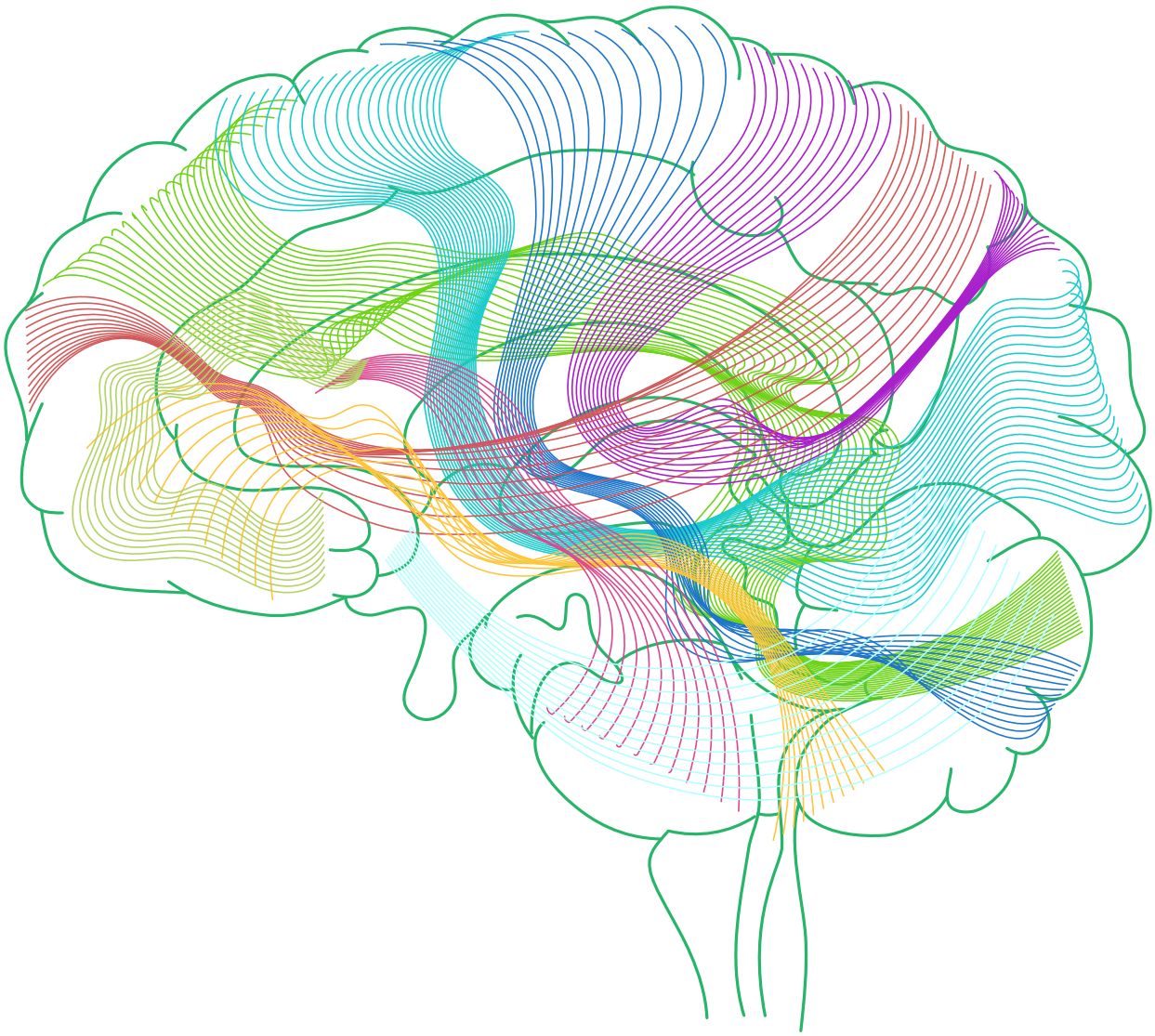
Psychedelic-Assisted Psychotherapy

Trauma, PTSD, and Suicide Risk

Brain & Behavior MAGAZINE

SEPTEMBER 2021



How COVID Infections Can Damage the Brain & Cause Psychiatric Symptoms

PRESIDENT'S LETTER

This September issue of *Brain & Behavior Magazine* showcases the impact that research funded by BBRF is having in the field of neuropsychiatry.

At this time the COVID-19 pandemic has claimed over 600,000 American lives and an estimated 4 million worldwide. Over the last year, research performed by BBRF grantees and Scientific Council members has helped to build a growing body of evidence linking COVID infections with damage to the brain. This is the subject of our **SCIENCE IN PROGRESS** and **COVID & MENTAL HEALTH** articles in this issue. This new research suggests how, in some cases, the virus may be exacerbating existing brain and behavior disorders, and in other cases may be giving rise to symptoms that were not present prior to a COVID infection. The research also suggests that some people with psychiatric disorders are at significantly greater risk for contracting the virus, and for having worse outcomes relative to COVID patients who don't have a psychiatric diagnosis.

Our **PATHWAYS TO THE FUTURE** story seeks to summarize some of the most important findings to date about the possibility of using psychedelic compounds to treat individuals with psychiatric illness. The article features comments from experts in the field (several of them members of BBRF's Scientific Council), who have been generally supportive of this idea, but consistently careful, stressing what is known and what remains unknown about psychedelic-assisted psychiatric treatments. They have raised important questions about who should and should not be considered a candidate for psychedelic-assisted psychotherapy, about the optimal conditions in which psychedelics should be administered, and about what still needs to be clinically demonstrated in people with psychiatric disorders before these powerful compounds can be recommended for wider use outside the research setting.

In our **ADVICE ON MENTAL HEALTH** piece, we talk with Dr. Kimberly Carpenter of Duke University. Dr. Carpenter and colleagues have performed important research on preschoolers with overly sensitive senses—children who are intensely bothered by stimuli such as loud or high-pitched sounds, or the sensation of clothing rubbing on the skin. Her research has shown that these children are at greater risk for developing an anxiety disorder by school age. In our Q&A Dr. Carpenter discusses these and related findings, including her inquiry into the relationship between early-life sensory over-responsivity and the risk for developing anxiety in children with autism spectrum disorder.

In **A RESEARCHER'S PERSPECTIVE** we highlight a presentation given by Lynnette Averill, Ph.D., a clinical psychologist affiliated with the Baylor College of Medicine, Yale University, and the Department of Veterans Affairs. Dr. Averill's clinical neuroscience research is focused on understanding the causes and consequences of trauma-related psychopathology and suicidality, and investigating novel rapid-acting interventions. She has special interest in the role that ketamine and psychedelics (including psilocybin and MDMA) can potentially play in the treatment of veterans and others with severe PTSD who are at high risk for suicidal thoughts and behaviors.

Our shared goal of a world free from debilitating mental illnesses relies first and foremost upon you, our donors—in partnership with the numerous researchers chosen by the BBRF Scientific Council, who are working to transform your donations into improved treatments, cures, and methods of prevention for our loved ones. I am inspired by the magnitude and scope of the discoveries that are being made by the scientists we fund together and appreciate your ongoing generous support.

Sincerely,

Jeffrey Borenstein, M.D.

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

CONTENTS

PUBLICATION CREDITS

Writers
Fatima Bhojani
Lauren Duran
Peter Tarr, Ph.D.

Editors
Lauren Duran
Peter Tarr, Ph.D.

Designer
Gene Smith

BBRF-Supported Scientists Address How COVID Infection May Damage the Brain and Affect Mental Illness Symptoms & Mortality

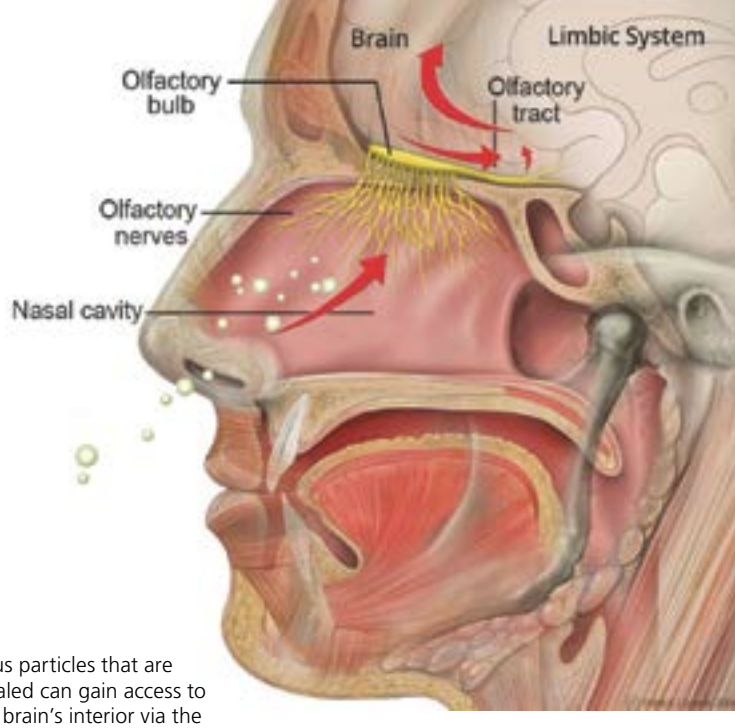
Maura Boldrini, M.D.

Over the last year, research performed by BBRF grantees and Scientific Council members has helped to build a growing body of evidence linking COVID-19 infections with damage to the brain.

This research suggests how, in some cases, the virus may be exacerbating existing brain and behavior disorders, and in other cases may be giving rise to symptoms that were not present prior to a COVID infection. The new research also suggests that some people with psychiatric disorders are at significantly greater risk for contracting the virus, and for having worse outcomes relative to COVID patients who don't have a psychiatric diagnosis. Finally, recent research on COVID's impacts indicates how racial and socioeconomic factors can exacerbate risk and pose obstacles to care for those who are underserved by the healthcare system [see companion story, p. 9].

In a striking example of how support for basic research can contribute to urgently needed practical knowledge in moments of crisis, a team of investigators at Columbia University in March 2021 published a report in the journal *JAMA Psychiatry* explaining the potential causes of a wide range of neuropsychiatric symptoms seen in some patients infected with the COVID-19 virus.

The report's lead author, **Maura Boldrini, M.D.**, a neuropathologist and psychiatrist, is a 2014 BBRF Independent Investigator and 2006 and 2003 Young Investigator. She was joined by Peter Carroll, M.D., Ph.D., a pathologist and cell biologist also at Columbia, and Robyn Klein, M.D., Ph.D., an expert in pathology, immunology, and neuroscience at Washington University St. Louis.



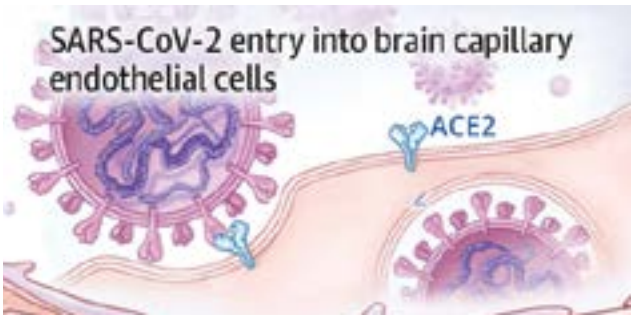
Virus particles that are inhaled can gain access to the brain's interior via the olfactory system.

In addition to anosmia—a loss of the sense of smell commonly reported by COVID-19 patients and therefore linked to the brain's olfactory processing system—the researchers noted a range of other reported neuropsychiatric symptoms in COVID patients. These include cognitive and attention deficits ("brain fog"), new-onset anxiety, depression, psychosis, seizures, and suicidal behavior.

Symptoms such as these have been present in COVID patients before, during, and after respiratory symptoms caused by the infection, the researchers noted, and importantly they appear to be "unrelated to respiratory insufficiency." Rather, they said, these brain and behavior symptoms "suggest independent brain damage" attributable to COVID-19 infection.

Research on COVID-19's impact on the brain is preliminary. Patient follow-ups conducted in Germany and the UK found post-COVID neuropsychiatric symptoms in 20% to 70% of patients—a very wide range reflecting their still uncertain prevalence. The symptoms were seen in young adults as well as older adults, and in some instances lasted months after the resolution of COVID's respiratory symptoms. This evidence suggested to Dr. Boldrini and colleagues that "brain involvement" due to COVID-19 infection persists in many cases.

In search of biological processes which may be interrupted by COVID-19, the researchers began with the question of how the virus enters the body. This is thought frequently to occur at cellular receptors (called ACE2 receptors) that stud the surface of cells found in cells of the lungs and arteries, but also in the heart, kidneys, and intestines.



One way the COVID-19 virus likely enters the body is by "docking" at ACE2 receptors and using these as a passage into cells—here, endothelial cells that line blood-carrying capillaries in the brain.

The "spike proteins" that project from the surface of COVID-19 viral particles latch onto ACE2 receptors, enabling the virus a point of entry into such cells. Once inside, the virus "hijacks" the cells' genetic machinery in order to produce thousands of new copies of itself, which are then released into the space between cells, spreading the infection.

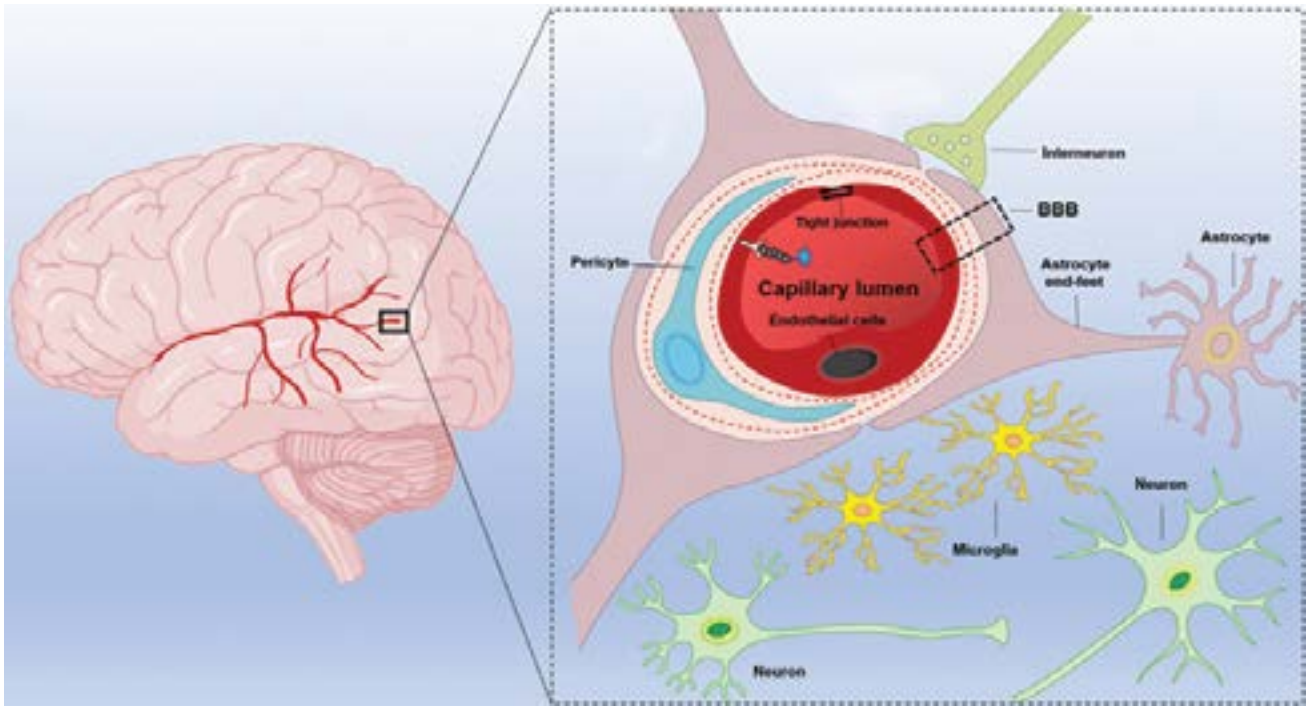
DAMAGE FROM INFLAMMATION

In various organs of the body, the virus can enter endothelial cells which line the interior of vessels and arteries, and damage them. This in turn can cause inflammation. Inflammation has a wide range of impacts in the body, varying according to where it occurs. If it occurs in blood vessels inside the brain, Dr. Boldrini and colleagues noted, it can cause the formation of blood clots (thrombi), and lead to brain damage.

When inflammation becomes systemic in the body, it can have many effects. Among these are decreased production of monoamines and trophic factors—brain proteins involved in neurotransmission and maintenance of neuronal growth.

Inflammation also leads to the activation of microglia. These are immune cells unique to the brain and spinal cord which have the crucial role of removing plaque-like build-ups in the central nervous system (CNS) as well as removing damaged or unnecessary neurons and synaptic connections.

Substantial reduction in microglia numbers has been associated with increased activity of the excitatory neurotransmitters glutamate and NMDA. Such heightened activity can sometimes result in what scientists call



Looking straight down the lumen or "tube" formed by a brain capillary, this drawing shows the BBB, or blood-brain barrier, the membrane designed to protect the capillary and the blood within from viral particles and other toxins. This depiction also suggests other elements: pericytes and immune system components called microglia and astrocytes. The "end feet" of astrocytes make contact with the outer surface of the BBB.

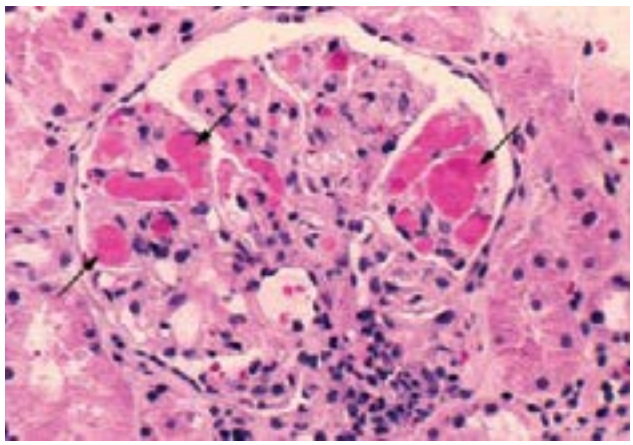
excitotoxicity, a kind of damage caused by overactivation of excitatory neurons and their receptors.

The researchers note that COVID-19 proteins have been found in the lining of blood vessels in the brain. While evidence is still lacking as to whether COVID-19 infects the brain directly, the researchers describe how viral particles might leak through the blood-brain barrier (BBB), a membrane that is designed to protect the brain from viruses, toxins, and other harmful factors. Another possible entry point into the brain, they note, is via the circumventricular organs, highly permeable capillaries around the brain's fluid-filled 3rd and 4th ventricles. These capillaries lack a blood-brain barrier.

The researchers speculate that loss of the sense of smell as well as nausea and vomiting may be related to viral invasion of brain and CNS vasculature. They further suggest that other short- and long-term neuropsychiatric symptoms "are more likely due to neuroinflammation and hypoxic injury"—a deficiency of oxygen due to interruption of blood flow in the brain.

COVID-19 infiltration of the brain stem, they add, may be involved in problems with the autonomic nervous system, which controls heart rate, respiration, and digestion, and has components that manufacture the main neurotransmitters (serotonin, dopamine, norepinephrine). Damage to these components can lead to cardio-respiratory shutdown, gastrointestinal symptoms, and emotional and cognitive symptoms, including depression, anxiety, and an inability to concentrate ("brain fog"), which have affected COVID-19 patients, the team points out.

In explaining other impacts of the virus upon the brain and CNS, the researchers note that when the virus enters the endothelial cells lining the blood vessels of the brain, cells called neutrophils and macrophages are activated, and thrombin is produced. These are among the factors leading to the production of "microthrombi" within blood vessels—tiny clots. "Neuropsychiatric symptoms of COVID-19 could result



Tiny blood clots, or microthrombi (bright pink), block capillaries in this cross-sectional slice of tissue.

from micro-strokes and neuronal damage," they say, with the specific symptoms varying in patients according to where in the brain or spinal cord such events occur.

In a paper appearing in July in *Nature Medicine*, researchers at UCSD led by Joseph Gleeson, M.D., and including first author **Lu Wang, Ph.D**., a 2019 BBRF Young Investigator, reported another mechanism through which COVID may infect brain cells. The team created "assembloids"—stem cell-generated research models consisting of various brain-cell types. These revealed that pericytes, support cells that wrap around the brain's blood vessels (see illustration, p. 6), express ACE2 receptors. Entering pericytes via these receptors, the virus might then reproduce and subsequently infect astrocytes. Or, the team said, infected pericytes might generate inflammation in blood vessels, thus triggering damaging impacts upon the brain like those described by Dr. Boldrini and colleagues.

Pathologies induced by COVID-19, as best as they can be deduced now, suggest to Dr. Boldrini's team a variety of potential interventions to lessen their impact. These include: administering agents which suppress cytokines, the immune-signaling molecules involved in generating the "cytokine storm" associated with pathology in severe COVID-19 cases; administering agents such as ketamine which suppress NMDA receptors; and administering agents such as aspirin and celecoxib (Celebrex) which have an anti-inflammatory effect.

Researchers have found that negative symptoms in people with schizophrenia, including social withdrawal, blunted affect, decreased motivation, and inability to experience pleasure, were often accentuated during the pandemic.

HOW PATIENTS ARE AFFECTED

At a different level of analysis, other researchers have studied whether and how people with psychiatric illnesses or heightened vulnerability to them are affected by COVID.

A team led by BBRF Scientific Council member **Nora Volkow, M.D.**, studied the health records of over 61 million Americans aged 18 and over, 11.2 million of whom (18%) had a history of a mental disorder at some point in their life. Dr. Volkow, a scientist who has made important discoveries about the biological bases of addiction, is Director of the NIH's National Institute on Drug Abuse.

Her team focused on 15,110 people among the 61 million, who had been infected with COVID-19. About 36% of these individuals had been diagnosed with a mental disorder, and nearly 63% of this subset had been diagnosed within the prior 12 months. The study revealed that people with a lifetime history of mental disorder had increased risk of contracting COVD-19 infection, and that those diagnosed in the last year were especially at risk, not only of getting the virus but of having a bad outcome. Indeed, 8.5% of those diagnosed in the last year died due to COVID infection—a rate more than four times that in the general population. (In the U.S. as a whole at the time of this writing, over 33 million have contracted COVID and over 600,000 have died, a mortality rate of about 1.8%).

In their paper, Dr. Volkow and colleagues identify individuals with mental disorders as a "highly vulnerable population for COVID-19 infection." They note that those with mental illness have "life circumstances that place them a higher risk for living in crowded hospitals or residences, or even in prisons," environments in which infections can spread rapidly. Also, "people with disabling mental illnesses are likely to be socioeconomically disadvantaged," a fact which "might force them to work and live in unsafe environments. Homelessness and unstable housing may affect their ability to quarantine.

People with a lifetime history of mental disorder had increased risk of COVID-19 infection. Those diagnosed in the last year were especially at risk, not only of getting the virus but of having a bad outcome.

Stigma may result in barriers to access to healthcare for patients infected with COVID-19, or make them reluctant to seek medical attention for fear of discrimination."

HIGH RISKS IN SCHIZOPHRENIA

Delusions and hallucinations are among the symptoms of psychosis, a condition which occurs most often in people with schizophrenia, but also in some people with bipolar disorder and more infrequently in severely depressed individuals.

A study conducted in a major New York City hospital system found that people with schizophrenia had 2.7 times the risk of dying within 45 days if they were infected with the COVID-19 virus. Higher mortality was not seen, however, in people with depression or anxiety who contracted the virus.

The study, appearing in *JAMA Psychiatry*, was based on medical records complied in the spring of 2020 at the NYU Langone Medical Center. **Donald C. Goff, M.D.**, of NYU Langone was senior member of the team. He is a 2009 and 2003 BBRF Independent Investigator. The team also included 2005 BBRF Distinguished Investigator **Mark Olfson, M.D., MPH**, of Columbia University.

Their study was based on electronic medical records of 26,540 patients tested for COVID within the multi-center NYU Langone health system over a several-month period. The mortality result for people with schizophrenia was second highest of any subgroup in the study, after that of elderly people. Drs. Goff, Olfson and colleagues noted that the elevated risk in schizophrenia remained significantly elevated even after statistically adjusting for various comorbidities and other risk factors associated with schizophrenia.

The particular risk COVID poses for people with schizophrenia was the subject of another study, which appeared in the *European Archives of Psychiatry and Clinical Neuroscience*. First author **Gregory P. Strauss, Ph.D.**, 2018 BBRF Young Investigator, and colleagues at the University of Georgia focused on how COVID infection may have impacted patients' "negative symptoms."

Negative symptoms in schizophrenia include social withdrawal, blunted facial and vocal affect, decreased motivation, and the inability to seek pleasure (anhedonia). The researchers sought to determine whether social isolation, physical distancing, and other public health precautions had the effect of exacerbating patients' negative symptoms.

They found that this was indeed the case, in a sample of 32 individuals with chronic schizophrenia who were compared with 31 healthy controls. The study also studied 25 individuals considered to be a "clinically high risk" of psychosis based on family history, genetic factors, or mild, potentially "pre-psychosis" behaviors, comparing them with a group of 30 healthy controls.

The investigators found that a wide range of negative symptoms, involving speech production, blunted affect, anhedonia, lack of volition, and social withdrawal, were worse, on average, in the schizophrenia patients while the pandemic was in progress, compared with before it began. Among the "high-risk" group, anhedonia and lack of motivation was worse during the pandemic compared with before it began.

Dr. Strauss and colleagues said their study suggests that negative symptoms "should be a critical treatment target during and after the pandemic" in people diagnosed with schizophrenia as well as in others on the schizophrenia spectrum, given the chance that they will have worsened during this time of great stress.

❖ **PETER TARR**

Researchers Study How Pandemic-Related Stresses Affect Families, Parenting, and Child Mental Health

In 2020 alone, the COVID-19 virus killed 375,000 Americans, making it the 3rd-leading cause of death in the country, after heart disease and cancer, according to government statistics. An additional 240,000 Americans died of the virus in the first 7 months of 2021, estimates indicate. By any standard, the pandemic represents an immense threat to public health.

The implications for mental health may be somewhat less obvious on the surface but are no less serious, according to a team of researchers led by BBRF Scientific Council member **Kathleen R. Merikangas, Ph.D.**, a senior investigator at the National Institute of Mental Health. In a recent paper appearing in *Scientific Reports*, Dr. Merikangas and colleagues note that "the pernicious mental health effects of the pandemic may result from death of loved ones, disease severity, social isolation and quarantine, unemployment, financial hardship, domestic violence, and educational disruptions." Each of these factors, they stress, has been "independently associated with psychological comorbidities."

Members of the team, including the paper's first author, 2018 BBRF Young Investigator **Aki Nikolaidis, Ph.D.**, of The Child Mind Institute, say the pandemic may pose distinctive risks due to its prolonged nature, compared with other well-studied disasters such as terrorist attacks, natural disasters, or acute exposures to environmental dangers such as radiation leaks or oil spills. These well-defined events have been associated with increases in depression, PTSD, substance use, and generalized anxiety disorder, among other psychiatric illnesses—as measured by investigators in their aftermath. "Much less is known about the risk and protective factors for well-being during and after prolonged threats like the pandemic, which continues to unfold," the researchers point out.




Individuals' perceptions of COVID-19 risk, their prior mental health status, and changes in lifestyle were key predictors of current mood state during the pandemic. Factors affecting a sense of wellbeing included media use, sleep, physical activity, and substance use.

Dr. Merikangas' team specifically set out to address this gap in knowledge, with the aim of testing a survey instrument that can be easily and rapidly deployed to help experts gauge, and address in real time, pandemic-related injuries to the psyche, to relationships between people—in short, to mental health generally, across the population. They created the Coronavirus Health and Impact Survey, or CRISIS, and conducted a pilot study, testing it over an 11-day period in April 2020 in 5,646 volunteer respondents in the U.S. and UK.

Among their chief goals was to identify, based on the answers to survey questions, factors in individuals that would reliably predict who was at greatest risk of acute and longer-term mental health issues due to pandemic conditions. Another goal was to identify which factors in the CRISIS survey appeared to have a protective effect.

The CRISIS survey asked questions about the following matters: household composition and crowding; physical and mental health of household members 3 months prior to the pandemic; COVID-19 exposure and infection status; life changes due to the pandemic; concerns and worries associated with COVID-19; current self-assessment of "well-being"; and what the team calls "behavioral factors," which include media use, sleep, physical activity, and substance use. Long and short versions of the survey were developed, both deployed via the internet.

Results of the pilot test of CRISIS revealed that individuals' perceptions of COVID-19 risk, their prior mental health status, and changes in lifestyle were key predictors of current mood state during the pandemic.

"Fear and worry about COVID and resulting changes in routines and daily life" were "significant drivers of adverse mental health outcomes associated with the pandemic," Dr. Merikangas and colleagues reported.

Interestingly, among children whose data were captured in the CRISIS survey (which was supplied by their parents) "current mood" during the pandemic was more strongly related to changes in life routines or circumstances than worries about COVID. This finding was consistent, the team said, with past research stressing the importance of regular, predictable daily routines for pediatric mental health.

The findings "suggest that attending to changes in children's lives may be key to predicting those at greatest risk for negative psychological impact." Specifically, "current mood" was more negative in respondents reporting family and social-isolation stress in both adults and children. The team also noted that subgroups of children with greater family and social isolation stress also experienced greater stress due to financial and food security. "This underscores the impact of multi-factor physical, educational, emotional, interpersonal, social and financial stressors which converged during this pandemic," the team said.

PARENTAL BEHAVIOR CAN HELP OR HURT

In a study seeking to understand more about how COVID-related stress affected children in a family setting, a team of investigators led by 2015 BBRF Young Investigator **Dylan Gee, Ph.D.**, of Yale University, focused on the impact of "buffering" behaviors by parents, as well as parental behaviors that potentially exacerbated the effect of children's exposure to pandemic-related stress.

As noted by Dr. Gee and colleagues, "nearly all aspects of family life were

disrupted during the spring of 2020," when they conducted their study via a carefully designed internet-based questionnaire. "Parents were required to work remotely without access to childcare or to work in essential roles while risking disease transmission for themselves and their families. Children transitioned to online schooling, with an increased burden for managing learning falling on parents. Many families faced additional concerns related to job loss and food and housing insecurity, as well as long-term effects of isolation on family members' mental and physical health."

The team gathered data from a sample of 200 parents, average age in the late 30s, 85% married and 52% female. Over a several-day period in April 2020 they sought to assess the impact of parental stress and behaviors on "internalizing" and "externalizing" symptoms in children. Examples of internalizing problems are anxious and depressive symptoms, loneliness, sadness, as well as social withdrawal. Externalizing problems often take the form of aggressive, oppositional, and delinquent behaviors that are manifested outwardly.

The study generated preliminary evidence for a linkage between a "wide range of COVID-19-related stressors and heightened internalizing and externalizing symptoms" in children, the team reported in *Research on Child and Adolescent Psychopathology.*

The results suggested to the investigators that specific parental factors "may buffer or exacerbate" the impact of COVID-related stress on children. "Specifically, parents who reported engaging in relatively higher levels of emotion coaching of children's negative emotions and who reported that they were able to more stably maintain children's home routines were more likely to effectively buffer the effects of pandemic-related stress."

Conversely, buffering was less common in parents who reported higher stress levels and anxiety due to the pandemic.

Dr. Gee and colleagues said their study "underscores the importance of considering parent-level factors and parents' potential to either buffer or exacerbate children's stress" in any attempt to deal with the effects of an event like the pandemic across large populations. "Public health efforts should consider the importance of targeting parental wellbeing, thereby promoting parents' capacity" to shield their children from the potentially harmful effects of ongoing stress.

The investigators cited a number of measures taken along these lines during the pandemic: recommendations for parents to increase communication with children about the pandemic and to continue to maintain children's typical home routines to the extent possible during a time of disruption.

Regular, predictable daily routines are vital for pediatric mental health. One way parental behavior can buffer children's stress is to involve them in activities they might not previously have been part of, making them feel involved in the response to the family's altered circumstances.

STRESS, BRAIN FUNCTION, AND PARENTING

In a similar vein, another recent study in which Dr. Gee participated, published in *American Psychologist* and co-led by BBRF Scientific Council member **Amy F. T. Arnsten, Ph.D.**, of Yale University, focused on the impacts of "an unanticipated and uncontrollable chronic stressor" such as the pandemic on the behavioral health of children and families. Such continually stressful events, which, they said, have disproportionately impacted families that are disadvantaged or marginalized, have "consequences on parent-child functioning."

Based on neuroscience and clinical evidence, the researchers presented evidence that "sensitive parenting is a vital avenue of intervention against the toxic effects" of a stressor such as the pandemic. Dr. Arnsten, a neuroscientist, is also a 2015 BBRF Goldman-Rakic Prize winner, a 2008 BBRF Distinguished Investigator and 1998 Independent Investigator. She and colleagues noted a strong body of evidence demonstrating that exposure to uncontrollable stress "rapidly impairs the functioning of the prefrontal cortex (PFC)," which performs higher cognitive functions including the guidance of flexible, goal-directed behavior, as well as top-down regulation of emotion, attention and action.

The prefrontal cortex is engaged during a pandemic, the team noted, "in using abstract reasoning to imagine the potential harm in once-habitual behaviors like hugging a friend."

Sensitive parenting is a vital avenue of intervention against the toxic effects of a stressor such as the pandemic, according to Dr. Arnsten and colleagues.

Prefrontal circuitry is also needed for effective, sensitive parenting, "as it supports mentalizing functions that allow a parent to understand their child's state of mind in response to new challenges such as disruptions in family routines and planning of effective strategies to help children cope with restrictions in learning and socializing.

The PFC is also engaged in operations in the brain which mediate attachment and empathy, as well as self-regulation that comes into play in trying to cope with frustration caused by disruptions in work and social life. The researchers noted that the PFC accomplishes these multiple functions via extensive connections throughout the brain, and can inhibit brain areas such as the amygdala and basal ganglia which are involved in reactive, emotional responses like shouting and aggression.

One way the PFC accomplishes its higher-order functions is via excitatory circuits that rely upon neurotransmitters such as glutamate, acting at NMDA receptors. These receptors are blocked by kynurenic acid, the precursor for which has been found to be highly elevated in the plasma of COVID-19 patients, particularly in men, the researchers noted. Blockade of NMDA receptors "could potentially weaken functions such as working memory and inhibitory control that depend on the PFC."

Similarly, "high levels of norepinephrine and dopamine are released in the brain upon exposure to uncontrollable stressors like COVID-19," and can weaken critical PFC connections needed for cognitive functions and top-down control. In contrast, they note, high levels of such neurotransmitters in the amygdala and basal ganglia "simultaneously strengthen the more primitive, emotional responses, shifting the brain from a more reflective state to a more reflexive one, which could be maladaptive" when coping with a remarkable enduring stressor like the evolving pandemic. ❖ **PETER TARR**

PLAN YOUR FUTURE, SHAPE YOUR LEGACY

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

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

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

"My late husband Arthur and I have supported BBRF for 30+ years, and as part of our estate plan, we were looking to fund the extraordinary work of the foundation's Young Investigators in the future. My husband recently left a generous bequest gift and I have identified BBRF as a beneficiary from my IRA account."

– Miriam Katowitz, BBRF Board Vice President

To learn more, please contact us at **646-681-4889** or **plannedgiving@bbrfoundation.org.**

Psychedelic-Assisted Psychotherapy: What We Know, and Still Don't Know

On May 9th of this year, a front-page headline in *The New York Times* announced: "The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same." According to the story's subheadline,"Psilocybin and MDMA are poised to be the hottest new therapeutics since Prozac." Six days earlier, a story appearing on the inside of the newspaper had reported "A Psychedelic Drug Passes a Big Test for PTSD Treatment."

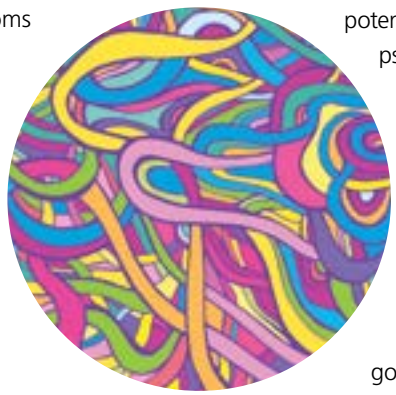
Readers who could remember the 1960s might well have done a double-take. Psychedelics? A "revolution"? Hadn't society "been there, done that"—over half a century ago?

In a way, yes. "Excitement over psychedelic drugs led to extravagant claims about their vast potential to expand human consciousness, elucidate the psychological architecture of the brain, and treat mental disorders," recalls **Dr. Jeffrey Lieberman**, a BBRF Scientific Council member, 2-time BBRF Distinguished Investigator and 2006 Lieber Prize winner, in a recent editorial in the *New England Journal of Medicine*. By the mid-1960s, LSD had been prescribed to approximately 40,000 U.S. patients and spawned over 1,000 scientific papers. At the same time, as noted by Dr. Lieberman, "recreational use of these drugs, encouraged by countercultural icons like Dr. Timothy Leary, spread. "Appeals to 'tune in, turn on, and drop out' propelled unsupervised use to leap-frog medical research," while "people experiencing 'bad trips' filled emergency departments."

Widespread, unregulated use of psychedelics was one factor leading Congress in 1970 to pass the Controlled Substances Act, under which psychedelic compounds including psilocybin (the psychoactive ingredient in "magic mushrooms") and MDMA (a type of amphetamine sold since the 1980s as the "club" drug "Ecstasy," also known as "Molly") were listed as Schedule I substances—unlawful to possess and officially regarded as "having no currently accepted medical use."

The 1970 law has not since reclassified psilocybin, MDMA, or other psychedelic substances including mescaline, LSD, and DMT (the active ingredient in ayahuasca). But around the year 2000, research in a few academic labs did resume, legally, on all of these psychedelics—most influentially, psilocybin and MDMA.

Since then, a new body of data has been building about how consciousness-altering psychedelic substances affect the operation of the brain. Among other impacts, psychedelics act upon the serotonin neurotransmitter system, which plays an important role in mood regulation. Psilocybin is known to stimulate several types of neural serotonin receptors, especially the serotonin 2A receptor; such stimulation has a wide range of "downstream" pharmacologic effects in the brain and body, which remain poorly understood but could impact symptoms of mood disorders such as depression and anxiety.



Animal studies have shown that MDMA, which has a distinct mechanism of action, induces serotonin release by binding to serotonin transporter proteins. There is evidence the drug may enhance the extinction of fear memories and modulate fear-memory reconsolidation and thus it holds promise in treating PTSD and anxiety, among other disorders.

While the pharmacology and mechanisms of action of psychedelics continue to be a subject for study, their impact on human consciousness has often been described: pronounced changes in sensory perception, including euphoria, sensory illusions, and auditory and visual hallucinations—which are experienced variably in different users and on different occasions, on a wide scale ranging from "magical" and "revelatory" to deeply sad and terrifying.

In recent years, researchers have begun to scrutinize, some under rigorous clinical trial conditions, how psychedelics might be used *in conjunction with* psychotherapy to treat a variety of mental health conditions.

Both psilocybin and MDMA have been given "fast-track" designation by the U.S. Food and Drug Administration (in 2018 and 2017, respectively) as potential treatments in psychiatric disorders. Dozens of U.S.-registered clinical trials are under way in a wide range of mental health conditions, some partly funded by the government and others by independent advocacy foundations and/or small drug companies with a financial interest in the research. Leaders of some of the new studies include established investigators at major academic and research institutions including Johns Hopkins University, New York University, and The University of California in the U.S., and Imperial College London and the Medical Research Council in the U.K.

Researchers are scrutinizing how psychedelics might be used in conjunction with psychotherapy to treat a variety of mental health conditions.

Several recently published studies have received widespread public attention. In November 2020, a study of psilocybin-assisted psychotherapy appearing in *JAMA Psychiatry* and led by Drs. Roland Griffiths and Alan Davis of Johns Hopkins University, reported "large, rapid, and sustained antidepressant effects" in a group of 27 participants with major depressive disorder.

In April 2021, a team led by Drs. Robin Carhart-Harris and David Nutt of Imperial College London reported in the *New England Journal of Medicine* on a phase 2 trial involving 60 patients with major depressive disorder, half of whom received psilocybin and half the conventional SSRI antidepressant escitalopram (Lexapro) over 6 weeks. While both groups, with psychotherapeutic support, showed improvements, the trial "did not show a significant difference in antidepressant effects between psilocybin and escitalopram," although results tended to favor psilocybin in a number of "secondary" measures, the team said.

In May 2021, as reported in the *Times,* a team led by Dr. Jennifer Mitchell of the University of California, San Francisco reported in *Nature Medicine* results of the first-ever Phase 3 trial using MDMA to treat patients with severe PTSD. Among the those in the MDMA-assisted therapy group, 67% no longer qualified for PTSD diagnosis after their three MDMA-assisted therapy sessions and 88% of participants experienced a clinically significant reduction in symptoms.

What to make of these recent studies, each involving the use of psychedelic-assisted psychotherapy in fewer than 100 individuals? Those most hopeful about the potential benefits of psychedelics in psychiatry point to reports of their positive effects on mood and outlook—some proposing that they can "open the mind" to new insights in psychotherapy that can lead to significant therapeutic gains. But science has yet to explain exactly how this might occur or which individuals are most likely to benefit.

REVIEWING THE EVIDENCE

As evidence about psychedelic-assisted psychotherapy has steadily grown, generating much discussion but no consensus, the American Psychiatric Association (APA) formed a study group to perform "an evidence-based summary of the literature of the clinical application of psychedelic drugs in psychiatric disorders." In May 2020, the group published a paper in the *American Journal of Psychiatry (AJP)* reviewing the evidence.

Of the *AJP* paper's eight named authors, six have BBRF affiliations: corresponding author **William McDonald, M.D.**, 1999 BBRF Independent Investigator; **Ned Kalin, M.D.**, BBRF Scientific Council member and AJP's Editor-in-Chief; **Carolyn Rodriguez, M.D., Ph.D.**, BBRF Scientific Council member and 2014 and 2009 BBRF Young Investigator; **Charles Nemeroff, M.D., Ph.D.**, BBRF Scientific Council member, 2003 and 1996 BBRF Distinguished Investigator, and 1996 BBRF Selo Prize winner; **Alik Widge, M.D., Ph.D.**, 2014 BBRF Young Investigator; and **Linda Carpenter, M.D.**, 1997 BBRF Young Investigator.

Some experts suggest psychedelics can "open the mind" to new insights in psychotherapy which can lead to significant therapeutic gains. But science has yet to explain exactly how this might occur and in which individuals.

The recent resurgence of interest in psychedelics is traced to several studies. One of these was led by Dr. Griffiths of Johns Hopkins, reporting in 2006 that a single high dose (25mg) of psilocybin, given in a psychotherapeutic setting, produced long-lasting positive changes in mood and wellbeing in *healthy* volunteers. This led Dr. Griffiths and others to question whether *depressed* individuals would have a similar experience.

Also influential were several brain-imaging studies conducted in the 2010s, led by Drs. Carhart-Harris and Nutt. These suggested that psilocybin produced "profound and meaningful alterations in brain function, especially of the default mode network (DMN), consistent with an antidepressant effect."

The DMN is a circuit connecting a number of brain areas whose activity reflects "baseline" activity when an individual is not actively performing a conscious mental task. In depressed individuals, DMN connectivity is elevated compared with non-depressed individuals. It may reflect looping, self-referential, "ruminative" thinking that is seen in many depressed individuals. DMN activity has been shown to be lowered in individuals under the influence of psilocybin, as it has been in individuals experiencing successful antidepressant treatments.

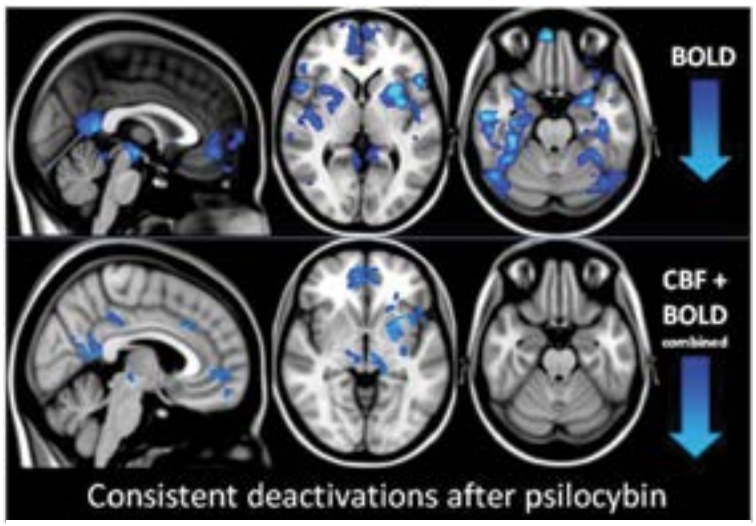
Observations such as these begin to suggest in biological terms what users of psychedelic substances have historically described in emotional and experiential terms. Plant-derived psychedelics have been used for thousands of years for medicinal and religious purposes in traditional cultures of Mexico and Central and South America, among others, but have carried an aura of profound mystery which science now seeks to penetrate.

Comments about the importance of the psychedelic experience in the larger context of users' lives have been generated in many early studies of the drugs. Such testimonials were especially impressive in preliminary trials of psilocybin in advanced-stage cancer patients, whose poor prospects had plunged them into deep depression and/or anxiety. In 2011, a small pilot study led by Dr. Charles Grob of UCLA was conducted in 12 individuals with advanced-stage cancer, all suffering from anxiety. Each received two treatments, weeks apart: one with a moderate dose of psilocybin, the other with niacin, which served as an "active placebo" (niacin has a "flushing" effect, sometimes also experienced after ingestion of psychedelics). Cancer patients' anxiety scores didn't change in the 2 weeks following treatments, but were significantly improved in the psilocybin group at the 1- and 6-month follow-ups.

A few years later, Dr. Griffiths' group conducted a double-blinded study involving 18 terminal cancer patients with anxiety or mood disorders who were treated with psilocybin administered in two sessions, one at high dose, the second at a negligible dose. As the team reported in a 2016 paper, at the 6-month follow-up, 78% of participants with depression were still experiencing a response (at least a 50% reduction in symptoms from baseline), as were 83% of those with anxiety. Remission was experienced, respectively, by 65% and 57% in each group 6 months following the end of the trial.

Another small but impressive preliminary trial led by Dr. Griffiths, involving 15 subjects, showed psilocybin to help people quit smoking. The 2014 paper reported remarkable rates of success, compared with conventional smoking-cessation programs.

A preliminary trial by Dr. Michael Bogenschutz and colleagues at NYU testing psilocybin combined with psychotherapy in 10 participants with alcohol dependence



Brain imaging by Drs. Carhart-Harris, Nutt and colleagues has shown that certain brain areas have lowered neural activity during a psilocybin "trip."

reported in 2015 that abstinence significantly increased after the first psilocybin session at 4 weeks and was largely sustained at 36 weeks.

Dr. McDonald and members of the APA review team, after studying results from 14 papers which they judged to be of the highest quality among several hundred involving psychedelics, concluded that while evidence published to date "is insufficient for FDA approval of any psychedelic compound for routine clinical use in psychiatric disorders at this time, continued research… is warranted."

JOHNS HOPKINS
Center for Psychedelic & Consciousness Research

Dr. Roland Griffiths founded the Center for Psychedelic & Consciousness Research at Johns Hopkins University in 2019.

The APA reviewers observed that researchers often noted correlations between reductions in patient symptoms and their descriptions of their psilocybin experiences as having been "mystical" or "personally meaningful." But they and others have noted that the psychedelic experience has a flip side. While "hallucinogens such as psilocybin are not thought to precipitate new psychotic illness, they may unmask a psychotic disorder in those who are susceptible," the APA reviewers noted.

Concern about how psychedelics might destabilize vulnerable individuals helps explain the caution with which many commentators on recent psychedelics research approach the prospect of the "mainstreaming" of psychedelics in uncontrolled community settings. Particularly worrisome is the growing practice of "microdosing." This involves taking psychedelics such as psilocybin, LSD and MDMA repeatedly over short periods of time in very small quantities that do not induce psychedelic experiences. No one knows whether such unsanctioned and illegal practices have any potential therapeutic benefits. One worry is that positive publicity over the encouraging results of recent psychedelic research trials may be misinterpreted by some as giving the public a green light to use the substances in non-research settings.

'SET' AND 'SETTING'

Concerns about patient safety and research rigor have helped guide what has emerged as standard protocol in current (and fully legal) psychedelic-assisted psychotherapy research. The protocol addresses what practitioners call the "set" and "setting" of psychedelic sessions. These seek to identify appropriate patients for these treatments, to protect their interests, and above all their safety. They also seek to optimize trust and cooperation between patient and therapist—the "therapeutic alliance"—deemed by many psychiatrists as a crucial factor in generating therapeutic insights.

Drs. Carhart-Harris and Nutt of Imperial College London, among the recent innovators in testing psychedelics in the clinical setting, describe "set and setting" in a 2020 commentary published in *JAMA Psychiatry*. "In depression trials, the model is becoming standardized as a 4-stage process," they note, involving assessment, preparation, experience, and integration. They explain:

"**Assessment** determines if the patient is suitable for psychedelic therapy, from both a mental and physical perspective." Those with a personal or family history of psychosis or bipolar disorder are excluded, as are those with conditions such as hypertension "because psychedelics transiently increase blood pressure." Medications that block the serotonin 2A receptors which are stimulated by "classic psychedelics" are stopped or tapered down—including SSRI antidepressants like Prozac, which reduce sensitivity of the receptor.

"**Preparation** sessions typically take place the day before the drug administration." The participant is "prepared" by one or two therapists, often referred to as guides. "An overview of the dynamics and nature of psychedelic experiences is explained, including how it can be challenging for many people, how such challenges can be confronted, and how the participant can get the most out of the experience."

Therapist-"guides" are at the patient's side to reassure or provide support during the drug experience and after it ends. In the days and weeks following the experience, psychotherapy seeks to develop insights uncovered during or after the drug experience.

"During the psychedelic **experience** [i.e., drug administration], the participant is placed in a room with comfortable seating and low lighting; "is offered eyeshades, and earphones to listen to a music compilation that has been prepared [by the patient] in advance." Oral psilocybin sessions typically last 4 to 6 hours. "Verbal engagement with the therapists is not expected, and most patients go deep into their own visions, thoughts, and memories and do not want to be disturbed. But the guides are present, and, with permission, they can hold the patient's hand to reassure that he or she is being looked after."

"The next day is the **integration** session, during which the same guides talk through the experiences and help the patient make sense of it." While this portion of treatment will vary according to the practitioner, Drs. Carhart-Harris and Nutt suggest a "small number of standard talk-based psychotherapy sessions" be made available to deal with issues that emerged during the psychedelic experience and need to be processed. Treatment studies conducted to date, they note, have typically been limited to one or two psychedelic administrations, weeks or months apart, with psychotherapy varying to include, for instance, a standard 10- to 20-week abstinence-based program in treatments for addiction.

Drs. Carhart-Harris and Nutt take up the question of why psychedelic-assisted therapy might work in a wide range of disorders—depression, anxiety, addiction, PTSD—which presumably have distinct underlying biological causes. "We suggest this may be because these conditions are all *internalizing disorders*. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addiction, drug craving drives behavior that is specific, narrow, and rigid: individuals ruminate on the drug—where to get it, how to pay for it, etc. In OCD and anorexia, there is excessive rumination about threats to the person, from contamination or the effects of eating and overeating, respectively."

Drs. Carhart-Harris and Nutt propose: "The psychedelic experience opens a therapeutic window that disrupts entrenched thinking and allows insight, which with psychotherapeutic support can lead to a recalibration of one's spectrum of [mental] associations." But Dr. McDonald and the APA reviewers note in their APA review paper that "it is unclear whether it is the psychedelic drug itself, the psychedelic-assisted psychotherapy experience, or drug-facilitated enhancements in the therapeutic alliance that promote change" in patients.

QUESTIONS AND CONCERNS

How safe—or dangerous—are psychedelic drugs? "Hallucinogens are not associated with drug-seeking behavior," note the APA review authors. "Animals [such as mice] cannot be trained to self-administer" them, in contrast to addictive substances such as nicotine, alcohol, and cocaine. This is not to say, however, that psychedelics are safe. MDMA, an amphetamine, is one psychedelic thought to have potentially addictive properties. And while psychedelics are cleared from the system in a matter of hours, everyone involved in studying them stresses that responses to the actual experience of the psychedelic "trip" can vary widely.

It is unclear whether it is the psychedelic drug itself, the psychedelic-assisted psychotherapy experience, or drug-facilitated enhancements in the therapeutic alliance that promotes change in patients.

While "these drugs on a relative basis are considered quite safe and don't have classic addiction potential," notes Dr. Griffiths of Johns Hopkins, "that doesn't mean they're safe for everybody and under all circumstances. People who have vulnerability to psychotic illnesses may get exposed and end up with a diagnosis of schizophrenia, and that would be awful. We also know it is almost certain that some people who take these substances under unconstrained conditions are going to become frightened and engage in behaviors that put themselves or others at risk."

Drs. Carhart-Harris and Nutt, in their 2020 *JAMA Psychiatry* commentary, note that "patient demand [for psychedelics] is growing, as is interest in the general population, with the possibility that expectations are outpacing the current data on what outcomes can be confidently foreseen." They caution: "Psychedelics are neither a cure for mental disorders nor a quick fix for an unfulfilled life and should not be portrayed as a panacea."

With respect to specific results obtained in preliminary studies of psychedelics, **Alan Schatzberg, M.D.**, of Stanford University, a BBRF Scientific Council member and 2005 BBRF Falcone Prize winner, in a 2020 commentary in the *American Journal of Psychiatry* asks whether or not, for example, therapeutic benefits experienced by advanced-stage cancer patients after psilocybin-assisted psychotherapy more broadly "tells us something [useful] regarding the use of psilocybin in refractory major depression." He asks: will psilocybin-assisted therapy help patients with anxious depression? Milder depression? "It is possible that clinical trials now under way may be targeting the wrong population or the wrong outcome."

Dr. Schatzberg also notes that some of the promising results obtained in psychedelics-assisted psychotherapy have occurred in "open-label" trials, in which patients know they are receiving the treatment under study (i.e., there is no placebo). This relates to a problem that he says is inherent in trials with psychedelic drugs: it is very difficult to find credible placebos against which to compare them. People who take psychedelics know that they have done so—the experience is vivid, and perhaps impossible to mimic convincingly with non-hallucinogens. And, says Dr. Schatzberg, "without an appropriate placebo, what are we to conclude?"

While generally supportive of the APA review paper's recommendation for continued research, Dr. Schatzberg, who was not part of the review team, stresses that "we need to be sure we are asking the right questions: In which types of patients? How severely ill?" The research process, he says, must seek "rational conclusions," and not be swept up in a wave of enthusiasm.

This view is consistent with that expressed by **Robert Malenka, M.D., Ph.D.**, a BBRF Scientific Council member, also of Stanford, whose commentary about psychedelics research appeared in *JAMA Psychiatry* in 2019. With co-author Boris Heifets, M.D., Ph.D., Dr. Malenka stresses the importance of "learning whether these drugs' benefits are specific to specific constellations of symptoms." For this reason, he and Dr. Heifets urge a "circuits-first approach." By using modern neuroscience tools to "define the [brain-]circuit adaptations that contribute to a drug's behavioral and therapeutic effects, studies can be conducted which could reveal new molecular targets in brain cells or circuits" which can be used as a basis

Different people will react differently to psychedelic substances; and the same user can react differently on different occasions. "Trips" have been described in vastly different terms, ranging from "revelatory" and "mystical" to deeply sad and terrifying.

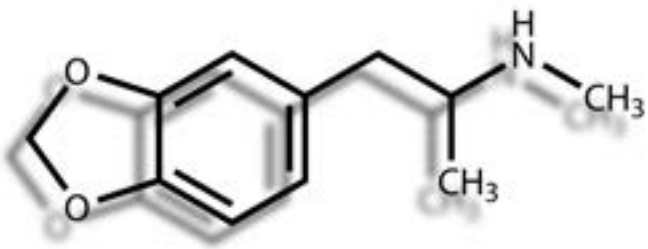
for developing novel drugs that are more effective and cause fewer side effects than psychedelics.

Dr. Jeffrey Lieberman, in his *New England Journal of Medicine* editorial, similarly notes the "fundamental question [as to] whether the putative therapeutic effects of psychedelics require a patient to have a mystical experience or would occur in its absence through the pharmacologic effects on the serotonin system or remodeling of neural circuitry. To answer this question, compounds are being engineered that have the pharmacologic properties of psychedelics but that do not cause mind-altering effects." More generally, Dr. Lieberman, writes, "given the controversial history, unique properties, and ambitious claims surrounding psychedelic drugs, their development must be guided by the most enlightened science and with the utmost methodologic rigor."

Drs. Malenka and Heifets, like Dr. Schatzberg, stress the need for developing effective placebo controls for psychedelics. They further ask, with reference to psilocybin trial data "suggesting that the mystical aspect of the acute drug experience scales with the therapeutic benefit": "Are *all* patients capable of generating this kind of subjective state?"

In the much-publicized 2020 psilocybin trial in patients with major depression led by Drs. Griffiths and Davis, reference was made to participants' "experiences of sadness, crying, grief, loneliness, despair, and imagining of their own deaths while under the influence of psilocybin," notes **Charles Reynolds III, M.D.**, winner of the 2016 BBRF Pardes Humanitarian Prize in Mental Health, in a 2020 *American Journal of Psychiatry* commentary. This leads Dr. Reynolds to compare the psychedelic trip with psychotherapy for prolonged grief disorder. In the latter, "the therapist encourages patients to revisit the circumstances of the death and to repeatedly confront the painful affects associated with reminders of the deceased…. Such grief work, exquisitely painful and emotionally arousing, becomes a pathway to accepting and coming to terms with the finality of the loss and enabling the bereaved to find new meaning in life."

Psychedelics-assisted psychotherapy may work in an analogous way, Dr. Reynolds suggests. But before it can be adopted outside of the research context, he cautions, "it is important scientifically and clinically to highlight the questions and caveats." Among other things, a way must be found, he says, to compare psilocybin-assisted therapy with similar therapy using a credible placebo, in order to determine whether it is the psychotherapy component or the drug that generates the greater part of the therapeutic benefit. ❖ **PETER TARR**



The MDMA molecule.

PTSD and Suicide: New Knowledge and New Treatment Possibilities

Lynnette A. Averill, Ph.D.

Associate Professor, Baylor College of Medicine
Clinical Research Psychologist,
Michael E. DeBakey VA Medical Center

Adjunct Assistant Professor, Yale School of Medicine
National Center for PTSD – Clinical Neurosciences Division,
VA Connecticut, U.S. Department of Veterans Affairs

2015 BBRF Young Investigator

Dr. Lynnette Averill is experienced in translational clinical neuroscience with work focused on informing our understanding of the causes and consequences of trauma-related psychopathology and suicidality, and the investigation of novel rapid-acting interventions. She is interested synaptic connectivity as a biomarker and treatment target, and has special interest in the role that ketamine and psychedelics (including psilocybin, MDMA, and 5-MeO-DMT) can play in biomarker testing due to their rapid effects on synaptic connectivity, behavior, mood, and cognition.

This text is adapted from a recent presentation Dr. Averill made to BBRF donors

The somewhat blurry pictures on this page are of my father, an enlisted U.S. Marine. One was taken in Vietnam, in his dress blues, and one with his treasured car in rural Montana where he and I both grew up. He and my uncle, his younger brother, served in Vietnam. My uncle died in Vietnam and I sometimes say my father did, too, though he came home fully alive. It wasn't until the early 1980s when PTSD was included in the DSM—the *Diagnostic & Statistical Manual* psychiatrists use to make diagnoses. My father, like so many veterans, struggled with what he had experienced in the war and was not able to get answers or effective treatments. Ultimately, he died by suicide when I was 3 years old.

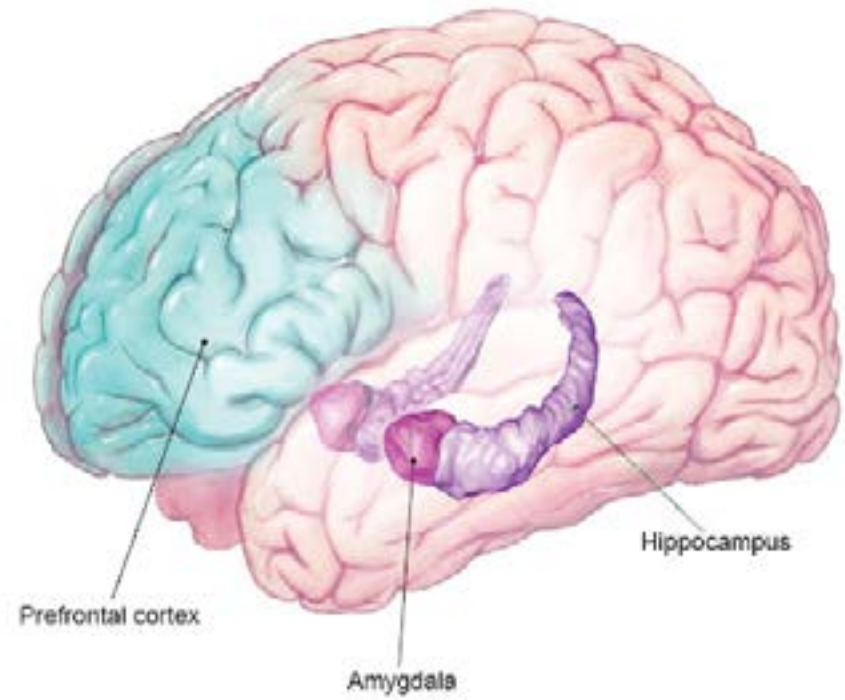
I have no memory of him at all, but I certainly grew up very aware of the effects of war, of stress, and of trauma—not only on the individuals who experienced those things themselves, but also the families, the friends, the communities, who, to a degree, experienced them in parallel and all too often end up losing loved ones to suicide.

Throughout my career as a researcher and clinician, I've asked: how can we effectively treat stress and trauma-related symptoms? How do we effectively treat suicidal ideation, specifically? I found a quote that I really like. It says, "Reality is the leading cause of stress among those in touch with it." It may seem silly. But I think it gets at the idea that reality, while beautiful and wonderful in so many ways, is also filled with stress and trauma. For the majority of the population, life will include trauma, sometimes in a single moment or event, and sometimes in chronic and persistent ways across days, months, or decades. Further, the experience of living day-to-day with PTSD, depression, suicidal thoughts, and related things are, in and of themselves, chronic stressors.

Suicidality, which includes suicidal thoughts and behaviors, is often related to stress and trauma. Right now, there isn't a formal diagnostic category for suicidal thoughts and behaviors in the DSM, although it has been proposed and is currently being considered for inclusion in the next addition.

We have a suicide epidemic in this country and also globally. Worldwide, we lose one person to suicide about every 40 seconds, which is a truly staggering number. Here in the U.S. it's approximately 130 people a day, of whom about 20 are veterans.

In view of these numbers, there's no debate and no question that we need to be doing something different, something more. This is what my career has been focused on: how we can improve treatments and outcomes. With support from the Brain & Behavior Research Foundation, the American Foundation for Suicide Prevention, the Department of Veterans Affairs, and some other groups, my research has been looking not only at the clinical and behavioral factors of risk and resilience related to PTSD and suicidality, but also at the neurobiological underpinnings.



"Over and over again we have seen evidence that three parts of the brain are significantly affected in various ways related to stress and trauma: the prefrontal cortex, amygdala, and hippocampus."

NEURAL FINGERPRINTS

It's been pointed out that mental illness has such a stigma in part because it's possible to look at an individual and say, "Well, I don't *see* anything immediately wrong with you. You don't have a cast, you don't have bandages. I don't see anything wrong—so there must not *be* anything wrong."

But we know from decades of neuroscience research that this really is not the case. There are "invisible injuries," neurobiological changes, that occur. Another quote I often share is by the writer Laurell Hamilton: "There are wounds that never show on the body, that are deeper and more hurtful than anything that bleeds…" Within stress and trauma, there are three primary brain regions that have been implicated: the prefrontal cortex, amygdala, and hippocampus. Over and over again we have seen evidence that these parts of the brain are significantly affected in various ways related to stress and trauma.

What does suicidal ideation or suicide attempts look like in the brain? Is there some sort of biological fingerprint that we can identify? We have some preliminary data that certain areas in the brain have significant changes in cortical thickness, which is used in this case as a measure of brain health, and can be affected, for instance, by injury or insult to the brain.

We have studied a sample of veterans with PTSD, some of whom reported they had thought of suicide and some who had never had such thoughts. Our data shows that there may be something unique, structurally, in the brains of individuals who report an experience of suicidal ideation. This data is very preliminary right now, and we're actively enrolling and recruiting additional participants who will add to this data set, as well as collecting much richer data around the experiences of suicidality.

In addition to brain *structure* we are also looking at *connectivity*, which tells us about brain function. Our attention is drawn to three networks. First, the salience network, which is kind of an alarm system that tells us what things we need to be paying attention to. Sometimes those are mundane things, sometimes they are potential threats or dangers. Second, the central executive network, which involves top-down regulation of emotion, decision-making, and planning. Third is the default mode network, the part of our brain that is most active when we are at rest, from a cognitive perspective.

The data shows that there are perhaps unique neural fingerprints, a neural signature in connectivity in veterans with suicidal ideation and behavior. The question is what we can do with this knowledge, presuming we are able to confirm it and learn more about it.

A NEW TREATMENT FRONTIER?

We know that traditionally available treatments quite rarely even scratch the surface of suicidal ideation for a lot of individuals, which of course is very concerning. It's said that the definition of insanity is doing the same thing over and over and expecting different results. If you want different results, at some point you have to try different approaches.

Over the last 5 to 10 years there has been an explosion in different approaches, which I think is really exciting. My perspective is that we're on the forefront of a new frontier in terms of psychiatric medicines that we might use to treat people with suicidal ideation and behavior. One is ketamine. There is also the possibility that psychedelic medicines may be useful.

Ketamine is a drug that we have done a lot of work with. It is really exciting in that it works in the brain in a way that is completely different from SSRIs, the serotonin reuptake inhibitor drugs usually used to treat depression. Ketamine has been shown to work rapidly in individuals with severe depression who have not found relief in standard antidepression therapies.

We have been able to give ketamine to individuals who are struggling with depression, PTSD, and suicidality, and generally within 24 hours they're feeling remarkably better, have a significant improvement in symptoms.

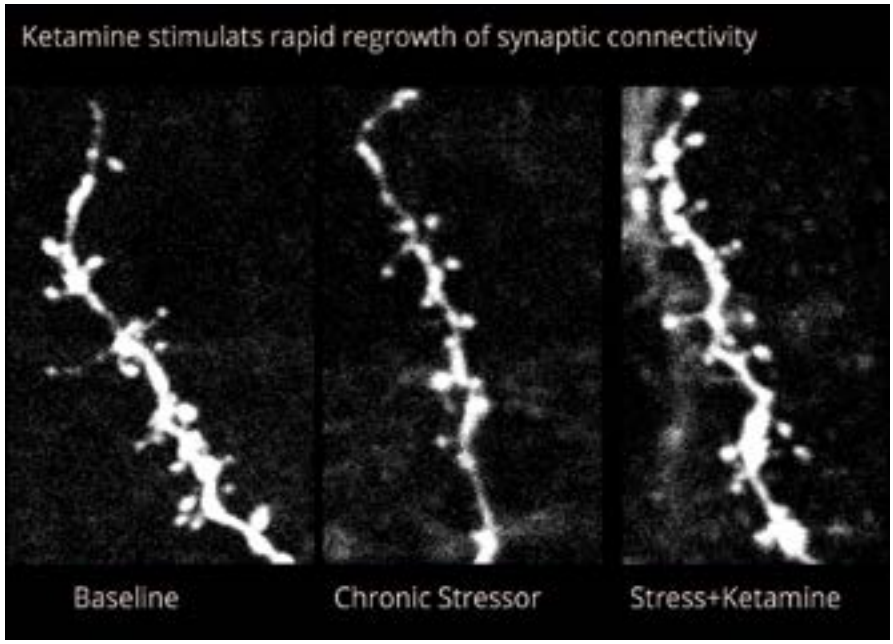
I want to note that SSRIs are incredibly important drugs and for the people that they work well for—they are literally life-saving. The problem is that for a lot of people they don't work well. That's why we're exploring what other things we can put into our toolkit.

We've been able to use MRI imaging and other sorts of tools to look at how ketamine is working, as well as how those changes in the brain seem to relate to changes in symptoms. Much of this seems to involve changes in synaptic strength—changes in the strength of connections between neurons, which we call plasticity. This may provide a biological target that will enable us to develop other treatments with the potential to improve and ultimately save lives.

I say other treatments with the same potential to help because ketamine is a dissociative anesthetic. That means people who take it can have dissociative experiences—people will talk about feeling that their thoughts are a bit jumbled or that they feel as if they are floating, disconnected from their body. Sometimes, people have visual or auditory hallucinations. In our experience with ketamine, side effects have been well tolerated and brief in duration, since ketamine has a short half-life in the body, lasting only minutes.

The image immediately below shows a dendrite in the mouse brain with little features called spines protruding from it. These are the points at which connections are made with other neurons. The image at LEFT is "baseline," i.e., before we subject the animal to stress. You can see the dendrite is pretty plumped up and there are a lot of spines on it. The MIDDLE image shows what happens when there is exposure to a chronic stressor. When there's stress, it kind of shrinks down, and some of those spines go away. Then, in the RIGHT image, you see what happens after we give ketamine following exposure to a stressor. You can see that the dendrite really plumps up again, which corresponds with increases in synaptic strength and synaptic density. The number of spines and dendrites has really expanded again.

That is incredibly positive, not only from a behavioral perspective, but also from a cognitive and symptoms perspective. Other research we've done tells us that within 24 hours of a ketamine infusion, abnormal connectivity in the brain in people with depression has shifted, and very closely resembles connectivity in the brain of unaffected, un-depressed individuals. I call your attention to this in order to suggest that not only does ketamine work rapidly to relieve



symptoms; it also works rapidly to change underlying neurobiology.

One of the potential drawbacks of ketamine is the short durability of its therapeutic effect. The response typically lasts a maximum of 10 days to 2 weeks. I was part of a large team based at Yale—it included many BBRF grantees—which last year demonstrated that pre-dosing individuals with the immunosuppressant drug rapamycin extended the therapeutic effects of ketamine in people who were depressed, in some cases for several additional weeks.

Recently we've gone back to that data and specifically looked at the individuals who reported suicidal ideation. Interestingly, we found that the trajectory of recovery and relapse for suicidal ideation is not at all the same as it is for depression symptoms generally. This suggests, perhaps not surprisingly, that suicidality is not simply a sub-symptom of depression, but is something unique, neurobiologically.

To be clear: suicidal ideation generally improved across the board, but it did have a very different trajectory than did symptom improvement in individuals with depression. This is leading us now to look for fingerprints in those connectivity networks I mentioned earlier—an approach we call "connectome fingerprinting." This means analyzing the connectivity profiles of individuals with PTSD and suicidality who respond to ketamine, and who don't respond to ketamine. We hope to compare their profiles with those of depressed people who do and don't respond to ketamine.

POTENTIAL OF PSYCHEDELICS

I also want to mention possible applications of psychedelic medicines and especially what we call psychedelic-assisted psychotherapy. Current research is conducted under what's called the medical model for these substances. You go to a hospital, are given the dosing by a qualified medical team, and you have trained mental health professionals to manage the psychotherapy portion of the treatment. This is called psychedelic-assisted psychotherapy. [Editor's note: see p. 14 in this issue.]

Psychedelic medicines are not a new thing, but in the last 5 to 10 years there has been a rebirth of interest in performing new research on their potential use in a variety of psychiatric illnesses, including severe depression, PTSD, and suicidality.

I have a collaboration with an investigator at Yale. We're looking at anti-suicidal effects of MDMA. This is a psychedelic drug that in its illegal street form is called Ecstasy. Like our experiments with ketamine in depression, our experiments with MDMA involve its use in highly controlled situations and dosages. We will also be looking at possible anti-suicidal effects of psilocybin, another psychedelic. Both MDMA and psilocybin have side effects in some people that include anxiety and increase in heart rate and blood pressure. This is why it's crucial to give these substances in an appropriate setting and under the guidance of highly trained professionals.

In July 2020, Alan Davis and I published a study in the journal *Chronic Stress* that looked at psychedelics specifically in Special Operations Forces veterans. These are the elite of our military personnel. They are selected for Special Forces because they have demonstrated not only exceptional physical strength, but also exceptional emotional and cognitive strength. Many have had considerable trauma exposure. The population that we had in our study averaged over 10 deployments each, some as many as 18, which is remarkable.

In this population, as with all veterans, but perhaps even more so, there's a great deal of stigma around mental illness, a great deal of stigma around admitting that they are struggling. They may have unexpressed concerns about PTSD and suicidality, and there are very high rates of suicide among them, unfortunately.

The Special Forces veterans in our analysis, nearly all of whom were Iraq/Afghanistan veterans, had completed a psychedelic clinical program in Mexico between 2017 and 2019. We asked them to recall, retrospectively, their mental health and cognitive functioning during the 30 days before and 30 days after treatment two plant-based psychedelics (ibogaine and 5-MeO-DMT).

Our study sample comprised 51 Special Forces veterans suffering from psychological and cognitive impairment. Results suggested that ibogaine and 5-MeO-DMT may offer a rapid and robust, and well-tolerated, treatment option for those suffering from a variety of psychiatric and cognitive symptoms. However, we noted that further research is needed to support this preliminary evidence, specifically, randomized, double blind, placebo-controlled trials to determine the safety and efficacy of these two substances. I should also note that our study did not assess any adverse effects or side effects.

I want to highlight significant changes in suicidal ideation, as well as in general mental health symptoms, that these and other veterans treated with psychedelic substances have reported. In the study I have just referred to, results indicated significant and very large reductions in retrospective report of suicidal ideation, as well as cognitive impairment and symptoms of PTSD. Some of this improvement may have been associated with increased psychological flexibility.

Most of the participants rated the psychedelic experiences as one of the top five personally meaningful (84%), spiritually significant (88%), and psychologically insightful (86%) experiences of their lives, which impressed us. We are preparing to evaluate prospective and longitudinal data from this same clinic.

"There are wounds that never show on the body, that are deeper and more hurtful than anything that bleeds…"

– Laurell Hamilton

We will be doing a study specifically looking at suicide in people with treatment-resistant PTSD and suicidal ideation. We hope to obtain connectome fingerprints, as we did in our ketamine research in depressed patients. We want to look for differences between those who seem to respond and those who do not, with an eye to using this knowledge to inform precision-medicine efforts. The idea is to take that kind of information and develop compounds that can target those same aspects of the brain, but with a different side-effect profile.

Right now, about 130 Americans are dying each day by suicide, including 20 or more veterans. Broadly speaking, I think the thing that's exciting about ketamine and psychedelic medicines is that if we can increase the number of approaches we have in our toolbox and improve our ability to know who might be the best candidates for which treatments, this will allow us to not only save lives, but to help people build lives they truly want to live. ❖

Sensory Over-response and Anxiety in Children With and Without Autism

Q&A with Kimberly L. H. Carpenter, Ph.D.

Duke University School of Medicine
Assistant Professor in Psychiatry and Behavioral Sciences
Assistant Research Professor in the Social Science Research Institute

2015 BBRF Young Investigator Grant

As researchers move closer to developing useful interventions for children at risk for anxiety before a full-blown anxiety disorder appears, one important objective is to identify factors or traits very early in life that correlate with elevated risk. Dr. Carpenter and colleagues may have found one such factor: sensory over-sensitivity. In one study, published in the Journal of Abnormal Child Psychology, *they examined over 900 children aged 2 to 5, 191 of whom were re-examined at age 6. They found that preschoolers with overly sensitive senses—who are intensely bothered by loud or high-pitched sounds, for instance, or the sensation of clothing rubbing on the skin, or bright lights—are at greater risk for developing an anxiety disorder by school age. In this Q&A Dr. Carpenter discusses these and related findings, including those probing the relationship between early sensory over-responsivity and the risk for developing anxiety in children with autism spectrum disorder.*

Dr. Carpenter, before we discuss the relationships you have identified between sensory over-response, early anxiety symptoms, and autism spectrum disorder (ASD), we'd like you to set the stage and talk first about anxiety disorders in young people. How prevalent are they?

Anxiety disorders are quite common in young children. About one in five preschool-aged children meet the criteria for an anxiety disorder. Furthermore, data from an important sample of children drawn from the general population that has followed them across the years—the Great Smoky Mountain Study—suggests that anxiety disorders are present across early childhood and adolescence.

The Great Smoky Mountain Study started at Duke University in the early 1990s to examine the prevalence and development of childhood psychiatric disorders using a sample of over 1,400 children who were recruited from rural counties in Western North Carolina.

To think that as many as one in five of these young people meet criteria for an impairing anxiety disorder by the time they are 26 tells you that this is a highly prevalent and early-emerging problem.

Anxiety disorders also increase the risk of lifelong difficulties with mood disorders. In fact, as data from the Great Smoky Mountain Study indicates, adolescent anxiety is associated with 2.8 times

About 1 in 5 preschool-aged children meet the criteria for an anxiety disorder. The rate is twice as high in children diagnosed with autism spectrum disorder.

greater odds of having anxiety as an adult and 1.85 times greater odds of having depression in adulthood. [Editor's note: this historic study was initially organized and directed by epidemiologist and 2007 BBRF Distinguished Investigator **E. Jane Costello, Ph.D.**, and her husband, **Adrian Angold, M.D.**, who in 2009 were awarded BBRF's Ruane Prize for Outstanding Research in Child and Adolescent Psychiatric Research.]

You say the prevalence of anxiety in children without autism is about 19% to 20%. What about in children who are diagnosed with autism?

In children with autism, the rate of anxiety is double that. One study shows that approximately 40% of all children with autism meet criteria for an impairing anxiety disorder. The problem is that despite the early emergence of anxiety symptoms and the long-term impacts on the lives of individuals with autism, many current interventions focus on alleviating anxiety symptoms in older children and adults who already suffer from an anxiety disorder.

The issue is that by the time most children receive these treatments, they've already developed a number of co-occurring challenges, including difficulties with sleep, recurrent stomach aches, and increased irritability. In addition to this, co-occurring anxiety has also been linked to increased core autism symptoms, including more difficulties with social interactions and more repetitive behaviors.

In order to prevent the significant impairment that results from anxiety, an ideal intervention would happen before full-blown anxiety emerges. The goal of such a strategy would be to reduce or prevent the onset of both the anxiety symptoms and the associated co-occurring challenges that I mentioned, rather than treat them after they've already become impairing.

Importantly, your research has identified hyperactive senses in preschoolers as a potential predictor of anxiety. We understand that you have studied this both in children who don't go on to develop autism as well as in children who do.

In general, we've found that one potential risk factor for anxiety in children with autism is sensory over-responsivity, characterized by heightened and unusual reactions to everyday sensory stimuli. Just about every aspect of our lives is driven by how our senses perceive our environment. Right now, I hope that readers' primary sensory input is the words they are reading on this page. They are probably not paying attention to the sound of the air conditioning or the feel of the tag of their shirt. But imagine if you weren't able to filter out that non-essential sensory information. That would be really hard, right? Well, this is what happens in about 56% of individuals who have autism.

What's even more striking is that sensory challenges are also one of the earliest and most persistent concerns reported by parents of children who go on to develop autism.

How could these early sensory challenges contribute to the high rates of anxiety in children with autism?

Imagine that instead of just being a nuisance that you can't ignore, a sensory experience actually causes you distress. Say you have a young boy, Tommy. Tommy's out to dinner with his parents and he needs to use the restroom. Just as he walks in to the restroom, someone activates the automatic hand dryer.

Everyday sensory inputs such as loud noises or the rub of a clothing tag against the skin can cause vulnerable children to enter a state of hyper-arousal or hyper-vigilance which can make life very difficult.

Now, unfortunately for Tommy, the sound causes his sensory system to react in a way that's similar to how I react when someone scrapes their nails on a chalkboard. Perhaps he will throw his hands over his ears. Perhaps he will run straight out of that restroom. Now, imagine that the following week, Tommy goes to the mall with his mom, and he again needs to use the restroom. Just as before, someone is using the automatic hand dryer as Tommy walks in.

At this point, Tommy's brain has made a very clear connection between the sound of the hand dryer and the public restroom. His brain is wired to be over-reactive to these experiences. Tommy has learned that in order to not have these negative sensory experiences, it's best he just avoids public bathrooms altogether, which he begins to do. This becomes a significant problem for both him and his family because they can no longer be away from home for extended periods of time. If they do find themselves away from home and Tommy has to go to the bathroom and they try to make him, he ends up resisting. A situation like this can cause the family to avoid leaving the house with Tommy unless it's absolutely necessary. You can see how this can very quickly become impairing for a family.

In other situations, everyday noises like a car horn or a lawnmower can cause distress. In such cases, the unpredictability of these sounds may cause these individuals to remain in a constant state of hyper-arousal and hyper-vigilance so that they are prepared to react the instant that they encounter any one of these negative sensory experiences.

This is in contrast, I take it, to the more predictable experience in the hand dryer example, where the predictability of the sound led Tommy to avoidance and phobia of bathrooms.

Right. And these two kinds of cases have led researchers in the field to suggest that these are two possible ways that sensory over-responsivity could lead an individual to develop an anxiety disorder. Our own group has found a positive relationship between sensory over-responsivity and anxiety symptoms in a study of 69 children with autism, ages 3 to 6. This replicates previous findings from a number of other research groups.

The next question is whether sensory over-responsivity is related to all kinds of anxiety or only to certain subtypes. In our study, we found that children with autism who had the greatest levels of sensory over-responsivity were 22 times more likely to meet criteria for generalized anxiety disorder and 10 times more likely to meet criteria for separation anxiety. Again, this replicates what others have found.

Together, our data and that of others suggest that there's a clear connection between sensory over-responsivity and anxiety in preschool-aged children with autism. But: it also suggests that there's more to the story, since not all children with co-occurring autism and anxiety also have sensory-over-responsivity.

In light of this, how do you think sensory over-responsivity and anxiety are linked—in children with autism and in children without autism?

In children with autism, it could be that sensory over-responsivity precedes anxiety, or it could be that sensory over-responsivity is an early manifestation of anxiety. Without longitudinal data, i.e., data that follows children over a period of years, it's impossible to know which of these is the case.

Luckily, other researchers have been able to explore this in a longitudinal sample of children with autism. In the first study that I'm aware of to explore the temporal relationship

between sensory over-responsivity and anxiety, researchers recruited a sample of young children with autism and measured their sensory over-responsivity and their anxiety when they were between 18 and 33 months of age, and then again, one year later.

Through this analysis, they were able to demonstrate that sensory over-responsivity predicts changes in anxiety over the period of toddlerhood. They did not, however, find the opposite to be the case. By this I mean that when children in the study had anxiety at a certain point in their development, the researchers did not find that this predicted that they'd develop sensory over-responsivity at some future time.

This supports the idea that sensory over-responsivity often does precede anxiety symptoms, at least in children with autism—but does not necessarily predict it.

What about children who don't have autism?

That's an important question, we think, because understanding this could have important implications for how one might approach treatment. If the pattern is the same, regardless of whether a child has autism or not, then the same treatment approaches may be applicable across individuals.

My colleagues and I set out to explore whether the same relationship between sensory over-responsivity and anxiety was true in 917 children who were recruited from three Duke pediatric primary care clinics (they were part of the Duke Preschool Well-Being Study). With this incredible sample, we were able to first explore baseline rates of sensory over-responsivity in a relatively large sample of preschool children drawn from the general population.

We found that 20.5% of our sample met criteria for at least one sensory over-responsivity during the preschool period. OK, then: how does sensory over-responsivity relate to anxiety in our sample? We found that, in this sample, 43% of children with sensory over-responsivity met criteria for at least one impairing anxiety disorder during the preschool period.

Luckily, a sub-sample of 191 of those 917 children returned to our lab a few years later to take part in a follow-up study, the Learning About the Developing Brain study, and we were able to obtain the same measurements that we did in their first visit. This allowed us to ask the question: if a child has at least one symptom of sensory over-responsivity when they are between 2 and 5 years old, are they more likely to meet criteria for an impairing anxiety disorder when they reached school-age?

We concluded that the answer to this is yes: sensory over-responsivity in the preschool period significantly and positively predicted anxiety symptoms at age 6 in children who were not diagnosed with ASD. Furthermore, this relationship was specific for anxiety disorders after accounting for other disorders that the children may have, such as ADHD.

Just as we saw in the children with autism, the opposite was not the case. Anxiety in the preschool period did not predict later symptoms of sensory over-responsivity.

So, to be very clear: this research led us to conclude that having at least one sensory over-responsivity as a preschooler is specifically associated with increased risk of having an anxiety disorder at 6 years old.

We know that some of your research focuses on neuroscience—about what may be going on in the brain to cause problems like sensory over-responsivity.

Yes. My lab has been looking at the question of how all of this relates to brain function. If we can start to understand the neurobiology of this relationship, we may be able to identify biologically relevant markers for these difficulties that could help us identify, for example, which children are most likely to respond to a particular treatment.

Or we may be able to identify biological endpoints that we can then use in clinical trials to track the success of treatment. If we understand the underlying neurocircuitry of sensory over-responsivity and anxiety, and how it affects different individuals, we may even be able to use that information to help us individualize treatments.

The way in which the brain processes potentially threatening stimuli is actually pretty well understood. Let me introduce you to my two favorite brain regions. First is the amygdala. The amygdala plays a critical role in driving our reactions to stimuli. Say, for example, you're walking along a trail and you see something that could be a snake. Your amygdala sounds the alarm that there is a potential danger and sets off the fight-or-flight response.

My second favorite region is the prefrontal cortex. What happens if you realize that you did not actually see a snake, but instead, just a coiled-up rope? Well, the prefrontal cortex plays a role in telling your amygdala that, and helps it put the brakes on that fight-or-flight response.

When the delicate balance between the prefrontal cortex and the amygdala gets disrupted, you move away from what we call adaptive anxiety—the kind of helpful anxiety that is warranted by, say, a dangerous or risky situation—and toward unchecked anxiety, which can lead to both hyper-vigilance and avoidance.

Is this similar to what may be happening in the brain of individuals with both sensory over-responsivity and anxiety?

Yes. As part of the follow-up to the Duke Learning About the Developing Brain Study, we had 83 children return to receive a functional MRI scan. We looked at how their brains processed faces depicting different emotions. We found that children who met the criteria for an anxiety disorder during the preschool period were more likely to have decreased connectivity between

the amygdala and the prefrontal cortex at age 6, the time they enter elementary school.

These same brain networks have also been implicated in sensory over-responsivity. This was one result of a recent study that looked at the functional brain response to sensory stimuli in children with autism, some of whom had sensory over-responsivity and some who did not have it.

The prefrontal cortex in children without sensory over-responsivity did a great job in dampening the response of the amygdala. However, the children with sensory over-responsivity had decreased connectivity between the prefrontal cortex and the amygdala, somewhat similar to what we found in our anxious preschoolers in whom the prefrontal cortex was not doing its job in putting the brakes on the amygdala.

What use can be made of these discoveries? How do you proceed from them?

Think about the brain being like your muscles. Just like you can do some bench presses to try to increase the strength of your chest muscles, there's evidence that therapies for anxiety can strengthen the connections between the prefrontal cortex and the amygdala.

For example, take cognitive behavioral therapy, or CBT, which is a common intervention for treating anxiety, and which has been demonstrated to significantly decrease anxiety symptoms in children with autism.

Is it a dangerous snake or just a coiled rope? The amygdala reacts first, but the prefrontal cortex, in processing the sensory data, can put the brakes on the fight-or-flight response. When this assessment process is disrupted, the result can be uncontrolled anxiety and hyper-vigilance and avoidance.

Now, CBT has two primary components that are affecting different aspects of brain function. The first is the cognitive part, which focuses on changing the thought patterns responsible for negative emotional and behavioral patterns. The second aspect is the behavioral therapy piece, which includes things like exposure to the stimuli that are causing anxiety, and includes helping the individual learn effective behaviors to replace their ineffective behavioral responses. These different components of CBT are basically training the prefrontal cortex to put the brakes on an overactive amygdala.

An MRI study of the brain in adults with social anxiety who improved after CBT demonstrated that the improvement was associated with increased plasticity in the amygdala. Plasticity refers to the ability of neurons to change the strength of their connections.

There are also newly emerging therapies that target executive functions, which are skills and processes that enable us to plan, or to focus our attention to achieve our goals. What's important to know about executive functions is that the prefrontal cortex plays a critical role in driving them. Differences in executive function are implicated across a number of disorders, including both autism and anxiety.

Can you give us an example?

For example, both children and adults with anxiety often present with a bias toward focusing on negative information in their environment over and above positive information. Specifically, threatening cues tend to capture the attention of individuals with anxiety. Once captured, they then have difficulty disengaging their attention away from that negative information. So, researchers have developed a treatment that aims to teach the brain to more flexibly shift attention away from threatening information.

It's called attention bias modification training or ABMT, and it's been shown to be effective for treating anxiety in children. Just like with CBT, the amygdala appears to play a role in driving this efficacy in treatment of anxiety.

Based on all of the findings you've shared, can you give us a picture of how they might help children and their parents in a clinical setting?

If we can identify children who struggle with sensory over-responsivity before they go on to develop an anxiety disorder and have a psychologist, occupational therapist, or other clinicians work with them to help them practice engaging that prefrontal cortex and decreasing the response to their amygdala when they experience negative sensory stimuli, then it is possible that we can help some children from progressing from sensory over-responsivity to a full-blown anxiety disorder.

What should a parent do if their child is experiencing sensory over-responsivity?

I think the first thing to do is always talk to your pediatrician. But I think if you're very concerned, please keep in mind that there are occupational therapists out there who specifically focus on this. It might make sense to find an occupational therapist or a psychologist to help you and help your child work through these issues so that they don't become an impairing problem, or don't evolve into one.

What should a parent do if they see that their child is experiencing significant anxiety at a young age or a little older in adolescence?

If you're worried, I always say, please seek help. Talk to your pediatrician, find a good child psychologist, find an occupational therapist. These people are amazing at what they do, and they know what they're doing.

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

The Klerman & Freedman Awards

The Brain & Behavior Research Foundation is pleased to honor and recognize the extraordinary work of six outstanding young researchers with our annual Klerman & Freedman Awards for exceptional clinical and basic research in mental illness. The Klerman and Freedman Awards recognize innovative thinking and remarkable talent across the field of neuropsychiatry.

The award winners are selected by committees of the Foundation's distinguished Scientific Council. Led by Dr. Herbert Pardes, this group of 178 prominent mental health researchers rigorously evaluates every BBRF grant application, identifying the most promising, high-quality science.

These six award winners have previously received awards through the BBRF Young Investigator Grant program, which supports early-career scientists as they gather pilot data and "proof of concept" for their innovative clinical and basic research. Our Young Investigator grants provide the seed funding early-career researchers need to pursue hypotheses, concepts, and strategies that our Scientific Council believes have the greatest chance of advancing the field.

We applaud these researchers for their exceptional work, and we thank our generous donors for their support of brain and behavior research to fund scientists working to produce better treatments, cures, and methods of prevention for mental illness.

More details on the 2021 awardees and honorable mentions can be found in the 2021 Program Booklet, which can be downloaded at: https://www.bbrfoundation.org/grants-prizes/klerman-freedman-prizes.

2021 KLERMAN PRIZE FOR EXCEPTIONAL CLINICAL RESEARCH

Nicholas L. Balderston, Ph.D.
University of Pennsylvania
Center for Neuromodulation in Depression and Stress

HONORABLE MENTIONS

Hengyi Cao, Ph.D.
Feinstein Institutes for Medical Research, Northwell Health
West China Hospital

Nolan R. Williams, M.D.
Stanford University

2021 FREEDMAN PRIZE FOR EXCEPTIONAL BASIC RESEARCH

Meaghan Creed, Ph.D.
Washington University in St. Louis
Washington University Pain Center

HONORABLE MENTIONS

Denise Cai, Ph.D.
Icahn School of Medicine at Mount Sinai

Tomasz J. Nowakowski, Ph.D.
The University of California, San Francisco

Recent Research Discoveries

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

Study Links PTSD Stress to Cortical Thinning and Shorter Expected Lifespan

For biological and genetic reasons some people are more resilient than others to the stresses that trauma places upon the human system, affecting both brain and body.

A team of researchers led by 2012 BBRF Young Investigator **Alicia K. Smith, Ph.D.**, and BBRF Scientific Council member **Kerry Ressler, M.D., Ph.D.**, set out to evaluate how trauma and PTSD affect the brain and the expected lifespan of sufferers, using brain scanning technology and a new assessment tool called GrimAge. Dr. Ressler is also a 2017 BBRF Distinguished Investigator, 2009 BBRF Freedman Prize winner and a 2005 and 2002 Young Investigator.

Publishing their results in the journal *Neuropsychopharmacology*, the team's findings were consistent with prior research indicating that trauma and PTSD appears to significantly accelerate cellular aging. And they generated direct evidence that PTSD in some people is likely to shorten expected lifespan as well as increase the risk of neurodegeneration by thinning portions of the brain's cortex.

A total of 854 people registered in the Grady Trauma Project based in Atlanta were selected for inclusion in the study by the team. The Grady project seeks to gauge the influence of genetic and environmental factors on responses to stressful life events in a predominantly low-income, urban African-American population. Over 90% of participants in the PTSD study were African-American and 70% were female. The average age was about 43.

Half (427) of the study subjects were controls; they had been exposed to trauma during their lives but had no history of PTSD. One-fourth (218) of the participants had current PTSD symptoms, and one-fourth (209) had a history of PTSD but had no current symptoms.

The "GrimAge" tool used to predict the impact of traumatic stress on expected lifespan is based on detection of changes in the human genome called epigenetic changes. GrimAge focuses on methyl groups (CH_3) which attach themselves to the DNA that forms the human genome, sometimes impacting the way genes are activated. The presence or absence of methyl groups at particular locations in the genetic sequence can be altered by an individual's exposure to stress, both chronic and acute. In this way, therefore, epigenetic changes can reflect the degree to which a given trauma or series of traumas have affected human cells at the deepest—genetic—level.

The study found that a PTSD diagnosis at any age predicted shorter lifespan. Overall, people with current and "lifetime" trauma—but not people who experienced trauma without having post-traumatic stress reaction—had an "acceleration" in their GrimAge score, suggesting that the stress they have endured has shortened their predicted lifespan by some amount (which varies according to the individual).

For those with trauma at some point in their lifespan but not currently, the GrimAge acceleration applied only in those with trauma in their adulthood, not those with childhood trauma only, provided they never suffered from PTSD.

Sixty-nine of the 854 study participants—all women, to avoid potential biological differences generated by gender—formed a subgroup whose MRI brain scan results were correlated with the study's other findings. This portion of the study showed that

those with GrimAge acceleration—i.e., expected quickening of cellular aging and shorter predicted lifespan as a result of trauma—had a thinning in the right lateral orbitofrontal cortex and right posterior cingulate cortex, brain areas associated with the regulation of emotions and threats. No thinning was seen in the control group who had experienced trauma but never suffered PTSD.

Cell-type differences in study participants with GrimAge acceleration were found to most affect cells that play important roles in inflammation, suggesting at least one possible mechanism for the conversion of stress into biological damage to the brain and bodily systems. The team urges future research using a study cohort that can be followed up over the long-term, and to explore whether the current findings hold up in populations of greater gender and ethnic/racial diversity.

The team also included **Tanja Jovanovic, Ph.D.**, 2015 BBRF Independent Investigator and 2010 Young Investigator; **Charles Gillespie, M.D., Ph.D.**, 2007 BBRF Young Investigator; **Sanne van Rooij, Ph.D.**, 2018 BBRF Young Investigator; and **Adriana Lori, Ph.D.**, 2013 BBRF Young Investigator.

New Technology Enables Manipulation of Neurons in Peripheral Organs & Reveals a Mechanism of Appetite Suppression

A research team led by a 2018 BBRF Young Investigator, **Sung Il Park, Ph.D.**, reports that it has developed and tested a new technology enabling unprecedented exploration of nerve-cell function in organs of the body outside of the brain. The new technology, called optoelectronics, uses tiny wireless implantable devices to manipulate the activity of individual nerve cells in the organs of awake, freely moving animals. This makes possible experiments with the power to reveal the specific (and often multiple) functions of different kinds of nerve cells in the body's periphery. Such knowledge, which is still spotty, is a vital predicate of future experiments to test new therapeutic concepts.

As reported in *Nature Communications*, the novel wireless devices created by Dr. Park and colleagues at Texas A&M University were successfully implanted in the stomachs of laboratory mice, and enabled the team to discover an unexpected mechanism for suppressing appetite. This is a hint of the technology's potential utility in identifying new treatment targets—in this application, for obesity and eating disorders.

In the early 2000s, a team led by **Karl Deisseroth, M.D., Ph.D.**, with help from two BBRF Young Investigator grants, pioneered a revolutionary technology called optogenetics, whose reach the newly reported technology significantly extends. With optogenetics, Dr. Deisseroth, now a member of BBRF's Scientific Council and winner of the 2013 BBRF Goldman-Rakic Prize, discovered a way to switch individual neurons in the brain "on" and "off," by genetically adapting various neuronal types to activation by specific wavelengths of light.

Like optogenetics, the wireless "optoelectronic" technology invented by Dr. Park and colleagues can provide deep insights into what goes awry in illness by obtaining new knowledge about how cells and circuits function. In contrast with optogenetics approaches, which are used to explore neural and circuit function in the brain, Dr. Park's wireless technology is designed to work in the body's peripheral organs and to probe the complex highways of nerves that connect those organs with the brain.

Optogenetics is limited to the brain due to constraints associated with delivering light via fiberoptic technology to the

body's periphery. The new technology has no such constraints. At its heart are extremely small "microscale light-emitting diodes" with soft, highly flexible tethers, which are implanted into the peripheral organ of interest. The devices are externally controlled via wireless platforms on a single transmitter that can direct experiments in as many as eight animals (living in adjacent cages) at a time. Testing showed that the devices were effective for a month in freely behaving animals.

In their paper, the team explained that one "key priority for research is to attain cell-type and organ-specific manipulations of the vagus nerve, in animals that are awake." The vagus nerve is the body's most important nerve pathway connecting the heart, lungs, and digestive tract with the brain. Its function accounts for the body's remarkable ability to unconsciously regulate breathing, the pumping of the heart, and the breaking down of food into nutrients and waste products.

The focus of Dr. Park's team in their test of wireless optoelectronics were the endings of the vagus nerve within the stomach—known to be important in the regulation of appetite. The specific targeting made possible by optoelectronics enabled the team to concentrate on a type of neuron found in the stomach that is characterized by its expression of a gene called *Calca+*. They used their wireless device to selectively activate *Calca+* neurons which connected with nerve-endings from the vagus nerve in a part of the stomach called the corpus.

Compared with mice in which optoelectronics was not used to stimulate stomach neurons of this type, mice that did receive stimulation via wireless commands showed "robust suppression of food intake during feeding," the team reported. In other words, by activating specific vagus nerve endings in a specific area of the stomach, appetite was suppressed—to the point of almost complete suppression when the stimulation was increased in intensity.

It is widely believed that when the stomach is full and has stretched, information about its stretch is conveyed to the brain by receptors on the vagus nerve. "Our findings suggest that stimulating non-stretch receptors, those that respond to chemicals in the food, could also give the feeling of satiety [fullness] even when the stomach is not stretched," Dr. Park explains.

The team also discovered that activation of *Calca+* vagal nerve endings seems to trigger an aversive reaction which alters an animal's taste preferences. Thus, these early optoelectronics experiments resulted in identification of a role of vagus nerve endings in the stomach in appetite suppression, and a mechanism involving taste-aversiveness which causes the loss of appetite.

The team described the implications: "Identification of pathways that can either suppress or stimulate appetite will have direct clinical importance for potentially developing novel therapeutics for treating appetite disorders."

Study Links Low Maternal Vitamin D in Early Pregnancy with ADHD Risk in the Child

For the first time, researchers have found that a low level of maternal vitamin D during the early part of pregnancy raises the odds that a child born of that pregnancy will develop clinically diagnosed ADHD (attention-deficit/hyperactivity disorder) by adolescence.

ADHD is estimated to affect approximately 5% of the world's population. Some people don't begin to experience symptoms until adulthood, but most cases are diagnosed in childhood and adolescence.

The study making the connection between low levels of maternal vitamin D in early pregnancy and subsequent ADHD in the child suggests that the child's risk is about 1.5 times that of the average risk level.

This finding was arrived at by a team led by 2008 BBRF Independent Investigator **Andre Sourander, M.D., Ph.D.**, of the University of Turku in Finland. He and colleagues studied Finnish birth registries, which include blood samples taken in early pregnancy, and combined these data with national records including referrals of young people to "specialized" health services, including psychiatric services.

Dr. Sourander, whose colleagues included **David Gyllenberg, M.D., Ph.D.**, a 2015 BBRF Young Investigator, and **Alan S. Brown, M.D.**, 2019 BBRF Lieber Prize winner, 2015 BBRF Distinguished Investigator, 2004 and 2000 Independent Investigator and 1996 and 1993 Young Investigator, reported their findings in the *Journal of the American Academy of Child & Adolescent Psychiatry*. The paper's first author was Minna Sucksdorff, M.D.

The study cohort consisted of 1,067 mother-child pairs in which the child was diagnosed with ADHD within 12 years of birth, and an equal number of mother-child pairs, matched demographically, in which the child was not diagnosed with ADHD. Maternal vitamin D levels were based on blood samples taken during the first trimester or early in the second trimester of pregnancy.

The study provides a window into vitamin D's impact on the fetus during pregnancy in a population in which vitamin D levels naturally tend to be lower. This is due to Finland's high northern latitude, which sharply limits sunlight during winter. In addition to dietary sources, vitamin D is produced by the body through a process in which skin cells must be exposed to sunlight.

Dr. Sourander's team notes, "Early pregnancy is a critical period for fetal brain development." They say their study's finding connecting low vitamin D levels in the early months of pregnancy and subsequent ADHD in the child "suggests that insufficient *in utero* vitamin D may adversely influence fetal [developmental] programming and expose the offspring to a suboptimal [pre-birth] environment resulting in possible ADHD."

They explain that vitamin D receptors are expressed in the brain and that research has shown that vitamin D affects brain function via regulation of calcium signaling (between brain cells) as well as by affecting molecular factors which help support and protect neurons, helping them to mature and grow. They also note that rodent studies have shown that vitamin D depletion can lead to alterations in dopamine signaling, possibly giving rise to "hyperlocomotion."

The team notes that their findings, if replicated in a more diverse population, could have important public health implications. Although nutritional deficiency over recent decades has been markedly reduced in the developed world, they observe, vitamin D deficiency "still remains common… and is especially prevalent among pregnant women." ❖

Therapy Update

Recent news on treatments for psychiatric conditions

TRIAL TESTS 'LAUGHING GAS' IN SEVERELY DEPRESSED TREATMENT-RESISTANT PATIENTS

Peter Nagele, M.D.

Charles R. Conway, M.D.

Newly reported results of a phase 2 clinical trial indicate the potential utility of using nitrous oxide treatments in patients with severe major depression that has not responded to other forms of therapy.

Nitrous oxide (N2O) is often called laughing gas, and has been used as an anesthetic since the 1800s. Many people are familiar with N2O because of its use in dentistry, as a mild pain reliever and anti-anxiety agent.

Peter Nagele, M.D., the Chair of Anesthesia and Critical Care at the University of Chicago, was awarded a BBRF Independent Investigator grant in 2016 to perform the study just reported, which appeared in the journal *Science Translational Medicine*.

Dr. Nagele and his co-investigator, 2007 BBRF Young Investigator **Charles R. Conway, M.D.**, were interested in testing nitrous oxide in part because of research showing the effectiveness of another anesthetic, ketamine, in alleviating the symptoms of severe major depression in treatment-resistant patients. Dr. Conway directs the Resistant Mood Disorders Center and Treatment-Resistant Depression and Neurostimulation Clinic at Washington University, St. Louis.

When ketamine is given to depressed patients, it is delivered intravenously (or intranasally in the case of esketamine, an FDA-approved drug based on the ketamine molecule). Importantly, the dose is far below that used in anesthesia, a fact which improves the side-effect risks of ketamine considerably.

Drs. Nagele, Conway and colleagues studied whether nitrous oxide, also an anesthetic at high concentrations, might show rapid antidepressant effectiveness at sub-anesthetic dosages. A prior placebo-controlled study had shown that a single one-hour administration of nitrous oxide—inhaled through a face mask—did enable severely treatment-resistant depressed patients to experience rapid antidepressant relief which lasted for at least 24 hours.

The new study sought to test nitrous oxide in severely treatment-resistant depressed patients at two concentrations vs. placebo: at 50%, the concentration used in the prior study, as well as at 25%. The patients had been depressed for an average of 17 years and had not been helped in four or more antidepressant treatment courses, on average.

Twenty patients received three hour-long treatments, each one month apart: one treatment with N2O at 50%, one with N2O at 25%, and one with a placebo (ambient air and oxygen). The patients were assigned to receive the three treatments in randomized order.

Results were positive and in some ways surprising. Nitrous oxide at both 50% and 25%, given in one-hour treatment sessions, was effective compared with placebo in significantly lowering the severity of depression symptoms. In the hours and days immediately following treatments, there was little difference in the magnitude of the improvement seen in the patients, regardless of whether they had received N2O at 25% or 50% concentration.

The researchers were surprised that the antidepressant benefits persisted well beyond the first week after an N2O treatment and, in some cases, up to a month after treatment. This would suggest that N2O, similar to ketamine, has persistent antidepressant benefits in some treatment-resistant patients after a single dose. Drs. Nagele and Conway said

future studies will be required to optimize dosing in treatment-resistant depression.

The researchers noted that side effects of N2O treatments were not uncommon but mild, and in each case resolved within hours of a treatment. They included nausea, light-headedness, headache, and dizziness. Importantly, side effects at 25% N2O were one-fourth as common as in 50% N2O, suggesting to the team that if the treatment is ultimately approved, on a risk-benefit basis it could make sense to use N2O at the lower dosage at the outset in patients, and escalate to 50% dosage in patients who remain resistant to treatment.

The team cautions that their trial was small and must be replicated in much larger populations, but they were cheered to note that giving N2O at the lower dosage not only resulted in fewer side effects, but was nearly as effective as treatments at twice the dosage.

LONG-ACTING INJECTABLE ANTIPSYCHOTIC TREATMENT LENGTHENED TIME TO FIRST SCHIZOPHRENIA HOSPITALIZATION

One of the most important goals in the treatment of people with schizophrenia is preventing relapses, which often lead to periods of hospitalization.

One common cause of the destabilization seen in many relapses is patients' non-adherence to antipsychotic medication. Psychosis, a major debilitating symptom of schizophrenia, can result in delusions, hallucinations, paranoia, or disordered thought. One recent study showed that 35% of patients admitted for a first hospitalization had stopped taking medication within 30 days of discharge, and 54% within 60 days.

The return to the hospital that such non-adherence necessitates can cost patients dearly, not only in terms of emotional suffering but also because second episodes of psychosis in the same individual tend to respond less well to same treatment used in the first episode.

With this fact in mind, a team led by **John M. Kane, M.D.**, a 1992 BBRF Lieber Prize winner at Zucker Hillside Hospital, set out to test a way to increase adherence to antipsychotic medication in newly diagnosed or early-stage schizophrenia patients, using a long-acting injectable form of the antipsychotic aripiprazole.

Although the evidence is not entirely clear, many practitioners believe one way of keeping patients on an antipsychotic regimen is to reduce the number of times the drug must be taken in order to maintain stability.

John M. Kane, M.D.

The team, which included **Delbert Robinson, M.D.**, a 2005 BBRF Independent Investigator, **Christoph U. Correll, M.D.**, a 2007 BBRF Young Investigator, and **Nina R. Schooler, Ph.D.**, a BBRF Scientific Council member and 1998 Distinguished Investigator, recruited 489 early-stage schizophrenia patients, aged 18-35. Three-fourths were men and the average age of the cohort was 25. Forty-six percent of the subjects had 1 year or less of prior antipsychotic use.

Delbert Robinson, M.D.

So that the study treatment modeled usual clinical care, the team decided to randomize treatment by clinic. Clinics were randomly assigned to either 1) offer participants treatment with long-acting aripiprazole or 2) provide treatment to their participants based upon the clinic staff's best clinical judgment. All participants at a particular clinic received the same treatment. Nineteen clinics with a total of 234 participants were randomized to offer long-acting aripiprazole treatment and twenty clinics with a total of 255 participants were randomized to offer clinician-choice treatment.

Participants were followed for 2 years. They were interviewed by telephone every other month to obtain data on hospitalizations and emergency/crisis unit use. Every 4 months they completed a medical service-use form; data were checked against medical records where available. Overnight stays in crisis stabilization units and in psychiatric emergency departments were regarded as hospitalizations. Admissions related to substance detoxification were not, for purposes of the study.

Use of a long-acting antipsychotic produced a 44% reduction in the incidence rate of first hospitalizations compared with use of antipsychotics as conventionally delivered. According to the team, which reported results in *JAMA Psychiatry*, for every 7 patients treated with the long-acting form of antipsychotic medication, 1 hospitalization was prevented, on average.

"Many attribute the low rate of long-acting injectable antipsychotic medications in clinical practice to patient refusal," the team said. But their trial, they said, "demonstrates that with proper training, practitioners are able to communicate potential advantages of long-acting injectables, even in early illness stages, and engage patients in shared decision-making resulting in high acceptance rates."

"It is human nature to have difficulty taking medication on a long-term basis," the researchers acknowledged. "The phenomenon of non-adherence needs to be normalized and de-stigmatized." They suggested that results of their trial suggested one potential way to move toward these objectives.

MEDICINE TO TREAT PREMENSTRUAL MOOD DISORDER IS TESTED

Cynthia Neill Epperson, M.D.

In a proof-of-concept trial, researchers have obtained encouraging results for a medicine to treat premenstrual dysphoric disorder (PMDD)—a mood disorder affecting 3% to 5% of women of childbearing age.

Classic behavioral symptoms of PMDD include mood swings, irritability, depression, and anxiety in addition to physical symptoms associated with the disorder (bloating, swelling of the breasts, gastrointestinal problems).

PMDD is likely caused by fluctuations in sex hormones, especially progesterone. Symptoms usually occur during the "late luteal" phase of the menstrual cycle, between ovulation and menstruation. When a new egg is not fertilized, levels of progesterone and other hormones that rise in preparation for possible pregnancy begin to fall rapidly. These ovarian hormone shifts correspond with the onset of PMDD symptoms, which affect quality of life and in some cases can be debilitating.

A research team based in Sweden and led by Inger Sundström-Poromaa, M.D., Ph.D., of Uppsala University, performed a randomized, double-blind clinical trial of a medicine called ulipristal acetate in a group of 95 women diagnosed with PMDD. **Cynthia Neill Epperson, M.D.**, a 2005 BBRF Independent Investigator and 1997 and 1995 Young Investigator, who played an important role in developing brexanolone, a rapid-acting antidepressant approved in 2019 for use in postpartum depression, was part of the team. Their results were published in the *American Journal of Psychiatry*.

Ulipristal acetate, or UPA, was given at a dose (5mg/day) and regimen already approved for use in treating uterine fibroids by regulators in the European Union in 2009 and by the FDA in the U.S. the following year. Forty-eight women received UPA in the trial and 47 received a placebo pill. The women ranged in age between 18 and 46 and had not been treated with psychotropic medications in the 3 months prior to their participation in the trial. The trial began in each participant on the first day of menses, and continued over three consecutive menstrual cycles.

UPA binds to and alters the function of two cellular receptors for progesterone. Among other places in the body, these are found in abundance in the amygdala and in other part of the brain involved in the processing of emotions: the hippocampus, the hypothalamus, the thalamus, and the frontal cortex. The drug's modulation of the receptors has the effect of inhibiting the synthesis and action of progesterone itself.

Each participant in the trial used a smartphone app to keep a daily log of mood and physical symptoms of PMDD, rating each on a scale ranging from "none" to "extreme." These self-reports generated a numerical score which was used to assess the comparative effects of UPA and placebo over three consecutive menstrual cycles.

While UPA showed no difference vs. placebo in moderating the physical symptoms of PMDD, women in the UPA group registered improvements in PMDD mood symptoms that the researchers found to be statistically significant. 85% of women in the UPA group experienced either a full remission (50%) or partial remission (35%) of mood symptoms by the end of three menstrual cycles. This compared with 52% of

participants who experienced full (21%) or partial (31%) remission in the placebo group.

The impact of UPA was especially significant in moderating symptoms of depression, anger/irritability, interpersonal conflicts, and lack of energy, the researchers noted.

Side effects were rare, they said, the most common being headache and nausea (each experienced by about 8% of those who received UPA) and fatigue (about 6%). The researchers were careful to note that in both the EU and U.S., UPA has been under post-approval study since 2018 for its possible role in rarely reported cases of liver injury. While these studies are still in progress, continuous monitoring of liver function over the first 3 months of the drug's administration is now routinely performed in patients as a precaution.

The team also noted that while the mechanism of the drug is still not fully understood, up to 80% of those who have taken it for uterine fibroids have experienced anovulation—a lack of ovulation. Neither ovulation nor progesterone levels were measured in the current trial; however, amenorrhea, or the skipping of a menstrual period, was experienced by 27.5% of those in the current trial who received UPA.

The researchers say UPA is "a promising drug" for treatment of the mood symptoms of PMDD, and encourage larger trials to validate their results and to more closely study the drug's potential impact on the liver and on changes in the menstrual cycle. They also note that UPA's modulation of progesterone receptors provides an insight into the molecular mechanisms underlying PMDD, and opens the way to developing other compounds that have similar impact. ❖

BENEFITS OF BECOMING A RESEARCH PARTNER

Personally choose & sponsor a scientist, selected by the BBRF Scientific Council, who is conducting research that is important to you and your family.

Receive annual scientific updates and progress reports

Interact one-on-one with your scientist partner through email, phone or a laboratory visit

Uniting Donors with Scientists

"My brother first exhibited symptoms of schizophrenia in 1960 at age 17. When we were able to support psychiatric research as a family, we found the Brain & Behavior Research Foundation. I became a Research Partner because the satisfaction of enabling a Young Investigator's work to unlock the pathways to understanding the sources of psychiatric illness is incredibly satisfying. Now I support three Young Investigators each year. My brother knew that whatever science discovered, it would be too late for him, but he wanted to know that others could avoid the illness that had ruined his life. I donate to honor his wish."

—Barbara Toll, Board Member & Research Partner

To learn more, please contact us at 646-681-4889
or researchpartner@bbrfoundation.org.
Visit bbrfoundation.org/research-partners.

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

Our Scientific Council

178 Scientific Council Members (20 Emeritus)
50 Members of the National Academy of Medicine
31 Chairs of Psychiatry & Neuroscience Departments
16 National Institute of Health Chiefs & Directors
9 Members of the National Academy of Sciences
3 Recipients of the National Medal of Science
2 Former Directors of the National Institute of Mental Health and the current Director
1 Nobel Prize Winner

PRESIDENT
Herbert Pardes, M.D.

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

Ted Abel, Ph.D.
Anissa Abi-Dargham, M.D.
Nii A. Addy, Ph.D.
Susanne E. Ahmari, M.D., Ph.D.
Schahram Akbarian, M.D.,Ph.D.
Susan G. Amara, Ph.D.
Stewart A. Anderson, M.D.
Nancy C. Andreasen, M.D., Ph.D.
Victoria Arango, Ph.D.
Amy F.T. Arnsten, Ph.D.
Gary S. Aston-Jones, Ph.D.
Jay M. Baraban, M.D., Ph.D.
Deanna M. Barch, Ph.D.
Jack D. Barchas, M.D.
Samuel H. Barondes, M.D.
Carrie E. Bearden, Ph.D.
Francine M. Benes, M.D., Ph.D.
Karen F. Berman, M.D.
Wade H. Berrettini, M.D., Ph.D.
Randy D. Blakely, Ph.D.
Pierre Blier, M.D., Ph.D.
Hilary P. Blumberg, M.D.
Antonello Bonci, M.D.
Kristen J. Brennand, Ph.D.
Robert W. Buchanan, M.D.
Peter F. Buckley, M.D.
Edward T. Bullmore, Ph.D.
William E. Bunney, Jr., M.D.
Joseph D. Buxbaum, Ph.D.
William Byerley, M.D.
Tyrone D. Cannon, Ph.D.
William Carlezon, Ph.D.
Marc G. Caron, Ph.D.
William T. Carpenter, Jr., M.D.
Cameron S. Carter, M.D.
Peter Jeffrey Conn, Ph.D.
Edwin H. Cook, Jr. M.D.
Richard Coppola, D.Sc.
Christopher W. Cowan, Ph.D.
Joseph T. Coyle, M.D.
Jacqueline N. Crawley, Ph.D.
John G. Csernansky, M.D.
Z. Jeff Daskalakis, M.D., Ph.D.
Karl Deisseroth, M.D., Ph.D.
J. Raymond DePaulo, Jr., M.D.
Ariel Y. Deutch, Ph.D.
Ralph DiLeone, Ph.D.
Lisa Beth Dixon, M.D., M.P.H.
Wayne C. Drevets, M.D.
Kafui Dzirasa, M.D., Ph.D.
Guoping Feng, Ph.D.
Robert L. Findling, M.D., MBA
Stan B. Floresco, Ph.D.
Judith M. Ford, Ph.D.
Alan Frazer, Ph.D.
Robert Freedman, M.D.
Aurelio Galli, Ph.D.
Mark S. George, M.D.
Elliot S. Gershon, M.D.
Mark A. Geyer, Ph.D.
Jay N. Giedd, M.D.
Jay A. Gingrich, M.D., Ph.D.
James M. Gold, Ph.D.
David Goldman, M.D.
Joshua A. Gordon, M.D., Ph.D.
Elizabeth Gould, Ph.D.
Anthony A. Grace, Ph.D.
Raquel E. Gur, M.D., Ph.D.
Suzanne N. Haber, Ph.D.
Philip D. Harvey, Ph.D.
Stephan Heckers, M.D.
René Hen, Ph.D.
Takao K. Hensch, Ph.D.
Robert M.A. Hirschfeld, M.D.
Elliot Hong, M.D.
Yasmin L. Hurd, Ph.D.
Robert B. Innis, M.D., Ph.D.
Jonathan A. Javitch, M.D., Ph.D.
Daniel C. Javitt, M.D., Ph.D.
Dilip V. Jeste, M.D.
René S. Kahn, M.D., Ph.D.
Ned H. Kalin, M.D.
Peter W. Kalivas, Ph.D.
Eric R. Kandel, M.D.
Richard S.E. Keefe, Ph.D.
Martin B. Keller, M.D.
John R. Kelsoe, M.D.
Kenneth S. Kendler, M.D.
James L. Kennedy, M.D.
Robert M. Kessler, M.D.
Mary-Claire King, Ph.D.
John H. Krystal, M.D.
Amanda J. Law, Ph.D.
James F. Leckman, M.D., Ph.D.
Francis S. Lee, M.D., Ph.D.
Ellen Leibenluft, M.D.
Robert H. Lenox, M.D.
Pat R. Levitt, Ph.D.
David A. Lewis, M.D.
Jeffrey A. Lieberman, M.D.
Kelvin Lim, M.D.
Sarah Hollingsworth Lisanby, M.D.
Joan L. Luby, M.D.
Irwin Lucki, Ph.D.
Gary Lynch, Ph.D.
Robert C. Malenka, M.D., Ph.D.
Anil K. Malhotra, M.D.
Husseini K. Manji, M.D., F.R.C.P.C.
J. John Mann, M.D.
John S. March, M.D., M.P.H.
Stephen Maren, Ph.D.
Daniel H. Mathalon, Ph.D., M.D.
Helen S. Mayberg, M.D.
Carla A. Mazefsky, Ph.D.
Colleen A. McClung, Ph.D.
Ronald McKay, Ph.D.
James H. Meador-Woodruff, M.D.
Herbert Y. Meltzer, M.D.
Kathleen R. Merikangas, Ph.D.
Richard J. Miller, Ph.D.
Karoly Mirnics, M.D., Ph.D.
Bita Moghaddam, Ph.D.
Lisa M. Monteggia, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.
Eric J. Nestler, M.D., Ph.D.
Andrew A. Nierenberg, M.D.
Patricio O'Donnell, M.D., Ph.D.
Dost Ongur, M.D., Ph.D.
Maria A. Oquendo, M.D., Ph.D.
Godfrey D. Pearlson, M.D., Ph.D.
Peter Penzes, Ph.D.
Mary L. Phillips, M.D., M.D. (CANTAB)
Marina R. Picciotto, Ph.D.
Daniel S. Pine, M.D.
Robert M. Post, M.D.
James B. Potash, M.D., M.P.H.
Pasko Rakic, M.D., Ph.D.
Judith L. Rapoport, M.D.
Perry F. Renshaw, M.D., Ph.D., M.B.A.
Kerry J. Ressler, M.D., Ph.D.
Victoria B. Risbrough, Ph.D.
Carolyn B. Robinowitz, M.D.
Carolyn Rodriguez, M.D., Ph.D.
Bryan L. Roth, M.D., Ph.D.
Laura M. Rowland, Ph.D.
John L.R. Rubenstein, M.D., Ph.D.
Bernardo Sabatini, M.D., Ph.D.
Gerard Sanacora, M.D., Ph.D.
Akira Sawa, M.D., Ph.D.
Alan F. Schatzberg, M.D.
Nina R. Schooler, Ph.D.
Robert Schwarcz, Ph.D.
Yvette I. Sheline, M.D.
David A. Silbersweig, M.D.
Vikaas S. Sohal, M.D., Ph.D.
Matthew W. State, M.D., Ph.D.
Murray B. Stein, M.D., M.P.H., F.R.C.F.C.
Stephen M. Strakowski, M.D.
John S. Strauss, M.D.
Carol A. Tamminga, M.D.
Laurence H. Tecott, M.D., Ph.D.
Kay M. Tye, Ph.D.
Flora M. Vaccarino, M.D.
Rita J. Valentino, Ph.D.
Jeremy M. Veenstra-VanderWeele, M.D.
Susan M. Voglmaier, M.D., Ph.D.
Aristotle N. Voineskos, M.D., Ph.D.
Nora D. Volkow, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Marina E. Wolf, Ph.D.
Jared W. Young, Ph.D.
L. Trevor Young, M.D., Ph.D., F.R.C.P.C., F.C.A.H.S.
Carlos A. Zarate, Jr., M.D.
Jon-Kar Zubieta, M.D., Ph.D.

MEMBERS EMERITUS
George K. Aghajanian, M.D.
Huda Akil, Ph.D.
BJ Casey, Ph.D.
Dennis S. Charney, M.D.
Bruce M. Cohen, M.D., Ph.D.
Jan A. Fawcett, M.D.
Fred H. Gage, Ph.D.
Frederick K. Goodwin, M.D.
Fritz A. Henn, M.D., Ph.D.
Steven E. Hyman, M.D.
Samuel J. Keith, M.D.
Kenneth K. Kidd, Ph.D.
Rachel G. Klein, Ph.D.
Steven M. Paul, M.D.
Steven G. Potkin, M.D.
Solomon H. Snyder, M.D.
John A. Talbott, M.D.
Ming T. Tsuang, M.D., Ph.D., D.Sc.
Jim van Os, M.D., Ph.D., MRCPsych
Mark von Zastrow, M.D., Ph.D.

GLOSSARY

ACE2 RECEPTORS (p. 5) One way the COVID-19 virus is thought to enter the body is by docking at cellular receptors called ACE2 receptors that stud the surface of cells found in the lungs and arteries, but also in the heart, kidneys, and intestines.

MICROTHROMBI (pp. 5–6) Inflammation has a wide range of impacts in the body, varying according to where it occurs. If it occurs in blood vessels inside the brain, for instance following COVID-19 infection, it can give rise to the formation of tiny blood clots called microthrombi which may cause brain damage.

EXCITOTOXICITY (p. 6) Damage caused by overactivation of excitatory neurons and their receptors. May be among the effects of COVID infection.

MICROGLIA & ASTROCYTES (p. 6) Components of the immune system specific to the brain and central nervous system (CNS) that are designed to keep out or destroy viral invaders and toxins.

PREFRONTAL CORTEX (p. 12) Exposure to uncontrollable stress can rapidly impair functioning of the prefrontal cortex, which performs higher cognitive functions including the guidance of flexible, goal-directed behavior, as well as top-down regulation of emotion, attention, and action.

"MICRODOSING" (p. 18) Involves taking psychedelic drugs such as psilocybin, LSD, or MDMA repeatedly over periods of days, weeks, or months in very small quantities that do not induce psychedelic experiences. Unstudied and illegal, the practice is not currently known to have any actual or potential therapeutic benefits.

CONNECTIVITY FINGERPRINTS (p. 24) Research suggests that connectivity changes in the brain's salience network, default-mode network, and central executive network may provide "neural" or connectivity fingerprints" characteristic of risk for suicidal thinking and behavior.

ATTENTION BIAS MODIFICATION TRAINING (p. 33) Has been shown to be effective for treating anxiety in children when they experience negative sensory stimuli by helping them practice engaging the prefrontal cortex and decreasing the response to signals from the brain's emotion centers including the amygdala. Potentially could help prevent children progress from sensory over-responsivity to a full-blown anxiety disorder.

OPTOELECTRONICS (p. 37) A new technology employing tiny wireless implantable devices to manipulate the activity of individual nerve cells in the organs of awake, freely moving animals. This makes possible experiments with the power to reveal the specific (and often multiple) functions of different kinds of nerve cells in the body's periphery.

Image credits: p. 5: JAMA, Wikimedia Foundation; p. 6: Wiley, Helmut Rennke, M.D.; p. 17: PNAS; pp. 18, 19: Johns Hopkins Center for Psychedelic & Consciousness Research; pp. 23, 25: Lynnette Averrill, Ph.D.; p. 24: UC Berkeley.

2021 INTERNATIONAL MENTAL HEALTH RESEARCH VIRTUAL SYMPOSIUM

Save The Date

Friday, October 29, 2021

Please join us for exciting virtual scientific discussions on innovative brain and behavior research by our 2021 Pardes Humanitarian Prizewinners & Outstanding Achievement Prizewinners.

For more information, please visit bbrfoundation.org/Symposium

BRAIN & BEHAVIOR
RESEARCH FOUNDATION
Awarding NARSAD Grants

747 Third Avenue, 33rd Floor
New York, NY 10017
646.681.4888 | 800.829.8289
info@bbrfoundation.org
bbrfoundation.org

RESEARCH FOR RECOVERY

30+ years

For more than 30 years the Brain & Behavior Research Foundation has fostered new research pathways and transformative breakthroughs.

70k+ donors

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

$430M+ awarded

Since 1987 the Foundation has awarded more than $430 million to fund more than 6,200 grants.

5,100+ researchers

Grants have been given to more than 5,100 leading scientists around the world.

100% OF EVERY DOLLAR DONATED FOR RESEARCH GOES TO RESEARCH

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