization that it is but one of many factors that influences the shape of the space between cells as well as the shape and permeability of the blood-brain barrier. Future research will seek to identify more factors that have these roles, any of which could potentially be future targets. Drs. Russo and Cathomas have co-authored studies on proteins such as claudins and adhesion molecules which are integral in establishing and influencing the behavior of the blood-brain barrier and hence may have value as therapeutic targets.

Still another issue that arises from the team's *Nature* paper concerns the impact that stress-generated immune activity, translated to the brain, has upon behavior. In the team's mouse experiments, the impact was seen specifically in social behaviors. As Dr. Cathomas points out, mice are extremely social creatures, and their avoidance of social contact after stress-related immune activation is therefore very important.



MMP8, released during chronic social stress by immune cells circulating in the body's periphery, can invade the brain and alter extracellular space (ECS), the space between neurons. LEFT: in the healthy brain, cells of the nucleus accumbens are close. RIGHT: in stress-susceptible mice, ECS opens up considerably. This has been associated with social withdrawal behavior in stressed mice.

Dr. Russo notes that data from humans suggests that "disturbances in systemic immunity and inflammation seem to be most associated with anhedonia." Anhedonia, or the avoidance of or inability to experience or seek out pleasure, is a classic symptom of depression, and is often expressed in terms of avoiding social relationships and human contact. "What Flurin's data suggests is that the mice in our experiments no longer found social targets rewarding, and that is why they were avoiding them."

But Dr. Russo thinks that research eventually will reveal immune-sensitive factors that influence behavior in non-social domains. He also is intrigued by thinking of the relationship between immune activation and behavior that may help us better understand some of the behavioral and mood effects of "long COIVD." Just as stress can cause cells in the periphery of the body to activate immune factors which in turn impact the brain, so too might the "cytokine surge" documented in COVID inflections. His lab is currently studying this.

Perhaps most of all, Dr. Russo is excited about what the recent work in his lab suggests about the co-morbidity of brain and bodily illnesses, a main focus of the Brain and Body Research Center that he directs. "Flurin's work has shown us that immune system honing signals not only reach the brain, but can also track to cardiovascular plaques"—buildups of fatty cells in the walls of the heart and vasculature that cause heart disease.

Studying brain-body biology may enable researchers to establish and comprehend linkages, for example, between cardiac symptoms, stress, immune activation, various individual risk factors, and, perhaps, outcomes like heart attacks.

"It's in this sense that we have begun to think of monocytes and other innate immune cells and their products as an anchor for comorbidities. You get stressed out, your bone marrow starts dumping immune cells into the circulation. They go to your brain and cause emotional disturbances. But also, it's conceivable that if you're at risk and you have a bad diet and you are overweight and have lots of plaque buildup, it's possible that inflammatory molecules go to the plaques and perhaps contribute to their rupture, causing a heart attack. This is how we are beginning to think about how brain and body systems interact." ❖ **PETER TARR**

2024 INTERNATIONAL MENTAL HEALTH RESEARCH SYMPOSIUM

Standing L to R: Dr. Carol Tamminga, Dr. Jeffrey Borenstein, Franca Ma-ih Sulem Yong, Dr. Cameron Carter, Dr. Deanna Barch, Dr. Nicole Karcher, Dr. Chistopher McDougle, Dr. Nolan Williams, and Geoffrey Simon. Photos by Chad David Kraus.

On Friday, October 25,2024 BBRF hosted its annual International Mental Health Symposium at the Kaufman Music Center in New York City, which was simultaneously live-streamed.

Later that same evening at its International Awards Dinner, BBRF presented the Outstanding Achievement Prizes in Mental Health to six scientists for their extraordinary work in advancing psychiatric research.

The BBRF Outstanding Achievement Prizes acknowledge and celebrate the power and importance of neuroscience and psychiatric research in transforming the lives of people living with mental illness. The recipients of this year's awards were recognized for their research achievements in schizophrenia, bipolar disorder, pediatric mood and anxiety disorders, and cognitive neuroscience. The Outstanding Achievement Prizewinners were selected by special committees of the Foundation's Scientific Council, a volunteer group of 195 mental health experts across disciplines in brain and behavior illnesses.

This year marked a celebration of the 25th anniversary of the Ruane Prize for Outstanding Achievement in Child & Adolescent Psychiatric Research. BBRF is thankful for the ongoing generous support of the Carmel Hill Fund, which has been funding this Prize since its inception.

Dr. Jeffrey Borenstein, BBRF's President & CEO, opened the Symposium with a welcome to all attendees, and noted, "We celebrate the Outstanding Achievement Prizewinners and acknowledge the importance of neuroscience and psychiatric research to transform the lives of people living with mental illness. These extraordinary scientists are advancing the development of new treatments, cures, and methods of prevention for mental illness. We applaud them, and we thank our philanthropic supporters whose generosity allows us to continue to support the most promising research in the field of neuropsychiatry."

Carol Tamminga, M.D., served as the Symposium moderator. The program featured presentations by the prize-winning scientists and the winner of the Pardes Humanitarian Prize in Mental Health, each speaking for about 20 minutes. In the pages that follow, we summarize the subjects covered in each Symposium talk.

Deanna Barch, Ph.D., started the scientific presentations by talking about *Identifying Risk For Developing Psychosis So We Can Promote Prevention*. Dr. Barch is Professor of Psychological & Brain Sciences, Psychiatry, and Radiology, the Vice Dean of Research, Arts & Sciences, and the Gregory B. Couch Professor of Psychiatry at Washington University, St. Louis. She is also a member of the BBRF Scientific Council, a 2013 BBRF Distinguished Investigator, a 2006 BBRF Independent Investigator, and a 2000 and a 1995 BBRF Young Investigator.

Dr. Barch's research, utilizing psychological, neuroimaging, and computational approaches across the lifespan, focuses on understanding normative patterns of cognitive function and brain connectivity, and the mechanisms that give rise to the challenges in behavior and cognition found in illnesses such as schizophrenia and depression.

In her presentation, Dr. Barch explained that one of the most important efforts in research on mental illness is to identify early predictors during development that might help us better understand causes. Ideally, we would be able to use such information to identify those children or adolescents who might benefit from early prevention or intervention.

Nicole Karcher, Ph.D., Assistant Professor of Psychiatry at Washington University School of Medicine, St. Louis, spoke about *Identifying Risk Factors For Early Psychosis Spectrum Symptoms.*

Dr. Karcher's research focuses on understanding the neural, genetic, cognitive, and environmental factors underlying the development and persistence of psychotic-like experiences in childhood and adolescence.

In her presentation Dr. Karcher focused on early psychosis spectrum symptoms, which include unusual thought content and perceptual disturbances, in childhood and adolescence. She presented results from a line of research examining the genetic, brain-based, and environmental risk factors for early psychosis spectrum symptoms. The results highlight the risk factors that show evidence of differentiating youth with transient experiences from those with clinically significant psychosis spectrum symptoms. Dr. Karcher's presentation provided evidence that early psychosis spectrum symptoms represent important targets for early identification and prevention efforts.

2024 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Deanna M. Barch, Ph.D.
Washington University in St. Louis

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Nicole Karcher, Ph.D.
Washington University in St. Louiss

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Nolan R. Williams, M.D.
Stanford University

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

John N. Constantino, M.D.
Pediatric Institute, Children's Healthcare of Atlanta
Emory University

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

Christopher J. McDougle, M.D.
Massachusetts General Hospital / Harvard Medical School

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE RESEARCH

Cameron S. Carter, M.D.
University of California, Irvine

Nolan William, M.D., presented *Breakthrough Rapid-Acting Therapeutics: Exploring Efficacy and Mechanisms in Treatment-Resistant Mood Disorders*. Dr. Williams is Associate Professor of Psychiatry and Behavioral Sciences; Director, Stanford Interventional Psychiatry; and Clinical Research Director, of the Stanford Brain Stimulation Laboratory at Stanford University. He won the 2019 BBRF Klerman Prize for Exceptional Clinical Research and was a 2018 and a 2016 BBRF Young Investigator.

Dr. Williams focuses on developing innovative technologies and therapeutics to modulate neural circuitry disrupted in mood disorders, OCD, and other neuropsychiatric conditions. His team employs neuroimaging-based approaches to target therapeutic delivery and predict treatment responses. Over the past decade, his lab has pioneered several novel therapeutic approaches, including Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) for treatment-resistant depression, which received FDA Breakthrough Device Designation and Clearance and is covered by Medicare New Technology Add-on Payment (NTAP)/New Tech Ambulatory Payment Classification (APC). SAINT is deployed in clinical and research settings worldwide. Dr. Williams also conducts mechanistic clinical trials on rapid-acting experimental pharmacological agents such as ibogaine and ketamine.

Dr. Williams discussed his team's efforts to develop novel therapeutic, pharmacological, and device approaches for treating mood disorders. The SAINT protocol for treatment-resistant major depressive disorder represents a revolutionary advancement in neuropsychiatry, offering hope to those unresponsive to conventional treatments. SAINT is an innovative form of repetitive transcranial magnetic stimulation (TMS), using functional MRI (fMRI) to precisely target brain regions based on individual brain connectivity, ensuring a tailored and effective approach. He also discussed the team's recent study of Stanford Traumatic Injury to the CNS (MISTIC) protocol, which combines ibogaine, a psychoactive substance, with a cardiac risk mitigation strategy using magnesium to enhance patient safety. Their research with this protocol has shown promising results in alleviating symptoms of depression and post-traumatic stress disorder (PTSD) in veterans with traumatic brain injuries and may offer new hope for individuals battling the wounds of war.

Thank you to our Bronze Sponsor Simon & Associates Wealth Management of Raymond James, our Benefactor Sponsor Miriam E. Katowitz, and our VIP Sponsor Rogers Research Center.

In his presentation, **John N. Constantino, M.D.,** discussed *New Horizons for Child Psychiatry From Research on Individual Differences in Early Social Development*. Dr. Constantino is Chair and Chief, at the Center for Behavioral and Mental Health, Children's Healthcare of Atlanta, and Professor of Psychiatry & Behavioral Sciences, Pediatrics, and Genetics at Emory University.

Dr. Constantino's research focuses on understanding genetic and environmental influences on disorders of social development in childhood, for the purpose of preventing or ameliorating lifelong impairment. He and his team developed and systematically validated the Social Responsiveness Scale, a quantitative scale for rating the characterizing traits and symptoms of autism that has been translated into over 60 foreign languages and is used worldwide as a measurement standard in research and clinical settings.

During his presentation, Dr. Constantino explained that decades of scientific advances have established that many pediatric psychiatric conditions represent extremes of normative variation in human behavior, caused by some of the same factors that give rise to individual differences in the general population. Tracing these factors to their early origins is beginning to inform higher-impact prevention and treatment of these illnesses. He discussed a series of research studies that have explored causal influences on variation in social development in relation to their clinical and

translational implications. Understanding these implications is helping to identify new opportunities for early identification, precision medicine, and the resolution of serious disparities in mental health outcomes that have long affected under-represented minority children in the U.S.

Christopher J. McDougle, M.D. presented *The Psychopharmacology of Childhood-Onset Neuropsychiatric Disorders Across the Lifespan*. Dr. McDougle is Director, Lurie Center for Autism and Professor of Psychiatry at Massachusetts General Hospital / Harvard Medical School. He is also a 1997 BBRF Independent Investigator and a 1994 and 1990 BBRF Young Investigator.

In his presentation, Dr. McDougle reviewed results from research studies conducted earlier in his career related to adults with obsessive-compulsive disorder (OCD), with and without co-morbid tic disorders, including Tourette's disorder. He discussed the transition in his career to research involving children, adolescents, and adults with autism spectrum disorder, and other neurodevelopmental conditions. He highlighted important findings from his research in clinical neuropsychopharmacology and how these results have contributed to improving clinical care and enhancing the quality of life of individuals with significant childhood neuropsychiatric disorders.

In his Symposium talk, **Cameron S. Carter, M.D.**, presented *A Cognitive Neuroscience Approach to Understanding Circuits and Symptoms in Psychosis*. Dr. Carter is Professor & Chair, Department of Psychiatry and Human Behavior at The University of California Irvine School of Medicine. He is also a BBRF Scientific Council Member, a 2007 BBRF Distinguished Investigator, Winner of the 2001 BBRF Klerman Prize for Exceptional Clinical Research, and a 1997 and 1994 BBRF Young Investigator.

Dr. Carter outlined a body of research, focusing on the dorsolateral prefrontal cortex (DLPFC) and related brain systems, that applies the tools and constructs of cognitive neuroscience. This work has sought to shed light on the mechanisms and timing of illness onset, relationship to cognitive deficits, clinical symptoms and functioning, as well as the developmental trajectory of frontal cortical dysfunction in schizophrenia and other forms of psychosis. In addition, he described recent work using these same tools to predict clinical outcomes and guide personalized treatment approaches in psychosis as well as recent work using animal model systems to provide insights as to how environmental risk factors such as maternal infections during pregnancy can disrupt DLPFC development and increase psychosis risk. Lastly, he discussed recent genetic studies that shed light on the molecular and cellular basis of altered DLPFC function in schizophrenia and bipolar disorder.

The entire BBRF symposium is available to watch free On-Demand at: https//bbrfoundation.org/event/international-mental-health-research-symposium

The BBRF International Mental Health Symposium also featured a presentation from **Franca Ma-ih Sulem Yong**, winner of the 2024 Pardes Humanitarian Prize in Mental Health, entitled *Navigating My ADHD Through Self Art Therapy*. Franca Ma-ih Sulem Yong is a Creative Art Therapist and Psychologist who has become known for her advocacy to promote tolerance, forgiveness, mental health and human fraternity as keys to sustainable peace.

In her presentation, she explored the challenges of navigating ADHD in Cameroon's unique cultural context. Art therapy became a powerful tool for managing symptoms, she found, offering creative expression and self-regulation. She shared personal experiences and tips to help those with ADHD embrace their strengths and develop coping strategies. ❖ **LAUREN DURAN**

2024 International Awards Dinner

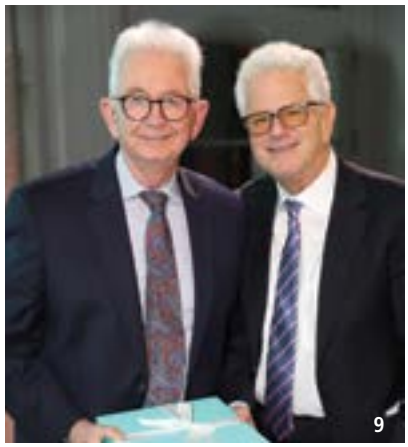
The BBRF International Awards Dinner was held on Friday, October 25, 2024 at The Pierre Hotel in New York City. The event celebrated the progress being made in neuroscience research and honored the BBRF Outstanding Achievement Prizewinners and the winner and honorary winner of the Pardes Humanitarian Prize in Mental Health. Prizewinners spoke earlier in the day at the BBRF Symposium.

(Names in each picture listed L–R):
1. Dr. Mark George and Dr. Nolan Williams **2.** Dr. Jeffrey Borenstein, Dr. Judith Ford, and Geoffrey Simon **3.** Dr. Judy Genshaft and Miriam Katowitz


1


2


3



4. Dr. Nicole Karcher and Dr. Jeffrey Borenstein
5. Dr. Christopher McDougle and Dr. Jeffrey Borenstein
6. Geoffrey Simon and Marc Rappaport
7. Dr. Deanna Barch and Dr. Jeffrey Borenstein
8. Dr. John Constantino and Dr. Jeffrey Borenstein
9. Dr. Cameron Carter and Dr. Jeffrey Borenstein
10. Geoffrey and Andrea Simon, Janice Lieber, and Dr. Jeffrey Borenstein
11. Marty and Janie Borell
12. Dr. Carol Tamminga and Dr. Joshua Gordon
13. Olivia Neu, Carole and Harvey Mallement

PHOTOS BY CHAD DAVID KRAUS

2024 Pardes Humanitarian Prize in Mental Health

Awarded to Franca Ma-ih Sulem Yong

Dr. Jeffrey Borenstein and Franca Ma-ih Sulem Yong

On Friday, October 25, 2024 at The Pierre Hotel in New York City, BBRF presented the 2024 Pardes Humanitarian Prize in Mental Health at its International Awards Dinner.

Franca Ma-ih Sulem Yong received the 2024 Pardes Humanitarian Prize in Mental Health for serving as an extraordinary advocate for tolerance, forgiveness, mental health, and human fraternity. She is a champion of mental health rights and a leading force for healing in Africa.

"Franca Ma-ih Sulem Yong is an extraordinary humanitarian who has consistently emphasized the importance of personal healing, mental health, and spiritual well-being as necessary components of sustainable peace, human rights, and prosperity. We applaud her tremendous work," said Dr. Jeffrey Borenstein, president and CEO of the Brain & Behavior Research Foundation.

The Pardes Humanitarian Prize in Mental Health, which carries an honorarium of $100,000, is awarded annually to recognize an individual or organization whose contributions have made a profound and lasting impact in advancing the understanding of mental health and improving the lives of people who are living with mental illness. It focuses public attention on the burden mental illness places on individuals and society and the urgent need to expand mental health services globally. Established in 2014, the Pardes Prize is named in honor of the late Herbert Pardes, M.D., the internationally renowned psychiatrist, outspoken advocate for the mentally ill, and the award's first recipient.

The 2024 Honorary Pardes Humanitarian Prize in Mental Health was awarded to the **Graham Boeckh Foundation** for serving as a catalyst for transformational changes that significantly improve the lives of people living with, or at risk of, mental illness.

Dr. Borenstein noted that BBRF salutes the Graham Boeckh Foundation "for its outstanding contributions in mental health advocacy and support of programs that bring mental health services to young people."

(L–R): Tony Boeckh, Raymonde Boeckh, Dr. Jeffrey Borenstein, and Ian Boeckh

THE PRIZEWINNERS

PARDES HUMANITARIAN PRIZE RECIPIENT

FRANCA MA-IH SULEM YONG

Franca Ma-ih Sulem Yong is a Cameroonian Art Therapist/Psychologist whose advocacy to promote tolerance, forgiveness, mental health, and human fraternity has made her a leading force for healing in Africa. She is the founder and president of the Afrogiveness Center, coined from the words "Africa" and "Forgiveness," which provides a safe space for mentally traumatized individuals, offering an antidote to hate crimes, retaliatory emotions, and violent extremism. Her work fosters forgiveness, dialogue, mutual understanding, and peaceful coexistence among youth from diverse backgrounds. The Center offers psychosocial, educational, legal, and socio-economic support to mentally traumatized survivors of conflict and intolerance.

Before founding Afrogiveness, Franca Ma-ih Sulem Yong was a journalist seeking to change the way mental illness is perceived and represented in society. She is also the founder of Positive Youths Africa (PYA), a nonprofit magazine aimed at inspiring, engaging, and empowering young people to live positive and purposeful lives. Drawing on the principle that unresolved trauma can perpetuate cycles of violence, she has consistently emphasized the importance of personal healing, mental health, and spiritual wellbeing as necessary components of sustainable peace, human rights, and prosperity.

2024 PARDES HONORARY PRIZE RECIPIENT

THE GRAHAM BOECKH FOUNDATION

The Graham Boeckh Foundation is a private foundation created in 1990 by J. Anthony Boeckh, his wife Raymonde, and their family to honor their son who died from complications related to schizophrenia in 1986. Its mission is to change the mental health care system, help save lives and improve outcomes for Canadian families. The Boeckh Foundation has done this primarily by focusing on the development of Integrated Youth Services hubs across all the Canadian provinces and territories, including in cities, rural and remote areas, and Indigenous communities. Integrated Youth Services provides a holistic suite of services that are easily accessible to youth aged 12 through 25. The collection of data from the hubs is a key component in the Foundation's drive to create a learning health care system that will greatly improve the delivery of services to patients and families suffering from psychiatric illnesses.

❖ **LAUREN DURAN**

PAST PARDES PRIZE WINNERS

2023
SPECIAL OLYMPICS INTERNATIONAL
Honorary Tribute:
Henry Jarecki, M.D.

2022
Altha J. Stewart, M.D.
Robert van Voren, FRCPsych (HON)
Honorary Tribute:
Clubhouse International
Sean Mayberry

2021
Kay Redfield Jamison, Ph.D.
Elyn R. Saks, J.D., Ph.D.
Charlene Sunkel
Honorary Tribute:
John M. Davis, M.D.
Michael R. Phillips, M.D., MPH
Norman Sartorius, M.D., Ph.D.

2020
Myrna Weissman, Ph.D.
Sir Michael Rutter CBE
Honorary Tribute:
E. Fuller Torrey, M.D.

2019
William T. Carpenter, Jr., M.D.
Honorary Tribute:
Cynthia Germanotta &
Born This Way Foundation

2018
Judge Steven Leifman
Honorary Tribute:
Suzanne and Bob Wright

2017
Doctors Without Borders/
Médecins Sans Frontières
Honorary Tribute:
Constance E. Lieber

2016
Vikram Patel, Ph.D., F.Med.Sci. &
Charles F. Reynolds, III, M.D.
Honorary Tribute:
Senator Edward M. Kennedy

2015
Beatrix (Betty) A. Hamburg, M.D.
and David A. Hamburg, M.D.
Honorary Tribute:
Rosalynn Carter

2014
Herbert Pardes, M.D.

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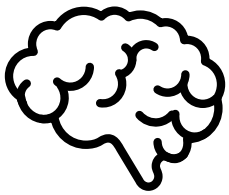

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Carlos A. Zarate, Jr., M.D.
Jon-Kar Zubieta, M.D., Ph.D.

A Precision-Health Approach to Bipolar Disorder

By Sarah H. Sperry, Ph.D.

Assistant Professor of Psychiatry
The University of Michigan

2022 BBRF Young Investigator

The following story combines ideas shared by Dr. Sperry in a BBRF webinar presentation she made on September 12, 2023 with results from her ongoing research.

IN BRIEF
Evidence based on mood records from bipolar disorder patients collected over extended periods of time calls into question the assumption in clinical medicine that periods between low and high mood in bipolar disorder are ones of "normal" mood. Dr. Sperry's finding of considerable "mood instability" between major episodes of depression and mania/hypomania could lead to future efforts to treat such mood fluctuations and in so doing potentially improve quality of life for patients.

I'd like to share with you findings from my BBRF Young Investigator Award project that will hopefully challenge the way you think about bipolar disorder. If you're living with bipolar disorder or have a loved one with the disorder, what I say here will suggest the importance of engaging in *ongoing mood monitoring*. The objective and hope is that such monitoring can help us develop new strategies to treat patients more effectively, to help them better function in the world and live productive lives.

For those who don't know, bipolar disorder is one of the top 10 leading causes of disability worldwide. Despite this, progress in terms of diagnosis and treatment has been slow. I want to suggest why this might be—what we might be missing and how we might be able to move forward to catalyze change in the field.

Let me briefly review our current diagnostic criteria so that we're all on the same page. Bipolar disorder is comprised of mood episodes, either manic, hypomanic, depressive, or mixed episodes. I'll briefly review what each is.

Manic episodes involve feelings of elation, euphoria, and/or agitation and irritability; increased energy and a reduced need for sleep; feeling grandiose, or invincible, or superior; talking more and faster than normal; having racing thoughts; being hyper-focused on an activity or goal; pacing or feeling really restless and fidgety; being impulsive or reckless. And for some, experiencing delusions and hallucinations. For something to be categorized as a manic episode, these symptoms have to last at least one week (or shorter If they require hospitalization). Critically, they cause significant impairment in one's health, work, and social life.

Hypomanic episodes are similar to manic episodes, but differ in intensity and duration. They involve the same set of symptoms, but in hypomania, the symptoms only have to last

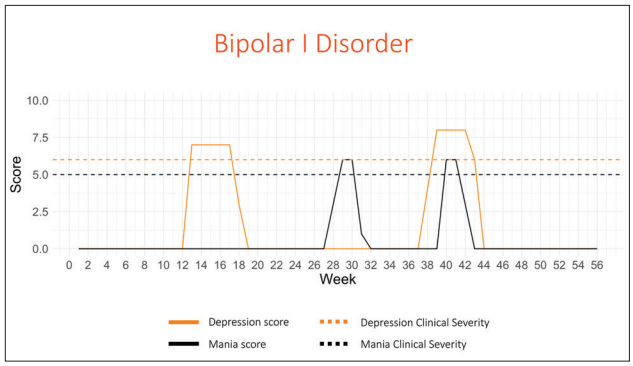
4 days. Unlike in mania, they tend not to cause clinically significant impairment. But they do involve a recognizable and observable change in somebody's affect and behavior. This is often apparent to family and friends.

People with bipolar disorder also experience **depressive episodes.** These can include prolonged sad and low mood, loss of energy, loss of interest in pleasurable activities, feelings of worthlessness or guilt, withdrawal from social activities and family, changes in appetite and weight, difficulty concentrating and making decisions, sleep changes such as insomnia or hypersomnia, and thoughts of death or suicide. For diagnostic purposes, these symptoms must be present for at least 2 weeks and cause clinically significant impairment.

Finally, people with bipolar disorder sometimes experience **mixed episodes,** in which they have symptoms of mania or hypomania *and* depression at the same time.

The type of episode one experiences determines which bipolar diagnosis they receive. We have four primary possible diagnoses in our current diagnostic system, based on the DSM-V manual. These are **bipolar I disorder; bipolar II disorder; other or unspecified bipolar disorder** (previously known as bipolar NOS, "not otherwise specified"), and **cyclothymic disorder**. Individuals with bipolar I disorder must have a history of manic episodes. It's not required that they have experienced depressive episodes. However, the majority with this diagnosis do experience depression in addition to mania.

Let's take a look at what bipolar I looks like in graphic form. This is a hypothetical classic case:

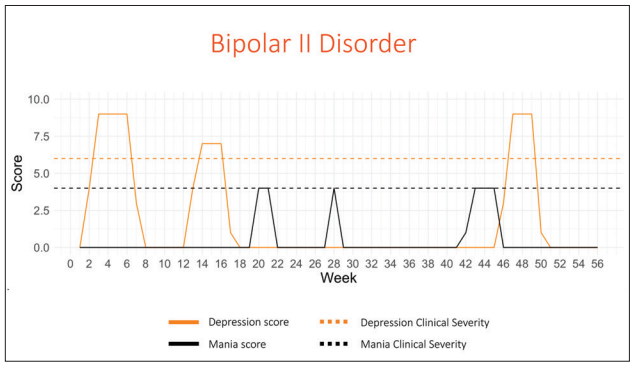


The bottom axis of the graph measures time—here, a 56-week period. The other axis shows the intensity of the symptom score this patient had during these weeks.

The horizontal orange dashed line is the threshold for a depressive episode; the horizontal black dotted line is the threshold for a manic episode. Anything above these lines (in this and subsequent graphs) means the patient is having an "episode."

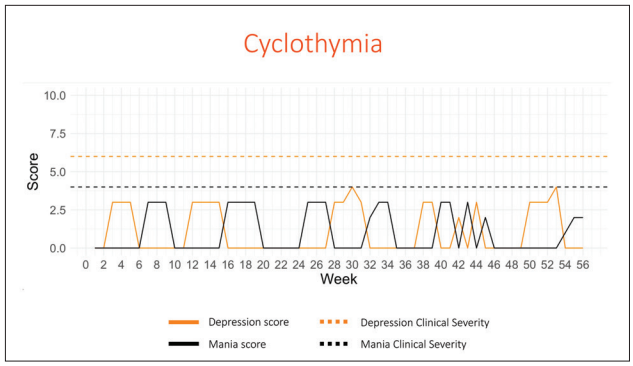
This graph tells this story: over the past 56 weeks, this individual has had one pronounced depressive episode, one pronounced manic episode, and one mixed episode (experiencing symptoms of both mania and depression). Please notice that between episodes, this person has no mood disturbances—their symptom scores are all the way down to zero. This is important because extant research and clinical theorizing often emphasizes that in bipolar disorder, there is a return to normal or what we call "euthymia" in between depressive or manic/hypomanic episodes.

Now consider this hypothetical individual with bipolar II disorder.



Individuals with bipolar II disorder by definition have to have at least one hypomanic episode and also experience depressive episodes. This chart is set up the same as the last, but the black dashed line is lower. This represents the lower intensity of hypomanic symptoms compared to manic symptoms. What we see in this chart is that the individual has three prominent depressive episodes and three hypomanic episodes over a 56-week period. One of the hypomanic episodes (the last one) partly overlaps in time with the third depressive episode. Here again, you see that when the individual is not experiencing either depressive of hypomanic episodes, symptoms go down to zero and the individual is "euthymic."

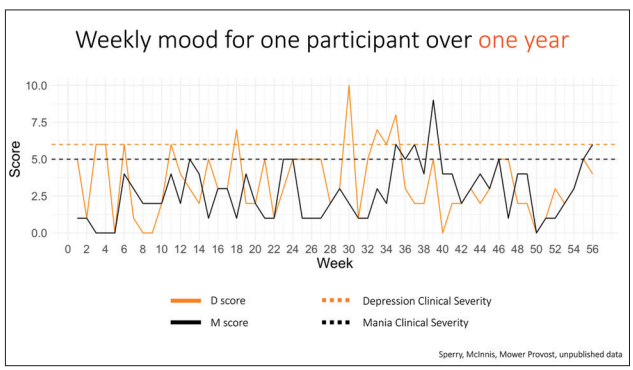
My third chart shows what a person with cyclothymia looks like, according to the official definition.



Remember, cyclothymia is when an individual has symptoms of both hypomania and depression that do not rise above the threshold for an official episode, either in intensity of symptoms or duration. But these "subthreshold" symptoms must be present for a significant amount of time, cumulatively. So, you'll see this person experiences a lot of variability in mood, a lot of vacillation between symptoms, and less time overall spent in "euthymia," without mood disturbances.

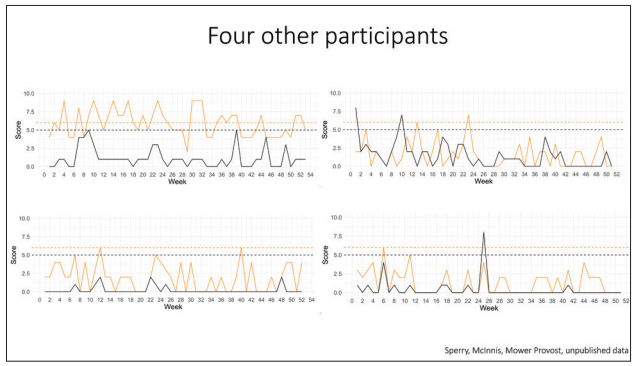
My point in showing you these charts is that they map onto our diagnostic criteria very nicely. But my message to you is that things do not look this clean when we're looking at the majority of actual patients and their moods over time.

The charts I will now show you are based on data my colleagues and I gathered in a study we called PRIORI, conducted at the University of Michigan. We had 18 individuals with bipolar I or bipolar II disorder complete weekly ratings of depression and mania symptoms (or their absence) over 12 months. They did so on an application on their smartphone developed by our group at Michigan. The questionnaire includes six items that result in a depression score or D-score, and mania score or M-score. The app is very easy to use and can be filled out in less than a minute, which makes it more likely participants in our study will actually use it every day.



At the lower left of this page is a chart of real-world data for one of our participants who completed the full 12-month study and a few weeks extra, 56 weeks in all. One thing you can see is that *there were very rarely periods of time when this person's mood symptoms were zero, or "euthymic."* Rather, the person vacillated between symptoms much more like the theoretical cyclothymic individual I showed you. But this person does have times where their symptoms spiked, and they had distinct clinically significant episodes. You'll also note that this person often had some level of depressive and manic symptoms at the same time. What you don't see is a clear-cut differentiation between depression and mania.

Here are four other real-world participants who recorded their moods over 56 weeks on our app.



You will notice some individual differences in these patterns. For example, the individuals on the bottom spend more time at zero in terms of manic symptoms (black lines), so they look a bit closer to our textbook-definition examples of bipolar I and II disorders that I showed you earlier. But they have a lot more variability and depressive symptoms (orange lines). You'll note that the individual on the top left experiences frequent but small shifts in manic symptoms, whereas their depression is consistently high and variable.

Over the 8 years of my initial research, data I had generated on people with bipolar diagnoses suggested that individuals differ significantly in their presentation and course. This "heterogeneity" within bipolar disorder is complex and a challenge for research and treatment.

I also want to emphasize that mood instability is present throughout much of the course of bipolar illness, *even outside the context of distinct mood episodes.* One implication is: the conceptual theory of "euthymia" in between mood episodes doesn't seem to be typical of many people with bipolar disorder if you carefully chart the pattern of their moods over time. The question I started to ask myself was: *can we stratify individuals based on these patterns of affective instability?* This, as opposed

to stratifying them based on the type of episodes they experience ("manic" or "depressed") or the diagnosis they come to us with (bipolar I, II, or cyclothymic).

I had the thought: If I took those five time-series charts from the PRIORI study I showed you, I could use models to describe how these individuals differ from each other—I mean, in the actual dynamics of their depression and mania. Thankfully, BBRF liked this idea, as did Thomas and Nancy Coles, who sponsored the Young Investigator Award that supported my project to attempt this non-traditional stratification of bipolar patients.

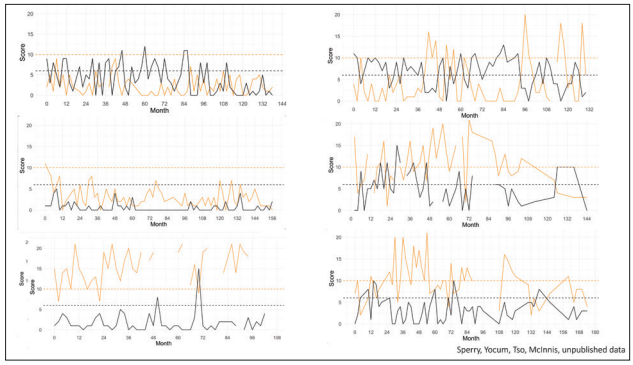
The aim has been to model and thereby be able to predict mood dynamics. I think of this as a **"precision health" approach to bipolar disorder.** In this project, which started mid-2022, I proposed to look at a unique cohort of individuals with bipolar disorder over a period of time, the Prechter Longitudinal Study of Bipolar Disorder (PLS-BD) at the University of Michigan. This unique cohort includes about 1,400 individuals who have been followed from anywhere from zero to 16 years. Although we took a snapshot of the existing data in 2022, the PLS-BD is an ongoing study, recruiting new participants, and following participants already enrolled.

Of the 1,400, about nearly 70% have a bipolar spectrum disorder. About 20% have no psychiatric diagnosis and are considered healthy comparison subjects. Others had non-bipolar psychiatric diagnoses. I proposed to focus on those individuals with a bipolar I, II, or NOS diagnosis who had at least 5 years of data we could model. This allowed me to have a sample size of 731 individuals. About 70% have bipolar I, about 20% have bipolar II and just shy of 10% have a bipolar NOS diagnosis.

When people enrolled in the study, they went through a baseline assessment that included an extensive diagnostic interview. They gave biological samples and filled out many questionnaires, and did interviews about trauma history, personality, temperament, family history, and neurocognitive functioning. After enrollment, every 2 months they completed self-report measures of mood and functioning. Every 6 months, they completed self-report measures on substance use and sleep quality. Each year, they underwent a clinical assessment where we rated their manic and depressive symptoms. They also completed some additional measures on family dynamics over time, and did a medications update. At year 2 or every 2 years, they underwent a comprehensive interview that updated their medical and psychiatric diagnostic and treatment history, and also any new history of suicidality. And every 5 years, they had a reassessment of their neurocognitive functioning and personality.

It's exciting that for many of these individuals, we were able to integrate this data with their electronic health record data, allowing us to really garner a lot of deep information that can be used to try to predict treatment response, trajectories of change, and so on.

Here are mood charts of six individuals who have been in the PLS-BD cohort for over 10 years. As you can see at a glance, there are lots of different patterns.



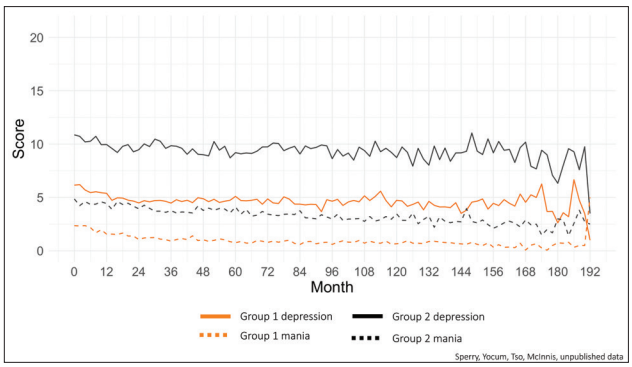
What do we do with all of this data? First, we can calculate the "mean" or middle point of each person's depression and mania over time. We think about these "means" as the average level of depression or mania that somebody experiences. Another way of putting it is that they are somebody's "home base," emotionally. It's the place that their body inherently goes back to most of the time. Next, we can look at what's called variability. This is how much a person deviates away from their home base. At any point in time you can ask: how intense or less intense are the symptoms at this point compared to what they look like on average? From this information we can compute, statistically, to what extent mood at one point in time predicts mood at the next point in time.

You can think about this as a way of showing how long it takes an individual to "return to baseline" when they do have a mood shift. It can also show, among other things, how mood may be consistent over periods of time.

For each of the 731 individuals with bipolar disorder in my data, I can put their time series of depression and mania data through my model (which is more complex than is necessary to explain here). The next question is: based on the data, can I group people, or stratify people, based on the temporal dynamics of their mood?

In our 731 individuals with bipolar disorder, we found two meaningful groups. I'm just going to call them Group 1 and

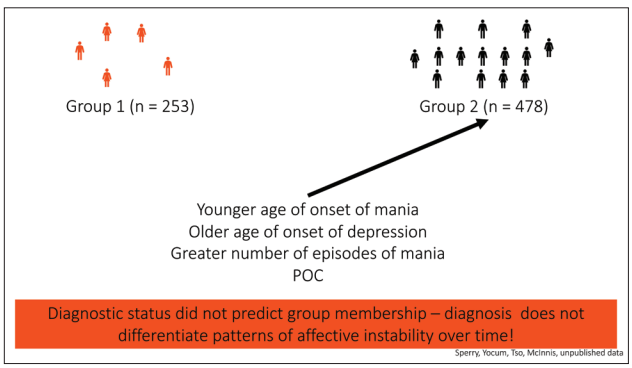
Group 2 for simplicity's sake. 253 of our individuals fell into Group 1 and 478 fell into Group 2. I took everybody's data and I found the average level of depression and mania for each group at each point in time.



The solid black line represents depression for everybody in Group 2, over time. The black dashed line represents Group 2's mania over time. The solid orange line represents Group 1's depression, and the orange dashed line represents Group 1's mania. Right off the bat, you can see that Group 2 tends to have higher average levels of depression and mania. You can also see that Group 2 seems to have more variability in their scores.

After lots of additional analysis, we were able to conclude that Group 2 are individuals with bipolar disorder whose emotional course is characterized by a high intensity of symptoms, but more importantly to me, *high variability* in these symptoms.

The next question is: are there predictors that help us know who is likely to be classified as Group 1 or Group 2? There are many diagnostic and demographic variables that might help us understand some differences about these two groups.



What we found is that these four variables predicted group membership. Those with a younger age of onset of mania or hypomania, older age of onset of depression, and a greater number of episodes of mania, were more likely to be classified as Group 2. The 4th variable is that Black, Indigenous, Hispanic, Asian and other people of color people of color were also more likely to be in Group 2.

What I want to stress here is that the **standard "diagnostic status" (i.e., bipolar I or II, etc.) did not predict group membership.** And if you remember, traditional diagnostic criteria are supposed to tell us something about the course and episodic nature of the illness. But here, the data suggests that DSM-V *diagnosis alone doesn't differentiate somebody's level of affective instability.*

The next important question I asked is: does group membership predict *outcomes*? Does being in Group 1 or 2 predict a person's mental and physical health functioning? We found that people in Group 2 have lower mental and physical health functioning over the course of their illness, by a significant amount that's very noticeable.

To recap all the big lessons we've learned so far:

1) Individuals with bipolar disorder experience considerable instability in mood between mood episodes—the typical pattern does not seem to be that you return to "euthymia," or no mood symptoms, after having either a manic or depressive episode.

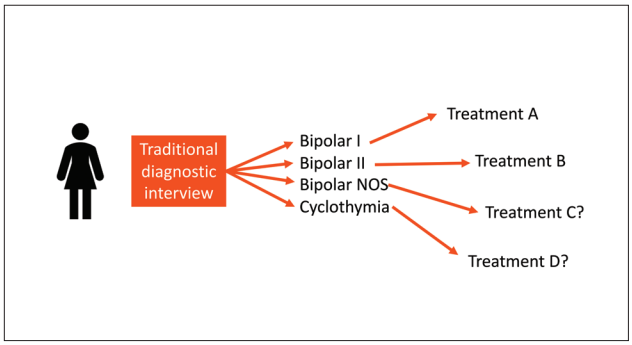
2) Individuals with bipolar disorder can be stratified by their level of mood instability.

3) Demographics and age of onset differentially predict levels of mood instability.

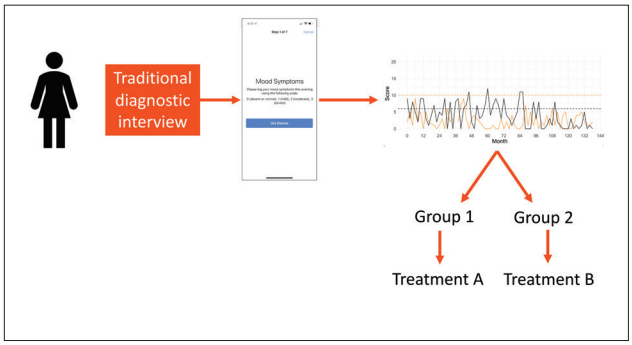
4) Levels of mood instability predict how well or poorly, in relative terms, that you will function both mentally and physically.

In our ongoing work, we hope to refine our models incorporating larger amounts of data, confirm the number of mood instability "classes" we identify, and look at other factors that might enable us to predict which group that someone with bipolar disorder will fall into, as well as how group membership may predict outcomes. We're going to be looking at whether sleep and circadian rhythms, trauma history, personality and temperament, family history, and health comorbidities, predict group membership. Regarding outcomes, we'll look at things like ER visits and hospitalizations, substance use, neurocognitive functioning, suicide risk, quality of life, medication history, and therapy response.

In the system as it stands today (see graphic immediately below), we choose treatments for patients based on the diagnosis, and if treatment doesn't work, we reevaluate, we try something else. We have second-line treatments, third-line treatments, and go from there.



What I'm proposing (see graphic below)—it could be the basis of a precision-health approach to bipolar disorder—is that when somebody comes in for a diagnostic interview, the process includes mood monitoring. What if our patients and our research participants filled out our questionnaire once a day for 14 days? That would give us a time series for them in terms of their depression and mania. We are currently exploring what the minimum amount of time is that would need to be measured to calculate a meaningful metric of mood instability.

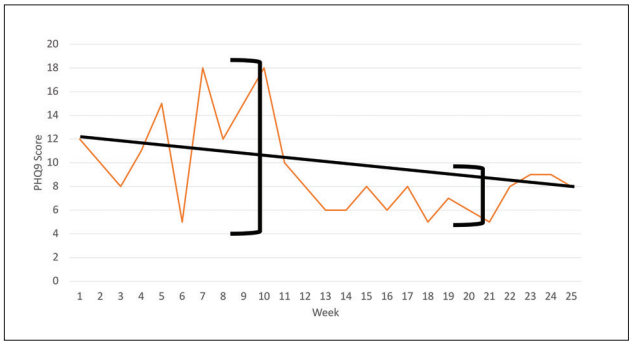


This might enable us to classify them, and determine whether they're more like those with the illness in Group 1 who have low variability and a more episodic course, or those in Group 2 who have chronic variability.

We might then think of developing treatments for "mood or affective instability," rather than based on whether someone is diagnosed with, say, bipolar I or II. This is my opinion, based on my program of research to date, and I know that it's probably controversial. But the data shows me that *classifying people by mood instability is potentially more meaningful than by diagnosis alone.* What if we had treatments that mapped onto the actual pattern of a patient's symptoms rather than on their diagnosis? That's my dream.

Although my research program is still in its early days, what I've been able to do so far, with BBRF's help, enables me to suggest this takeaway: affective instability in bipolar disorder is something we must pay more attention to. I would like to propose that reducing the reactivity and variability of mood in our patients could be an important way of judging the outcomes of the treatments we provide. We may find that reducing the variability of depressive or manic episodes could be an important way to improve functioning in people with bipolar disorder.

This final graphic shows what that might look like.



The orange line registers variations in the intensity of a hypothetical patient's depressive mood over a period of 25 weeks. The change from the initial reading of symptoms at week 1 and the final level at week 25 is significant but not that large (the slope of the solid black line connecting levels at week 1 and week 25 is shallow). Further, the week-1 vs week-25 levels do not tell the story of what the patient experienced between those time points. Compare the range of variability in symptom intensity through week 9, which is large (black bracket "A"), with the much smaller range at, say, week 20 (black bracket "B"). It's possible that such a patient, over the latter half of the treatment period, would have been better able to function because his or her symptoms tended to vary less, and at levels much lower than were experienced during the first 9 weeks of the treatment course. We might call this a success. ❖

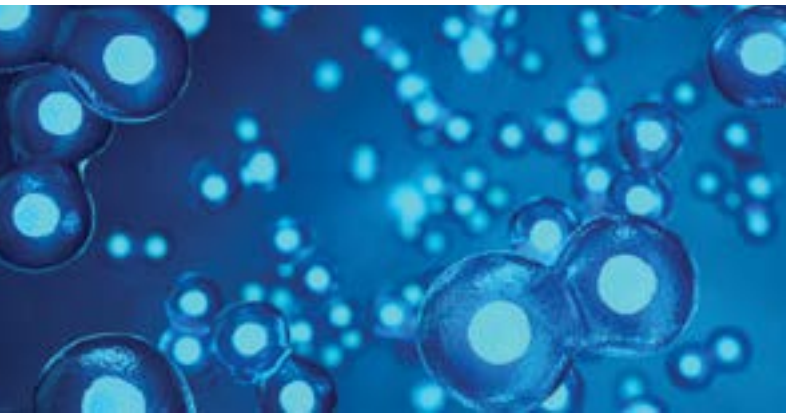
Recent Research Discoveries

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

A Potential Stem Cell-Based Therapeutic 'Rescue Strategy' is Developed for Timothy Syndrome, an Autism Spectrum Disorder

A team of researchers led by two-time BBRF grantee **Sergiu Pasca, M.D.**, of Stanford University, has published results of experiments demonstrating a potential "rescue strategy" using stem cell-based models for a devastating neurodevelopmental disorder called Timothy Syndrome (TS).

TS is widely considered to be among the autism spectrum disorders, with patients often having severely impaired communication and socialization skills, as well as delayed development of speech and language. TS also can have other serious impacts on health including epilepsy and a cardiac



disorder called long QT syndrome that affects heart rhythm. The newly reported experiments, while specifically targeting pathology in severe TS, could have future applications in other illness involving the brain including schizophrenia, bipolar disorder, and intellectual disability.

The new research, reported in a cover story in the journal *Nature*, has its origins over 15 years ago in the Pasca lab. Dr. Pasca received his first grant from BBRF in 2012 (Young Investigator) and in 2017 he received a BBRF Independent Investigator grant. He is among the pioneering researchers who have harnessed stem-cell technology to grow human brain cells in the laboratory. His lab developed guided neural "organoids" from stem cells and has pioneered the first "assembloids" that model circuit formation in three dimensions in the lab setting. In a more recent innovation, they have transplanted organoids into living animal brains, where they make connections and take part in functional circuits. This has made possible unprecedented experiments to reveal pathologies in human brain illnesses, particularly those like schizophrenia and autism which in some forms likely have origins in the first months of life, during development of the fetal brain and other organ systems.

The organoids used by Dr. Pasca and others are based on cells harmlessly sampled from patients; skin or blood cells, for example, can be reprogrammed in the lab to redevelop as cells of the brain, heart, or any organ. Importantly, every reprogrammed cell bears the genome of the patient-donor. If the donor has genetic mutations linked with an illness like Timothy Syndrome, then a novel kind of experiment becomes possible. One can watch these cells from their earliest days as they develop and begin to manifest pathologies caused (at least in part) by their illness-related variant genes.

As reported last year in this magazine (September 2023), Dr. Pasca's team engrafted cortical organoids derived from cells donated by patients with a severe kind of Timothy Syndrome called type 1 (TS1). These organoids, after transplantation into a living rodent, integrated with the host brain in ways that clearly revealed pathologies consistent with the illness. This provided key insights that led to the dramatic experiments just reported.

It began to be clear even from earlier experiments in test tubes that neurons grown from cells donated by TS patients displayed certain characteristic pathologies. For example, these cells had problems regulating the flow of calcium into and out of neurons, a flaw that is associated with abnormally high levels of neural excitation. There were also pathologies affecting the way neurons migrate in the brain.

These defects are caused by a mutation in a gene called *CACNA1C*, known to be mutated in TS (and several other psychiatric illnesses) and, much more specifically, the way in which the *CACNA1C* gene is processed in cells to ultimately give rise to *CACNA1C* proteins.

Every gene in our bodies, when activated, generates a "message" in the form of RNA ("messenger RNA") that tells a cell to manufacture a specific protein. Under normal conditions, the *CACNA1C* gene produces several variants, or "alternate" messenger RNAs (mRNAs). These alternate messages are the result of a process called "alternate mRNA splicing" that occurs just before the message is sent to cellular protein production factories called ribosomes. These messages contain instructions for making the *CACNA1C* protein. The variant of *CACNA1C* carrying the TS mutation is present early in the developing brain and patient-derived neurons seem to make even more of it than those from healthy controls. As development progresses, the *CACNA1C* RNA "message" normally transitions to a slightly different, more mature form. Dr Pasca reasoned that interfering with RNA splicing to yield the more mature non-mutated form might prevent defects associated with Timothy Syndrome type 1.

To achieve this, his lab created chemically modified pieces of RNA called antisense oligonucleotides (ASOs). The ASOs act like missiles within cells, homing in precisely on specific spots in pre-spliced RNA messages of a gene, causing the splicing of the message to be slightly modified. This ASO was designed to interfere with the splicing of *CACNA1C* favoring the variation not carrying the TS1 mutation.

In rats that had received cortical organoid transplants grown from the cells of TS patients, the team injected the tiny ASO molecules into the fluid that bathes the spinal cord and brain. These did indeed alter the splicing of RNA messages in the human cells growing inside the rodent brains, resulting in "robust" reversal, or "rescue" of pathologies in the neurons caused by the mutation—those involving calcium flow as well as migration.

The proof-of-concept experiment was successful, but much more work needs to follow before ASOs can be considered for treating people with Timothy Syndrome. It is not yet clear what impact treatments would have on pathology that happens to predate the treatment. Also, long-term tests must be performed in animals to evaluate toxicities potentially related to the treatment.

Yet the strategy is a promising one, the team believes, and illustrates how this platform involving stem cells and organoids could be used to study other neuropsychiatric diseases and to evaluate the therapeutic efficiency and safety of ASOs and other approaches including small molecule candidate drugs. ❖

Study Reveals New Details About Relationship Between Suicidal Ideation/Attempt and Alterations in the Immune System

Inflammation in the body causes physical pain each day for untold millions of people, and in that respect it is a well-known and well-understood medical problem. Much less well understood is the role of inflammation in psychiatric illness—a silent phenomenon that has been the subject of speculation for decades and in recent years the focus of increasingly intense research (see pages 10–15 of this issue). Inflammation is one of the byproducts of immune system activation.

With support from his 2019 BBRF Young Investigator grant, **Federico Manuel Daray M.D., Ph.D.,** of the University of Buenos Aires, Argentina, embarked on research dedicated to better understanding the possible roles of the innate and adaptive immune systems in the development and maintenance of depression. That work has begun to generate results, including in a paper recently published in the journal *Brain, Behavior & Immunity – Health* reflecting a study involving 105 individuals recruited from five Buenos Aires-area hospitals.

The aim of the current study, which grows out of Dr. Daray's search for an "immune signature" that might characterize people having a major depressive episode, was to more specifically explore immune system responses in individuals with suicidal ideation or attempts (both current and prior) in comparison with healthy controls. Of the 105 individuals analyzed in the study, whose average age was about 40, 21

had current suicidal ideation or suicide attempt; 42 had a lifetime history of one or both but not current; and 42 were controls. Of those with current or lifetime suicidal ideation or attempts, about half were diagnosed with major depressive disorder and half with bipolar disorder.

The innate immune system is the body's first line of defense against infections and is made up of defense mechanisms that are present from birth. This system includes physical barriers like the skin and mucous membranes, as well as specialized cells like macrophages and neutrophils, which can engulf or destroy pathogens in a nonspecific manner. In contrast, the acquired ("adaptive") immune system is specific to each pathogen and develops throughout a person's life in response to exposure to different microorganisms. This system includes cells like B cells and T cells, which produce antibodies and coordinate specific immune responses against specific pathogens.

Dr. Daray and colleagues note that in past studies involving patients with suicidal ideation or who have recently made a suicide attempt, immune changes (relative to healthy controls) have been noted in the blood, the cerebrospinal fluid that circulates in the body's central nervous system, and postmortem brain samples. But these studies have focused almost exclusively on the humoral component of the immune system and not on the component characterized by *cell-mediated* immunity. Both the innate and adaptive immune systems have humoral and cellular components. Humoral components include antibodies, which can neutralize pathogens and mark them for destruction by killer cells. Cellular components include cells like macrophages, T cells, and neutrophils, which can envelop pathogens and destroy them directly.

After drawing blood from study participants, the researchers were able to study the composition of peripheral immune cells (i.e., those in circulation in parts of the body excluding the CNS and the brain) as well as humoral immune biomarkers, comparing readouts from individuals currently experiencing suicidal ideation or attempts with those who had a history of the same but were not currently exhibiting such behavior, and also with the healthy controls.

The analysis yielded many potentially important insights, broadly showing that both the innate and acquired immune systems are altered in patients with suicidal ideation or attempts, both current and lifetime. The study participants with suicidal ideation or attempts had significantly elevated monocyte counts relative to controls. Monocytes are white blood cells manufactured in the bone marrow; high levels indicate the body is actively fighting an insult and are associated with inflammation. Additionally, there was a change in the proportion of the three subtypes of circulating monocytes.

Regarding acquired immunity, no difference among the three groups of participants was noted in the total number of lymphocytes (cell-mediated immunity components such as T cells and B cells). But the team found an increase in markers of "T-cell exhaustion" in patients with suicidal behaviors compared with controls. These biomarkers are inhibitory receptors located on immune cells. In great numbers, they signal continuous stimulation by antigens that possibly exhausts the effectiveness of T cells. Detection of these exhaustion markers has not been reported previously, neither in major depression nor in patients with suicidal behaviors, the team said, and could represent a "groundbreaking development in our field, as it holds the promise of opening new avenues for therapeutics."

The researchers also found higher levels of "a potentially novel and likely more specific biomarker for neuroinflammation in individuals with lifetime suicidal ideation/attempt [vs. controls]," a protein receptor mainly expressed in microglial cells called sTREM2. Microglia are an immune cell type that occurs only in the brain. sTREM2 "plays a critical role in microglial activation, survival, and apoptosis [programmed cell death]." Alterations in the protein have been linked with microglial activation in neurodegenerative and neuroinflammatory illnesses. This potential pathological process in microglia is another target for future study.

Dr. Daray commented: "These findings have potential therapeutic implications, suggesting that for patients with suicidal ideation or attempts, addressing inflammation may be necessary in addition to treating previously identified depressive symptoms." ❖

Team Develops an Innovative, Implantable Ultrasound Device to Stimulate Neurons in Deep-Brain Regions

A research team led by 2018 BBRF Young Investigator **Canan Dağdeviren, Ph.D.**, of the Massachusetts Institute of Technology, reports in *Nature Communications* that it has designed, developed, and successfully tested a tiny, implantable neurostimulation device that uses ultrasound to modify the activity of neurons deep in the brain. **Steve Ramirez, Ph.D.**, a 2016 BBRF Young Investigator, was a member of the team.

Although still an experimental device, their neural stimulator, called ImPULS, in the team's view has promise to become "a potent neuromodulatory tool" for therapeutic applications in people in illnesses ranging from major depression to Alzheimer's. It may also prove useful in basic research on the brain.

ImPULS stands for "implantable piezoelectric ultrasound stimulator." Ultrasound consists of sound waves that vibrate at greater than 20,000 cycles per second (20 kHz), a frequency that is very close to the upper limit of human detection.

ImPULS is not the first device that uses ultrasound to stimulate the brain and alter the activity of neurons. Ultrasound has also been used, on a limited basis, to stimulate the brain non-invasively. In transcranial-focused ultrasound (tFUS) treatments in depression, Alzheimer's, and epilepsy, low-intensity ultrasonic waves are transmitted through the skull. Unlike the most common form of non-invasive neurostimulation, transcranial magnetic stimulation (TMS), which uses magnetism rather than sound waves to alter neuronal activity, tFUS has the advantage of being able to reach much deeper into the brain. It is thought ultrasound exerts its effects by affecting the tiny pores called ion channels that regulate the electrical activity of neurons. tFUS beams can be precisely focused (on the scale of millimeters), and penetrate several centimeters into regions far "beneath" the brain's cortex, which lies immediately below the skull. Structures in the deeper subcortical regions include those such as the hippocampus and amygdala that play a central role in mood, memory, and learning.

Yet, as the MIT-led research team notes, "ultrasound, when transmitted from outside the human skull, faces significant scattering and reflection." This can cause the stimulation of brain areas beyond the therapeutic target(s), and in some cases can potentially cause damage to the brain. These unintended "off-target" impacts are among the chief motivations for the MIT team's work. Dr. Dağdeviren's 2018 Young Investigator grant supported her work on developing a new, implantable interface that could precisely target areas of the brain known to be involved in Parkinson's disease. The current project is related to that effort, in that it also seeks to develop and test a device that can be surgically implanted in the brain to deliver ultrasound with a specificity and precision that exceeds what is possible in tFUS and other non-invasive ultrasound applications.

"A miniaturized, non-genetic platform for localized stimulation is needed to fill the gap for next-generation neural interfaces to reach high standards of safety and longevity," the MIT team says. Some early attempts at making ultrasound devices that fit this description have been proposed, but they may not be suitable for implantation deep in the brain "due to their rigid form factors, material composition, or high power requirements," the researchers say.

ImPULS, the implantable piezoelectric ultrasound device they developed, has no active electrochemical elements. It is highly

miniaturized, engineered at the micron-scale (1000 microns = 1 millimeter), is biocompatible, and uses very little power. Piezoelectricity is the electric charge that accumulates in certain solid materials, such as crystals, certain ceramics, and biological matter, in response to applied mechanical stress. ImPULS is designed to be implanted in deep-brain regions, where its emission of ultrasound energy alters the behavior of adjacent neurons.

For the initial tests described in their paper, the ImPULS device was connected to an external printed circuit board via a special cable. The extremely thin probe whose implanted 100 micron-wide tip delivers the ultrasound energy was used in the laboratory to excite neurons in a preserved slice of mouse hippocampal tissue. Then, implanted deep in the brain of an anesthetized mouse, ImPULS was used in the living setting to prompt neurons to express a specific gene called c-Fos. Perhaps most intriguing, ImPULS was used in living mice to stimulate neurons that release dopamine in a part of the brain called the substantia nigra pars compacta. Careful application of ultrasound enabled the team to modulate dopamine release over a specific period of time. In Parkinsons's disease, large numbers of dopamine neurons in this region at the back of the brain die or cease to function.

The team says the fabrication process enables them to scale ImPULS devices to target larger areas of the brain, if wanted. In future studies, they seek to gain finer control of neural stimulation and evaluate potentially distinct effects such as excitation vs. inhibition in a variety of cell types, neural circuits and brain regions. The team also hopes to produce versions of the device that can deliver ultrasound carrying greater energy. They will also study the durability of the device, hoping to demonstrate that it can survive a month-long implantation. ❖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Therapy Update

Recent news on treatments for psychiatric conditions

A POSSIBLE BIOMARKER FOR COCAINE MISUSE AND A NOVEL TREATMENT FOR COCAINE ADDICTION BASED ON COMPOUND IN ROSEMARY

Kevin T. Beier, Ph.D.

Researchers led by 2017 BBRF Young Investigator **Kevin T. Beier, Ph.D.**, have discovered a way to predict individual behavioral responses to cocaine in mice never exposed to the drug, and have also found that carnosic acid, which is found in extract from the herb rosemary, can reduce volitional cocaine use in mice by reducing activity in a key brain circuit that controls cocaine-induced behavioral changes.

Dr. Beier, of the University of California, Irvine, is among researchers who in recent years have studied the system that regulates release of the neurotransmitter dopamine from a region called the ventral tegmental area (VTA). Dopamine release from cells in this area has been implicated in all phases of substance misuse (not only cocaine), from the initial rewarding effect to withdrawal and ultimately to compulsive drug-seeking.

But as Dr. Beier and colleagues note in their new paper, appearing in the journal *Neuron*, "it is precisely because the dopamine system is central to so many functions that it has proved to be a poor target to combat substance abuse." Given dopamine's ubiquity in the brain, rather than try to regulate the dopamine system as a whole as a way of modifying drug addiction, researchers including Dr. Beier and colleagues have turned to the idea of modulating signaling in particular dopamine subcircuits.

In prior research, Dr. Beier's team demonstrated the role of a key subcircuit centered on dopamine-releasing cells in the VTA that contributed to some of the later stages of substance misuse including withdrawal and reinstatement of use after forced cessation. In the team's new experiments just reported, they sought to map circuits that control the earliest stages of substance use disorder (SUD)—those that mediate drug reward as well as the urge to take the drug.

While most SUD research has focused on several brain regions involved in reward and aversion processing including the VTA, nucleus accumbens, and medial prefrontal cortex, Dr. Beier's team has focused on a less-explored region called the globus pallidus externus (GPe), which appears to play an important role in mediating behavioral changes that occur following use of an addictive drug like cocaine.

The question in the new study was which areas of the brain controlled individual differences in behavioral response to cocaine. While cocaine is an addictive drug, not everyone who uses cocaine develops an SUD; Dr. Beier's team was interested in whether individual differences in behavioral responses to cocaine could be predicted prior to repeated use of cocaine. Through a series of experiments in mice, the team was able, first, to implicate the GPe "as the central mediator" in cocaine reward as well as in sensitization to the drug (responding more strongly to each subsequent drug exposure).

Beyond this, they were able to show that by dampening the activity of parvalbumin (PV)-containing cells in the GPe, they could reduce volitional cocaine intake in mice. This likely occurred through modulating activity in a subset of dopamine cells in the VTA that critically regulate cocaine reward. PV is a protein whose presence is used to distinguish a particular subset of neurons in the brain.

Importantly, the researchers identified a specific mechanism that appeared to be essential in getting this response: they "dampened" GPe cell activity by activating proteins called KCNQ3 and KCNQ5. These are proteins that help regulate the flow of charged molecules (ions) of potassium into and out of nerve cells. The flow of ions like potassium is one of the essential ways that nerve cells regulate their activity—whether and how often they fire.

The experiments demonstrated that in cocaine-naïve mice, levels of firing activity of PV-containing GPe cells correlated directly with how rewarding a mouse found a subsequent cocaine dose to be. Cocaine-naïve animals with high levels of activity in such cells were more susceptible to long-lasting behavioral effects of cocaine than those with low levels of activity.

This provided a rationale to test whether artificially lowering the activity level in PV-containing GPe cells would lower the behavioral response to cocaine, including the desire of animals to self-administer it when offered. This proved to be the case. The effect was the same in mice of both sexes and was thought by the team to occur via the blocking or lowering of reward from taking the drug.

There were two important takeaways. One is that measuring the baseline activity of PV-containing cells in the GPe is a potential biomarker for cocaine sensitivity—perhaps in people, as in mice. This is important, says Dr. Beier, because "only a subset of people is vulnerable to developing substance-use disorder, but we cannot yet identify who they are. If globus pallidus cell activity can effectively predict behavioral responses to cocaine, it could serve as a biomarker for the most vulnerable, which could be an important method for reducing dependence and ultimately, substance misuse."

The second major takeaway was that the method used to lower the activity of PV-containing GPe cells—administration of carnosic acid obtained from rosemary extract—is a potential novel treatment for cocaine-use disorder and perhaps for other substance use disorders.

The team noted: "Carnosic acid has [previously] been reported to exhibit wide-ranging health benefits, however, to our knowledge, this is the first report of its potential as an anti-addictive agent. As such, we should note that much remains unknown about carnosic acid's effects on the brain, both acutely and long term."

Translation of results in rodents to humans is a major undertaking. The next steps in the research include thoroughly assessing any negative side effects of carnosic acid, and determining optimal dosages and timing of treatments. This would precede any tests of efficacy in people. The team is also interested in testing carnosic acid's effectiveness in reducing the desire for other drugs. ❖

Celso Arango, Ph.D.

A SCHOOL-BASED INTERVENTION TO REDUCE BULLYING AND THE PSYCHOLOGICAL HARM IT CAUSES

In nations around the globe, systems of primary and secondary education have gradually been making an important transition: from those that traditionally set special-needs children apart (when it served these young people at all) to school systems in which such children are "mainstreamed"—brought into classes to take their place among their peers.

This development has been widely hailed as enlightened, a long overdue lifting of a largely unspoken and unacknowledged burden placed upon those with special needs. Yet the enlightened approach is "not without risks," note authors of a newly published paper. Those authors—psychiatrists, psychologists, education professionals and social workers—who report on the results of a novel clinical trial they have conducted, remind us that children with special needs are most often the targets of peer aggression, typically taking the form of bullying. For purposes of the study, "special needs" is defined as having mental or physical health challenges.

Some studies suggest that as many as one person in three experiences bullying at some point in life. Young people, and most of all the very young, in primary school, stand to be hurt most. Past research has shown that bullying and other kinds of childhood adversities are among the most consistent risk factors for development of severe mental disorders.

The research team, led by 2005 BBRF Independent Investigator **Celso Arango, Ph.D.,** of the Gregorio Marañón University General Hospital and the School of Medicine at Universidad Complutense, CIBERSAM, Madrid, Spain, noted "few studies have focused on bullying behavior on the vulnerable population of children and adolescents

with special education needs (SEN), and even fewer have addressed the efficacy of anti-bullying interventions in this population."

Dr. Arango and colleagues tested a novel anti-bullying school-based intervention delivered at no charge over the web, involving students in 20 primary and secondary schools (10 each) in 2018 and 2019. Results of the intervention included post-intervention assessments 6403 of 6542 students who received the intervention. The very high percentage indicates the intervention was well accepted and did not prove onerous to those who participated. The intervention lasted 12 weeks. The follow-up analysis was based on responses gathered a year after the end of the trial, a delay due to the advent of the COVID pandemic.

The participating students were divided into two groups. One received the anti-bullying intervention, which focused on reducing discrimination and promoting inclusiveness; the other group experienced what the team describes as "conventional" school practices—they received no particular education or training about bullying. The anti-bullying training was "multi-modal": it involved different modules for students randomly assigned to receive anti-bullying training, as well as their teachers and parents. Much of the intervention consisted of education about bullying and its harmful effects. It also sought to raise awareness about the prevalence and present and future impacts of bullying. Among the young people, both victims and perpetrators of bullying were exposed to the training, which addressed the perspectives of each.

The mean age of the children across the trial groups was about 12. They were equally divided among boys and girls. All were from the Madrid area, and about two-thirds were from large, urban schools. About half in each group were from families in the middle or upper-middle income range. A bit less than one-third of the students were in primary school. About 5% of all students in the trial, irrespective of group, had "special educational needs." About the same percentage were assessed to have been bullied according to reports based on interviews.

The anti-bullying intervention that was tested—which is called LINKlusive, and incorporates significant aspects of a prior intervention tested with some success in Madrid schools—was found to "reduce bullying victimization" in schools enrolling students with special educational needs, the team reported in its paper published in *The Lancet*. But it had this impact only among students in primary schools enrolling SEP students, not secondary schools.

The team also found that among students who had already been bullied before the study began, "the intervention was associated with a significant decrease in depressive symptoms and improvement in quality of life." These findings were based on the assessments made a year after the study ended.

The results need to be replicated, the researchers noted. Interestingly, even though the LINKlusive intervention was adapted for delivery to students of different ages, "our results would suggest potential efficacy … only in the younger group," the team said.

Those who had been bullied before the start of the study were found most likely to benefit, and to have the greatest benefit relative to those who had not been bullied. This suggested to the team that there may be temporal "windows" for prevention in at least this aspect of mental health: the intervention was more likely to help those children who had been bullied and more likely to prevent bullying, compared with its effect on adolescents in the secondary grades. This could be because brain development in the older children, while still highly plastic compared with adults, may already be more resistant to modification by an intervention like the one tested in the trial.

"Given the current tendency to integrate students with special needs into mainstream schools and the lack of current interventions to reduce bullying," the researchers said, their results justify studies aimed at replicating their results. The results also suggest that the intervention they tested, or ones like it, "could be effective" for students of both age groups, both younger and older, if they are targeted to those who were seen to benefit in the trial. ❖

Boris Birmaher, M.D.

DIALECTICAL BEHAVIOR THERAPY DECREASED SUICIDE ATTEMPTS IN YOUTHS WITH BIPOLAR DISORDER

Among young people under 18 who are diagnosed with disorders on the bipolar spectrum (BD), as many as one in two attempts suicide. Of all psychiatric diagnoses in this age group, BD is associated with the highest risk of suicide death, psychological autopsy-based research has indicated.

Peter Franzen, Ph.D.

Bipolar disorder beginning before 18 is considered "early-onset" by psychiatrists who specialize in treating it—most often with a combination of drug therapy (e.g., mood stabilizers) and talk therapy. "Several psychosocial interventions have demonstrated efficacy" for stabilizing mood and lowering the rate of recurrence," note a team of researchers at the University of Pittsburgh School of Medicine. "Yet to our knowledge, no treatment expressly targets suicidal behavior in this patient population."

To make the situation even more frustrating, clinical trials that have been effective in lowering suicidal ideation and behavior in adolescents across psychiatric diagnoses have, for a variety of reasons, often specifically excluded youth with BD from participating.

These were among the chief motivations for the Pittsburgh team, who recently reported results of a clinical trial testing a specific form of psychotherapy, dialectical behavior therapy (DBT), in young people diagnosed with bipolar spectrum disorders. DBT is an evidence-based psychosocial treatment that was developed for adults with borderline personality disorder (BPD). DBT has been shown to reduce suicidal behavior in BPD patients, but also, more broadly, in reducing suicidal ideation, self-harm, and suicide attempts in suicidal youths who don't have BPD—although not, to date, including those with bipolar diagnoses, who have been largely excluded from prior trials.

The new Pittsburgh trial, led by Tina R. Goldstein Ph.D., was reported in *JAMA Psychiatry*. The team's senior member was **Boris Birmaher, M.D.**, winner of BBRF's Ruane Prize for outstanding child and adolescent psychiatric research in 2022 and the BBRF Colvin Prize for outstanding mood disorders research in 2013. Three other BBRF grantees were members of the team.

One hundred young people took part in the randomized clinical trial. All had BD diagnoses—14 with Bipolar type I, 28 with Bipolar type II and 58 with unspecified Bipolar Disorder. Bipolar disorder type I involves more pronounced manic episode(s), while in bipolar disorder type II, elevated periods are called hypomania. Forty-seven participants were randomly assigned to receive 1 year of DBT sessions (DBT therapy included a number of "family skills training" sessions involving at least one family member of the participants as well as individual DBT therapy sessions); in the comparison group, 53 received "standard-of-care" psychotherapy delivered by clinicians experienced in treating youth with BD. Participants in both groups continued to receive drug therapies.

The average patient was White, female, and about 16 years old. Over 40% of participants had a history of psychiatric hospitalization; over 60% had a history of suicide attempt; the average age of BD onset was about 13; about three-fourths had a co-occurring anxiety disorder and over one-fourth had been diagnosed with comorbid ADHD. Both groups reported similar suicide attempt rates at the time they were recruited for the trial.

Analysis revealed that youths who received DBT had fewer suicide attempts over 1 year. Further, suicide attempts declined to a greater extent over time among those who received DBT compared with those receiving standard of care psychotherapy. This was particularly true among participants who had a recent or lifetime history of suicide attempt.

The study results also indicate that the decreased rate of suicide attempt in the DBT-treated group was a result of the degree to which the therapy helped reduce emotional dysregulation—particularly among those for whom emotional

dysregulation was especially acute at the start of the trial.

DBT and standard psychotherapy were associated with similar amounts of improvement in depression and hypomania/mania over the 1-year period of the trial. Both therapies delivered in this trial were "more rigorous and intensive" than that received typically by young people when treated in the community, the team said.

Importantly, though, standard of care psychotherapy was found to have "minimal impact on suicide risk," the team noted. "To our knowledge, this is the only study to date to demonstrate a treatment effect on suicide attempts among adolescents with BD."

"Data provide particularly strong support for DBT among adolescents with BD with a history of suicide attempt. Yet for up to 60% of individuals, their first suicide attempt is lethal, and for those who survive, risk of death increases with each successive attempt." For this reason, the team stressed, it remains very important for future research to enhance the ability to predict first attempts among youths with BD.

The team suggested that their findings offered additional empirical support for the theory that DBT exerts its beneficial effects in reducing suicidality by helping patients manage emotional dysregulation.

The team also included: **Peter Franzen, Ph.D.**, 2016 BBRF Independent Investigator; **Dara Sakolsky, M.D., Ph.D.**, 2008 BBRF Young Investigator; and **Danella M. Hafeman, M.D., Ph.D.**, 2019 BBRF Young Investigator. ❖

GLOSSARY

EEG (p. 6) Electroencephalography, "a window onto the brain." In EEG, electrodes are placed on the scalp and recordings are made of electrical activity generated by the workings of the collectivity of neurons, billions of them. The waves are measured in several key wavelengths (among them, alpha, beta, theta, and delta), which have been found to correspond with particular mental operations.

BLOOD-BRAIN BARRIER (pp. 12–15) A protective layer in the brain that shields us from toxins, viruses, as well as pro-inflammatory immune molecules that circulate in the blood. (The brain has its own unique immune cells.) Pro-inflammatory immune molecules introduced into the bloodstream, it was once assumed, should not be able to penetrate the blood-brain barrier. But the barrier may "leak" when modified by stress, as research by Drs. Russo and Cathomas reveals.

NUCLEUS ACCUMBENS (NAc) (pp. 13–14) When modified by stress, the blood-brain barrier in mice leaks a bit, allowing the entry of circulating proteins into the brain that normally cannot pass through. One region in the brain particularly affected by such invasion following stress, in mice and perhaps also in people, is the NAc, which is central in the processing of rewards and also in the response to aversive stimuli.

EXTRACELLULAR SPACE (ECS) and **EXTRACELLULAR MATRIX (ECM**) (pp. 14–15) The ECS, as the name implies, is the space between cells. The ECM is a dense web-like material that individual neurons in the brain extend out into ECS. Both are related in important ways to the blood-brain barrier, including its integrity. Experiments by Drs. Russo and Cathomas show that when mice are subjected to repeated social stress, they tend to withdraw from social contact. This behavior is associated with remodeling of the ECS, which has the effect of increasing the space between once-adjacent neurons.

MMP FAMILY (pp. 14–15) Proteins in the MMP (matrix metalloproteinase) family are enzymes. MMP8, like other enzymes in the MMP family, has roles in shaping and regulating the space between neurons, the extracellular space (ECS). MMP8, which is released during chronic social stress by immune cells circulating in the body's periphery in mice and possibly people, can invade the brain perhaps due to damage to the blood-brain barrier, and alter the shape of ECS and ECM in the brain's NAc and possibly other brain areas. This may account mechanistically for the appearance of social withdrawal behavior in stressed individuals.

EUTHYMIA (p. 27) In clinical medicine, it has long been thought that in bipolar disorder (BD), the periods between episodes of high (mania or hypomania) and low (depressed) moods in many patients are essentially euthymic, i.e., characterized by normal mood. To the extent "normal mood" is defined as the absence of symptoms qualifying (according to the DSM diagnostic manual) as manic/hypomanic or depressed, this may be correct. But research by Dr. Sarah Sperry involving over 700 BD patients whose moods were charted at short intervals over long stretches of time (up to 10+ years) suggests that "affective instability" between clearly defined high- and low-mood episodes may be prevalent enough in a significant subset of patients to justify trying to treat them to improve disease course and quality of life.

Image credits: pp. 10, 14: Ichan School of Medicine at Mount Sinai; p. 13: Rochester Institute of Technology (apadpted); p. 15: Dr. Flurin Cathomas, Russo Lab, Mount Sinai (adapted); pp. 27–31, Dr. Sarah H. Sperry University of Michigan.

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