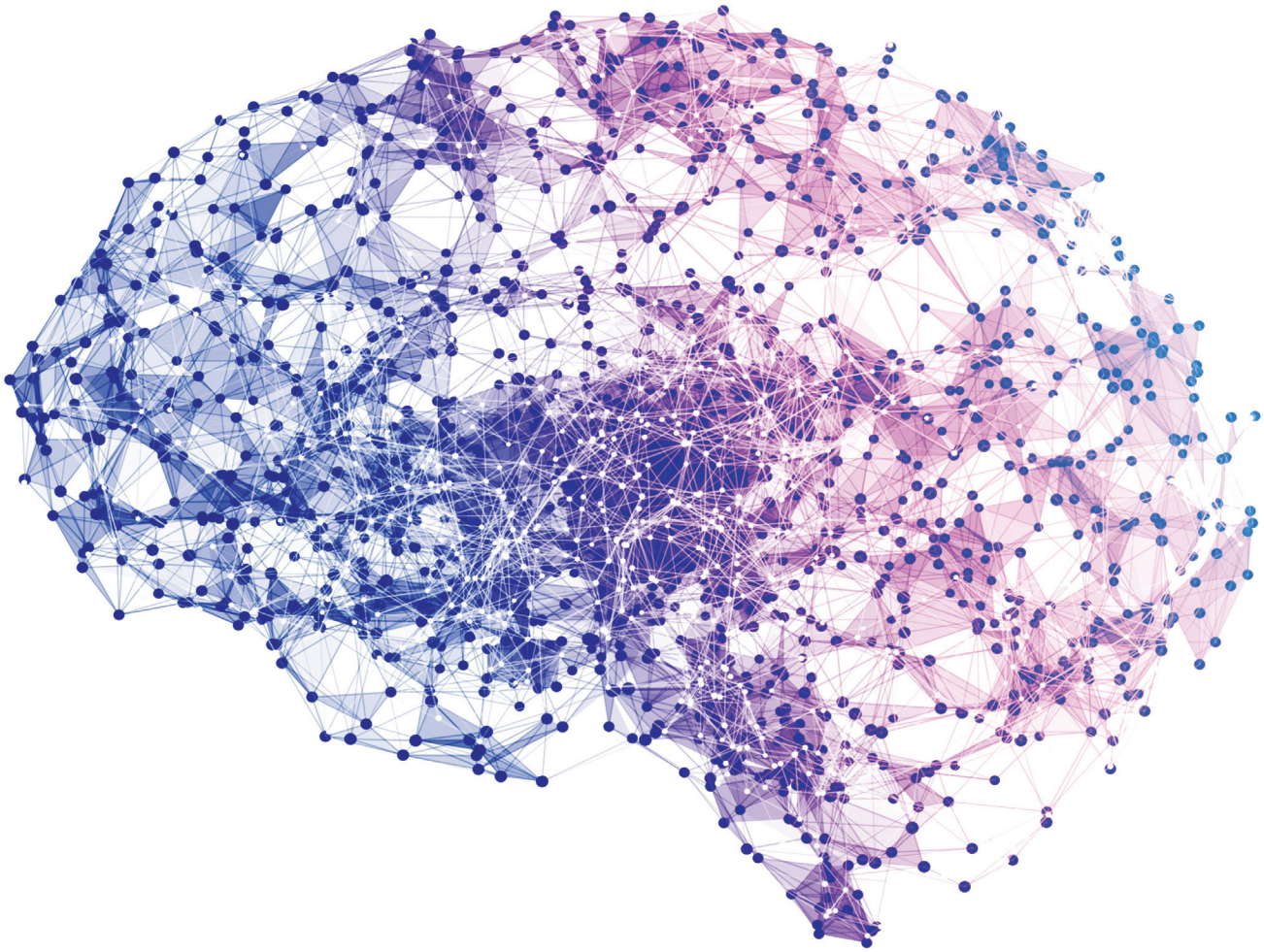
BBRF Mental Health Research Virtual Symposium

Cannabis: What Parents Should Know

MAGAZINE

Brain&Behavior

JANUARY 2022



Highly Individualized Deep-Brain Stimulation for Severe, Treatment-Resistant Depression

PRESIDENT'S LETTER

In this issue of *Brain & Behavior Magazine*, readers will find two stories that reflect the central importance of basic research, and which provide notable examples of how your donations are having a real, tangible impact on a goal all of us share—better treatments, cures, and methods of prevention for mental illness.

Our **PATHWAYS TO THE FUTURE** article tells of a novel idea to address brain-based disorders that has moved from theory to bedside in the short span of three years. Two teams at the University of California, San Francisco, led by three of our grantees (one of whom is also a member of the Scientific Council) have been involved in this research. The innovation involves testing "closed-loop neuromodulation" in a patient with treatment-resistant major depression. "Closed-loop" stimulation of the brain, via a surgically implanted deep-brain stimulation (DBS) device, is innovative because it delivers electrical signals to a specific spot in the brain briefly and intermittently, when a particular EEG brainwave pattern is detected. In this instance, the stimulation-triggering EEG pattern corresponds directly with the onset of the patient's symptoms. Closed-loop neuromodulation has become an FDA-approved treatment for refractory epilepsy and also is used to help patients with Parkinson's. As our story explains, the first test of this new, highly individualized approach in DBS-based therapy has generated a remission in the patient which continues to endure months since the trial began. At the same time, the researchers are careful to stress that this is one test of a new idea in a single patient. While the result is encouraging, it needs to be tested and validated in many more patients.

Our lead story in **ADVANCING FRONTIERS OF RESEARCH** features a second innovation in treating refractory depression. It involves using non-invasive stimulation of the brain—an enhancement of an FDA-approved technology called rTMS (repetitive transcranial magnetic stimulation). The enhancement, called SNT (Stanford Neuromodulation Therapy), has now received its first randomized, placebo-controlled trial. Seventy-nine percent of the small group of patients who received SNT were able to achieve remission of their refractory depression within 4 weeks of the conclusion of the 5-day neurostimulation protocol. If further validated in larger patient populations, this non-invasive way of treating refractory depression could be quite useful since it appears to generate large reductions in symptoms within days and thus could help hospitalized patients who are experiencing a crisis. The same technology could also have broader applications, although these still need to be tested and validated.

Both of the novel technologies discussed in these stories were pioneered by early-career BBRF grantees who are now members of our Scientific Council: Helen S. Mayberg, M.D. (DBS) and Mark S. George, M.D. (rTMS).

This issue also highlights our 2021 International Mental Health Research Virtual Symposium, the winners of the 2021 Pardes Humanitarian Prize for Mental Health, and features recent news on treatments for psychiatric conditions in our **THERAPY UPDATE** and important research advances that are moving the field forward in our **RECENT RESEARCH DISCOVERIES**.

I continue to be inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing support. Together we will continue to fund innovative and impactful research that is making a difference in the lives of those living with brain and behavior disorders.

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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PUBLICATION CREDITS

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Highly Individualized Deep-Brain Stimulation Helps a Patient With Severe Treatment-Resistant Depression

Over the past three years, researchers at The University of California, San Francisco (UCSF)—three of them BBRF grantees and one a member of BBRF's Scientific Council—have published three papers that have led to an experimental new approach to treating brain and behavior disorders, using deep-brain stimulation (DBS).

All three papers are notable, describing the progression of an idea from laboratory to bedside. The most recent, appearing in *Nature Medicine* in September 2021, was the subject of a *New York Times* story. It signaled that a concept which until then had been theoretical had now reached the point of helping a patient: "A 'Pacemaker for the Brain': No Treatment Helped Her Depression—Until This."

The patient who received the new treatment had been depressed since childhood and had not been helped by 20 different combinations of medicines, or by electroconvulsive therapy (ECT) or non-invasive transcranial magnetic stimulation (TMS). "Within a few weeks" of the beginning of her new treatment, she told the *Times*, "the suicidal thoughts just disappeared. Then it was a gradual process where it was like my lens of the world changed. The device has kept my depression at bay, allowing me to return to my best self and rebuild a life worth living."

Deep-brain stimulation treatment for patients with severe and unresponsive depression was pioneered on an experimental basis beginning in 2005 by **Helen S. Mayberg, M.D.**, and colleagues. Dr. Mayberg is a BBRF Scientific Council member, three-time BBRF grantee and 2007 winner of BBRF's Falcone Prize. This story will explain the concept behind a new application of DBS and will explore its potential implications for patients with depression and perhaps other psychiatric illnesses. Although the initial results have been both intriguing and encouraging, researchers involved in designing and delivering the treatment are the first to point out that it has only been tested in a single patient. At this point, they caution, it is impossible to know how it will work in other patients.

Andrew D. Krystal, M.D.
1997, 1993 BBRF Young Investigator
Professor and Director, Dolby Family Center for Mood Disorders, UCSF

Katherine W. Scangos, M.D., Ph.D.
2018 BBRF Young Investigator
Assistant Professor, Dolby Family Center for Mood Disorders, UCSF

Vikaas S. Sohal, M.D., Ph.D.
BBRF Scientific Council
2009 BBRF Young Investigator
Associate Professor, Dolby Family Center for Mood Disorders, UCSF

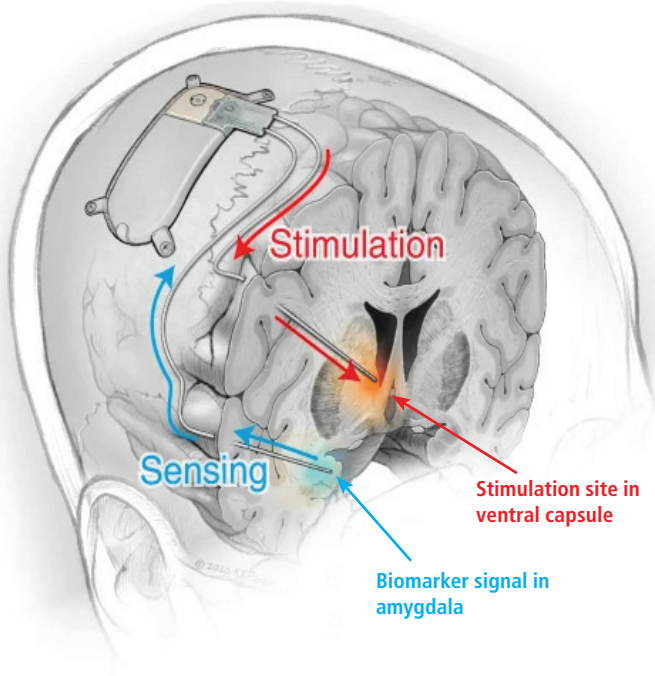
Testing of the new treatment was the focus of a 2018 BBRF Young Investigator grant to **Katherine W. Scangos, M.D., Ph.D.**, first author on the new paper. Inklings of the unconventional idea driving the research trace farther back, perhaps most distantly to two BBRF Young Investigator grants awarded in the 1990s to **Andrew D. Krystal, M.D.**, a psychiatrist and expert on brain stimulation and mood disorders. Dr. Krystal is co-leader of the UCSF research team that delivered the treatment, along with Edward F. Chang, M.D., a neurosurgeon and authority on using implantable DBS devices to treat epilepsy.

The team's September 2021 paper described the application of the new approach in just a single patient. A battery-powered DBS "pacemaker" was surgically implanted within the brain of a 36-year-old woman and programmed to deliver electrical stimulation at specific moments over the course of each day. It was placed in a location where its pulses were expected to help alleviate symptoms of major depression.

Unlike past "open-loop" tests of DBS in treatment-resistant depression, in which stimulation is delivered constantly following implantation of the device, this was a proof-of-concept test for a "closed-loop" approach. The DBS device would be activated intermittently throughout each day for only seconds at a time, and—here is the most notable innovation—only at moments when a sensor placed in another part of the brain detected a specific brain-wave pattern linked in prior tests with the onset of this particular patient's depressed moods (see illustration, top right).

What is new, then, about the approach is not just that the stimulation is intermittent—and limited to 300 times per day, maximum—but that it is triggered by a signal coming from elsewhere in the brain and relayed to the device. This highly personalized treatment design was not arrived at by guesswork, but only after a 10-day-long brain-mapping process in which brain-wave signals in this patient, as measured by EEG (electroencephalography), were painstakingly correlated with fluctuations in the patient's moods.

Implantable sensing and stimulation DBS system



A KEY INITIAL DISCOVERY

When Drs. Krystal, Chang, and Scangos performed their bold clinical test of closed-loop neuromodulation, they were building upon research in which Dr. Chang had previously been involved. Dr. Chang co-led a team with BBRF Scientific Council member **Vikaas S. Sohal, M.D., Ph.D.**, a 2009 BBRF Young Investigator who had trained in the Stanford University lab of BBRF Scientific Council member, two-time grantee and recent Lasker Award winner **Dr. Karl Deisseroth**.

In November 2018 Drs. Sohal, Chang and colleagues reported in the journal *Cell* their discovery of a "subnetwork" (or "subnet") in the brain connecting the amygdala and hippocampus, two areas centrally involved in the processing of emotions. They were surprised to find that recurrent and highly specific variations in EEG signals emanating from this subnetwork were directly correlated with worsening mood in 13 human subjects, attributable by the subjects to the onset of anxiety. The variations occurred in the EEG bandwidth called the beta band, which registers neurons oscillating at between 13 and 30 times per second.

It has long been assumed that human brain networks somehow encode variations in mood, although precisely how they do so remains unknown. The insight provided by Drs. Sohal, Chang, and colleagues was among the fruits of President Barack Obama's "Brain Initiative" and backing by DARPA, the Defense Advanced Research Projects Agency, and the Dolby family. The researchers made a direct connection between the beta-band signal in the amygdala-hippocampus

"subnet" which corresponded directly with a specific change in mood—and not just in one individual but in 13. The team was surprised by this result.

Interestingly, the mood signal was detected in 13 of the study participants, but not in 8 others. All 21 subjects suffered from epilepsy that had resisted treatment with medications. (The study was conducted to learn more about their brain activity prior to brain surgery designed to prevent seizures). But the anxiety signal was seen only in the 13 who had been assessed previously with comparatively high levels of anxiety—none of the others.

Dr. Krystal notes that the "DARPA subnets" study of 2018, as he and others call it, was notable in part because the EEG signal correlated with the presence of anxiety in the 13 subjects. This suggested to Drs. Krystal, Chang, and Scangos that it might be possible to find other biomarker-like signals in specific patients that would signal the onset of other psychiatric symptoms.

Their follow-up work would focus on the 36-year-old patient with childhood-onset treatment-resistant major depression—her name is Sarah—who became the first patient with psychiatric illness to benefit from closed-loop neuromodulation.

"What happened is the thing we had hoped for—but weren't really sure was possible. We're picking up something driving this patient's depression and delivering stimulation before she has any sense of being depressed."

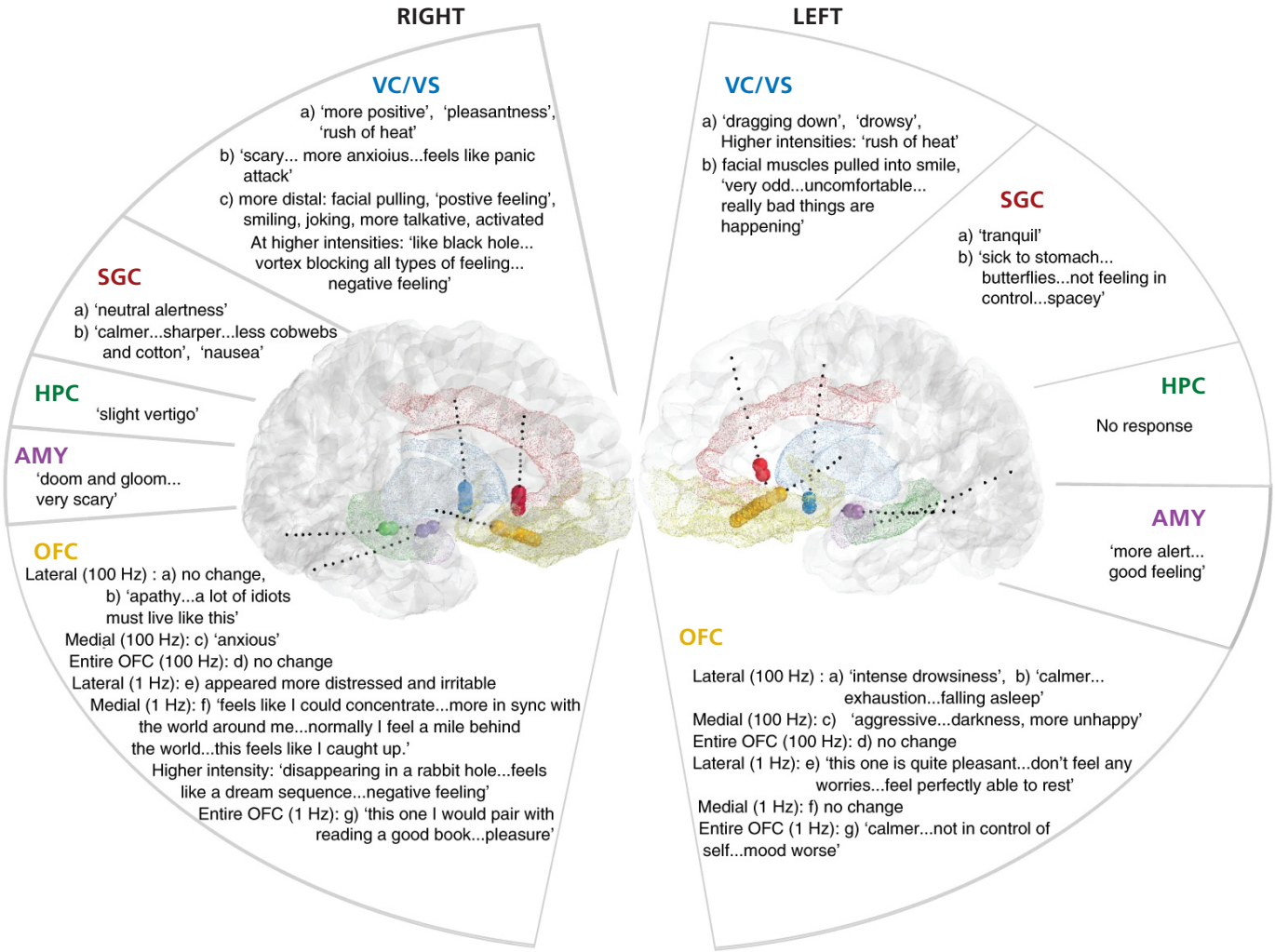
PREPARING THE FIRST PATIENT

The work advanced in two major steps. The first step involved implanting electrodes in Sarah's brain—an invasive procedure requiring surgery—and systematically assessing her response over 10 days when the team applied electrical stimulation across the brain, with particular attention to five brain areas: the subgenual cingulate, amygdala, hippocampus, ventral capsule (part of the striatum), and orbitofrontal cortex. Cautiously, the team delivered stimulation at varying intensity at each of the locations. As they did, they communicated continuously with Sarah, who conveyed what impact each stimulation had on her mood and feelings.

The result [see illustration, right] is captured in a graphic conceived by Dr. Scangos and which appeared in the team's January 2021 paper, published in *Nature Medicine*. It summarizes what Sarah experienced at each step of the experiment—what Dr. Krystal calls "the clinical effects of neurostimulation," delivered widely across both hemispheres of the brain.

Here, the team observed something that had also been seen in the earlier "DARPA subnets" study. "We saw in that study that you could elicit changes in emotion-related symptoms—quickly and immediately—when applying stimulation at specific locations," Dr. Krystal explains.

This is exactly what they now saw in Sarah, over the 10-day "stimulation-response" mapping period. "We asked the patient to rate her depression



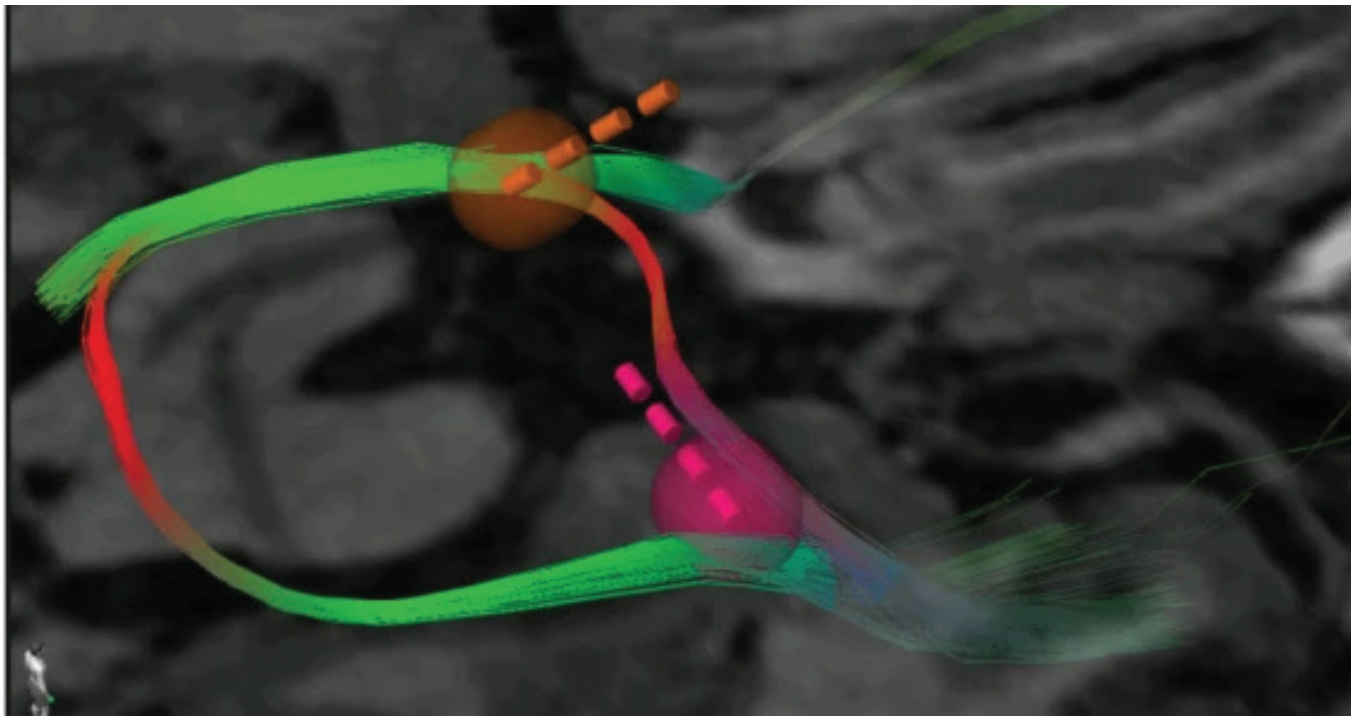
Over a 10-day period, researchers carefully stimulated Sarah's brain in multiple areas including 5 key regions in both the left and right hemispheres (color-coded here: VS/VS=ventral capsule/striatum; SGC=subgenual cingulate; HPC=hippocampus; AMY=amygdala; OFC=orbitofrontal cortex). Electrodes delivered current at various levels of intensity, while the team recorded Sarah's EEG and mood-state, as well as her remarks about how she felt at each step. This yielded a wide range of emotions, from very pleasant to very unpleasant. In the end, the team selected a site in the ventral capsule on the brain's right side in which to direct brief pulses of stimulation when an EEG pattern detected in the amygdala signaled an impending worsening of Sarah's mood.

severity and related symptoms as we proceeded," he says. They focused on Sarah's mood, gauging fluctuations in her depression, as well as in anxiety and her energy level. Sarah's responses are summarized in the illustration on this page, above.

Based on research to this point, the team reported: "We found an elaborate repertoire of distinctive emotional responses that were rapid in onset, reproducible, and context- and state-dependent. These results provide proof of concept for personalized, circuit-specific medicine in psychiatry." By context- and state-dependent, the team meant that stimulation in certain spots in the brain could generate different responses, which depended in a consistent and predictable way on Sarah's mood state and level of alterness at the time of the stimulation.

To be clear, the researchers had not yet tried to treat Sarah; they had just completed the essential preliminary step of stimulating her brain in many locations and noting impacts on her mood and feelings. This work was followed by analysis, aided by computer-driven machine learning, of the already recorded EEG data. In this analysis they sought to find a place or places in Sarah's brain where changes in her mood were directly reflected in distinct brainwave patterns. This was the search for an individualized biomarker of her depression, very much like the biomarker in the "DARPA subnets" study which was associated with anxiety in 13 epilepsy patients.

"We asked: 'What patterns are present in the EEG signals as the patient rated her depression as worse; and how did that signal differ when the patient was feeling better?'" Dr. Krystal explains. The team and patient were very fortunate. "In this, our first patient, we found that when there was elevated high-frequency activity (neural oscillations in the "gamma band," 30+ cycles per second) in the amygdala, that's when she got more depressed. And with her, it was a very strong relationship."



Here is the brain subnetwork involved in the closed-loop neuromodulation Sarah has received. The circuit it forms is shown in the green and red fiber tracts. The EEG biomarker signaling Sarah's shift toward depressed mood is detected by an electrode placed in the amygdala (pink circle, below); the site stimulated by DBS when the signal is detected, located in the ventral capsule, is shown by the orange circle, above.

In Sarah's case, the team was similarly fortunate to have found a single location—an area called the ventral capsule—where electrical stimulation at levels beneath the threshold of Sarah's ability to detect it, "took her depression away," as Dr. Krystal describes the effect.

"What was extremely moving for me," Dr. Krystal remembers, "and I think it had a big impact on everybody on the team and on our patient, was that in our early attempts to explore levels of stimulation in her ventral capsule,"—this was in 2020, when they mapped Sarah's responses to many stimulation intensities at many sites over 10 days—"she had a profound and immediate response. She said: 'I haven't felt this way in 10 years. I feel like my old self again!'"

The mapping procedure helped the team know which stimulation site or sites was most likely to help the patient without adding to her problems. At one point, Dr. Krystal recalls, "We stimulated in one place and she said, 'That feels really good—but I wouldn't want to *live* that way. It feels like I'm artificially happy and almost like it's a "high," which is not where I want to be.' Then we stimulated at another place and she said, "That feels really good and that's what I want to feel like."

IMPLANTING THE DBS DEVICE

In the second step of the process, it was time to implant a DBS neurostimulation device in Sarah's brain, a second invasive surgical procedure that followed the protocols which Dr. Chang had perfected, using the same DBS device to prevent seizures in epilepsy patients. The device is made by a company called NeuroPace, and the procedure for its use in epilepsy was approved by the FDA in 2019.

The team placed one electrode in Sarah's amygdala that would detect the biomarker signal—of an impending shift toward depressed mood; and one electrode in her ventral capsule, which would deliver precisely the stimulation that prior experiments had shown would make her feel better, in the way that she preferred.

"I wasn't sure how it was going to work," Dr. Krystal says.

What ended up happening, he says, "was the thing I had hoped for but wasn't really sure was possible. The biomarker we selected is close enough to the drivers of this patient's depression that she no longer gets depressed. She never even senses it. We are picking up something driving her depression and delivering stimulation before she has any sense of being depressed."

The device appears to be functioning much like a thermostat, which is a closed-loop system that senses the temperature in a room and then activates heating or cooling systems to keep the temperature in a desired range. In this case, the DBS device when triggered by the biomarker sensor appears to do a very good job keeping Sarah's depression "at bay," as she has described it.

It's not that she doesn't have shifts in mood. "I think it's very important to convey the idea that there is a difference between feelings like sadness, grief, and irritation, when bad things happen in our lives, and depression," Dr. Krystal observes. "Sarah tells us, 'I still have normal ups and downs. When something good happens, I feel good. When something bad happens, I feel bad. What's different now is that in the past there were all these triggers that would make me feel sad, and then another process where I would then get more and more depressed. That is not happening now.'"

Dr. Krystal makes approving reference to an observation once made by Dr. Helen Mayberg, a DBS pioneer. The purpose of the new treatment, Dr. Krystal says, is that "we're not trying to make people 'happy'; rather, we are trying to eliminate their depression.'"

This is what Sarah seems to be reporting, after living for a year with the implanted DBS device. She's not artificially happy in the sense that she reported when, in the preliminary stimulus-response mapping phase of the research, stimulation at a certain site made her feel "high"—not a feeling she desired and which actually made her feel uncomfortable.

According to Dr. Krystal, the amount of stimulation delivered in Sarah's ventral capsule by the DBS device has gradually dropped over time, although not dramatically so. While the antidepressant effect of the treatment was immediate, her symptoms of depression reached the point of remission about 4 months after the device was activated and she remains in remission at the time of this writing.

Dr. Krystal has always been a strong believer in integrating behavioral therapy (e.g., talk therapy) with therapies like brain stimulation. And in Sarah's case, to date, there is some evidence, he notes, that the "closed loop" delivering stimulation to her brain is generating modifications in the way she responds to typical triggers or challenges from day to day, for instance in the context of relationships with others. Such a changed response pattern could conceivably generate another kind of "closed loop," in the register of behavior. Events that formerly were triggers to a downward spiral in mood, leading to deep depression, are still capable of bothering Sarah, he says, "but now she responds differently because she's not depressed. This has the potential to shift the dynamic in her relationships, because now, people in her life are going to respond differently to her."

WHAT NEEDS TO BE PROVEN

There are many unknowns, beginning with the observation, in Dr. Krystal's words, that "we are not sure if we will ever see a response like this again, when we try this in other patients." It is not that he lacks optimism or enthusiasm; he and the team are simply unable to make projections based on results in a single patient. They were fortunate in finding a single biomarker signal in Sarah's case which reliably predicted a worsening of her mood; and equally lucky to have found a single spot in her amygdala where delivery of stimulation that she can't even feel is able to either counteract or cancel out that signal, so that Sarah is no longer depressed.

Among the outstanding questions: whether the region of the brain being stimulated adapts over time, decreasing or increasing the therapeutic effect, or if the relationship between brain activity and depression shifts, making the biomarker less effective. So far, this has not happened. Also, based on results in Sarah's case and in several other patients with whom the team is now working to deliver the same kind of therapy, it is not yet known if in different subjects—even those with similar symptoms—the

"For patients and their families, it's important to be clear: We won't know if this approach is going to be helpful to people generally at least until we do a careful, randomized, double-blinded placebo-controlled trial."

stimulation and biomarker sites will be the same, or similar, or entirely different. For this reason, the entire concept remains highly experimental.

Dr. Krystal and colleagues already believe, however, that multiple potential stimulation sites will probably be found in most patients. They say this based on having found several sites in Sarah's brain which to varying degrees and in the context of her different mood-states, had some beneficial impact on some of her symptoms.

Dr. Krystal makes clear that Sarah's depression tends to feature low energy and anhedonia (the inability to experience pleasure). Other patients say they are, in contrast, often anxious and hyper-aroused when depressed. Even Sarah has anxious moments, and interestingly, a stimulation site was found to diminish that feeling—but she said such stimulation had minimal impact on her depression.

It's possible, Dr. Krystal says, that as DBS devices become more sophisticated, they might be programmed to deliver pulses to address multiple symptoms at different moments. The condition for such a multi-faceted impact on symptoms would be identifying reliable biomarkers for each symptom and deploying sensors to detect them. No one at this point knows whether, if such treatment one day becomes technically possible, how addressing one symptom might impact a patient's other symptoms, in real time.

The purpose of the new treatment, Dr. Krystal says, is that "we're not trying to make people 'happy'; rather, we are trying to eliminate their depression."

Is "closed-loop neuromodulation" a breakthrough? Dr. Krystal is clear: "We've established a number of proof-of-principles. But it is very important to be circumspect, very cautious, because we are talking about one patient. In 5 years, if I can come back to you and report on experiences with more patients—20, or 100—then I will be in a better position to answer. But for patients and their families, I feel it's important to be clear that we won't know if this approach is going to be helpful to people generally at least until we do a careful, randomized, double-blinded placebo-controlled trial."

If more patients can be helped with the approach, then it is certainly possible that as the number grows, certain patterns could emerge, Dr. Krystal says. There are almost certainly different major subtypes of depression—and other psychiatric illnesses—so knowledge of what works in multiple patients with similar subtypes could reveal important things about where and when to apply therapeutic stimulation in the brain with DBS.

It's conceivable that the emergence of patterns, if they are robust, could eliminate the laborious and invasive "stimulus-response mapping" that Sarah bravely endured prior to implantation of the DBS device. Highly robust patterns could also conceivably inform the targeting of non-invasive stimulation for depression or other conditions.

While all of these possibilities are no more than matters of speculation at this point, the team is encouraged to see that when stimulation is effectively applied, results can be rapid and can be repeated consistently over time. This may also be the case in other patients and could occur in the application of this approach to the treatment of symptoms in other psychiatric illness.

Most immediately, Drs. Krystal, Chang, Scangos and colleagues are eager to discover the extent to which the method works for others who suffer from treatment-resistant depression, a highly complex illness that varies considerably among individuals. Depending on the results, they and other researchers will be equally curious to test the concept to address symptoms in other psychiatric disorders. ❖ **PETER TARR**

The 2021 International Mental Health Research Virtual Symposium

This year BBRF awarded its Outstanding Achievement Prizes in Mental Health to nine scientists for their extraordinary work in advancing psychiatric research. The Prizewinners serve as the featured presenters at the 2021 International Mental Health Virtual Symposium, along with the winners of the Pardes Humanitarian Prize in Mental Health. The Symposium is available to watch free On-Demand at https://www.bbrfoundation.org/event/international-mental-health-researchsymposium

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 are recognized for their research achievements in autism, depression, schizophrenia, bipolar disorder, and childhood psychiatric disorders, as well as cognitive neuroscience.

Dr. Jeffrey Borenstein, BBRF's President & CEO, opens the Symposium with a welcome to all attendees, noting that "The 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." He goes on to say that, "Through these extraordinary scientists, the world is gaining new insights and making significant advances in finding new treatments, cures, and methods of prevention for mental illness."

Dr. Herbert Pardes, President of the BBRF Scientific Council, provides opening remarks for the Symposium and notes that "We celebrate and honor the 2021 Outstanding Achievement Prizewinners for their scientific accomplishments and exceptional achievements in brain and behavior research. From their work, we are making great progress in our understanding of the brain and how to treat and potentially cure psychiatric disorders."

An overview of the entire Symposium is provided by **Dr. Robert Hirschfeld,** a BBRF Scientific Council member who has served as the moderator at the in-person Symposium since its inception more than 30 years ago.

The Symposium program features the prize-winning scientists, each speaking for about 20 minutes as they take the audience through a slide presentation explaining their research results. In the five pages that follow, we summarize the subjects covered in each Symposium talk.

2021 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH

Ezra S. Susser, M.D., Dr.PH
Columbia University,
Mailman School of Public Health
New York State Psychiatric Institute

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH

Lawrence H. Yang, Ph.D.
School of Global Public Health,
New York University

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH

Katherine E. Burdick. Ph.D.
Brigham and Women's Hospital
Harvard Medical School

Aleksander Mathé, M.D., Ph.D.
Karolinska Institute

Colleen A. McClung, Ph.D.
University of Pittsburgh
School of Medicine

RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH

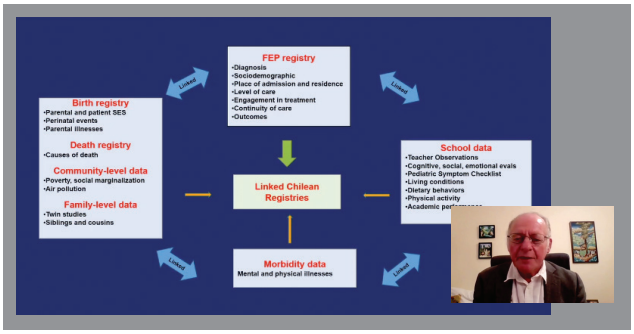
Kenneth A. Dodge, Ph.D.
Duke University

John T. Walkup, M.D.
Lurie Children's Hospital of Chicago
Northwestern University
Feinberg School of Medicine
Johns Hopkins University

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE

Elisabeth A. Murray, Ph.D.
National Institute of Mental Health

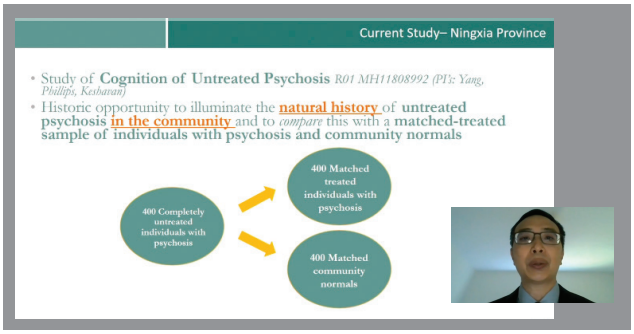
György Buzsáki, M.D., Ph.D.
New York University



Ezra S. Susser, M.D., Dr.PH, delivered a Symposium talk entitled *Living with Schizophrenia During the Covid-19 Pandemic*. Dr. Susser is a Professor of Epidemiology and Psychiatry at the Mailman School of Public Health at Columbia University, and at New York State Psychiatric Institute. He is also a 2008 BBRF Distinguished Investigator, 1995 BBRF Independent Investigator, and a 1987 BBRF Young Investigator.

Dr. Susser has contributed groundbreaking research on prenatal exposure to starvation and serologically-measured biomarkers in maternal serum samples. He has also done extensive research on neurodevelopmental disorders evident in childhood, such as autism spectrum disorders. His work has encompassed the determinants of the onset and the course of schizophrenia and childhood neurodevelopmental disorders at many levels. His past and current work has had a major focus on global mental health, in regions including Latin America, Sub-Saharan Africa, India, and China. It has also encompassed the HIV/AIDS and COVID-19 pandemics, including their relation to mental disorders.

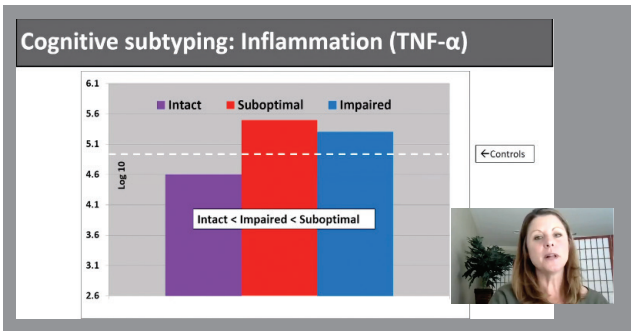
His Symposium talk discusses ways in which the pandemic has affected the lives of people with schizophrenia in the United States and has illuminated unmet social and medical needs. He explores how inequalities in pandemic response are reflected in the lives of people with schizophrenia across regions of the globe.



Symposium speaker **Lawrence H. Yang, Ph.D.**, addressed *Global Mental Health and Stigma: Advancing Science by Reaching the Most Vulnerable Groups with Psychosis*. Dr. Yang is an Associate Professor of the Department of Social and Behavioral Sciences at NYU–School of Global Public Health. Dr. Yang also directs the Global Mental Health and Stigma Program and is Associate Director of the Global Center for Implementation Science at NYU. He is also an Adjunct Associate Professor of Epidemiology at Columbia University. He is a 2010 BBRF Young Investigator.

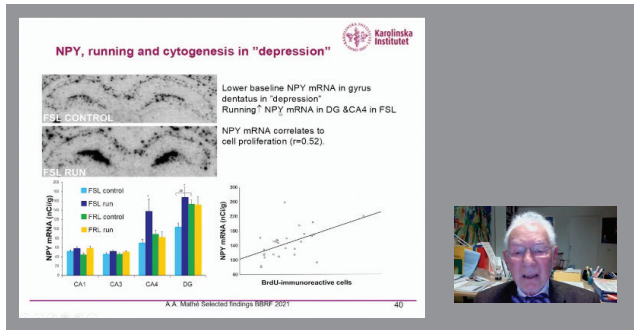
Dr. Yang's work focuses on psychosis, early detection of psychosis risk, and global mental health. He discusses his work evaluating the preventive potential and risks associated with the "clinical high-risk" state for psychosis (CHR) designation, particularly as it concerns potential stigma. He has completed the first and largest systematic study of stigma among youth identified as CHR in North America via a NIMH-funded grant. Since concern about stigma affecting designation of an individual as CHR is a significant barrier preventing its universal adoption, findings from this study could aid in guiding the implementation of this diagnosis among youth worldwide.

Dr. Yang also talks about his work examining cognition in people with untreated psychosis in China. This research examines the "natural state" of cognition in a large untreated community sample of individuals with psychosis who have not yet received antipsychotic medications; they are being compared with a treated sample and with healthy controls. Prior studies have not been able to disentangle whether cognitive deterioration associated with psychosis onset is predominantly attributable to the disease process or exposure to antipsychotic medication. Dr. Yang notes data showing that cognitive performance may continue to decrease as the duration of untreated psychosis becomes prolonged. These findings have the potential to shift scientific thinking about schizophrenia by suggesting possible processes contributing to pathophysiological variations later in the natural course of chronic psychosis.



Katherine E. Burdick. Ph.D., gave her presentation on *Cognitive Impairment and Functional Disability in Bipolar Disorder—How Can We Optimize Outcomes?* Dr. Burdick is the Jonathan F. Borus, M.D. Distinguished Chair in Psychiatry and the Vice Chair for Research in Psychiatry at Brigham and Women's Hospital (BWH) in Boston. She is also Director of the Mood and Psychosis Research Program at BWH and is Associate Professor of Psychology in Psychiatry at Harvard Medical School. She is a 2014 BBRF Independent Investigator and a 2005 BBRF Young Investigator.

Dr. Burdick explains that many patients with bipolar disorder suffer from persistent cognitive impairments, even during periods of remission, which contribute directly to functional disability. At the group level, the severity of these deficits is three-fourths to one full standard deviation below average; however, she notes, substantial heterogeneity exists. Some patients function very well throughout their lives, while others struggle to hold down a job. Dr. Burdick's work has focused on gaining a better understanding of these differential outcomes to identify: 1) which patients are likely to follow a declining cognitive and functional course and which are resilient; 2) clinical factors and biological mechanisms that drive poor outcomes in bipolar disorder; and 3) modifiable targets for intervention. Her overarching goal is to promote full recovery in every patient with bipolar disorder.

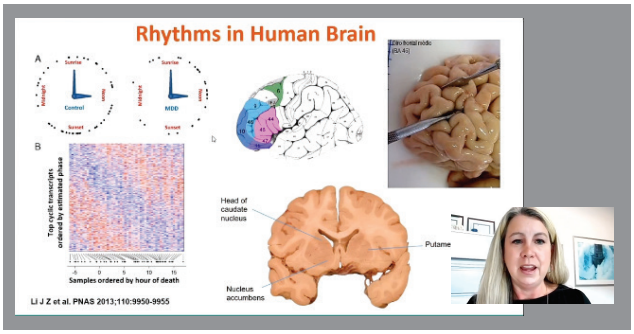


Aleksander Mathé, M.D., Ph.D. discussed *Neuropeptide Y in Normal Brain Function and in Mood Disorders*. Dr. Mathé is an Associate Professor of Psychiatry and a Professor and Head of the Neuropeptide Laboratory, Department of Clinical Neuroscience at the Karolinska Institute.

Dr. Mathé notes that our understanding of the pathophysiology of mood disorders remains limited and that optimal treatments continue to be lacking. While dysregulated neurotransmission may be sufficient to cause depression, he suggests, this is not a necessary condition; extensive evidence shows that changes in other endogenous compounds, such as neuropeptides, also play a role in depression.

Dr. Mathé focuses on research he has led on a class of compounds called peptides and discusses findings regarding neuropeptide Y (NPY). Peptides are chains of amino acids and are found in all living organisms. They play a panoply of basic physiological roles. NPY is of particular importance as it plays many roles in a wide variety of normal brain functions and is altered in depression and PTSD. Consistently in models of depression and chronic stress, researchers have observed decreased NPY expression in brain regions involved in depression and anxiety.

Dr. Mathé notes the dysregulation of the NPY system in preclinical models, and cites clinical data of reduced NPY in cerebrospinal fluid in depression and PTSD patients as well as findings that NPY treatment rescued pathology in animal experiments. He describes the testing of NPY treatment in depressed patients, including his team's demonstration in a double-blind placebo-controlled trial of NPY administration that NPY significantly alleviates major depressive disorder. He suggests that this is an opening to new treatment possibilities.

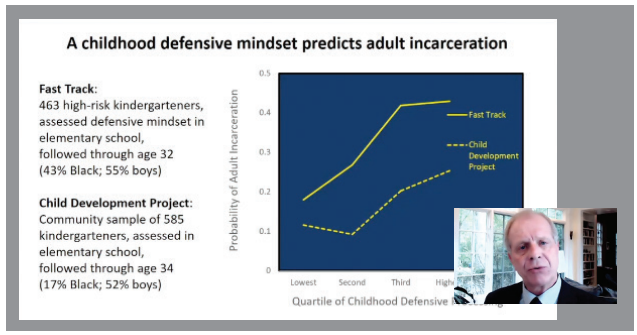


The Symposium talk given by **Colleen A. McClung, Ph.D.** addressed *Circadian Genes, Rhythms, and the Biology of Bipolar Disorder*. Dr. McClung is a Professor of Psychiatry and Clinical and Translational Science, and the Director of the Center for Adolescent Reward, Rhythms and Sleep at the University of Pittsburgh School of Medicine Department of Psychiatry. She is also a 2016 BBRF Independent Investigator and a 2007 and 2005 BBRF Young Investigator.

Dr. McClung has made important contributions to our understanding of the molecular basis of bipolar disorder, focusing on the role of circadian genes and central rhythm disruptions in the development and progression of this and other psychiatric diseases. Through work in mouse models, her team has identified some of the key mechanisms by which circadian genes are involved in the regulation of the brain's reward and mood-related circuitry. They have found that specific types of circadian gene disruptions in mice can lead to behavioral profiles which are strikingly similar to human mania or depression, suggesting a causative role for these disruptions.

In studies in human postmortem brain, they have identified the changes in molecular rhythms that occur in patients with psychiatric diseases, findings which have challenged ideas about what is causing these gene expression changes and how they are involved in disease pathology. This work has led to the development and testing of novel therapies.

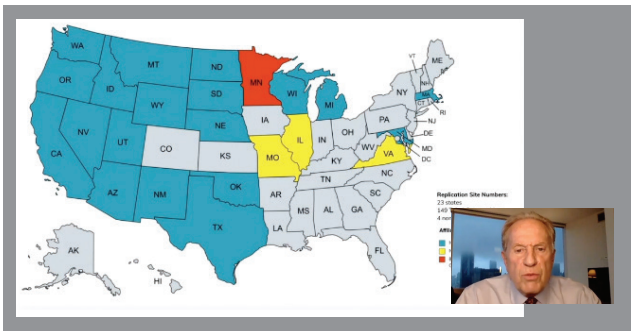
Dr. McClung discusses work from her group and others illustrating the strong relationship between circadian rhythm abnormalities and bipolar disorder. She notes data from her laboratory which has identified some of the ways that circadian genes control processes in the brain that regulate mood, and suggests how disruptions of their function can lead to mood-related episodes. She explains how this knowledge is informing development of therapeutics targeting the circadian clock for the treatment of bipolar disorder.



Kenneth A. Dodge, Ph.D. gave his Symposium talk on *The Development, Consequences and Prevention of a Defensive Mindset*. Dr. Dodge is the William McDougall Professor at the Sanford School of Public Policy at Duke University.

Dr. Dodge's laboratory experiments and longitudinal studies have led him to formulate a social information processing model of the development of aggressive behavior that asserts that early adverse life events lead some children to develop a defensive mindset that includes hypervigilance, hostile attributional bias, and impulsive decision making. This pattern, in turn, leads to increasingly violent behavior across the lifespan. Dr. Dodge's work has led him to develop interventions to prevent aggressive behavior and to pursue the prevention of early child abuse.

In his presentation, Dr. Dodge notes that the difficulty of treating chronically violent adolescents has led to the search for an understanding of how this pattern develops and might be prevented. Laboratory studies show these children enter social situations with a defensive mindset that includes hypervigilance to threat, a bias to attribute hostile intent to others, and impulsive decision making that ignores long-term consequences in favor of immediate safety. Although adaptive in truly threatening circumstances, a defensive mindset leads to social failure in the long term. Longitudinal studies show that early adverse events such as physical abuse and chronic peer rejection predispose children to develop a defensive mindset. According to Dr. Dodge, structured intervention can steer this mindset toward more adaptive behavior, with modest success. Greater promise, he contends, lies in prevention of child abuse in the first several years of life.

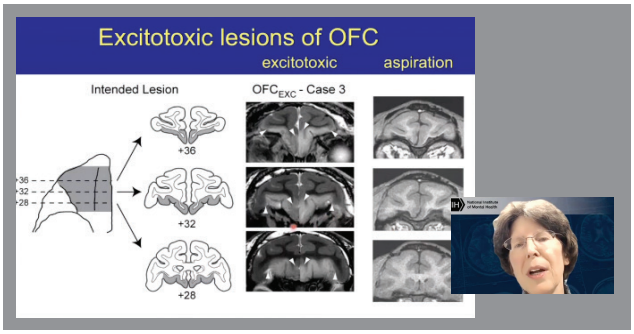


The Symposium presentation given by **John T. Walkup, M.D.** was titled *From Clinical Trials to Population Health: Closing the Mental Health Gap and Meeting the Needs of Children and Families*. Dr. Walkup is Head of the Pritzker Department of Psychiatry and Behavioral Health at Ann & Robert H. Lurie Children's Hospital of Chicago and a Margaret C. Osterman Professor of Psychiatry and Behavioral Science.

Dr. Walkup's work with movement disorders, specifically Tourette disorder, uniquely spans psychiatry, child psychiatry, and neurology. His expertise in child and adolescent psychiatry clinical trials focuses on the development and evaluation of psychopharmacological and psychosocial treatments. He also has been involved in developing and evaluating interventions to reduce the large mental health disparities facing Native American youth, specifically focusing on drug use and suicide prevention.

Dr. Walkup began by studying Tourette disorder and expanded his focus to include obsessive compulsive disorder, anxiety disorders, ADHD in young children, depression, suicide, and bipolar disorder. These early studies significantly expanded the evidence base that clinicians worldwide rely on to effectively treat children with psychiatric disorders.

Dr. Walkup discusses how he pursued a concurrent line of research with the team at the Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, to develop interventions delivered by members of the Native community that reduced the substantial mental health disparities facing Native American youth in substance use and suicidal behavior. This work has direct applicability to the population health approaches he is now using in Chicago. He stresses that locating mental health care in the community and focusing on prevention and early intervention holds promise to improve access and reduce the mental health disparities facing all youth and families who live in large urban communities.

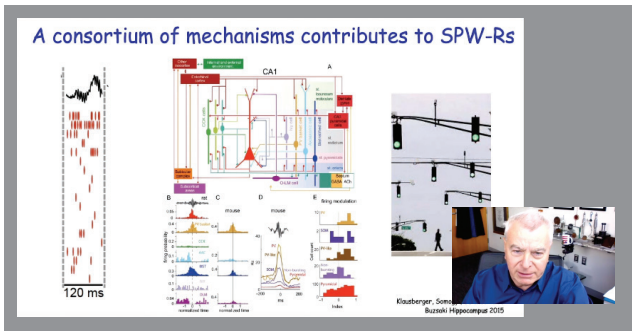


Elisabeth A. Murray, Ph.D.'s presentation was titled *From Knowledge to Action: Roles of the Primate Prefrontal Cortex*. Dr. Murray serves as the Chief of the Laboratory of Neuropsychology and Chief of the Section on the Neurobiology of Learning & Memory at the National Institute of Mental Health.

Dr. Murray and colleagues seek to develop a causal theory of the functional interactions between the amygdala and the prefrontal cortex (PFC). Specifically, they seek to understand how the primate prefrontal cortex and amygdala process feedback, produce decisions, and generate both autonomic and emotional responses.

In her presentation, Dr. Murray explains that some of the most sophisticated behaviors of primates, including humans, depend on the prefrontal cortex, yet there are few well defined and experimentally verified functional specializations within the primate PFC, especially at a causal level. Recent work from

her laboratory has contrasted the functions of two parts of the PFC: the ventrolateral PFC (VLPFC) and the orbital PFC (OFC), which they found play complementary roles in updating representations of value used to translate acquired knowledge into behavioral goals for action. Dr. Murray explains this work and another study, which addressed social cognition. In the second study she found that the anterior cingulate cortex (ACC) is essential for expressing prosocial tendencies. These findings suggest that three parts of the primate PFC make different contributions to goal selection, which collectively promoted the survival of our anthropoid ancestors and influence human behavior to this day because we have inherited these areas from those ancestors, albeit in modified form.



György Buzsáki, M.D., Ph.D., discussed *Preconfigured Dynamics in Our Brains* at the Symposium. Dr. Buzsáki is the Biggs Professor of Neuroscience at the NYU Neuroscience Institute, Department of Neurology at New York University, Langone Medical Center.

In the early 1980s, Dr. Buzsáki introduced the concept of feedforward inhibition, which is now a widely recognized property of neural circuits. He went on to develop the two-stage model of memory formation in the hippocampus, which is still the dominant model for consolidation of hippocampal memory. More recently, he has developed a conceptual framework to understand the fundamental synaptic mechanisms underlying brain rhythms, including theta, gamma, and sharp-wave ripple oscillations.

In his talk, Dr. Buzsáki states that skewed distributions of anatomical and physiological features permeate nearly every level of structural and functional brain organization. This organization implies that the brain comes with a preconfigured and self-organized dynamic that constrains how it acts and views the world and stores experiences. Instead of constructing representations from scratch, an alternative view, he explains, is that preexisting "nonsense" brain patterns become meaningful through action-based experience. He discusses recent experiments that support this framework.

The Symposium also featured presentations from the winners of the 2021 Pardes Humanitarian Prize in Mental Health and recipients of the Honorary Pardes Prize, who discussed personal stories of living with mental illness and their work in research and helping individuals living with illness (see pages 18–20).

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– Miriam Katowitz, BBRF Board Vice President

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2021 Pardes Humanitarian Prize in Mental Health Awarded to Three Women Striving to Improve Treatment, Expand Access, and Empower People with Psychiatric Illness

On September 28, 2021 BBRF announced the winners of the 2021 Pardes Humanitarian Prize in Mental Health. This year's winners are: **Kay Redfield Jamison, Ph.D.**, for her profound contribution to mental health awareness as an advocate drawing on her own struggles with bipolar disorder; **Elyn R. Saks, J.D., Ph.D.,** for her pioneering work as both a therapist and legal advocate for the mentally ill while living with schizophrenia; and **Charlene Sunkel**, Founder and CEO of the Global Mental Health Peer Network, for helping to empower other people who live with mental health problems.

Three 2021 Pardes Honorary Prize Recipients were also announced and acknowledged for their groundbreaking work in mental health. They are: **John M. Davis, M.D.**; **Michael R. Phillips, M.D., MPH**; and **Norman Sartorius, M.D., Ph.D., FRCPsych**.

The Pardes Humanitarian Prize in Mental Health carries an honorarium of $150,000, and is awarded annually to recognize individuals whose contributions have made a profound and lasting impact in advancing the understanding of mental health and improving the lives of people 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.

In making the announcement, Dr. Herbert Pardes, President of BBRF's Scientific Council and for whom the prize is named, said, "The 2021 Pardes Prize recipients have applied their scientific knowledge, deep understanding of human behavior and compassion for people to improve the lives of millions suffering from mental illness. We applaud their important work."

BBRF President and CEO Dr. Jeffrey Borenstein added, "These talented and accomplished leaders have expanded our scope of mental illness treatment globally. They serve as extraordinary advocates for mental health and exemplify how to use our knowledge for the greater good. They truly represent what it means to be world-class scientists and compassionate humanitarians."

PAST PARDES PRIZE WINNERS

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.

THE 2021 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORING

KAY REDFIELD JAMISON, PH.D.

Dr. Jamison, a clinical psychologist, writer, and professor at Johns Hopkins University, serves as an inspiration to countless people living with bipolar disorder, and has helped transform how society sees those living with mental illness.

She has made a profound contribution to mental health awareness through her autobiography, *An Unquiet Mind*, detailing her own struggles. With remarkable honesty about very personal elements of her experience, Dr. Jamison courageously identifies stigma as prejudice and makes a case for the relationship between bipolar disorder and creativity, which in turn has made it easier for many people to enter into treatment.

She describes the relationship between bipolar disorder and creativity in her book, *Touched with Fire: Manic-Depressive Illness and the Artistic Temperament*, and elaborated further on this in her 2018 Pulitzer Prize finalist biography of the poet Robert Lowell. Dr. Jamison is a renowned spokeswoman and advocate for the mentally ill who inspires us to use our knowledge toward the greater good for all humanity.

THE 2021 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORING

ELYN R. SAKS, J.D., PH.D.

Dr. Saks's pioneering contributions to our understanding of mental illness are seen through her work as a legal advocate for the mentally ill, a volunteer at a psychiatric hospital, a therapist, an educator, and as an author.

Her best-selling book, *The Center Cannot Hold: My Journey Through Madness*, in which she provides a first-person account of her transition to psychosis and a lifetime spent as a person living with schizophrenia, has helped to transform our thinking about mental illness.

A distinguished law professor and academic lawyer, Dr. Saks uses her position to reduce and eliminate stigma, and to make psychosis more approachable and understandable to others, bringing a wisdom that reflects both her experience and compassion. Dr. Saks has made a profound and lasting contribution to mental health awareness in her profession, her publications, and her daily work, with a deep impact on individuals, families, and the global community.

THE 2021 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORING

CHARLENE SUNKEL

Charlene Sunkel is the Founder and CEO of the Global Mental Health Peer Network, the first group of its kind in the world that promotes and supports the empowerment of people who live with mental health problems. Ms. Sunkel herself has the experience of living with schizophrenia and is a great leader not only in her country of South Africa, but also around the world.

In South Africa, she has worked for a number of mental health advocacy organizations and collaborated with other civil society groups, academic centers, and the government. She also served on the South African Presidential Working Group on Disability and Ministerial Advisory Committee on Mental Health.

At the global level, Ms. Sunkel has held a number of leadership roles including her position as a Commissioner on the Lancet Commission on Global Mental Health and Sustainable Development. A recipient of numerous international awards, she has, most of all, made it impossible for any global mental health initiative to be implemented without the active and meaningful involvement of people with lived experience.

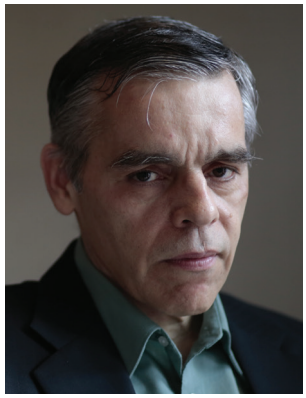
2021 PARDES PRIZE HONORARY RECIPIENTS

John M. Davis, M.D.

Dr. Davis is a tireless advocate and humanitarian in the mental health field, including his support for programming and services that provide better treatment for people with mental illness internationally. A mental health lobbyist, a defender of forensic psychiatry, and a devoted champion of young scientific investigators, he is the author of the first science-based textbook on psychopharmacology as a guide for psychiatrists seeking to use medications more effectively.

Dr. Davis's support of others has made it possible for many professionals to advance care for the mentally ill, for institutions to remain dedicated to their care, and for elected officials to understand and support mental illness programs.

Michael R. Phillips, M.D., MPH



Dr. Phillips has dedicated his professional and personal life to serving as a mental health advocate in China. Having lived most of his career there, Dr. Phillips has not only brought mental health issues in China to the attention of the world; he has also provided leadership on culturally sensitive interventions to address the problems he uncovers.

His advocacy includes coordinating multi-center collaborative projects on suicide, depression, and schizophrenia, as well as running research training courses for Chinese and foreign graduate students, thus improving the quality, comprehensiveness, and access to mental health services around the country. By inspiring generations of Chinese psychiatrists to conduct research and publish their work, he has utilized the strengths of academic psychiatry to make a major impact on mental health care in China and beyond.

Norman Sartorius, M.D., Ph.D., FRCPsych

Dr. Sartorius has helped to shape the field of mental health and psychiatry over the past 50 years through his humanitarian efforts, research, and work to advance the understanding of mental health. He has provided hope and healing worldwide for people who are living with mental illness, particularly those who live in low-income countries.

Dr. Sartorius served as the first director of the World Health Organization's Department of Mental Health, bringing together a variety of stakeholders in areas of mental health classifications, human rights, epidemiology, ethics, stigma, comorbidity, workforce development, and the optimization and humanization of treatment. His tenure launched the world's largest program against the stigma of mental illness and key initiatives designed to protect the human rights of the mentally ill.

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

❖ **LAUREN DURAN**

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—Barbara Toll, Board Member & Research Partner

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What Research Tells Us About Cannabis Use — And What Parents Should Consider

Q&A with Martin Paulus, M.D.

Scientific Director and President
Laureate Institute for Brain Research
Deputy Editor, JAMA Psychiatry

2000 BBRF Young Investigator

Martin Paulus has published over 300 scientific papers and has been funded continuously by federal grants since 1997. Among his current projects, he is a member of the NIMH's Adolescent Brain Cognitive Development (ABCD) study, which is closely following some 11,000 youths from age 9–10 to adulthood to determine how the brain changes during the course of adolescence and how these changes put adolescents at risk for substance use. The Paulus lab is also engaged in several studies involving the impact of cannabis upon the brain, as well as research exploring the possible utility of pharmacological modifiers of the body's own cannabinoid system to treat anxiety and depression.

Dr. Paulus, cannabis is a substance that until recent years was illegal. Today, many states have legalized cannabis, some for recreational use, some for "medicinal use" only. Either way, this represents a major shift. We wonder whether the trend to legalize cannabis is accompanied by a solid body of research that would assure the parents of an adolescent, for example, that the use of cannabis from an early age is harmless.

The short answer is that research to date is not able to support such a reassurance. I don't want to be an alarmist, but it is crucial that we try to understand what research so far has revealed about cannabis, and in that context, to consider why people use cannabis and what its impacts are on the brain and behavior—both in adults and young people. Also, it's important to try to distinguish among those who use cannabis. Research suggests that some people are likely at greater risk than others.

In your own research, we understand that you and colleagues are investigating the possibility of using modifiers of the body's own, naturally occurring cannabinoid system to treat anxiety and depression. We will write at a later date about this very interesting work. In this conversation, we'd like to focus on cannabis that is derived from plants, and how ingesting it—whether by smoking it, vaping it, or eating it in the form of various foods or even cannabis-infused candies—may or may not pose risks for young people, in particular. After decades of public discussion and debate about cannabis, we're

curious: why hasn't research managed to resolve the ambiguities about safety and risk?

There is much we still do not know, and there are reasons for this. As you noted, many of the states have moved ahead quite vigorously to legalize the use of cannabis and cannabis-based products such as those containing CBD (cannabidiol, a non-psychoactive component in cannabis). But there is a real disconnect between liberalized state laws and federal law.

Federal law still considers cannabis a Schedule I substance, considered to have a high potential for abuse and no currently accepted medical use. That's the same designation that is given to LSD, heroin, cocaine, mescaline, and heroin. Because cannabis is still a Schedule I drug, it is very difficult to do federally funded studies with it. You need to have a special license from the Drug Enforcement Administration. These are hard to obtain. Also, the federal classification of cannabis means that researchers, when they are authorized to study it, have to obtain it from regulated federal sources. The National Institute on Drug Abuse (NIDA) makes cannabis available to researchers, but the concentration of THC is much lower, meaning it has much less effect on users compared with the cannabis that people regularly purchase and consume in various forms today. So you're not really studying the same drug that people are using on a day-to-day basis.

Is the cannabis that is now being sold to the public different than the cannabis people consumed in the 1970s and 1980s?

Today's cannabis is far more potent. THC is the main psychoactive ingredient in cannabis. Its concentration in street-use cannabis was in the single-digit percentage range in the '70s and '80s. But the formulation that people buy today in, say, Colorado or California, or even here in Oklahoma, is much more concentrated, with THC in the 20%–30% range.

We have heard that in some formulations of the product—the "concentrate," for example—the THC content can be 70% or higher.

This is indeed true. The point is that the makeup of the drug itself has changed dramatically over the years. There are several things to consider about this. One is that when people say, "There's nothing wrong with cannabis; I smoked it in the '70s, so I know it's fine," they are talking about a different era that may not be a good guide to potential risks of the cannabis in use today. Another is that not having access to the currently consumed form of cannabis due to federal classification is a real problem for research; it makes it very difficult to study the long-term health impacts, positive or negative, associated with cannabis consumption.

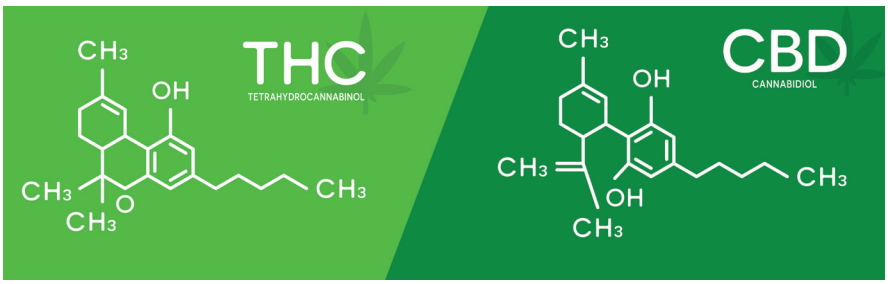
A bill has been drafted by several senators to "de-schedule" cannabis by removing it from restriction under the Controlled Substances Act. What are your thoughts on this?

This would be of great benefit to research because we would then have the chance to much more thoroughly research cannabis—

which must be the basis of responsible recommendations to the public.

Before we go further, can you tell us a bit about how cannabis works? And about the body's own cannabinoid system, called the endogenous cannabinoid system?

THC, the main psychoactive ingredient in the cannabis plant, is one of over 100 known compounds in the plant that affect the body in one way or another. CBD—cannabidiol—is the other main ingredient of cannabis, considered by some people to be "the good sister" of THC. It has no psychoactive effects and may have some therapeutic effects in the brain and body, although this remains to be proven.



THC is the psychoactive ingredient in cannabis; CBD (cannabidiol) is non-psychoactive, but claims of its medicinal properties are unproven.

The human body has its own system that produces cannabinoids—the endogenous cannabinoid system. There are two cannabinoid receptors, CB1 and CB2, which are widely distributed throughout the brain. These receptors are where the cannabinoids made by the body "dock." These receptors are also occupied when we ingest plant-based cannabis. I'll return to this later, but for now I want to note that ingesting cannabis creates competition for the receptors with the body's own cannabinoid system.

Why do we even have an endocannabinoid system? Why does the body make this substance?

That's a good question, because it helps explain why people seek to supplement it by ingesting plant-based cannabis. There are many systems in the brain that have evolved over the eons to enable individuals to modulate their responses to the vast range of stimuli and situations that we confront. Think of the many neurotransmitter systems like dopamine and serotonin. Or CRH, the corticotropin-releasing hormone, which helps modulate the response to stress. Or norepinephrine, which is released when we need to pay attention to something. Each of these systems has specific pathways and receptors that make their effects possible. The endocannabinoid system is one of these many regulatory systems. It's involved in our level of approach or avoidance toward an object or a situation that may make us anxious.

In the slowdown period following exercise, for example, there's an increase in the level of naturally occurring cannabinoids in the system. The system scales our readiness for relaxation in the context of the environmental conditions we are facing—as I said, one of many systems that help adjust the readiness of the brain to perform different operations.

What about the urge to smoke marijuana? What is behind the urge, biochemically?

Say I'm going out to a party and I know I will need to socialize, talk to people. That can cause some people to experience stress, anxiety. A person might worry, "Other people will be judging me." Many people ingest cannabis to feel more relaxed when they feel stress.

Is it correct to say this comes from the experience of experimenting with cannabis and feeling the "high"?

Yes, but smoking cannabis, and especially the high-potency cannabis that is everywhere today, is like using a very blunt instrument to deal with stress. Cannabis with single-digit THC concentration is one thing—somewhat akin to taking an alcoholic drink. But smoking high-potency cannabis, some recent research has suggested, carries risks. People with mild anxiety might get some relief from ingesting cannabis, but taking high THC-concentration cannabis will flood the body's cannabinoid receptors and may dysregulate the body's own endocannabinoid system. Then, rather than reducing anxiety, you may end up becoming much more anxious.

It's like two sides of the same coin. You ingest cannabis to deal with anxiety; but high-potency cannabis has the potential to make you even more anxious. Why?

"Ingesting high THC-concentration cannabis will flood the body's cannabinoid receptors and may dysregulate the body's own endocannabinoid system."

A bit of biochemistry will help to explain this seeming paradox. The body's own cannabinoid system is finely balanced, with action at the two receptors, one of which is active on the psychoactive side, the other the non-psychoactive side. THC affects one of the two receptors, the CB1 receptor. The body makes an enzyme called FAAH whose action reduces the level of endocannabinoids in the system. It attaches to endocannabinoid molecules and thus changes their shape, making it impossible for them to dock at the receptors.

This is how the body regulates the action of its own cannabinoids. When you ingest high-potency cannabis, the endogenous system says, "there's too much coming our way; we have to try to limit the impact." What's the consequence? In response, the system down-regulates itself—it tries to become less sensitive so that you are not overly stimulated. But this creates a new problem. This means that the body's own system, after the "high" has ended and when it next has to respond to stress, is starved of endocannabinoids. This can make one irritable; it is what happens when high-potency cannabis use leads to withdrawal. The user may be relaxed when ingesting the drug, but afterward may feel anxious, stressed, and irritable.

So you have bombarded the system by ingesting high-potency cannabis; the body's own cannabinoid system has responded by down-regulating itself; and now you have dysregulated the system, creating an imbalance that only ingesting more cannabis can (temporarily) relieve.

Both THC and CBD (cannabidiol) can now be ingested in various non-traditional ways, from vaping THC concentrate to eating sugar-coated candies. These products are unregulated.

Yes, this is the risk of becoming *tolerant* of high-potency cannabis with high THC concentration. Your irritability is the consequence of coming down from your high and then saying, "Okay, let me take some more, so I can feel good again." The endocannabinoids you make naturally can no longer compete; they're sort of side players now, and so what would naturally help you to relax—the body's own cannabinoid system—doesn't do that anymore. The body's own system is very sensitive and quite subtle; it has evolved to balance itself.

One of the tasks of current research is to discover more about the impact of high-potency cannabis on the natural balance, and what the potential impacts are, and how these might affect different users. We want to know who is at risk, when, and why.

In your work for *JAMA Psychiatry*, you have edited several papers on cannabis over the last two years. Please tell us about what these have revealed about these and related questions. Then perhaps we can consider "best advice," based on this evidence.

In June 2020, we published a paper based on research led by Kent Hutchinson, Ph.D., of the University of Colorado. He has done some fantastic work, doing something very difficult to do, which is using the real cannabis product—the cannabis that people actually use. The study involved 121 healthy volunteers, who were randomly

THC in highly concentrated form (left)—as high as 70%–90%—can be smoked or vaped (right). Research is beginning to explore the potential risks posed by such products.

assigned to groups that purchased and then consumed either relatively low-potency cannabis or a kind of cannabis we call "concentrate," with a much higher THC content.

We read in that paper that in the "lower-potency" cannabis group, the THC concentration ranged from 16% to 24%—much higher than the single-digit THC percentages in the cannabis commonly used decades ago. In the "concentrate" group, which Dr. Hutchinson and colleagues note is "made by extracting plant cannabinoids into a form with a much higher THC concentration," THC content was a remarkable 70% to 90%. Even though these concentrates are in widespread use, "there are virtually no data on the relative risks associated with using these higher-strength products," the researchers note.

They found that in the short-term, cannabis use *in both groups* resulted in acute delayed memory impairment as well as impairment in balance. These effects are well known. More surprising was that the lower- and higher-concentration types of cannabis resulted in similar levels of intoxication, as measured by the reports of the participants themselves.

This seems counterintuitive. But the researchers' commentary in the paper echoes what you told us about the biochemistry. They note that high-potency users may develop a tolerance to the effects of THC. The similar levels of intoxication would suggest that the cannabinoid receptors might become saturated with THC in high-potency users, meaning that beyond a certain level, there's a diminishing effect of additional THC.

Yes. And so one important implication of this study is that high-potency users may be at a higher risk for developing cannabis-use disorder because of increased exposure to THC. This is important because in Colorado and other places, concentrates have become popular. So for me, it's a cautionary tale; we need to know more about the long-term consequences of exposure to high-potency cannabis.

Tell us about the second of the *JAMA Psychiatry* papers you edited.

Published in May 2020, it comes from researchers in England, who looked at mental health consequences of high-potency cannabis use in adolescents. In over 1,000 participants, 141 (13%) reported using high-potency cannabis. After adjusting for variations in the low- vs. high-potency users, the researchers found that there was a significant elevation in anxiety disorders among the users of high-potency cannabis. We've discussed why this might be the case: the system down-regulates itself after being flushed with so much THC; this dysregulation impairs the function that the system normally plays in relaxing us—resulting in anxiety.

The same paper also noted that use of high-potency cannabis was associated with increased *frequency* of cannabis use. So, this paper adds to the potency question a question about frequency. If you use high-potency cannabis a lot, you may be at increased risk of developing cannabis-use disorder.

That's right.

And now tell us about a third paper, from Denmark, published in *JAMA Psychiatry* in September 2021. It takes up the very important question of whether there is a relationship between cannabis use and schizophrenia.

It's a pretty remarkable study because it covers the entire Danish population—the national health records of over 7 million people. This gives you enormous sensitivity to detect relationships that otherwise you wouldn't be able to detect. Also, the researchers were looking over a period of time—all people born before

the end of 2000 who were alive and reached their 16th birthday at any point between 1972 and 2016.

The records enabled them to see that there was both an increase in cannabis use in this period, and also a slight increase in the prevalence of schizophrenia.

They were able to conclude, after doing a great deal of statistical work accounting for all kinds of variables with the ability to distort the analysis, that about 8% of the schizophrenia cases in Denmark over the period covered by the study could be causally related to cannabis use.

What does this mean? We know that schizophrenia is a complex disease with a strong genetic component and a developmental component—both *in utero* and early childhood. It also has a social component, having to do with what your brain is exposed to as you go through life. All these things matter.

All of this suggests that there is a certain threshold of risk factors (let us assume it varies among individuals)—a threshold beyond which a person develops schizophrenia. For example, you may have a certain genetic risk, you may experience some developmental event when still *in utero*, and you may have grown up in a high-stress environment. If you had two of these you may not develop the illness but if you had two and you also used cannabis you may develop schizophrenia. In this hypothetical, which I mention for explanatory purposes, the additional cannabis added to the existing risk factors leads to an active disease process.

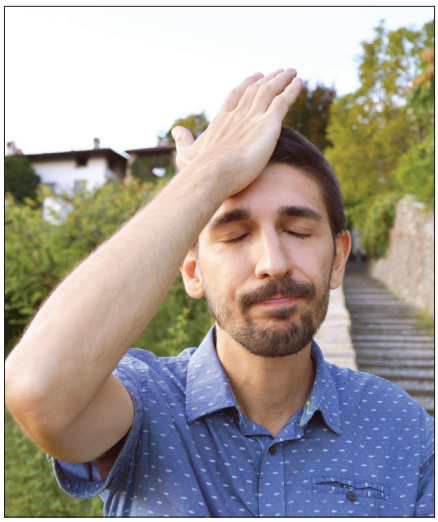
To clarify what you just said about a threshold: the Danish study tried to account for all of the background factors, and then looked at the incidence rate of schizophrenia across the population. They wanted to know how many of the cases during the study period could be attributed to the potential risk factor of cannabis use.

Yes. And, as we discussed, when you expose yourself to high-potency cannabis, the endocannabinoid system changes; the stress and relaxation systems are imbalanced. That is on top of whatever environmental, social, developmental, and genetic factors affect you as an individual. What this paper suggests is that the extra push provided by the unbalancing of the endocannabinoid system may put some people—8% in this study—over the edge and into schizophrenia. And that is a tragedy. I say this having worked with many first-episode schizophrenia patients.

Is there a lesson in this, then, even though this result needs to be verified in other populations?

What you want to tell a parent is: "Listen, I am not saying everybody who uses high-potency cannabis will develop schizophrenia,"—not by any means. But if you notice certain aspects of your child, odd behaviors, difficulty with differentiating between real and imagined events, having few friends, or having a difficult time experiencing positive feelings, you need to consider that cannabis might make these symptoms worse, not better.

It may be that an unhappy or anxious adolescent may be looking for something to make them feel better. In fact, as we have noted, using high-potency cannabis may make a problem like anxiety worse because it dysregulates the brain even further and in some number of cases, not a trivial number if this third study is right, it may contribute to a process that results in schizophrenia.



Two well-documented short-term effects of cannabis ingestion are memory loss and problems with balance. Less well understood are potential risks of developing cannabis-use disorder or exacerbating an underlying vulnerability to mental illness.

"Research is needed to discover more about the impact of high-potency cannabis on the body's cannabinoid system, what the potential impacts are, and how these might affect different users. We want to know who is at risk, when, and why."

Regarding the risk of high-potency cannabis raising the risk not of schizophrenia but of cannabis use disorder, how would you characterize cannabis? Where would you place it on the scale of addictiveness?

Ten years ago, I would have put it on the low end of the scale because of the relatively lower potency of the drug then in common use. Today we confront a changed situation.

As far as parents are concerned, I think it is useful to think about the question of why adolescents start to use cannabis. Clearly, there's a social component; "I'm part of a group and they're using it, so I'll try it." Another motivation is to address a problem. Something doesn't feel quite right; the child wonders, "How can I feel better?" Through trial and exploration, they come to cannabis. And they might say, "When I smoked it, I felt pretty relaxed. I didn't feel bad. It must be a good thing."

For the parent, I think it is the latter situation that you want to be alert to. When the child is not feeling right, not feeling good, is searching for something. That's when I think it's important to have a conversation about "What's happening?" "What is not feeling right?" "Is it excessive anxiety? Are you having odd thoughts? Mood swings? Unable to sleep?" You want to try to find out what drives the child to think that cannabis is really doing something for them.

How general is this advice?

As I have noted, we still need to do more research, with the kind of cannabis product that is now in common use. It is also crucial to remember that everyone's brain is a little different. We have to allow for the possibility that for some people, the endocannabinoid system may be so fragile that it may be problematic to take any cannabinoids at all. We don't know yet who these people are and that points again to the need for more research. We especially need to identify those people for whom cannabis might put them over a threshold and into a tragic illness.

We want to have empirical evidence about the responsible use of cannabis. If we do find that there's significant potential of negative consequences for some people, then we have to be prepared to say, "At these doses and this frequency, at this potency, we need to be very, very careful." Like with alcohol: some people are able to consume alcohol on a regular and recreational basis and maintain function over periods of time. Some people cannot. We need to identify, for cannabis, who these people are.

All the more because I don't think we can turn the tide back. It appears that cannabis, recreational cannabis, will be legal in most states within the next 10 years. It's going to be available and people are going to use it. We have to know what it does to us so we can act responsibly.

For parents, what is your suggestion based on what we know today?

Somewhat similar to what I say regarding the use of computer and smartphone "screens" and social media, which have created a lot of worry. What I always say is: "Find out what your kid is doing and why, and how it makes them feel. By understanding that process, you can, as a parent, have a lot more insight and can potentially judge if there is or is not a problem. I should say, at the same time, that in a study I did with Dr. Susan Tapert at UCSD, in which we looked at cannabis users in high school, the striking thing to me was that in most cases the parents had no idea. The kids were using and the parents did not know.

This is a major missed opportunity. It's really important between parents and children to know what is happening and why; what the experience is like; and to do this in a non-judgmental way. To judge or to lecture accomplishes nothing. It shuts down the conversation.

❖ **WRITTEN BY PETER TARR AND FATIMA BHOJANI**

Recent Research Discoveries

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

Non-Invasive Brain-Stimulation for Treatment-Resistant Depression Enabled 79% to Experience Remission

In its first randomized, placebo-controlled test, an enhanced form of non-invasive brain stimulation called SNT (Stanford Neuromodulation Therapy, formerly called SAINT) generated "a large antidepressant effect" that enabled 79% of treatment-resistant patients to experience remissions within 4 weeks of the conclusion of the 5-day course of treatment, its developers have reported in the *American Journal of Psychiatry*.

A research team at Stanford University led by **Nolan R. Williams, M.D.** first reported in April 2020 on their experimental protocol designed to improve the effectiveness of FDA-approved rTMS (repetitive transcranial magnetic stimulation) therapy. Dr. Williams is a 2018 and 2016 BBRF Young Investigator and winner of the 2019 BBRF Klerman Prize for Exceptional Clinical Research. The team also included **Alan Schatzberg, M.D.**, a member of BBRF's Scientific Council.

The initial test reported in 2020 was "open-label," conducted in 21 patients with treatment-resistant depression who knew they were receiving the new therapy, as did the doctors providing the treatments. Optimized for each patient who receives it, the new approach delivers a full course of treatment, using multiple treatments sessions per day, over a 5-day period, compared to single-session treatments over 4 to 6 weeks in standard rTMS therapy.

In the test reported in 2020, by the end of the 5th day of treatments, when the course was completed, 90% of the participants were in remission. The newly reported test of the therapy was a "gold-standard" placebo-controlled double-blinded trial involving 29 patients with treatment-resistant major depression. Fourteen of the participants received SNT, while 15 received a placebo version of it that was designed to be indistinguishable from active SNT, both to recipients and the doctors administering the treatment. Trials like this are of superior value in research because they attempt to control for the placebo effect, which tends to elevate success rates.

The results of this trial were also impressive. For those in the group that received active SNT treatments, 78.6% experienced remission at some point during the 4 weeks after completing the 5-day treatment course. The remission rate in the placebo group was so much lower (13%) that the trial was halted early, so that all participants could have the opportunity to benefit from SNT. Over a 4-week period following the treatment course, over 85% of participants who received SNT responded, meaning that their depression, as measured on a standard symptom scale, was reduced in intensity by 50% or greater.

In the view of the research team, both the brevity of the SNT treatment course, compared with standard rTMS therapy, and its high rate of effectiveness, "presents an opportunity to [use SNT] to treat patients in emergency or inpatient settings [e.g., in-patient psychiatric facilities] where rapid-acting treatments are needed."

In treatment-resistant patients with major depressive disorder, standard rTMS on average enables an estimated 20% to achieve remission, although it helps a larger percentage of individuals who are not treatment-resistant.

SNT is a more efficient form of rTMS, its developers say. It employs iTBS (intermittent theta-burst stimulation) in 10 treatment sessions daily, each lasting 10 minutes and spaced

50 minutes apart. This protocol is the result of experiments by Dr. Williams and his colleagues aimed at delivering a higher overall dose compared with standard rTMS, over a much shorter number of days. Each iTBS session delivers 1,800 magnetic pulses compared with 600 in standard rTMS sessions; over each day of the 5-day course, the total dose of 18,000 pulses is equal to that of an entire 6-week course of standard rTMS.

Despite the higher dose, no severe adverse events occurred during the trial. The most commonly reported side effect was headache, which either self-resolved or resolved after nonprescription pain relief. Fatigue was also experienced by some participants.

The hypothesis behind the development of SNT, Dr. Williams has explained, is that some or most patients, and especially treatment-resistant patients, who have not been helped by conventional rTMS or iTBS, have not received enough stimulation quickly enough (in standard 4- or 6-weeks protocols) to reduce their depression. In SNT, the 50-minute "intersession interval" separating each of the 10 daily iTBS treatments is also thought to be a factor in enhancing efficacy. A third factor is the individualization of the treatment target in each patient receiving SNT.

Dr. Williams wants to hit the precise spot in the brain's dorsolateral prefrontal cortex (DLPFC) that has the greatest functional effect on another area, called the subgenual anterior cingulate cortex (sgACC), but each person is slightly different. The question then becomes: how does one hit this spot in the brain precisely when its position, relative to the outer skull, varies a bit from person to person?

For this reason, SNT begins with each patient getting an fcMRI brain scan—a functional scan of the brain in its resting state, when the individual is not focused on any particular mental task. This enables Dr. Williams' team to increase the specificity of the iTBS pulses "to the person's actual functional anatomy."

This second trial of SNT, like the first, involved a small number of patients. Subsequent trials must test the therapy in a larger patient population; they will likely test it against one or more active therapies in addition to placebo; and will test it in patients who both have and have not received fcMRI-guided targeting, to see if that step is in fact contributing to effectiveness. ❖

New Data on Prevalence of 'Long-COVID,' Including Cognitive & Psychiatric Symptoms

After many months of anecdotal reports and preliminary research about the long-lasting impacts of COVID-19 infection, a team of researchers has now provided a more specific idea of how common "long COVID" is, which patients are most likely to be affected, and which symptoms they are likely to report, including those impacting cognition and mental health.

Among the COVID patients assessed in the study (average age 46, 55% female), 57% had one or more "long-COVID" symptom at some point in the 6-month period following their initial diagnosis; 37% experienced one or more symptoms in the 3- to 6-month period after diagnosis.

The study revealed that cognitive symptoms were markedly more common in patients who were elderly as well as in those who were hospitalized or who needed intensive care. The single most frequently reported long-COVID symptom was anxiety/depression (23% of patients within 6 months of COVID diagnosis; 15% in months 3 through 6 after diagnosis); the corresponding figures for cognitive symptoms were 8% and 4%.

Led by senior team member **Dr. Paul J. Harrison**, a psychiatric neuroscientist and 2004 BBRF Independent Investigator, and Dr. Maxime Taquet, both of Oxford University in the UK, the researchers drew upon data in 59 institutional electronic health records, mostly based in the U.S., capturing the health histories of 81 million people, including 273,618 who were diagnosed with COVID-19 infection in 2020 and were alive 6 months later.

The analysis also included a matched group of patients who contracted influenza during the same period. Study results were reported in *PLOS Medicine*.

The researchers used two time periods to assess nine "core" symptoms of "long COVID": one, covering the first 180 days (6 months) following diagnosis; another to capture the core symptoms that were present between 90 and 180 days (3 to 6 months) following diagnosis. The latter period captures long-lasting or long-developing symptoms.

The nine core symptoms related to long COVID that were measured in the study were: breathing difficulties; fatigue; chest/throat pain; headache; abdominal symptoms; muscle pain; other pain; as well as two neuropsychiatric phenomena: cognitive symptoms (notably, "brain fog") and anxiety/depression.

For the researchers, one of the most important takeaways of the study was that 1 in 3 patients had one or more features of long COVID between 3 and 6 months following original diagnosis; 40% of these patients had no record of the long-COVID symptoms in the first 3 months after being diagnosed with COVID.

The team pointed out that the risk of having long-COVID symptoms, including cognitive symptoms and anxiety or depression, was higher in patients with more severe COVID, and slightly higher among females. White and non-white patients were equally affected.

The fact that risk of long-COVID features is higher after COVID diagnosis than after influenza diagnosis, the researchers said, suggests their origin may in part directly involve a mechanism specific to COVID or the body's response to it, not just a general consequence of viral infection. But the study was not designed to determine the origins or mechanisms behind symptoms. Another observation supported by the study's data was that long-COVID features were recorded in children and young adults, and also in more than half of non-hospitalized patients, "confirming that they occur even in young people and those who had a relatively mild illness. This is significant in public health terms given that most people with COVID-19 are in the latter group," the researchers noted.

Finally, the fact that some long-COVID features appeared only after the 3-month mark following diagnosis suggests that in some patients there may be a delayed onset. Reasons for this phenomenon are one of several subjects that will likely be pursued in follow-up studies. ❖

Study Links Schizophrenia Medicines' Anticholinergic Impact to Risk of Cognitive Impairment

An important study led by BBRF grantees has closely examined a commonplace pharmacologic property of many antipsychotic and other medications commonly prescribed to people with chronic schizophrenia and has concluded that this property can "substantially" contribute to the risk of cognitive impairment. Medications with anticholinergic properties were the focus of the study.

Anticholinergic compounds are those which block the action of the neurotransmitter acetylcholine at synapses. Many antipsychotic medications, both "first-generation" agents like chlorpromazine and "second-generation" agents such as clozapine, have anticholinergic properties, although the degree to which antipsychotics (and other psychiatric medications) block acetylcholine varies from medicine to medicine. Many have a small to moderate anticholinergic impact, but some have a comparatively large impact, as assessed by pharmacologists.

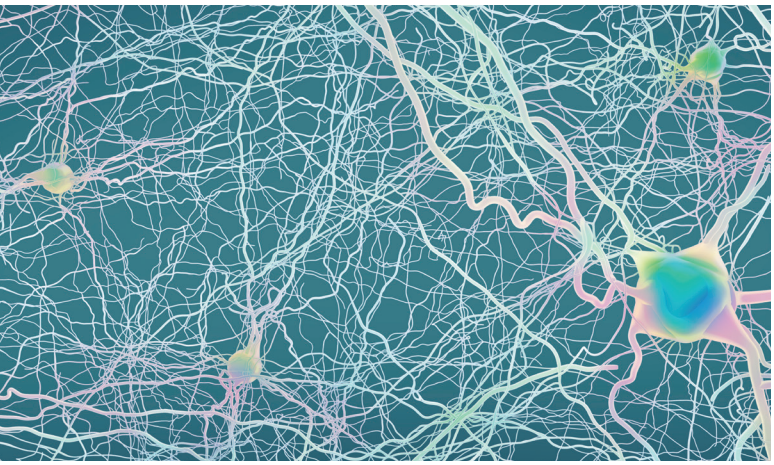
Increasingly, the anticholinergic properties of medications are being scrutinized for their impacts on brain health. One recent study of healthy adults aged 55 and over highlighted the negative cumulative impact of anticholinergic medication exposure and suggested "strong and potentially causal associations between increased burden of anticholinergic medicines and both cognitive impairment and risk of dementia."

This is particularly relevant for those living with schizophrenia, since cognitive impairment is often a major symptom of the illness. It affects a wide range of functions including attention, learning, memory, executive functioning, and social cognition.

Indeed, cognitive impairments are "directly linked to poor psychosocial outcomes," say authors of the new study. Appearing in the *American Journal of Psychiatry*, the study was led by **Yash B. Joshi, M.D., Ph.D.**, and **Gregory A.**

Light, Ph.D., both of the University of California, San Diego. Dr. Joshi is a 2018 BBRF Young Investigator; Dr. Light is the 2014 winner of BBRF's Baer Prize for Outstanding Schizophrenia Research, and is a 2013 BBRF Independent Investigator and 2006 and 2003 Young Investigator. Nine other BBRF grantees, prize winners and Scientific Council members were involved in the study.

The study assessed the total burden of anticholinergic medications taken by 1,120 chronic schizophrenia outpatients, 58% of whom lived in board-and-care or transitional living programs. The average age of participants was 46; nearly 70% were male; the average participant had been diagnosed with schizophrenia at age 22, and took a single antipsychotic medicine. One-third of participants also took an antidepressant medicine and/or other medicines, including mood stabilizers or anti-anxiety agents such as benzodiazepines.



Guided by previously established research protocols, the researchers assigned each prescribed medicine a numerical score, rating it on a scale from having no anticholinergic effect (0) to having a high effect (3). The study rated participants with a combined medication score of 3 or greater to have a "high" anticholinergic burden. In the prior study of healthy older adults, scores of 3 or greater for 3 years or more were associated with a 50% increase in the odds of developing dementia over that study's 11-year duration.

"We found that many patients [in our study] have medication regimens with high anticholinergic burden, with an average score of 3.8," the researchers reported. Overall, 63% of the 1,120 participants had a score of at least 3, and one-fourth had a score of 6 or greater. The authors noted that participants in their study were not included if they had major medical issues. Since individuals with schizophrenia may be more vulnerable to a variety of health issues, and medications used to treat these health issues may have anticholinergic properties, the team speculated that total anticholinergic burden may be even higher for many individuals in the community living with schizophrenia.

Consistent with findings in the prior study of healthy older adults, the new study found that "anticholinergic burden was significantly associated with generalized impairments in cognitive functioning in schizophrenia patients." Antipsychotic medicines contributed more than half of the total anticholinergic burden, they said, with other medicines accounting for the remainder. The researchers stressed that their results point to the total score—total anticholinergic burden—as being the key factor in contributing to risk for cognitive impairments, as opposed to any particular medication or medications considered individually.

The researchers said it was important that their results be understood in the proper context: working "to optimize outcomes" in chronic schizophrenia patients. "Psychotropic medications, especially antipsychotics, are critically important in schizophrenia, have substantially improved the lives and outcomes for countless patients living with the illness, and represent an essential staple of comprehensive treatment," they stressed.

They suggested that their results, if validated, might help guide prescribing physicians making medication decisions for their patients. On the one hand, "psychotropic medications are necessary to reduce symptoms [such as hallucinations and delusions] and to help patients achieve or maintain functional gains," they said. On the other hand, "the longer-term impact of all medications may contribute to longer-term cognitive disability."

The research team also included: **Ming T. Tsuang, M.D., Ph.D.**, BBRF Scientific Council, 2010 BBRF Lieber Prize winner, 1998 Distinguished Investigator; **Raquel E. Gur, M.D., Ph.D.**, BBRF Scientific Council, 2009 BBRF Lieber Prize winner, 1999 Distinguished Investigator; **Neal R. Swerdlow, M.D., Ph.D.**, 2016 BBRF Distinguished Investigator, 1990 Independent Investigator, 1990 Young Investigator; **Bruce I. Turetsky, M.D.**, 2001 BBRF Independent Investigator; **Debby W. Tsuang, M.D., Ph.D.**, 2009 BBRF Independent Investigator, 2001 Young Investigator; **Tiffany A. Greenwood, Ph.D.**, 2008 BBRF Young Investigator; **William S. Stone, Ph.D.,** 2000 and 1997 BBRF Young Investigator; **Ruben C. Gur, Ph.D.**, 2007 BBRF Distinguished Investigator; and **David L. Braff, M.D.**, 2014 BBRF Lieber Prize winner and 2007 Distinguished Investigator. ❖

Therapy Update

Recent news on treatments for psychiatric conditions

POSITIVE PHASE 3 TEST OF RAPID-ACTING ORAL MEDICINE FOR POSTPARTUM DEPRESSION

Handan Gunduz-Bruce, M.D.

An investigational medicine called zuranolone has generated significant, rapid, and enduring symptom reduction in women with postpartum depression. The drug was compared with placebo in a phase 3 trial conducted at 27 sites in the U.S.

Postpartum depression (PPD) affects about 13% of American women and is among the most common medical complications during and after pregnancy, according to the research team that conducted the trial. Reporting in the journal *JAMA Psychiatry* and led by Kristina Deligiannidis, M.D., of Zucker Hillside Hospital and Feinstein Institutes for Medical Research, the team included **Handan Gunduz-Bruce, M.D.**, a 2007, 2005 and 2003 BBRF Young Investigator.

PPD "is underdiagnosed and undertreated and can persist for years," the researchers noted. "Complications of untreated PPD include maternal suicide, lasting negative effects on infant and child development, and depression in partners."

Zuranolone has a mechanism of action similar to that of brexanolone, a fast-acting (within 3 days) drug for PPD approved by the FDA in 2019. Significantly, however, zuranolone is delivered orally, in contrast with brexanolone which is delivered via infusion. Zuranolone's pharmacology profile makes it suitable for once-daily dosing, the investigators said. In the phase 3 trial, nearly all patients self-administered the drug as outpatients.

Brexanolone, the first medicine ever approved specifically to treat PPD, was developed over a 25-year period, through basic research that included important contributions by **Cynthia Neill Epperson, M.D.**, whose early work on PPD was supported in part by 1995 and 1997 BBRF Young Investigator grants and later by a 2005 BBRF Independent Investigator award.

PPD has been linked to disruptions of signaling by the inhibitory neurotransmitter GABA. These disruptions are thought to be related to dramatic changes in the period just before and after childbirth of circulating levels of the hormone allopregnanolone, which modulates neural receptors for GABA. In her pioneering research, Dr. Epperson mapped changes in cortical GABA levels across the menstrual cycle and in postpartum women.

In brain regions involved in emotion and self-perception, neural connectivity supported by GABA signaling correlates with allopregnanolone levels in a way that distinguishes women who develop PPD from those who do not. GABA has also been linked in animal models with the stress pathway called the hypothalmic-pituitary axis, which is implicated in PPD.

A total of 153 women, average age 28, were recruited for the randomized, double-blind outpatient trial of zuranolone. Half received 30mg of zuranolone orally each evening for 2 weeks. The other half received placebo. Participants were diagnosed with PPD 6 months or less postpartum, with major depression beginning in the third trimester of pregnancy up to 4 weeks post-delivery. To qualify for the study, participants must have ceased lactating at screening or agreed to stop breastfeeding from just prior to receiving zuranolone until 7 days after taking the last dose.

The researchers reported that women receiving zuranolone demonstrated "rapid (within 3 days), clinically meaningful, and sustained antidepressant effects," measured through the 45th day of the trial. They also demonstrated "rapid and sustained improvements in anxiety and improved global and maternal functioning compared with placebo."

Noting that "a high proportion of patients" remained in remission over the 45 days, the authors said zuranolone's "sustained effect is clinically meaningful and similar to effects

observed in brexanolone infusion studies." While the drug's effect past 45 days is unknown, the trial made a convincing case for zuranolone's "short-term outpatient utility in PPD," the researchers concluded.

"The need for rapid and effective resolution of PPD symptoms cannot be overstated," they added, "given the prevalence of PPD and the negative effect untreated PPD can have on mothers, children and parents."

Several team members including Dr. Gunduz-Bruce are employees of Sage Therapeutics, the developer of zuranolone. Dr. Deligiannidis and others on the team reported consulting and/or funding relationships with the company. ❖

PHONE-BASED MINDFULNESS APP HELPED YOUNG TEENS RUMINATE LESS

Christian Webb, Ph.D.

New research suggests that certain freely available smartphone apps featuring "mindfulness" exercises can be useful in helping some adolescents ruminate less.

Rumination refers to repetitive and negative self-focused thinking, often concerning stressful or negative past events. Called a "transdiagnostic" symptom, rumination is often seen in adolescents who are anxious or depressed, and studies have shown that it is a style of thinking that can predict the onset of both disorders.

Mindfulness training tries to focus attention on the present moment and an awareness of what one is thinking and feeling while those thoughts and feelings are occurring—what psychologists call "metacognitive awareness."

Past studies have suggested that intensive, in-person meditation training can be useful in learning mindfulness and in mobilizing it to reduce both stress and the tendency to ruminate. These studies have often involved adults, taking courses that spanned several months.

Christian Webb, Ph.D., a 2018 and 2015 BBRF Young Investigator at Harvard Medical School and McLean Hospital, in collaboration with Lori Hilt, Ph.D. and their colleagues, sought to test a smartphone-based mindfulness app in a group of 80 adolescents, average age 14. The team was not only interested in the degree to which teens would use the app, but also whether information about them gathered before the trial began would be useful in predicting who among them would be most likely to benefit.

The upside, the researchers noted in a paper appearing in the journal *Mindfulness*, was clear: "mindfulness apps offer a highly scalable, convenient, cost-effective, and potentially engaging means for teens to access brief mindfulness training via their smartphones." They noted that over 260 such apps are now available and have millions of monthly users. The apps typically consist of brief (1- to 10-minute) guided mindfulness exercises, offered via daily "courses" that last a few weeks or sometimes longer.

The app used in the study, called CARE, was downloaded on each of the participants' phones and they were taught how to use it. Based on their inputs of sleep and wake times, users are prompted via random notifications within that time window to engage the app. Each time they use the app, they take a survey to assess whether they are ruminating and to what degree, and to indicate their current mood. Participants had a higher likelihood of receiving a mindfulness exercise from the app if they reported worse mood. Mindfulness training sessions varied from 1 to 12 minutes, based on users' reply to the question of how much time they had available. Immediately following a session, users were asked to complete another survey about their current mental state.

90% (72 of 80) of the adolescents completed a 3-week trial with the CARE app, with the typical user completing a total of 29 mindfulness training sessions, an average of 1 and a half sessions per day, with session length being 1 minute 91% of the time they engaged the app.

Reductions in rumination were assessed over two time intervals—"immediate" (i.e., pre- to post-mindfulness exercise) and "cumulative" (i.e., overall change in rumination over the course of the 3-week trial). Use of the app led to better immediate success among girls and older adolescents. Those with higher levels of rumination at the beginning of the study, and those who suppressed their emotions less had

better cumulative outcomes. Levels of anxiety and depression symptoms prior to the trial did not predict who would most likely be helped.

The researchers propose that those with a more habitual tendency toward repetitive negative thinking (i.e., higher rumination) may be more likely to benefit from a targeted intervention like mindfulness training focused on cultivating attentional control and present-moment awareness. The finding about emotional suppression is more complicated to interpret given the brief nature of the mindfulness training, the researchers said. It may be that "more sustained, intensive meditation practice" would help emotionally suppressed individuals more, as they "may learn and gradually internalize a more adaptive, open and receptive relationship with emotional states" through acquisition of mindfulness skills that can take time to cultivate. ❖

MINDFULNESS TRAINING PLUS tDCS STIMULATION TO TREAT COGNITIVE DECLINE IN OLDER PERSONS WITH DEPRESSION OR ANXIETY

Tarek K. Rajji, M.D.

In older adults, there is a well-established association between cognitive decline and depression and anxiety. Yet, as of now, "there are no evidence-based interventions for older adults that target cognitive difficulties in the context of depression or anxiety," a newly published study points out.

Authors of that study, appearing in *Mindfulness* and co-led by 2010 BBRF Young Investigator **Tarek K. Rajji, M.D.**, at the Centre for Addiction and Mental Health at the University of Toronto, designed an intervention to address both declining cognition and depression/anxiety in older adults. The approach combined mindfulness training with a form of non-invasive brain stimulation called transcranial direct current stimulation, or tDCS.

Mindfulness involves paying attention to the present moment in a non-judgmental way, "merely accepting it with an open and inquisitive nature," according to the researchers. Put another way, it means learning to accept one's thoughts and feelings as they occur, and identifying problems and finding ways to cope with them.

The pilot study adapted a form of mindfulness training called Mindfulness-Based Stress Reduction, or MBSR, which is group-based and taught and practiced with a trained instructor, weekly over a 2-month period. The version used in the study involved home-based application of mindfulness training (after a period of in-person instruction) combined with self-administration, also at home, of tDCS.

tDCS is an experimental form of non-invasive electrical stimulation of the brain that targets low levels of electrical current to specified brain regions in order to modulate the activity and plasticity of neural circuits. Lower in power than FDA-approved methods of stimulation such as transcranial magnetic stimulation, or TMS, which must be delivered by trained personnel in medical facilities, tDCS has been used safely in many studies and can be self-administered, the user wearing a mesh-like cap bearing electrodes.

The small study enrolled 26 people at least 60 years old (the average age was about 70) who had self-reported cognitive issues and also suffered from at least moderate depression or anxiety. All participants attended a thorough preparation program in which they were introduced to mindfulness training and were trained how to use a tDCS device. Some of the participants received active tDCS stimulation during their mindfulness sessions (30 minutes was advised); for purposes of comparison, others received a placebo version of tDCS.

While one in-person group mindfulness session was held during each week of the trial, the main idea was to have the participants practice mindfulness at home each of the other days of the week, while at the same time using the tDCS device. It was hoped that the two therapies would work synergistically to alleviate both cognitive symptoms and depression and anxiety.

The primary aim in the study was to test whether home administration of both therapies was feasible, measured by the degree to which participants complied with the protocol. Results were generally positive, with 54% average "attendance" at daily home sessions in which mindfulness and tDCS were applied simultaneously.

The study did show that older adults could self-administer tDCS and practice MBSR at home; and that the treatments were safe and well-tolerated, with tDCS side effects limited to such symptoms as skin itchiness or redness, and headache, typically only while the treatment was being given.

As for impact on symptoms, the team reported medium to large effects in reductions in anxiety, increases in everyday mindfulness, and improvement in social functioning. Effects sizes were smaller for reductions in depression and improvements in cognitive performance. This being a pilot study, these findings can only be considered suggestive, the researchers said.

The team believes their results justify further exploration of the approach. Improving the user interface and including more individualized tDCS training might encourage more patients to participate, and perhaps, benefit, they said.

The team also included **Daniel M. Blumberger, M.D**., 2010 BBRF Young Investigator, and **Sanjeev Kumar, M.D.**, 2014 BBRF Young Investigator. ❖

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GLOSSARY

CLOSED-LOOP NEUROMODULATION (p. 5) Electrical stimulation is delivered (via an implanted deep-brain stimulation device) at a precise location in the brain, intermittently throughout each day for only seconds at a time, and only at moments when a sensor placed in another part of the brain detects a specific EEG brain-wave pattern linked (in the example of a depressed patient) with the onset of the patient's depressed moods.

VENTRAL CAPSULE and AMYGDALA (p. 6) In the first clinical test of closed-loop neuromodulation for treatment-resistant depression, stimulation was delivered intermittently to an area called the ventral capsule, part of the brain's reward system. Such stimulation was given only when a biomarker signal consisting of specific EEG brainwave patterns was detected by a sensor placed in the patient's amygdala, an emotional processing area. These two sites were selected after rigorous testing of the patient's response to stimulation at many sites in the brain, and to analysis of how area-specific EEG patterns in the patient correlated with the onset of depressed mood.

THC and CANNABIDIOL (p. 23) Respectively, the principal psychoactive and non-psychoactive components of cannabis. Medicinal properties have been attributed to cannabidiol, but so far such claims have not been scientifically confirmed.

ENDOGENOUS CANNABINOID SYSTEM (p. 24) The body has its own ("endogenous") system which regulates endocannabinoid molecules (cannabinoids generated within the body). The endogenous system is one of these many regulatory systems that, among other things, helps adjust our level of approach or avoidance toward an object or a situation that may make us anxious. The endogenous system may be dysregulated when exogenous, plant-based THC at high concentration is ingested; cannabis-use disorder may be one consequence of such dysregulation of the body's own cannabinoid system.

CANNABINOID RECEPTORS (p. 24) Both endogenous (naturally occurring) and exogenous (plant-based) cannabinoid molecules generate effects by docking at the body's cannabinoid receptors, called CB1 and CB2, which are plentiful in the brain. Psychoactive plant-based THC engages the CB1 receptor, where its occupancy can potentially contribute to dysregulation of the body's own cannabinoid system.

ANTICHOLINERGIC COMPOUNDS (p. 31) Anticholinergic compounds block the action of the neurotransmitter acetylcholine at synapses. Many antipsychotic medications have anticholinergic properties, both "first-generation" agents like chlorpromazine and "second-generation" agents such as clozapine. Researchers are trying to determine if this property can contribute to the risk of cognitive impairment.

RUMINANTION (p. 34) Repetitive and negative self-focused thinking, often concerning stressful or negative past events. Called a "transdiagnostic" symptom, rumination is often seen in adolescents who are anxious or depressed.

MINDFULNESS (pp. 34) Mindfulness training tries to focus attention on the present moment and an awareness of what one is thinking and feeling while those thoughts and feelings are occurring—what psychologists call "metacognitive awareness."

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