Dealing with 'An Epidemic Of Loneliness'

BBRF's Virtual Mental Health Research Symposium

MAGAZINE

Brain&Behavior

DECEMBER 2020

The Promise of Stem-Cell Biology in Diagnosing, Treating, and Preventing Mental Illness

PRESIDENT'S LETTER

While all of our lives have been impacted by COVID-19, we are continuing forward in our important mission to alleviate the suffering caused by mental illness by awarding grants that will lead to advances and breakthroughs in scientific research. This issue of *Brain & Behavior Magazine* features a number of articles that highlight the impact research funded by BBRF is having, with broad implications for better treatments, cures, and methods of prevention for mental illness.

This past October, since we could not come together in person for our annual International Mental Health Research Symposium, we hosted a virtual symposium with presentations by the seven BBRF 2020 Outstanding Achievement Prizewinners who share new breakthroughs and insights on schizophrenia, bipolar disorder, depression, autism, cognitive neuroscience, and childhood psychiatric disorders, as well as a presentation on familial risk for depression by a recipient of the 2020 Pardes Humanitarian Prize in Mental Health. If you have not yet had a chance to view the presentations, they are still available to watch On-Demand on the BBRF website. Our **EVENTS** stories discuss our 2020 prize winners and summarize this year's Symposium presentations.

In our **PATHWAYS TO THE FUTURE** story we focus on the exciting research of Dr. Kristen Brennand, a scientific pioneer who in recent years has adapted stem cell technology to the problems of psychiatric illness. A two-time BBRF grantee and member of our Scientific Council, Dr. Brennand hopes one day to be able to identify and treat people at high risk of illness very early in life, before they actually develop the outward signs of mental illness. She and her team can reprogram skin or blood cells sampled from individuals with disorders such as autism and schizophrenia, and direct them to re-develop into multiple types of brain cells. This enables them to observe early cellular processes that contribute to disease causation, even those that occur in the fetal period and the first years of life. This same technology may also revolutionize the testing of medications to reverse early brain-cell pathologies that contribute to psychiatric illness.

Our **ADVICE ON MENTAL HEALTH** feature has an interview with Dr. Dilip Jeste, a former president of the American Psychiatric Association, a BBRF Scientific Council member and past grantee. In our discussion, Dr. Jeste speaks about what he has termed "an epidemic of loneliness," which, he explains, affects not only our senior population, but millions of people worldwide, across the lifespan. He has advocated the concept of "wisdom" as a way of reducing loneliness—and in our article he explains what he means by the term and how wisdom can be cultivated by anyone with the willingness to better their life.

In our **RECENT RESEARCH DISCOVERIES** article you will find a timely summary of research conducted by Dr. Nora Volkow, a BBRF Scientific Council member who has led the NIH's National Institute on Drug Abuse since 2003. After studying the health records of 61 million American adults, Dr. Volkow and colleagues have found that people with a recent diagnosis of a mental disorder have a significantly increased risk for COVID-19 infection and tend to have worse outcomes than people infected with COVID-19 who do not have a mental disorder. The study highlights the vulnerability of people with mental health diagnoses, and the need for new and more effective mental health treatments.

Together, we will continue to fund innovative and impactful research. Our shared goal of a world free from debilitating mental illnesses relies first and foremost upon you, our donors—in partnership with the exceptional scientists chosen by the BBRF Scientific Council—who are working to transform your donations into better treatments, cures, and methods of prevention for mental illness.

Sincerely,

Jeffrey Borenstein, M.D.

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

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The Promise of Stem-Cell Biology: Treating People at High Risk for Psychiatric Illness Before They Become Patients

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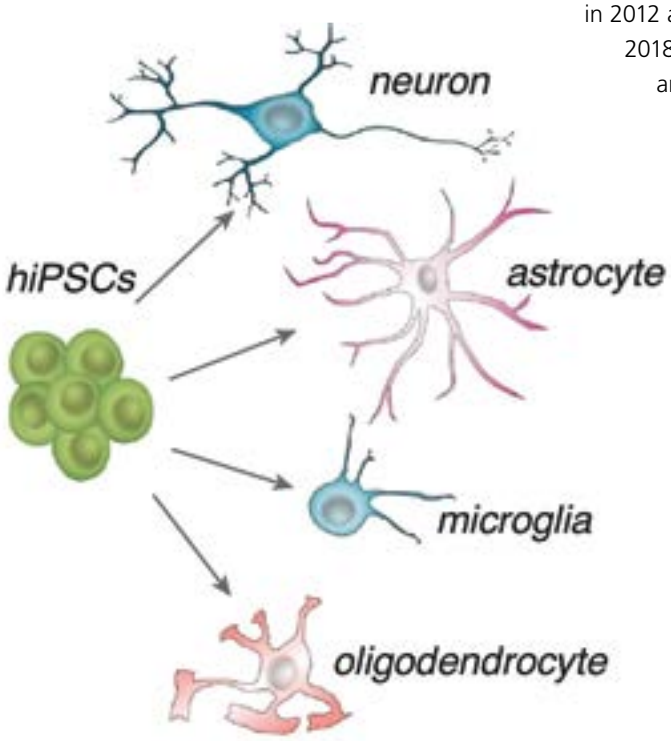
BBRF Scientific Council
2018 Maltz Prize winner for Innovative & Promising Schizophrenia Research
2016 BBRF Independent Investigator Grant
2012 BBRF Young Investigator Grant

"Why would you treat schizophrenia after the first psychotic episode—if you could intervene when someone was 10 years old, before the first symptoms appear? Why would you treat Alzheimer's disease in 60-year-olds who already have neurons in their brain that are dying—if you could prevent those cell-deaths in 30-year-olds? Our ultimate goal is to treat patients *before* they become patients."

This is the vision that drives the research of Kristen Brennand, Ph.D., whose early-career successes, which grew out of preliminary studies she performed with BBRF grants in 2012 and 2016, have led to multiple career-supporting NIH grants. In 2018 Dr. Brennand was honored with BBRF's Maltz Prize for Innovative and Promising Schizophrenia Research and in 2019 her leadership and expertise were recognized when she was asked to join BBRF's Scientific Council.

She has come a long way in just a few years, reflecting great strides she and her colleagues have made in one of the most promising areas of biological research: applying what we know about stem cells to the problems of psychiatric and neurodevelopmental illness.

Stem cells are the "mothers" of all cells and come in several varieties. Dr. Brennand works with those that are "pluripotent"—stem cells that have the power to develop into the many different types of cells that make up the organs of the human body, including the brain.



Left: hiPSCs—pluripotent stem cells created from skin or blood cells sampled from patients—can be made to re-develop as different types of cells that make up the human brain and central nervous system.

Stem-cell technology provides a chance to observe, from inception, pathology in brain illnesses with genetic roots that are thought to begin at the dawn of life.

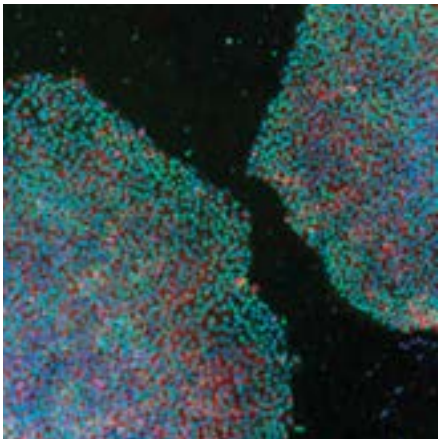
The focus of Dr. Brennand's research is something that 20 years ago might have sounded like science fiction: taking skin or blood cells sampled from psychiatric patients, reprogramming them to a pluripotent stem-cell state, and then directing them to redevelop as brain cells.

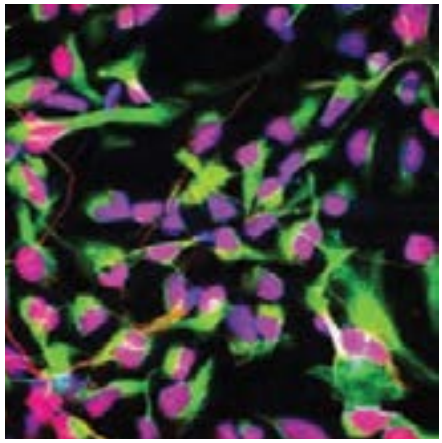
The technology as it stands today is particularly useful in studying pathology in illnesses like schizophrenia and autism that are rooted in developmental processes at the very beginning of life, when the brain is forming.

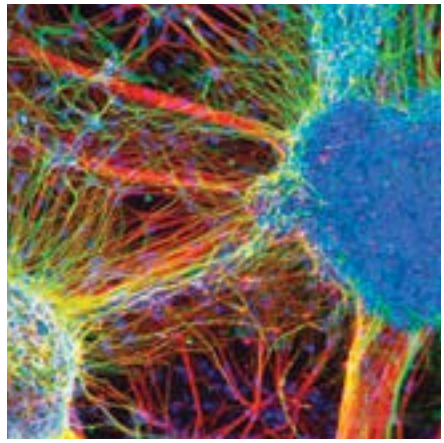
BACK IN TIME

How can a mature cell be forced to go "back in time"? In 2006, Dr. Shinya Yamanaka, a scientist in Japan, demonstrated this was possible by taking single cells and activating the genes of four transcription factors (regulators of gene activity). Once they reverted to the pluripotent state, the cells could then be brought forward, by application of specific chemical factors, so that they matured into different kinds of somatic cells—specialized cells that comprise the organs. For these breakthroughs, Dr. Yamanaka in 2012 was awarded the Nobel Prize.

Dr. Brennand's career has advanced along with this revolutionary technology and has contributed significantly to its maturation. In her lab, she takes skin or blood cells donated by a patient with illness and uses a variety of methods to induce them to differentiate into, say, dopamine neurons, or neural support cells called astrocytes, or glial cells which are immune cells unique to the brain. Each of these reborn cells is grown in a petri dish, and will bear the genetic code of the patient who supplied the original cells. Importantly, the cells reprogrammed from the pluripotent state—they can be generated as many times as desired and







This stunning sequence of images shows the remarkable transformation of pluripotent stem cells (left) into neural progenitor cells (center) and then into excitatory neurons (right), which readily form intricate connections just as in the living human brain. The stem cells at far left were created by Dr. Brennand and colleagues by reprogramming skin cells sampled from several individuals with schizophrenia.

grow into functional, interconnected groupings—do not resemble mature neurons, astrocytes and glia. Rather, they are almost identical to immature versions of these cells that are found in the fetal brain.

This fact makes the new technology, called "human induced pluripotent stem cell" (hiPSC) technology, uniquely valuable for psychiatry. It provides a chance to observe, from inception, pathology in brain illnesses with genetic roots that are thought to begin at the dawn of life. It's a chance to see what goes awry in cells of a specific patient; and to compare those results with similar experiments in other patients, and in comparative experiments with healthy controls.

An important premise of hiPSC research and its future applications is that it will be easier to prevent or lessen in intensity a pathological process when it has just begun, or even before it begins, than it is to treat its system-wide effects once an illness has fully manifested.

Making that vision a reality will depend on knowing in advance who tomorrow's "patients" are most likely to be—before symptoms emerge. And the key to this, in disorders like schizophrenia and autism that are strongly rooted in genetic variations, is the ability to obtain an individual's genetic sequence at birth or shortly after, and based on that read-out, apply interventions that are most likely to minimize or prevent early pathologies from developing.

"Assume you have my DNA sequence," Dr. Brennand postulates. "What we want to know is which genes are differentially expressed in which cell types—and what does that mean for my disease risk and for my drug responses? If someone knew you carried risk factors that changed gene expression in your neurons, increasing the risk of psychiatric illness, then your disease risk could be predicted when you were born. And then you have a whole lifetime for preventive or therapeutic intervention."

UNTANGLING COMPLEXITY

A longstanding obstacle to progress in treatments, she explains, is that schizophrenia is highly heterogeneous, meaning that different patients experience different combinations of symptoms. This *clinical* heterogeneity is thought to strongly reflect schizophrenia's *genetic* heterogeneity. Studies that have scanned the genomes of several hundred thousand patients and healthy controls over the last 20 years have identified over 200 locations in the genome ("risk loci") where the DNA sequence is different in people who have schizophrenia (or are at high risk for it). Most of these "risk variations" in the

genome are small stretches of DNA, and do not, by themselves, disable vital genes, but instead mostly affect parts of the genome that regulate genes. These risk variations for schizophrenia are *common*—nearly every human being has one or several of them. What remains to be explained is how, in a bit less than 1 percent of the human population, different numbers of small risk variations, perhaps in combination with environmental and other factors, result in schizophrenia.

How then can we untangle the complexity of this illness? Stem cell technologies, to begin with, solve a problem that always has limited brain research: difficulty accessing human brain tissue and the functioning brain in living people. Useful studies have been made of postmortem brains of individuals who have lived with schizophrenia and other psychiatric illnesses. But these brains reflect a lifetime of disease impact and can't tell researchers enough about how pathology emerges.

Because of this difficulty, researchers have turned to animal models. But again, there are limitations. When a rodent is repeatedly exposed to stress and begins to show behaviors that are analogous in certain respects to human behavior in depression, it is possible to look at brain cells and circuits and make observations about changes that are occurring. But it is impossible to generate a realistic rodent version of schizophrenia or autism; these are uniquely human illnesses, with effects that alter thinking, speaking, and perception.

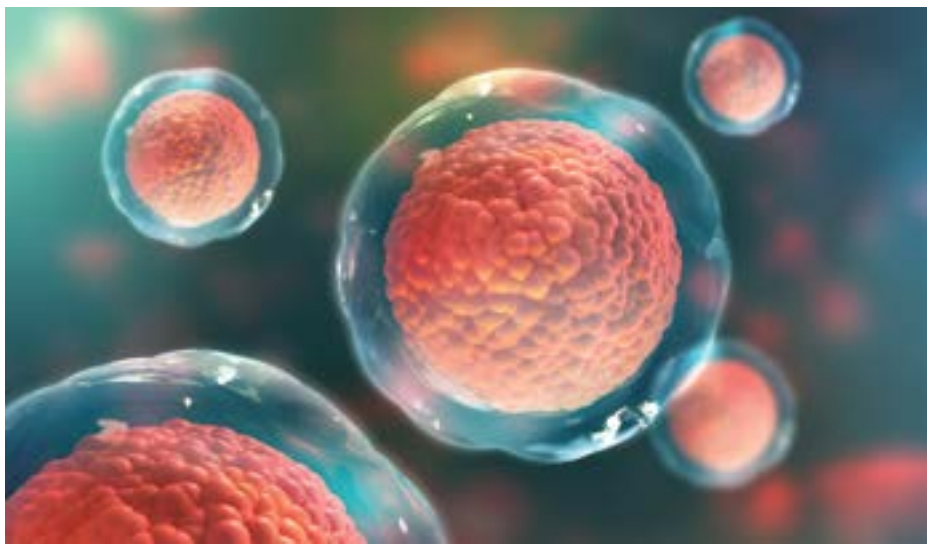
'HOW BIG CAN WE GO?'

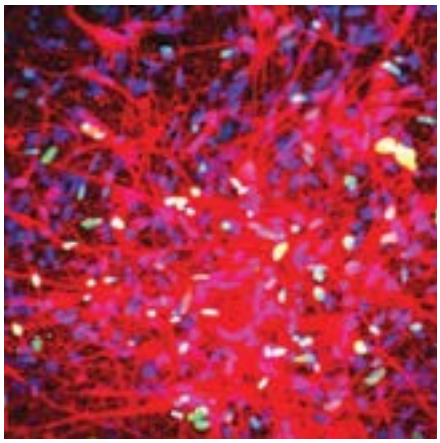
Stem-cell technology enables researchers to generate virtually limitless quantities of live human neurons, every cell perfectly representing a patient's genetics in all its complexity. But this fidelity can be both a blessing and a curse.

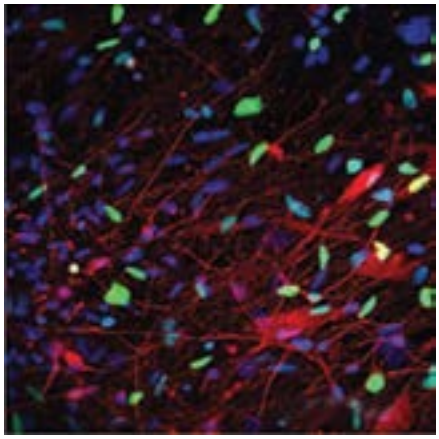
In 2011 Dr. Brennand, at the time a postdoctoral researcher, and her mentor at the Salk Institute for Biological Studies in San Diego, Fred Gage, Ph.D., a BBRF Scientific Council member and 2013 Distinguished Investigator, published in *Nature* the first study in which a living model of schizophrenia was created using stem cells grown from skin cells donated by schizophrenia patients.

'We can now ask what the same mutation in 10 different people leads to, and how much the effects vary between the cells we generate from each person'

After reprogramming the derived stem cells to become neurons and observing their function as they grew in a lab dish, the team was able to document diminished neuronal connectivity (compared with neurons from healthy people), as well as decreases in the function of glutamate receptors, and changes in gene expression, among other things. They exposed the newly created neurons to five antipsychotic medicines, and found that one of the five reversed a number of the changes seen in the patient-derived cells.







After reprogramming patient-derived stem cells to become neurons and observing their function as they grew in a lab dish, Dr. Brennand and colleagues observed diminished neuronal connectivity (lower image), compared with similar neurons in healthy people (top image). It's a vivid example of how stem-cell technology can reveal pathological processes that may have occurred in patients (in this case, with schizophrenia) before birth or in the early years of life. These experiments also provided the researchers with a chance to "treat" the cells with various drugs, one of which, in this case, reversed pathology.

Based on samples from only four schizophrenia patients, this study was only a hint of what soon would be accomplished. A key moment for Dr. Brennand came after her first BBRF grant, a 2012 Young Investigator award, supported a project that generated data needed to secure her first large NIH grant. "What I did with BBRF support and that first NIH grant was ask, 'How big can we go with this?' And the most ambitious thing I could imagine at the time was a study with 13 patients and 13 controls. We made two to three lines of stem cells from each."

What she and her team came to appreciate was the inherent difficulty of determining how the genomes of these 26 individuals were (or were not) related to irregularities seen in the neurons grown from their donated cells. Since every human has DNA variations, and only some of these are relevant to disease (most in fact are not) how can specific variations be matched reliably with specific effects on how cells behave?

Using the gene-editing technology called CRISPR to make cells "isogenic"—genetically identical except for one or more variations under study—"you can ask, for example, what the same exact mutation in 10 different people leads to, and how much the effects vary between the cells we generate from each person," Dr. Brennand says. Or, "you can use CRISPR to introduce one variation, then two, then three, keeping everything else the same, and ask: what is the effect? Or, a patient may have two risk variants; if I use CRIPSR to fix one, is that sufficient to change the pathology we saw in the original cells?"

Isogenic brain cells grown from stem cells also make possible an experiment impossible to conduct in mice—to study the interplay of hundreds of DNA "risk variants" at once, across a multitude of cells types. They can be studied cell type by cell type, or in combinations with one another—either in petri dishes or in 3-dimensional assemblages of cells called organoids.

"No cell exists in isolation," Dr. Brennand notes. "In ALS (Lou Gehrig's Disease), pathology is defined by motor neuron death. But a lot of the risk variants that have been identified in ALS are expressed not in neurons but in astrocytes." In that case, growing them together makes great sense.

Making isogenic lines of patient-derived cells also opens a new vista on drug discovery. In 2018 Dr. Brennand and colleagues published a pioneering study in which hiPSC technology was used to generate neural cells from 12 people with schizophrenia and 12 controls. A drug screen was performed: the cells were exposed systematically to 135 drugs, generating 4,320 unique drug-response signatures based on changes in gene activity within each cell line. This enabled the team to identify 18 existing drugs that were able to reverse gene-expression changes that had been seen in the brains of schizophrenia patients that were examined in a postmortem study. There will be many more stem cell-enabled drug screens to come in the years ahead.

Dr. Brennand suggests that the integration of stem-cell and genomic technologies may make possible the identification of people at high risk for psychiatric illnesses from the time of birth, opening a long window for intervention. Once symptoms of illness are evident—in schizophrenia, typically in the late teens or 20s—the opportunity for prevention has passed and doctors face the immense challenge of reversing or lessening complex pathology.

FINDING THE SECRET OF RESILIENCE

Stem-cell technology also enables Dr. Brennand's team to approach the important question of why some people have severe illness and others have milder illness. "I think it's really important to know, for example, why some people with autism are high-functioning and others are low-functioning," she says. "Even if we never cured autism—but we were able to turn low-functioning patients into high-functioning ones, we would be doing an incredible amount of good."

The same applies to resilience. "I love the idea that there are biological cures walking around that we just haven't been able to recognize," she says. The secret may be in learning more about the genetic basis of resilience. "For example, we know that a person with two mutated copies of a gene called APOE4 has a 90% chance of developing Alzheimer's. But this still means that 10% of people with 2 bad copies of APOE4 *aren't* going to get sick. We have to find the pathways that confer this resilience, and find drugs that target them."

The prospects in psychiatric illness are equally exciting. "Wouldn't it be great," Dr. Brennand concludes, "if you could have a high-risk patient come into your clinic when they were 15, or 12, or 5, and be able to tell them: 'You're at extremely high risk for schizophrenia, or for bipolar disorder. Let's start treating you now.' That's our ultimate goal." ❖ **PETER TARR**

Dr. Brennand is featured guest on Episode 5 of this season's *Healthy Minds with Dr. Jeffrey Borenstein*. View at: **https://www.pbs.org/video/stem-cell-research-and-mental-health-g2kdp2/**

The 2020 International Mental Health Research Virtual Symposium

This year BBRF awarded its Outstanding Achievement Prizes in Mental Health to seven scientists for their extraordinary work in advancing psychiatric research. The Prizewinners serve as the featured presenters at the 2020 International Mental Health Virtual Symposium, along with Dr. Myrna Weisman, one of the recipients of the 2020 Pardes Humanitarian Prize in Mental Health. The symposium is available to watch free On-Demand at **https://www.bbrfoundation.org/event/international-mental-health-research-symposium**

The BBRF Outstanding Achievement Prizes acknowledge and celebrate the power and importance of neuroscience and psychiatric research in transforming the lives of people living with mental illness. The recipients of this year's awards are recognized for their research achievements in suicide prevention, schizophrenia, autism, bipolar disorder, childhood trauma and cognitive neuroscience.

Dr. Jeffrey Borenstein, BBRF's President & CEO, notes that "These exceptional scientists are on the cutting edge of finding new treatments, cures, and methods of prevention for mental illness. We celebrate their progress in brain and behavior research, which is paving the way for more people to live full, happy, and productive lives."

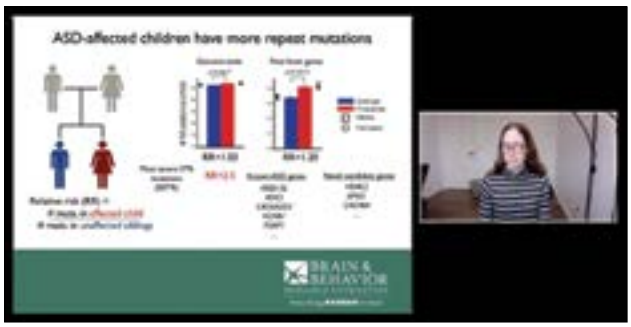
Dr. Herbert Pardes, President of the BBRF Scientific Council, provides opening remarks for the Symposium and observes that the 2020 Outstanding Achievement Prizewinners are "making extraordinary contributions to advancing psychiatric research and eliminating the stigma of mental illness. Their work is providing insights in our understanding of the brain and how to treat and potentially cure psychiatric disorders."

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

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

Anne S. Bassett, M.D., delivers a Symposium talk entitled *Identifying A Genetic Subtype of Schizophrenia That is Clinically Relevant for Patients and Families*. Dr. Bassett is Professor of Psychiatry & Director of the Clinical Genetics Research Program at the University of Toronto and the Centre for Addiction & Mental Health, and a 2002 BBRF Distinguished Investigator and 1997 BBRF Independent Investigator.

Her presentation highlights some of the technological advances making it possible to identify genetic changes with high impact that are clinically relevant for patients with schizophrenia and their families. These genetic changes, identifiable with a clinical blood test, can influence clinical care and are having important effects on our understanding of schizophrenia. Dr. Bassett is known for her work with individuals born with a piece missing from a section of chromosome 22, who have a one-in-four chance of developing schizophrenia. She has pioneered the world's first clinic devoted to adults with the associated 22q11.2 deletion syndrome. Dr. Bassett says that for schizophrenia in general, such a human model provides enhanced power to understand the interacting factors and mechanisms that lead to the illness and their relationship to other brain disorders, as well as contribute to new animal and cellular models for study.



Symposium speaker **Melissa Gymrek, Ph.D.**, discusses *Dissecting the Role of Repetitive Regions of the Genome in Schizophrenia and Autism*. An Assistant Professor in the Departments of Medicine and Computer Science & Engineering at the University of California San Diego, Dr. Gymrek's major research interest is to understand complex genetic variants underlying changes that lead to human disease. Her recent work focuses on repetitive DNA variants known as short tandem repeats (STRs), which she has utilized as a model for complex genetic variation. She develops computational methods for analyzing and visualizing complex variation from large-scale sequencing data. These tools are allowing researchers for the first time to answer many questions regarding STRs and other variant types, including their contribution to neuropsychiatric disorders in humans.

2020 PRIZEWINNERS

LIEBER PRIZE FOR OUTSTANDING ACHIEVEMENT IN SCHIZOPHRENIA RESEARCH
Anne S. Bassett, M.D., FRCPC
University of Toronto

MALTZ PRIZE FOR INNOVATIVE & PROMISING SCHIZOPHRENIA RESEARCH
Melissa Gymrek, Ph.D.
University of California San Diego

COLVIN PRIZE FOR OUTSTANDING ACHIEVEMENT IN MOOD DISORDERS RESEARCH
Martin Alda, M.D., FRCPC
Dalhousie University

Gustavo Turecki, M.D., Ph.D.
McGill University

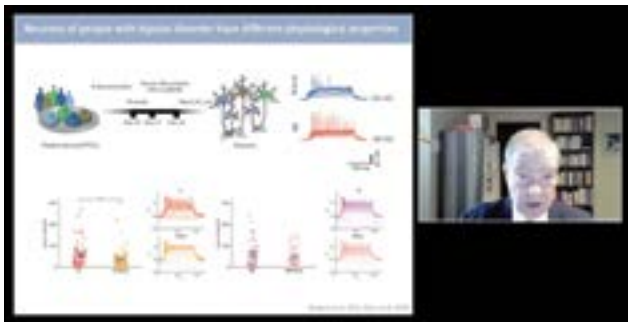
RUANE PRIZE FOR OUTSTANDING ACHIEVEMENT IN CHILD & ADOLESCENT PSYCHIATRIC RESEARCH
Joan L. Luby, M.D.
Washington University School of Medicine

GOLDMAN-RAKIC PRIZE FOR OUTSTANDING ACHIEVEMENT IN COGNITIVE NEUROSCIENCE
Robert Desimone, Ph.D.
Massachusetts Institute of Technology

Angela C. Roberts, Ph.D.
Girton College, University of Cambridge

In her lecture, Dr. Gymrek notes that repetitive regions of the genome are one of the largest sources of genetic variation across human populations and are well known to contribute to human traits. She observes that large sequencing efforts have largely ignored repeats, owing to the technical challenges they present. Hence, her team and others have sought to develop bioinformatics methods for analyzing genomic repeats at population scale. She explains her team's efforts to integrate analysis of repeat variants into genome-wide association studies as well as whole-genome sequencing studies. This research identifies novel risk areas in the genome, called risk loci, and demonstrates that genetic variation at repeat sequences plays a key, but often overlooked, role in neuropsychiatric traits including schizophrenia and autism spectrum disorders.

Martin Alda, M.D., FRCPC, discusses *Thinking Rationally about the Treatment of Bipolar Disorder* in his Symposium talk. A Professor of Psychiatry and Killam Chair in Mood Disorders at Dalhousie University, and a 2003 and 1999 BBRF Independent Investigator, Dr. Alda has worked at the junction of clinical and basic research, investigating genetic and neurobiological markers of mood disorders and response to treatment. His clinical, genetic, pharmacogenetic, and brain imaging studies are based on carefully characterized prospective clinical samples.



The aim of his lab is to develop methods of personalized treatment in psychiatry. Dr. Alda points out that most people with bipolar disorder require ongoing treatment to prevent recurrence of mania and depression. While several medications have been found to be effective in this indication, each works only in a proportion of patients, he stresses. The treatment in individual patients is usually chosen by trial-and-error, with each trial taking many months. As a result, he notes, most people achieve stability after a considerable amount of time. He discusses how his research guides the way to rational selection of long-term treatment. Starting with the "gold-standard" mood stabilizer, lithium, his team has shown that the response to it has a genetic basis and can be predicted reliably with a combination of clinical and genomic data. They have also shown that patients who respond to a different class of medications called anticonvulsants differ from lithium responders in important clinical features. It is the goal of their work, he suggests, to help institute early and effective treatment, shorten the time to full recovery, and reduce the negative impact of the illness.

Gustavo Turecki, M.D., Ph.D., speaks about *How Pain Shapes the Brain: The Impact of Childhood Trauma on Suicide Risk*. Professor and Chair of Psychiatry at McGill University, Dr. Turecki is a 2016 BBRF Distinguished Investigator, 2008 BBRF Independent Investigator, and 2000 BBRF Young Investigator. Pioneering research he has led has increased our understanding of how traumatic life experiences impact gene function in brain cells and increase long-term risk for suicide by regulating critical genes involved in stress responses and behavioral development.

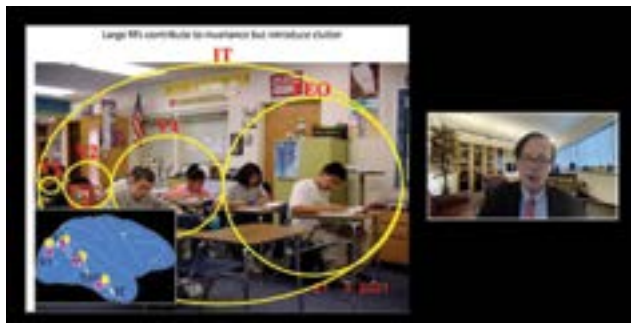
He discusses how childhood experiences have an important impact on the way emotional and behavioral brain processes are regulated. Childhood maltreatment or abuse, for instance, increase the likelihood of negative mental health outcomes, including increased risk of suicide over the lifespan. Dr. Turecki also discusses data from his research suggesting that childhood maltreatment leads to differential molecular regulation of a number of key brain molecular pathways. In turn, he suggests, these changes associate with differential behavioral and emotional trait regulation, which increases the risk of suicidal behavior.

Joan L. Luby, M.D., devotes her Symposium discussion to the question of *How Early Childhood Experiences Shape Brain Development and Influence Mental and Physical Health Trajectories*. Dr. Luby is Samuel and Mae S. Ludwig Professor of Psychiatry (Child) at Washington University School of Medicine. She is a member of the BBRF Scientific Council; a 2008 and 2004 BBRF Independent Investigator; the 2004 BBRF Klerman Prize winner for Exceptional Clinical Research; and a 1999 BBRF Young Investigator.

Dr. Luby's presentation reviews how early experience alters brain development—either for benefit or detriment—during sensitive periods. She notes the importance of caregiver nurturance on healthy brain development and how a more detailed understanding of sensitive periods can be used to harness proactive prevention and health enhancement strategies. Her talk underscores the power of the early psychosocial environment on child health and well-being and in setting lifelong health trajectories.

The Symposium talk given by **Angela Roberts, Ph.D.**, addresses *Prefrontal Circuits That Regulate Threat and Reward-Elicited Behaviors*. Dr. Roberts, Professor of Behavioral Neuroscience and Professorial Fellow at Girton College, University of Cambridge, UK, combines pharmacological, cardiovascular, neuroimaging, and genetic techniques to understand the brain basis of cognition and emotion. Her lab has worked to establish non-human primate models of positive and negative emotion regulation and trait anxiety.

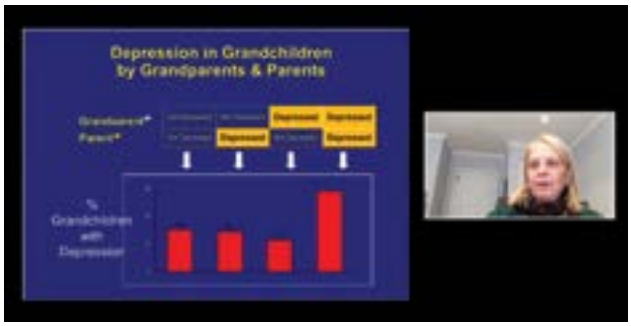
Dr. Roberts has revealed distinct prefrontal cognitive processes that may underlie the varied causation of affective disorders and has elucidated the role of dopamine- and serotonin-system modulation of these processes that are essential for the more effective targeting of current pharmacotherapies. In her talk, Dr. Roberts discusses what happens when there is an inability to regulate emotions—a core symptom of many psychiatric disorders including anxiety and depression and often associated with altered activity of neurons in the brain's prefrontal cortex. She explains that to further our understanding of its role in the prefrontal cortex's failure to regulate response to reward and threat in mood and anxiety disorders, her team is studying threat and reward-elicited behaviors in the marmoset, a primate. These studies are revealing the multiple dysregulated pathways and distinct cognitive impairments within the prefrontal cortex, as well as mechanisms of action of current treatments, providing insight into the probable multiple causes of, and hence potentially differential treatment strategies for, anxiety and depression.



Robert Desimone, Ph.D., speaks at the Symposium about *A Causal Analysis of the Attentional Network*. The Doris and Don Berkey Professor of Neuroscience at the Massachusetts Institute of Technology and Director of the McGovern Institute for Brain Research, Dr. Desimone studies how the brain deals with the challenge of information overload. By studying the visual system of humans and animals, he has shown that when we attend to something specific, neurons in parts of the brain concerned with vision filter out distracting information, allowing us to concentrate

on the task at hand. This visual filtering is under the control of parts of the brain, including prefrontal cortex, concerned with "executive function," working memory, and the control of sensory processing.

Dr. Desimone's discussion explores emerging insights from human and animal data about the network that supports attentive vision. He notes that the most behaviorally relevant stimuli in scenes we observe are selected for processing and control over behavior. The effects of selection on neuronal responses are widespread, he says, making it difficult to distinguish cause from effect in the attentional network. However, he suggests, the flow of control can be inferred through an analysis of the relative timing of neural signals and the use of methods such as pharmacological inactivation, optogenetics, and feedback training to establish the impact of one circuit upon another.



Also presenting at the BBRF Symposium is **Myrna M. Weissman, Ph.D.**, a recipient of the 2020 Pardes Humanitarian Prize in Mental Health (see story on facing page). Dr. Weissman devotes her Symposium discussion to *Thirty Years of Studying Families at Risk for Depression: What Have We Learned?* Dr. Weissman is Kemper Family Professor of Epidemiology in Psychiatry at the College of Physicians and Surgeons & Mailman School of Public Health, Columbia University, and Chief of the Division of Epidemiology at the New York State Psychiatric Institute.

Dr. Weissman's talk summarizes an historic multi-decade study she has led that has analyzed the impact over three generations of major depressive disorder, and notes the role of these findings in humanitarian work in which she has been involved. Overall, Dr. Weissman's work has shown that depression usually begins early in life; tends to recur in many people; runs in families; and is often highly amenable to treatment, with evidence-based methods. Her multi-generation study calls attention to differences in outcomes, focusing on families at high and low risk for depression. One important discovery of the study concerns the impact of maternal remission from depression upon offspring. The child of a parent who is depressed has a much higher risk of depression over the lifespan, Dr. Weissman notes. This is also true in families in which a child's parent and a grandparent have suffered from depression. But Dr. Weissman's research has demonstrated the power of treatment. For instance, if a depressed mother is promptly treated, with antidepressant medicines or psychotherapy or both, and her symptoms remit within 3 months, the studies show clearly that her children usually fare better as well.

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2020 Pardes Humanitarian Prize in Mental Health Honors Global Advocates for the Poor and Children with Psychiatric Illness

On September 30, 2020 BBRF announced the winners of the 2020 Pardes Humanitarian Prize in Mental Health. This year's winners are: Myrna Weissman, Ph.D, for her transformative work in the mental health care of disadvantaged persons suffering from depression; and Sir Michael Rutter, CBE, for advancing our understanding of and treatments for mental health problems in children.

An Honorary Pardes Humanitarian Prize was also awarded, to E. Fuller Torrey, M.D., for promoting the biological basis of mental illness.

The Pardes Humanitarian Prize in Mental Health carries an honorarium of $150,000, and is awarded annually to recognize individuals whose contributions have made a profound and lasting impact in advancing the understanding of mental health and improving the lives of people with mental illness. It focuses public attention on the burden mental illness places on individuals and society, and the urgent need to expand mental health services globally.

In making the announcement, Dr. Herbert Pardes, President of BBRF's Scientific Council and for whom the prize is named, said, "Recipients of this year's Pardes Prize have used their scientific knowledge, understanding of human behavior, and compassion to improve the lives of millions of people with mental illness, including children and people living in poverty. Through their work, we broaden the scope of mental illness treatment around the world and the use of knowledge for the betterment of our diverse global family."

THE 2020 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORING

MYRNA M. WEISSMAN Ph.D.

Dr. Myrna Weissman's humanitarian efforts reflect a deep personal commitment to both scientific excellence and bringing change to the world. Her transformative work has advanced the field of behavioral interventions for depression, including the development and dissemination of Interpersonal Psychotherapy (IPT), one of the most effective standardized approaches for treatment of depression in children, adults, and women post-partum. Her humanitarian spirit is exemplified by her donation of the copyright for IPT to the World Health Organization. Her visionary contributions have had a lasting and profound impact on individuals, families and the global community.

Dr. Weissman received her Ph.D. in epidemiology from Yale University School of Medicine in 1974. She is currently a Professor of Epidemiology in Psychiatry, Vagelos College of Physicians and Surgeons and the Mailman School of Public Health at Columbia University and Chief of the Division of Epidemiology at New York State Psychiatric Institute.

Dr. Weissman's research career has focused on studying depression in families, seeking ways to break the cycle of transmission across generations and to develop better understanding of the mechanisms underlying transmission. Her current research, using methods of epidemiology, genetics, and neuroimaging, focuses on understanding the long-term risks of mood and anxiety disorders in individuals and transmitted to families.

Inspired by her research, Dr. Weissman's humanitarian effort globally and in the U.S. has been transformative in the mental health care of disadvantaged

persons suffering from depression. She developed IPT with her late husband, Gerald Klerman, M.D., and, since his death in 1992, she has simplified and implemented it for health workers around the world. IPT addresses depression associated with disruption of attachments due to grief, disputes, transitions, or loneliness. These problems are universal and common in persons suffering natural disasters, war, and forced dislocation.

She also adapted IPT for African countries and donated the copyright to the World Health Organization. She participated in the first clinical trial of psychotherapy in sub-Saharan Africa, and modified IPT for the study. She actively contributes to Strong Minds, a humanitarian effort, providing IPT to over 70,000 depressed, impoverished women in Uganda and Zambia. This effort has won a number of major international awards. She also participates in an NIH-funded implementation project, PRIDE-SSA, which will improve mental health services in Mozambique.

THE 2020 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORING

SIR MICHAEL RUTTER, FRS

The transformative work of Professor Sir Michael Rutter, also known as the "father of child psychiatry," has challenged existing theories and allowed for a major change in earlier ideas about the relationship between maternal deprivation and mental health. Sir Michael's pioneering contributions to our understanding of mental resilience, the effects of maternal and institutional deprivation on subsequent mental health, and the turning points in adult life following psychosocial adversity in childhood have had a lasting and profound impact on individuals, families, and the global community.

Professor Rutter was trained in general medicine, neurology, and pediatrics before specializing in psychiatry. He was appointed the first consultant of child psychiatry in the UK and has been head of the Department of Child and Adolescent Psychiatry at the Institute of Psychiatry, London, and Honorary Director of the Medical Research Council Child Psychiatry Unit.

His studies of autism, depression, antisocial behavior, reading difficulties, deprived children, overactive children, school effectiveness, and children whose psychiatric problems have a clear organic component have resulted in many publications. One of the most influential is *Maternal Depression Reassessed*, in which he argues that it is the norm for children to form multiple attachments rather than a selective attachment to just one person.

Professor Rutter is recognized as contributing to the establishment of child psychiatry as a medical and biopsychosocial specialty with a strong scientific base. In 1994, he established the Social, Genetic and Developmental Psychiatry Unit at the Institute of Psychiatry. The goal of the center is to bridge the gap between "nature" (genetics) and "nurture" (environment) as they interact in the development of complex human behavior, for example in depression and attention-deficit hyperactivity disorder (ADHD) in children.

Professor Rutter was knighted in 1992 and is an honorary member of the British Academy, a Fellow of the Royal Society, and a founding Fellow of the Academia Europea and the Academy of Medical Sciences. The Michael Rutter Centre for Children and Adolescents at the Maudsley Hospital, London was named in his honor.

THE 2020 PARDES HUMANITARIAN PRIZE IN MENTAL HEALTH HONORARY TRIBUTE TO

E. FULLER TORREY, M.D.

Dr. Torrey is a model of citizen activism, a scientific leader and a fearless advocate for people living with mental illness and their families. His extraordinary contributions have had a profound impact on advancing the understanding of mental illness and educating the public about the biological basis of serious mental illness and the need to improve the treatment system. He is a tireless advocate for policy and legislative change and a champion of the mental illness advocacy movement.

He is currently Associate Director at The Stanley Medical Research Institute, where he is investigating the causes and treatment of schizophrenia and bipolar disorder, including ongoing collaborative research on infectious agents as a cause of these diseases.

In the 1970s Dr. Torrey introduced what was then a radically new and revolutionary approach, an infective/inflammatory etiology and pathophysiology of mental illness. Over the years, this hypothesis has led to the testing of many new treatments for mental illness. Dr. Torrey's early work on inflammation and infection in mental illness has been transformative, as hundreds of researchers and hundreds of millions of grant dollars are now devoted to research in this field. Anti-inflammatory and antibiotic drugs are being studied as potential treatments.

His other major contribution is in education and advocacy. For 40 years he has been responsible for hundreds of public lectures, radio and TV shows, reports by the National Alliance on Mental Illness (NAMI) and Treatment Advocacy Center, editorials, op-eds, and letters to the editor. He has written five books, all intended to educate the public about the biological basis of serious mental illness.

BBRF President & CEO Dr. Jeffrey Borenstein noted that "Dr. Weissman, Professor Rutter, and Dr. Torrey exemplify what it means to be world-class behavioral scientists and humanitarians. We were delighted to honor them for their outstanding commitment in the pursuit to alleviate the pain and suffering of mental illness. All three of this year's recipients inspire us all to use our knowledge towards the greater good for all humanity."

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

❖ **LAUREN DURAN**

WINNERS

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

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

2018
Judge Steven Leifman
Honorary Tribute:
Suzanne and Bob Wright

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

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

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

2014
Herbert Pardes, M.D.

‘An Epidemic of Loneliness and Despair’: How Wisdom Can Help

Q&A with Dilip V. Jeste, M.D.

University of California, San Diego

BBRF Scientific Council Member
2002 BBRF Distinguished Investigator

Dr. Jeste is the Senior Associate Dean for Healthy Aging and Senior Care, Distinguished Professor of Psychiatry and Neurosciences, Levi Memorial Chair in Aging, and Director of the Stein Institute for Research on Aging, at UC San Diego, and Co-Director of the UC San Diego-IBM Center on Artificial Intelligence for Healthy Living. He was previously Chief of the Units on Movement Disorders and Dementias at the National Institute of Mental Health. At UC San Diego he started a Geriatric Psychiatry program in 1986—today, one of the largest such programs in the world. He discusses many of the ideas raised in this Q& A in a new book, “Wiser.”

Dr. Jeste, you have said that we are currently in the middle of two epidemics, one being COVID, of course, but the other an epidemic of loneliness. You have written that loneliness acts as “a lethal behavioral toxin in our society.” Can you help us understand what you mean?

People don’t realize that this “other” epidemic of loneliness has been going on for the last couple of decades. One way to see this is through the average lifespan in the U.S., which had been increasing ever since the 1950s but started dropping a few years ago. This decrease is not because of new infections or new cancers. It is because of a marked increase in the numbers of opioid-related deaths and suicides, both of which are related to underlying loneliness. In 1999, there were 8,000 deaths from opioid overdoses. Last year, this number reached 50,000. Overall, the rate of suicide has increased by 30% in the U.S. from 1999–2017. The U.S. government estimates that 162,000 Americans die every year from loneliness and social isolation. That is greater than the number of Americans who die annually from lung cancer or from stroke.

The silent epidemic of loneliness doesn’t strike in a “crisis” sort of way, and yet it has been going on for 20 years. Stress is increasing. Loneliness is increasing.

These have been called “deaths of despair.”

Yes. And loneliness also contributes to other illnesses such as diabetes, obesity, heart disease, dementia, major depression, and generalized anxiety disorder. This is based on studies of several thousands of people who were followed over a period of years. We’re able to say that loneliness

Loneliness occurs throughout the lifespan, and tends to peak in people in their late-20s, mid-50s and late-80s.

increases mortality by 30%. That is the same or greater than mortality attributed to smoking 15 cigarettes a day or mild to moderate obesity.

What factors in the way we live are responsible for the increase in loneliness?

Two important factors for increased stress and loneliness in the last 20 years are globalization and the rapid growth of technology.

And yet: advocates of globalization and enthusiasts of new technologies say that these two forces are actually connecting us, making the world smaller.

There is no question that globalization and technology have many good effects, but the good effects are often neutralized by downsides.

In the realm of technology, I suppose you could cite social media as not just "connecting" people, but also, for many, and especially young people, increasing peer pressure tremendously.

Exactly. Some social media contribute to psychopathology, whereby some people hurt others psychosocially.

The COVID pandemic adds a whole new layer to this because of the very fact that we need to be physically isolated.

Social distancing is absolutely critical to reduce the spread of the disease; however, that social distancing is also causing greater loneliness and social isolation, which is increasing the risk of suicide, substance use, obesity and so on.

When we think of people who are lonely, we often think of those who are old. Who is empirically most at risk of being lonely?

Loneliness is common across the board. Something to keep in mind is that especially in recent years, the level of stress, loneliness, and suicides has increased, especially in younger people, including teenagers. Loneliness is common at all ages; however, there are some ages at which it peaks. In one of the studies my colleagues and I recently published, we found that there were three peaks: people in their late-20s, mid-50s and late-80s.

What circumstances mark those peak years?

Adolescence is a difficult period for most people, but then you reach 21, and you are supposed to be an independent adult and make lots of major decisions. There is a lot of stress and tremendous peer pressure. And you may feel that you are worse off than your peers, because you are always comparing yourself with peers seemingly doing better. The 50s is the time of the classical mid-life crisis, when people start noticing higher blood pressure or other physical changes, and see retirement looming. Their kids have left home, leaving an empty nest. And then the late 80s, of course, is the period when, often, you don't even have a spouse. You are worried about dementia. Your physical health is in decline and you may be disabled.

You study "wisdom," which is a word that means different things to different people. But you use it in a particular way. You're talking about wisdom as a concept that you're trying to measure empirically and to apply therapeutically for people who experience loneliness. How did you get interested in the idea of wisdom?

We did a study of about 2,000 people in the general community, ages 20 to over 100, and we found that physical health starts declining around age 45–50. But mental health actually tends to improve over the entire span from ages 20 to 90. This is what I call the

Empathy and Compassion: One of the components of wisdom. Images on this and facing page illustrate other components.

Emotional Regulation

Ability to Self-Reflect

paradox of aging. This finding has now been replicated by several other studies. The 20s is a period of considerable stress, depression, anxiety, loneliness. But the good news is that things start getting better, emotionally, for many people. It's not that the stress goes down, it's that you get better at handling it—and that's where the idea of "wisdom" comes from, as I use it.

How did you reach your definition of wisdom?

When I got interested in wisdom, the first thing I did was a literature review. We looked at all the scientific journal articles that had tried to define this term and found that wisdom is not understood universally as one thing. We found seven different components that were used across the studies on wisdom. These components are: pro-social behavior (i.e., empathy or compassion); emotional regulation; self-reflection; acceptance of uncertainty and diversity of perspectives; the ability to be decisive; the ability to give appropriate advice and support to others; and spirituality.

To do scientific research on this subject, you must define wisdom clearly and you must be able to measure it empirically. We developed a questionnaire that assesses people on a scale, the San Diego Wisdom Scale (SD-WISE). It measures each of these seven components. And we have four items for each of these subscales, so a total of 28 questions. The total score is called Jeste-Thomas Wisdom Index or JTWI.

Since you develop your definition based on studies published since the 1970s, does this mean that your idea of wisdom reflects only modern Western thinking?

We actually did a qualitative/quantitative study of wisdom as discussed in an ancient Indian scripture, Bhagavad Gita. We looked at the word "wisdom" and its antithesis, "foolishness," to see how often those words were used and in what context. For example, the Gita says that a wise person is somebody who is quite decisive when needed. That means that decisiveness is a component of wisdom. The Gita also says that a wise person is unselfish and looks out to other people's needs (what I call "pro-social behaviors"). We were really surprised to find that the components of wisdom in the Gita are almost identical to our modern definition!

It seems there's something almost eternal about this, or perpetual in human culture. Why do you think that is?

To me, it means that wisdom is biologically based. If it is based in biology in the brain, then it will not change over centuries and across cultures. We published a paper on the neurobiology of wisdom. We found that in the brain, the prefrontal cortex and the limbic striatum are involved in a major way in all of these wisdom components.

What you are saying is that there are probably biological correlates of the things that cause us to express in our behaviors the seven components of wisdom.

Exactly. Just as there are places in the brain that display abnormal functioning in conditions marked by a lack of wisdom—for example, antisocial personality.

Can wisdom be increased or inculcated?

Wisdom is a trait, and most traits are about 50% determined by genetics and 50% by environment and behavior. We recently published a meta-analysis of 57 randomized control trials interested in three of the components of wisdom that I've discussed: emotional regulation, empathy/compassion, and spirituality. About half of these studies showed significant improvement with the interventions they tested. Our analysis of these trials showed that components of wisdom can be increased. The question then becomes whether someone can increase the "whole"—living in a way that benefits themselves as well as others—from the behaviors and insights associated with wisdom.

Just a few months ago, my colleagues and I published a paper on that very question. It was a study of 89 older people in five retirement communities in three states. The purpose of the study was to increase resilience in these people, but we also were using the wisdom scale, and found a significant increase in the overall wisdom scale score—as well as an increase in resilience and decrease in stress.

What were the interventions that increased resilience?

We used psychosocial or behavioral interventions, group-based. These used the principles of cognitive behavioral therapy along with other approaches like keeping a "gratitude diary," in which you record something every day that you are grateful for.

That helps to increase self-reflection.

Yes, and also empathy/compassion, because when you start acknowledging that people around try to help you, it increases your desire to help them too. Coming back to your original question, yes, wisdom components can be improved. Even overall wisdom.

How do we improve our own wisdom in practice?

What I call "practical wisdom" is something that you can actually do in everyday life. What we need to do is improve our self-reflection, empathy/compassion, emotional regulation, acceptance of uncertainty, decisiveness, social advising, and spirituality.

The first step is to assess yourself in an unbiased way. You can start by going online and taking our SD-WISE questionnaire at: **aging.ucsd.edu**. You will respond to statements using a 1-5 scale, where you indicate the extent to which you agree with them. This way you can find out what components you are strong or weak in. We all have strengths and limitations. What we need is an unbiased evaluation. If we are to improve, we have to find out where we need help, right?

Would you agree that one condition of becoming wiser is that the individual has to want to do this?

People should want to improve. No question about that. But there are people who want to improve and don't know how, and that's why they give up.

Openness to Others' Points of View

Ability to Give Advice to Others

Spirituality

One can be lonely even when among others, or in a crowd.

Let's talk to the people who want to improve but don't know they can or what framework to use.

Let's say you need to be more self-reflective. What do you do? Practical wisdom means wise decision-making in everyday life. Almost every decision I make should be made around the seven components to the extent possible. Let's use as an example a recent fight with a good friend that is making me feel lonely. You can start with self-reflection: why did it happen? Did I do something wrong? Then secondly, emotional regulation. I'm being mad at him. But that doesn't help, so I should control my anger. Third is empathy. Empathy is both cognitive and affective. What is my friend's perspective? Where is he coming from? That doesn't mean I have to agree with him, but it helps me a lot to understand his rationale. Then comes the acceptance of uncertainty. I can accept the fact that he may have a different value system and that's okay. And finally, spirituality means being connected to something or someone that you don't see or hear or feel, whether it is God, nature, or whatever. You won't feel lonely if you are always connected. This is practical wisdom. We need to integrate it into all behaviors. In the beginning it takes time, but it should eventually become second nature.

Consider the hypothetical of an elderly person who has lost their spouse and many friends, and is feeling lonely. This is very common. Their world is getting smaller. Their physical health is declining. How can they apply practical wisdom to their life?

You can start with a kind of mindfulness, where you accept your emotions of grief and loneliness and what you are going through. You also get some perspective, realizing that you're not the only one feeling that way. Another way is to think about the times you've felt lonely in the past and subsequently came out of it when you found new friends or hobbies. It didn't last forever.

In senior living facilities, should staff organize programs that teach practical wisdom?

I think it is very important to have this type of training at all levels, provided by community staff. This is something that should start from kindergarten. I think we need it, in societal terms, because of the increased rates of suicides, that are now even happening in children as young as 10.

Our stress levels as a society keep on increasing. It becomes a vicious circle. Higher stress level leads to more depression. You don't do as well, and then there's more pressure. We need to change that. In our educational institutions, we emphasize hard skills. For example, in medical school we teach students how to be the best diagnostician and treatment-prescriber. We don't teach them how to take care of themselves, how to empathize, how to have self-reflection or self-compassion. We need to teach people how to get social support and to support others.

You did a study of seniors in San Diego County who were living in a facility with hundreds of people like themselves. Yet, 63% said they felt lonely. You commented: "The study shows why solutions to loneliness such as increased engagement on social media or going into public spaces does not work for all people.... We must stop thinking that we can cure loneliness just by increasing people's social relationships." Tell us about this and how it relates to the concept of "Oneliness."

Loneliness is subjective. This means you can be lonely in a crowd. Even if someone is in a group facility with many others like themselves, or on social media where they connect with hundreds, they can feel lonely. In contrast, an older person living by himself or herself can feel quite contented. This is "oneliness"—it refers to people who are happy or at least contented at being by themselves. It means not feeling isolated and distressed. Thus, you don't have to be with others all the time. For those who are spiritual, it is always possible to feel connected. Even if you do not have spirituality, if you are alone, you can say, "This is good, actually. I can read something, or I can watch a movie or whatever." The solution to loneliness is not outside the individual. The solution is inside.

❖ **FATIMA BHOJANI AND PETER TARR**

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"Marla and I donate to the Brain & Behavior Research Foundation in support of science and the hope of finding better treatments for mental illness.

"Better treatments came too late for my brother, Stewart, who lost his battle with schizophrenia, and too late for my father, Ken, who suffered from depression. But we believe that with ongoing research, it will not be too late for millions of other people thanks to BBRF. We know this because we have seen the scientific breakthroughs and results that have come from funding scientists. Marla and I are dedicated to helping people who live with mental illness and doing what we can to be a part of the solution by our continued giving to BBRF."

—Ken Harrison, Board Member

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

Recent Research Discoveries

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

Study Reveals Adults With Mental Disorders Are At Significantly Higher Risk of COVID-19 and Have Poorer Outcomes

A systematic study based on the health histories of over 61 million American adults has found that people with a recent diagnosis of a mental disorder have a significantly increased risk for COVID-19 infection and tend to have worse outcomes than people infected with COVID-19 who don't have a mental disorder.

"Recent diagnosis" in the study was defined as within the last year. Those recently diagnosed with depression had the greatest risk of COVID infection, followed by those recently diagnosed with schizophrenia.

For those recently diagnosed with a mental disorder who also contracted COVID-19, the death rate was 8.5%, far above the 4.7% death rate in COVID-19 patients in the study with no mental disorder.

The study showed that the negative impacts of COVID/mental health comorbidities were most pronounced in African-Americans and women. Among people with a recent diagnosis of a mental disorder, African-Americans were found to have a higher COVID-19 infection risk than Caucasians. Women with chronic or recent mental disorder diagnoses were more likely to be infected with COVID-19 than men.

Nora Volkow, M.D.

The study was led by **Nora Volkow, M.D.**, Director of the NIH's National Institute on Drug Abuse (NIDA). She is a member of the BBRF Scientific Council.

Her team examined electronic health records of 61.7 million Americans aged 18 or over, 11.2 million of whom (18%) had a lifetime diagnosis of a mental disorder—recently, within the last year, or prior. A total of

1.3 million in the database had a recent mental health diagnosis. Within the same set of 61.7 million people, 15,110 had been infected with the COVID-19 virus, and 5,450 of these individuals (36%) had a lifetime mental health diagnosis; of these, 3,430 were diagnosed within the last year. It was in this latter group—recently diagnosed and contracting COVID—that the death rate was 8.5%.

Importantly, the study, which appeared in the journal *World Psychiatry*, was designed to reveal correlations, but is not able to judge causality. Nevertheless, Dr. Volkow commented that "the proper control and management of mental disorders is one factor that will [tend to prevent] COVID-19 infection. If you're delusional or hallucinating, you're less likely to follow public healthy interventions. If you're depressed, you may be unmotivated or you may not care."

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 serious 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. 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."

The team also noted that "higher sensitivity to stress, common among patients with mental disorders, will make it harder for them to cope with the uncertainties, isolation, and economic challenges linked with the COVID-19 pandemic—increasing their risk for relapse and disease exacerbation."

Yet another factor which may help explain the unique risks faced by those with mental disorders who contract COVID-19 is the increased likelihood that they suffer another major medical comorbidity such as heart disease, diabetes, COPD (lung disease), or substance-use disorders. All of these can contribute to greater severity and poorer outcomes in people who contract the virus.

The researchers suggest that overlapping biological factors may also be implicated. One example is elevated inflammation in the body, which not only can exacerbate COVID response but is also suspected of contributing, in at least some cases, to causality in depression, schizophrenia, and bipolar disorder.

Dr. Volkow and colleagues express the hope that their results will highlight "the need to recognize and address modifiable vulnerability factors and prevent delays in the provision of health care" in people with psychiatric disorders who are infected with the COVID-19 virus.

New Insights About How Alcohol Withdrawal Changes the Brain Differently in Males and Females

Newly published research is helping to make sense of data indicating that males and females not only consume alcohol differently, but also respond differently when, if they are heavy users, they are forced abruptly to abstain from drinking. The results are relevant to efforts to develop new treatments for alcohol and other substance-use disorders.

A team led by 2018 BBRF Young Investigator **Nicole Crowley, Ph.D.**, of Pennsylvania State University, studied "forced abstinence" in mice that modeled alcohol-use disorder (AUD) in people. Their aim was to learn about how an involuntary cessation of habitual alcohol consumption affects interconnected networks of neural circuits that can generate depression and anxiety.

It has been proposed that symptoms and underlying neural pathology overlap in alcohol-use disorder and depression and anxiety disorders. Forced abstinence is known to generate depression and anxiety in some people, but patterns differ in males and females, both in mice and humans.

Dr. Crowley and colleagues were intrigued by experiments indicating that treatment with the experimental rapid-acting antidepressant ketamine can reduce binge drinking and depressive-like behavior in rodents. This finding suggests that some of the potentially overlapping neural circuitry in alcohol-

use disorder (AUD) and major depression involves a subset of inhibitory neurons in the brain called somatostatin-expressing neurons (SSTs).

SST neurons, like other inhibitory neurons, reduce communication between cells in the brain. Learning more about the role of SST neurons in parts of the brain involved in regulating emotions and adapting to stresses—such as forced abstinence in heavy alcohol users—was a focus of the research newly reported by Dr. Crowley's team in *Frontiers in Behavioral Neuroscience*.

The researchers randomly assigned male and female mice to two groups: one group had access only to tap water; the other to both tap water and alcohol. Mice in this second group were

free to drink alcohol if they chose to do so. Concentration of the alcohol was gradually increased from 3% in the initial days of the trial to 10% by the end of the 42-day trial period. For those mice consuming alcohol, abstinence was forced after the 42nd day—only tap water was offered to all mice at this point. The trial continued for 21 additional days.

As had been observed in past studies, both male and female mice showed a preference, generally, for alcohol over water, when available; and females drank more than males. Both sexes, also, showed an increase in various depressive-like behaviors when alcohol was withdrawn. Both sexes had symptoms corresponding with anhedonia, a lack of interest in seeking pleasure.

But there were differences in the responses of the sexes to certain tests given to mice to gauge their response to stressors like forced abstinence. This led the team to hypothesize that females transition to an abstinence-induced depressive state more rapidly than males.

Future research, the team suggested, should more closely study the way men and women progress over time through different mood states during alcohol withdrawal.

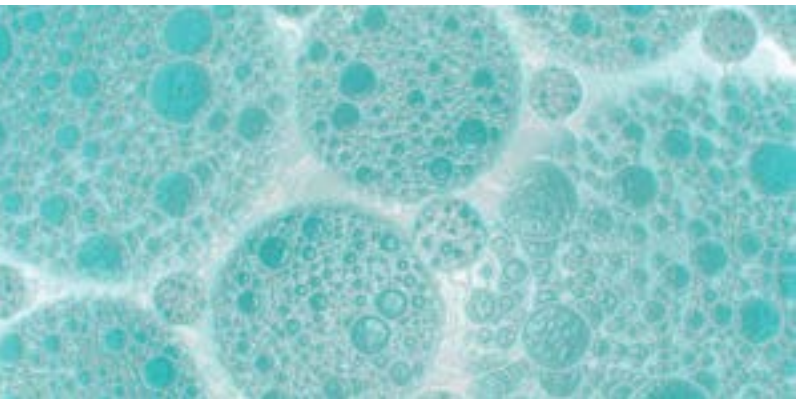

Nicole Crowley, Ph.D.

Behavioral adaptation to stress "may be more nuanced in female mice," Dr. Crowley and colleagues reported. The team's experiments suggested that forced abstinence induced sex-specific alterations in the prefrontal cortex (PFC)—dampening activation of excitatory neurons in the PFC in female mice (but not in males). In response to stress, abnormally low activation of part of the PFC called the medial prefrontal cortex, as well as changes in the amygdala, have been observed in people with major depression and alcoholism, the team noted.

SST neurons may confer resilience to stressors like forced abstinence—a concept that could have future therapeutic implications. Broadly, the research suggests that remodeling components of the brain's stress-response network could be an aim of future therapeutic strategies for alcohol-use disorder and perhaps other substance-use disorders.

Team Discovers Mechanism in Blood-Vessel Cells in the Brain That Promotes Resilience Against Stress

Thirty-five years after the first clue appeared, researchers now report they have assembled a detailed picture of one way in which inflammation can cause or help spur the development of depression and possibly other mood disorders.



The research reveals a molecular mechanism in blood-vessel cells that promotes resilience in the presence of chronic stress. Stress is one of the main "environmental" factors known to give rise to depression in vulnerable people.

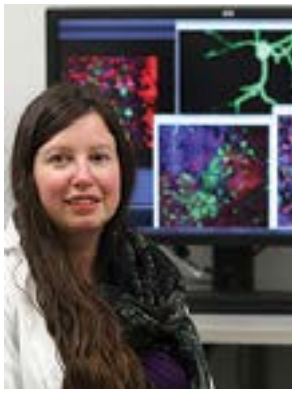
In the mid-1980s, a clinical study of depressed people first suggested a connection between leaks in the blood-brain barrier (BBB) and depression. The BBB selectively allows certain nutrients and other essential factors in the blood to pass into brain tissue, while keeping out pathogens, pro-inflammatory immune signals and other harmful elements.

Several years ago, research led by 2016 BBRF Young Investigator **Caroline Ménard, Ph.D.**, of Laval University and the CERVO Brain Research Centre in Canada, showed that in mice exposed to chronic social stress, BBB integrity was breached, due to a loss

of a protein called claudin-5 (cldn5). This protein forms "kissing" points that help to seal the junctions between endothelial cells that line blood vessels. In the brain, the "leakage" between cells was especially noted in an area called the nucleus accumbens, which is heavily involved in mood regulation.

Dr. Ménard and colleagues, including four other BBRF grantees, one of whom is a BBRF Scientific Council member, set out to clarify the mechanisms within neurovasculature (the vessels that bring blood to the brain) that cause leaks in the blood-brain barrier, promoting depression. They also sought to determine how the BBB is normally kept strong, hoping to identify factors that contribute to resilience amid challenges like chronic stress or inflammation.

Using tools that were unavailable 35 years ago when the first clue was noted, Dr. Ménard's team discovered changes at the cellular and sub-cellular levels in endothelial cells that line the vasculature. They linked these changes to different ways certain genes are regulated—switched on or off at different moments—and the way these changes impact still other molecular factors affecting the integrity of the BBB. The results were published in the *Proceedings of the National Academy of Sciences*.


Caroline Ménard, Ph.D.

Dr. Ménard's team confirmed their past research showing that the BBB was "normal" in mice that were naturally resistant to social stress. Immune signals circulating in the blood were prevented from crossing the BBB. In comparison: in mice without natural resilience that were exposed to chronic social stress, levels of the cldn5 protein were reduced.

This reduction in cldn5 was, in turn, linked with inflammation of the BBB. Loss of cldn5 and BBB leakage were associated with activation of pro-inflammatory signaling pathways (two important ones are TNF-alpha and NFK-b) in the endothelial cells of stress-susceptible mice.

These changes allow circulating inflammatory mediators, called cytokines, to "leak" through inflamed blood vessels into brain tissue, specifically within the nucleus accumbens. Mice with leaky BBBs developed depression-like symptoms.

The new research takes all of this an important step further, showing why and how levels of the key "cell-adhesion" protein cldn5, responsible for BBB integrity, dropped in vulnerable mice. The researchers documented blockage of the regulatory mechanism that causes the gene for cldn5 to become active.

Although the mechanism the team uncovered is more complex, the research confirmed that TNF-alpha, NFK-b, and a protein called hdac1 are all involved in mediating susceptibility to stress.

This is important because it raises the possibility of using drugs to alter the levels of these factors. This might alter the impact of stress on depression vulnerability. The team tested this concept in mice, finding that by using a drug that blocks hdac1 activity, they could reverse changes in the mice that made them vulnerable to loss of cldn5 and leakage in the BBB.

Clinical trials in humans are now under way seeking to discover if measures to alter pro-inflammatory signaling could therapeutically reduce inflammation and promote recovery in mood disorders.

Results obtained by Dr. Ménard's team suggest that this approach may also have promise in protecting the brain vasculature, ameliorating responses to social stress. Dr. Ménard notes that some depressed patients, particularly those resistant to commonly prescribed antidepressant treatments, have high levels of circulating proinflammatory cytokines in their blood.

"The possibility of modulating brain inflammation by acting directly on the neurovasculature is intriguing and appealing," the team wrote. While there is no known way to enhance cldn5 levels, they say, the new results suggest that targeting molecular pathways affecting cldn5 "might be a way to promote BBB integrity, neurovascular health and stress resilience."

The team also included: **Carol Tamminga, M.D**., a BBRF Scientific Council member, 2011 Lieber Prize winner and 2010 and 1988 BBRF Distinguished Investigator; **Gustavo Turecki, M.D., Ph.D.**, a 2020 BBRF Colvin Prize winner, 2016 Distinguished Investigator, 2008 Independent Investigator and 2000 Young Investigator; **Scott Russo, Ph.D.**, a 2008 and 2006 BBRF Young Investigator; and **Sam Golden, Ph.D.**, a 2018 BBRF Young Investigator.

Therapy Update

Recent news on treatments for psychiatric conditions

Studies Reporting on 2 Novel Therapies for Schizophrenia Make the Case for Their Continued Development

CLINCAL STUDY SUGGESTS EFFICACY OF DRUGS TARGETING THE GLUTAMATE SYSTEM IN SCHIZOPHRENIA

Jeffrey Lieberman, M.D.

In the continuing effort to develop new medicines to treat schizophrenia, a team led by BBRF Scientific Council member **Jeffrey Lieberman, M.D.**, and including nine other Council Members, BBRF grantees and prize winners, has reported encouraging results from a test of two drugs that target a novel mechanism in the brain. The study was a collaboration between researchers at Columbia, NYU, UC Davis, UCLA, Yale, and University of Alabama at Birmingham.

All currently approved antipsychotic medicines target the brain's dopamine neurotransmitter system, and specifically, act to inhibit the D2 dopamine receptor. Such medicines include antipsychotics of both the 1st generation (such as chlorpromazine and haloperidol) and 2nd generation (such as clozapine, risperidone and aripiprazole). The compounds tested in the new trial target the glutamate neurotransmitter system, and specifically, act to stimulate two receptors called mGluR2 and mGluR3.

While effective and safe, existing antipsychotic medicines have limitations and leave unmet clinical needs in the treatment of schizophrenia. The "positive symptoms" such as hallucinations and delusions of as many as 30% of people with schizophrenia do not respond to medications, and another 20%–30% of patients only partially respond. Moreover, medicines targeting the D2 receptor, which can have significant neurologic and metabolic side effects, do not have a therapeutic impact on schizophrenia's "negative symptoms," which include flat affect, social withdrawal, and the inability to experience pleasure.

There is substantial preclinical and clinical rationale for targeting the glutamate system in developing drugs to treat schizophrenia. The National Institute of Mental Health, hoping to spur development of new medicines to treat psychiatric disorders, has initiated a "Fast-Fail" clinical trial program, in which candidate drugs that have already proven safe in humans can be moved into phase 1B and 2A studies to determine if they engage the biological target(s) in the brain that their hypothesized effectiveness depends upon.

Dr. Lieberman and colleagues conducted an NIMH-supported study of one of the two glutamate-targeting drugs, called POMA (pomaglumetad) and simultaneously, in parallel, conducted a virtually identically designed trial of the other, called TS-134, which was sponsored by its developer, Taisho Pharmaceutical of Japan. In addition to serving on the BBRF Scientific Council, Dr. Lieberman, of Columbia University, is a 2006 Lieber Prize winner for Outstanding Schizophrenia Research and a two-time BBRF Distinguished Investigator.

His team posed the question: do POMA and TS-134 engage with their receptor-targets in brain cells, and if so, at what dosages? POMA had already been tested in a phase 3 study by its developer, Eli Lilly, and failed to generate therapeutic effects at a dosage of 80mg/day per patient. Lilly subsequently discontinued its program to develop the drug. Dr. Lieberman and colleagues postulated that POMA failed to generate therapeutic effects because the doses tested were too low, and perhaps too low to engage the drug's receptor-target. A parallel study of TS-134 using doses of presumably equal potency was performed in tandem. Such

comparisons of novel drugs in early development are highly informative but rarely done.

To determine if the drugs worked and which was better, they were tested in healthy volunteers who were administered the drug ketamine to produce a "pharmacologic model" of schizophrenia. These subjects were individuals aged 18-55 who volunteered to receive a single dose of ketamine, known to generate transient psychotic symptoms. In the POMA trial, data from 76 individuals were analyzed: 27 received the high dose (320 mg/day), 21 the low dose (80 mg/day), and 28 received a placebo treatment. The low dose was that used in Lilly's failed phase 3 trial.

The TS-134 study analysis included 59 healthy volunteers, 25 of whom received the high dose, 24 the low dose and 10 placebo treatment. The only differences in the two studies were: 1) in the POMA study participaints received 10 days of treatments, while those in the TS-134 study were treated for 6 days; and 2) TS-134 study subjects were hospitalized for the duration of the study whereas POMA subjects remained outpatients.

All of the participants were given functional MRI scans to determine whether the drugs were engaging with their receptor-targets, particularly in a region of the brain called the dorsal anterior cingulate cortex (dACC), important in glutamate activity. They were also carefully assessed clinically to determine if ketamine did in fact induce psychosis-like symptoms and whether or how much these were lessened by the administration of POMA or TS-134.

The results supported the studies' hypotheses and were interpreted by the investigators as warranting continued investigation. "Both drugs ameliorated ketamine-induced symptoms specific to schizophrenia," they reported in *Neuropsychopharmacology*, "although only the low dose of TS-134 demonstrated engagement with the target." They went on to propose that "prior negative results from Lilly's phase 3 studies may have been due to inadequate doses." Giving POMA at four times the dose "did show significant suppression of ketamine-induced symptoms," supporting the notion that the drug was in fact engaging its target. TS-134 appeared to be more potent, achieving target engagement and symptom reduction at the low dose but not at the high dose tested in the trial. Both drugs were generally safe, but generated some nausea and/or vomiting. TS-134 appeared to be the more potent in generating such effects, a side-effect issue the team dealt with by ramping up dosage gradually as treatments began.

The team concluded: "Our results demonstrate sufficient proof of principle and mechanism to support continued development of mGluR2/3 agonists as treatments for schizophrenia at empirically optimized doses."

In addition to Dr. Lieberman, the investigators included: **Daniel Javitt, M.D., Ph.D.**, BBRF Scientific Council member, 1995 Independent Investigator and 1990 Young Investigator; **John Krystal, M.D.**, BBRF Scientific Council member, 2019 Colvin Prize winner, 2006 and 2000 Distinguished Investigator and 1997 Independent Investigator; **Guillermo Horga, M.D., Ph.D.**, 2018 BBRF Maltz Prize winner; **Junghee Lee, Ph.D.**, 2012 BBRF Young Investigator; **Ragy Girgis, M.D.**, 2015 and 2010 BBRF Young Investigator; **Lawrence Kegeles, M.D., Ph.D.**, 2010 BBRF Independent Investigator and 1997 and 1995 Young Investigator; **Stephen Marder, M.D.**, 2016 BBRF Lieber Prize winner and 2011 Distinguished Investigator; **Adrienne Lahti, M.D.**, 2000 BBRF Independent Investigator; and **Donald Goff, M.D.**, 2009 and 2003 BBRF Independent Investigator.

EVIDENCE SUPPORTING RIGOROUS RE-TESTING OF OPIOID ANTAGONISTS TO TREAT SCHIZOPHRENIA

Anissa Abi-Dargham, M.D.

Trying to assess the value of an idea that first appealed to the research community in the 1970s, a team of investigators has published a careful statistical analysis of 30 past clinical trials in which people with schizophrenia were treated with a class of medicines called opioid antagonists. These medicines, which block the body's naturally occurring opioid receptors, were invented to treat opiate overdoses.

The meta-analysis (as studies of multiple past studies are called) found that four opioid antagonists, approved by the FDA in the 1970s, '80s and '90s, likely have some "significant" degree of effectiveness in treating the positive symptoms of schizophrenia, and perhaps negative symptoms as well. The findings appeared in the journal *Neuropsychopharmacology*.

In schizophrenia, positive symptoms refer to hallucinations and delusions as well as confused or disorganized thinking. Negative symptoms refer to flat affect, social withdrawal, and the inability to experience pleasure, among other symptoms.

In the 1970s, during clinical testing of opiate medicines designed to relieve pain, it was noted that some healthy volunteers experienced hallucinations and delusions similar to those experienced by people with schizophrenia and other illnesses with psychotic symptoms. This led to the question of whether blocking the cellular receptors for opioids would have some impact in reducing positive symptoms in schizophrenia patients.

A team led by Samuel Clark, M.D., Ph.D., the founder and CEO of Terran Biosciences, set out to review and assess clinical tests between 1979 and 2019 of opioid antagonists in patients with schizophrenia and related illnesses including schizoaffective disorder. The team's senior member was **Anissa Abi-Dargham, M.D.**, a member of BBRF's Scientific Council, winner of BBRF's 2018 Lieber Prize for Outstanding Achievement in Schizophrenia Research, and a 2008 BBRF Distinguished Investigator, 2000 Independent Investigator, and 1997 and 1993 Young Investigator. Dr. Abi-Dargham, a professor at Stony Brook University, is on Terran Biosciences' Board of Scientific Advisors.

The idea of using opioid antagonists to treat positive symptoms in schizophrenia, after many clinical tests, was abandoned by some academic researchers when the results proved to be mixed—substantial efficacy was shown in some trials, minimal efficacy in others, and no benefit in still others. Trying to make sense of this, Drs. Clark, Abi-Dargham and colleagues applied a set of stringent criteria to published reports, reducing thousands of academic references to 27 published papers reporting on 30 clinical trials.

For this meta-analysis the team only considered trials in which there was a "control" group, and in which doctors and participants were "blinded," i.e., did not know which participants were receiving an opioid antagonist and which were not. The 30 trials passing these and other quality-control criteria included 434 patients. In 28 of the 30 trials, two opioid antagonists, naloxone and naltrexone, were tested; one used nalmefene and another used buprenorphine.

One limitation of the meta-analysis of the 30 trials is that they varied considerably in their designs: in the kinds of patients they recruited (different ages, medication history, history of illness); in the way patients in the trials were assessed (e.g., the number of hours following administration of the drug or placebo at which they were assessed, as well as the assessment scales that were employed); and choice of study-endpoints (i.e., what defined a "response" in each trial).

Despite these differences, the team found that across the 30 trials, "significant decreases in symptoms following treatment with opioid antagonists were observed." Among these, they found significant improvements in participants' positive symptoms. Although there was some evidence of impact on negative symptoms, this evidence was "underpowered," meaning considerably more patients, data, and results are needed to make a meaningful assessment.

Many of the patients in the 30 trials were already taking antipsychotic medicines. There was evidence that the higher an individual patient's dose, the more muted any additional benefit of an opioid antagonist would be on positive symptoms. Still, the team suggested that the evidence across the 30 trials supplies sufficient rationale for a modern, carefully controlled clinical trial or trials to attempt to quantify and specify: if and how much benefit is to be gained from opioid antagonists, which patients might be most helped, and which antagonist(s) are likely to have the greatest therapeutic impact.

"These findings remain preliminary, but provide a strong rationale for a systematic effort to resolve the potential efficacy of opioid antagonists either alone or as adjunctive treatment, both for positive and negative symptoms," the team wrote.

Dr. Clark, whose company is developing a candidate medicine that specifically blocks one of the three main opioid receptors, believes the concept "could represent a paradigm shift" in schizophrenia treatment. In some patients, he believes, they might supplement or supplant antipsychotics, which block the D2 receptor for dopamine. Dr. Clark theorizes that kappa opioid receptors malfunction in schizophrenia, impacting the regulation of the dopamine system—hence his company's drug to block that specific receptor.

Two Forms of Non-Invasive Brain Stimulation Are Shown to Help Patients with PTSD and Fear & Anxiety

iTBS BRAIN STIMULATION CONTINUED TO HELP VETERANS WITH PTSD A YEAR AFTER TREATMENT

Mascha van't Wout-Frank, Ph.D.

Jennifer Barredo, Ph.D.

In two related published papers, a research team that included three recipients of BBRF grants has reported evidence suggesting that a form of non-invasive brain stimulation may be an effective new treatment for post-traumatic stress disorder (PTSD).

The evidence is based on a clinical test of iTBS (intermittent theta-burst stimulation) involving 50 veterans diagnosed with PTSD. Half of the participants received active iTBS treatments for 4 weeks. The other half received a placebo version of iTBS stimulation for the first two weeks of the trial, then received 2 weeks of active iTBS treatments. The groups were selected randomly and both participants and doctors administering the treatments were blinded as to which participants were in the two groups. The trials were conducted at the Center for Neurorestoration and Neurotechnology at the VA Providence Healthcare System; team members were also affiliated with Brown University.

Their results, appearing in the *American Journal of Psychiatry*, showed therapeutic benefits when assessed at the end of the second week in the group receiving active iTBS treatments from the start of the trial, as compared with the group that had only received placebo stimulation to that point. (The placebo treatments were designed to feel like active stimulation but did not deliver actual stimulation to the brain.)

"At 2 weeks, active stimulation improved social and occupational function," the team reported, and there were indications of reduced PTSD symptoms as well as relief of depression in participants whose PTSD was accompanied by depression. One month after the trial ended, reassessment of the participants found "clinically meaningful and statistically significant reductions in PTSD, depression, and social and occupational function."

iTBS is an FDA-approved form of non-invasive brain stimulation that delivers the same amount of stimulation given in rTMS (repetitive transcranial magnetic stimulation) treatments, first approved for depression 12 years ago and now also approved in obsessive-compulsive disorder. iTBS sessions are each 3-10 minutes in duration, compared with 37.5 minutes for standard rTMS sessions. While rTMS treatments for depression target the brain's left dorsolateral prefrontal cortex (DLPFC), this iTBS trial targeted the right DLPFC. During the trial, most of the participants continued taking various medications that they had been prescribed previously.

One intriguing result of the trial was the fact that most of the clinical improvements from stimulation occurred early, during the first week of active treatments. The team wanted to know more about the relationship between the amount of iTBS stimulation given and the impact on symptoms over time, beyond one month. Among those who benefited, did the effects last, and if so, for how long?

Hence, they conducted a second study that looked at 46 of the 50 participants of the original trial, assessing how they fared one year after the original 2- and 4-week active iTBS treatments ended. Those results were published in the journal *Neuropsychopharmacology*.

Of the 46 participants whose records were studied over the following year, 24 had received 4 weeks of active iTBS in the original trial and 22 had received 2 weeks of active treatment and 2 weeks of placebo treatments. 22 of the 46 (48%) relapsed over the following year: 1 died of an overdose, 3 were admitted to hospitals for psychiatric treatment, and 18 sought re-treatment with brain stimulation (all received rTMS, not iTBS).

Of those who had received only 2 weeks of active iTBS, 64% relapsed; of those who had received 4 weeks, the relapse rate was only 33%. Just as impressive, the average time until relapse in the "2-week" group was 182 days, compared with 296 days in the 4-week group.

The team says their results "provide real-world support" for the use of iTBS in treating PTSD, especially in view of the fact that the veterans they studied are part of a "difficult-to-treat population" that often has comorbidities including major depression, anxiety, substance abuse and suicidality.

The team said another aspect of their results was encouraging. Each of the 50 veterans taking part in the original study were given a "resting-state" fMRI brain imaging scan prior to the beginning of the trial. In their 1-year follow-up paper, the team concluded that functional connectivity of the brain's posterior cingulate cortex (PCC) as measured in the pre-treatment fMRI scans, was predictive of patient outcomes a year following treatment. Importantly, they identified two sub-regions whose connectivity consistently differed in participants who did and did not relapse within a year of the end of iTBS treatments. These are potential biomarkers to assist in future clinical applications of iTBS in treating PTSD, the team said. ❖

Mascha van't Wout-Frank, Ph.D., a 2010 BBRF Young Investigator, and **Jennifer Barredo, Ph.D.**, a 2019 BBRF Young Investigator, co-authored both studies. **Benjamin D. Greenberg, M.D., Ph.D.**, a 2000 BBRF Independent Investigator, co-authored the first study. Noah S. Philip, M.D., of VAPHCS and Brown University, led both studies.

rTMS BRAIN STIMULATION REDUCED FEAR AND ANXIETY IN A PRELIMINARY TRIAL

Researchers have reported success in a preliminary effort to use non-invasive brain stimulation to reduce fear and anxiety. The placebo-controlled trial involved 19 healthy human subjects who were exposed to stimuli designed to activate their "startle" response to an experienced or anticipated threat.

The experiments grew out of a project funded by a 2018 BBRF Young Investigator grant to **Nicholas Balderston, Ph.D.**, now at the University of Pennsylvania. Dr. Balderston and colleagues used repetitive transcranial magnetic stimulation (rTMS) to reduce excitation in a part of the brain called the parietal lobe. Specifically, they targeted a section called the IPS (intraparietal sulcus), which their past research had shown to be "hyperexcited" when individuals are experiencing or perceiving a threat.


Nicholas Balderston, Ph.D.

As Dr. Balderston's team noted, in a paper published in the journal *Translational Psychiatry*, nearly one American in five meets the criteria for an anxiety disorder each year, and less than half of these individuals receive treatment that is even "minimally adequate." While there are a number of pharmaceutical treatments for anxiety, as wells as various forms of talk therapy, the researchers said they wanted to "broaden the scope" of potential treatments by learning more about the potential of non-invasive brain stimulation to help patients.

rTMS has been FDA-approved for depression since 2008, and has an effectiveness profile that often compliments that of antidepressant medicines, which don't help every patient achieve remission. But rTMS has not been as successfully or broadly applied in anxiety disorders. Dr. Balderston's team wanted to test rTMS in a mode called "low-frequency," which reduces excitation in targeted brain areas—in this case, the IPS. ("High-frequency" rTMS, which increases cortical excitation, is used in treating depression.)

The team enrolled 19 subjects in a double-blinded trial of rTMS under a variety of test conditions. The subjects were healthy and averaged about 30 years of age; 13 were female. Participants were exposed to threats: brief, mild electric shocks to the wrist which were uncomfortable but harmless. These challenges were delivered in separate "runs": in some they were predictable and in others unpredictable. Fear and anxiety caused by the anticipation of predictable and unpredictable threats was measured by quantifying participants' startle response.

While these challenges were being presented, in successive rounds, all of the participants experienced them, in turn, while receiving low-frequency rTMS targeting the IPS; a simulated

(placebo) version of rTMS that did not actually deliver stimulation to the brain; and a "no-rTMS" mode where the equipment was not even present.

The team found that when rTMS was being directed to the IPS, there was a measurable reduction in the "startle" response caused by both fear and anxiety, compared with the startle response with placebo rTMS and no-rTMS.

The researchers think these results indicate that the parietal cortex plays a causal role in a state of elevated arousal that regulates the startle response. Further, they suggest that using rTMS to reduce excitability in the IPS can "reduce physiological arousal associated with fear and anxiety during threat."

Although additional research should help to clarify these ideas, the team believes that by inhibiting activity in the parietal cortex while a threat was being experienced, "it's possible that we were reducing subjects' tendency to shift their attention towards the shock threat," and in this way reducing their threat-related anxiety. This is interesting in part because the IPS region of the parietal lobe is known to be involved in focusing attention, among other things.

Based on its findings, the team thinks low-frequency rTMS is a potential treatment for anxiety disorders, a prospect they intend to explore in larger trials involving patients diagnosed with generalized anxiety disorder—trials that must also test what proportion of patients are helped, to what degree, and for how long.

Other members of the research team, in addition to Dr. Balderston, included senior member **Christian Grillon, Ph.D.**, a 1988 BBRF Young Investigator; **Sarah Lisanby, M.D.**, a 2010 BBRF Distinguished Investigator and 2003 Independent Investigator; and **Zhi-De Deng, Ph.D.**, a 2017 BBRF Young Investigator.

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—Barbara Toll, Board Member & Research Partner

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GLOSSARY

PLURIPOTENT STEM CELLS (pp. 4–9) Stem cells, which come in different varieties, are the "mothers" of the trillions of cells that make up the human body. They are found in the embryo (embryonic stem cells) as well as in the mature adult (in "niches" such as the bone marrow). The stem-cell technology that is revolutionizing biology centers on creating pluripotent stem cells—cells which can be directed to develop into many different kinds of specialized cells found in different organs of the body. A variety of human brain-cell types can now be generated in unlimited numbers by re-programming skin cells or blood cells from human donors. The donated cells are treated with proteins called transcription factors that "de-differentiate" the cells back to a pluripotent stem-cell state; these in turn are treated with chemical factors that direct them to redevelop as specific types of brain cells. This technology (called **hiPSC**—"human induced pluripotent stem cell") provides a limitless supply of human brain tissue for study, an advance of incalculable value in view of the limits on experimentation with the brain in living people. hiPSC technology is uniquely valuable in the study of disorders such as schizophrenia and autism with strong genetic roots and in which pathology is thought to begin prenatally, in many cases. hiPSC enables researchers to reprogram patients' skin cells to become immature brain cells that bear the precise genetic identity of the patient-donor, making it possible to observe and study pathologies as they emerge in the newly created cells.

DIFFERENTIATION (p. 5) The process in which a stem cell, which is wholly undifferentiated, i.e., unspecialized, is transformed into a specific, specialized cell of the human body—a neuron or heart cell or muscle cell, for example. Such cells are sometimes called "somatic cells."

CRISPR and **ISOGENIC CELLS (p. 8) CRISPR** is a gene-editing technique adapted by scientists from the bacterial immune system. The recent "integration" of CRISPR with hiPSC stem-cell technology (see above) is making it possible to generate **isogenic cells** in unlimited numbers: cells bearing precisely the same genetic variations—for instance, combinations of variations found in one of more individuals with a disorder such as schizophrenia. This provides a controlled means of studying the impact of the variations, one by one, to determine how they contribute (or do not contribute) to disease pathology.

WISDOM (pp. 18–22) A "trait" of human behavior that Dr. Dilip Jeste and colleagues have attempted to harness to address psychosocial problems such as loneliness. Dr. Jeste has identified seven components of wisdom: pro-social behavior (i.e., empathy or compassion); emotional regulation; self-reflection; acceptance of uncertainty and a diversity of perspectives; the ability to be decisive; the ability to provide support for others in a non-self serving way; and spirituality. Dr. Jeste believes the components of wisdom can be cultivated and learned by people of all ages.

ONELINESS (p. 22) The ability of some individuals to be happy even when alone.

BLOOD-BRAIN BARRIER (p. 26) The BBB selectively allows certain nutrients and other essential factors in the blood to pass into brain tissue, while keeping out pathogens, pro-inflammatory immune signals and other harmful elements. There may be a connection between leaks in the BBB and depression.

rTMS and **iTBS (pp. 31–33)** Two forms of non-invasive brain stimulation currently used to treat depression and obsessive-compulsive disorder. **rTMS** (repetitive transcranial magnetic stimulation) was first approved for treatment of refractory depression in 2008; sessions lasting 37.5 minutes are delivered once weekly over a period of 6 weeks. **iTBS** (intermittent theta-burst stimulation), approved in 2019, delivers the same amount of total stimulation, usually in 5 sessions per week lasting only 3 minutes each, over a period of 4 to 6 weeks. Accelerated versions of iTBS with possible rapid-antidepressant effects have been tested which deliver an entire course of treatment in just 5 days.

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