ADHD:
What You Need to Know

BBRF Distinguished
Investigators for 2025

MAGAZINE
# Brain&Behavior
SUMMER 2025

## Reverse Translation: Research That Begins and Ends With Patients

# PRESIDENT'S LETTER

Welcome to the Summer 2025 issue of *Brain & Behavior Magazine*.

Philanthropic support for research has never been more vital. With recent shifts in government funding, BBRF grants have become a critical force in driving forward bold, life-changing research and play an increasingly essential role in advancing innovative treatments and creating new therapies for individuals affected by psychiatric illness.

In this issue, our **PATHWAYS TO THE FUTURE** story features Dr. Akira Sawa, a champion of "reverse translation," a research approach that begins with observations made in psychiatric patients that call attention to unresolved questions about brain biology. Dr. Sawa leads a team at Johns Hopkins School of Medicine that uses patient data in laboratory-based experiments often involving animal models that seek to solve these mysteries, with the aim of then translating new insights back to the clinic in the form of novel diagnostic tools and therapies. As our story explains, Dr. Sawa believes this can be particularly powerful in advancing doctors' ability to practice precision medicine—tailoring treatments to individual patients or subgroups of patients.

Our **ADVICE ON MENTAL HEALTH** story details the conversation I had this past fall with Dr. Stephen P. Hinshaw of the University of California, Berkeley. A world expert in ADHD, Dr. Hinshaw advises parents and educators that he thinks ADHD is not an "attention deficit" per se, but rather, more of a regulatory disorder, often reflected in difficulty shifting gears between tasks, particularly those that are highly engaging vs. those that are routine. Ultimately, he suggests that ADHD is a "child-school-parent affair" in which "everybody needs to work together" for the child's benefit.

In **AWARDS & GRANTS**, we proudly announce the 10 recipients of BBRF's Distinguished Investigator grants for 2025. These awards, with a value of $1 million, are made possible by the generosity of the WoodNext Foundation.

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

Thank you for being an important part of the BBRF community. Together, we will continue to fund innovative and impactful research that will pave the way forward for scientific advancements that are making a difference in the lives of those living with 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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Lauren Duran

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Peter Tarr, Ph.D.

**Designer**
Gene Smith

# Research That Begins and Ends With Patients

## Starting with problems faced by psychiatric patients, Dr. Akira Sawa conducts research in the lab that seeks to bring solutions back to the clinic

**IN BRIEF**
Dr. Akira Sawa is a champion of "reverse translation," a research approach that begins with observations in patients that aren't well understood in terms of brain biology or mechanisms. These ultimately lead, via laboratory experiments, back to patients in the form of diagnostic tools and testable ideas for new therapies. He believes this can be particularly powerful in advancing doctors' ability to practice precision medicine—tailoring treatments to individual patients, or sub-groups of patients.

While studying for his M.D. degree, Akira Sawa, like his peers, thought carefully about what kind of medicine he wanted to practice. For a while, during a clerkship in surgery, he was captivated by the idea of becoming a surgeon. Observing with delight the art of experienced doctors performing liver transplants, he found the results to be "almost magical." Indeed, the high success rate of such transplants by the late 1980s did seem like magic, unless you understood, as Dr. Sawa notes, that such results were dramatically facilitated by the development of immunosuppressing drugs. These are medicines that greatly minimize the chance that the transplant recipient's body will reject the donor's organ—which the immune system recognizes, correctly, as "foreign tissue," and tries to attack.

Such innovations impressed young Dr. Sawa. Recognizing the significance of mechanism-driven medical research, his interest in surgery waned. "I began to think about what areas of medicine needed the most innovation" he remembers. "Which discipline was most underdeveloped? Unfortunately, it seemed to be psychiatry." He thought that if he went into psychiatry, "I could contribute to its daily practice through patient-based medical research and scientific innovation."

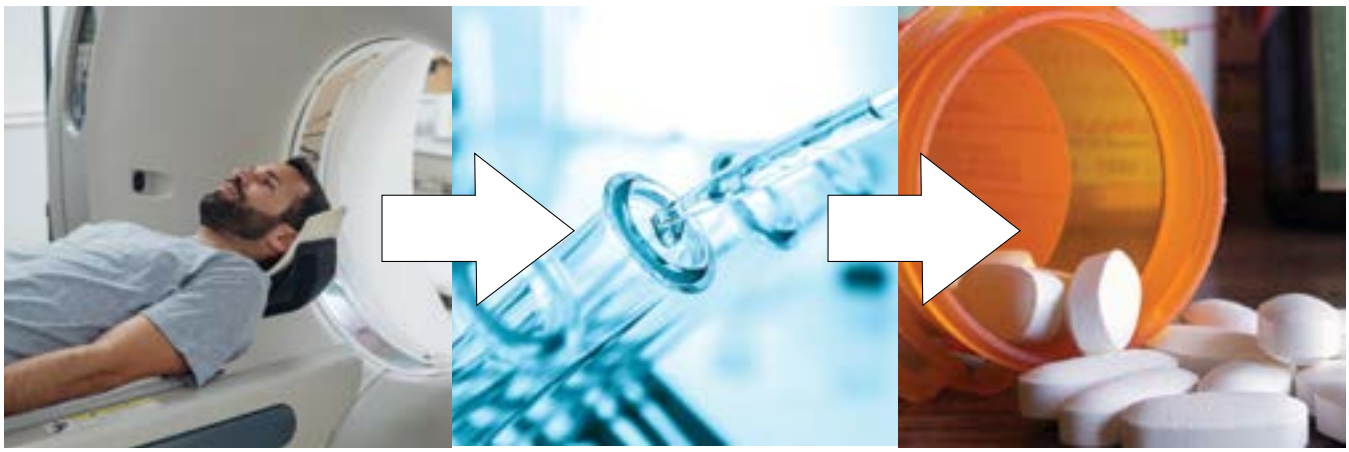
Today a figure of international renown, Dr. Sawa holds professorships at the Johns Hopkins School of Medicine and Bloomberg School of Public Health, in several fields: Psychiatry and Behavioral Sciences, as well as in Mental Health; Genetic Medicine; Pharmacology and Molecular Sciences; Biomedical Engineering; and Neuroscience. He also is Director of the Johns Hopkins Schizophrenia Center, where his direct involvement with patients continues, often in connection with his supervision of medical interns, along with his many research and administrative commitments.

**Akira Sawa, M.D.**

Professor, *Johns Hopkins School of Medicine and Bloomberg School of Public Health*
Director, *Johns Hopkins Schizophrenia Center*

BBRF Scientific Council
2011 BBRF Distinguished Investigator
2004, 2002 BBRF Young Investigator

The central idea that drives Dr. Sawa is closely related to that with which he began: he strives very consciously to connect what doctors observe of their patients in the clinic to the research projects they choose to undertake in the laboratory. Over the decades of his career, Dr. Sawa, who has received three BBRF research grants and is a member of BBRF's



The "reverse-translation" approach begins with data from psychiatric patients that doctors and researchers cannot explain biologically. These mysteries are investigated in animal models, in the lab, with the hope of generating new ideas that can be translated back to patients in the form of diagnostic tools or new therapies.

Scientific Council, has come to dedicate his energies to an approach called **"reverse translation."** To establish this approach, he has focused, especially over the past decade, in building clinical cohorts composed of patients with psychotic disorders, from whom he and colleagues collect not only clinical but also brain imaging and molecular and cellular data from biopsied tissues.

"We *always* start from the clinic—from our patients," he explains. "What we want to discover is how our clinical observations can be explained in terms of biological mechanisms, or how they can be understood in a biological context." The aim is to then translate this newly obtained biological insight back to the clinic—in the form of biomarkers to aid diagnosis, or new targets for better treatments, or even those treatments themselves. It's called "reverse translation" to distinguish it from "translational research" that proceeds from observations and discoveries made initially in the laboratory, which may or may not have a direct relationship with observations made in patients (in this case, those with psychiatric illness).

Both traditional translational research and reverse translation are vitally important. Both share the ultimate aim of improving the lives of patients, and Dr. Sawa would be the last to suggest that reverse translation is intrinsically more important. What he does strive to show, however, is that the approach that begins with patients and leads via the laboratory back to patients can be particularly powerful in advancing doctors' ability to practice *precision medicine*—the idea of tailoring treatments to individual patients, or sub-groups of patients, who might share a broad diagnosis like schizophrenia or depression but for whom the optimal treatment may differ.

The best way to explain the promise of reverse translation is through examples, of which there are several in the recent history of Dr. Sawa's lab. The three that we will summarize in this story might be thought of as three stories that begin with observations in psychiatric patients that posed a mystery to doctors and researchers—phenomena that were clearly occurring in patients but could not be accounted for based on the current understanding of human biology. These mysteries in each instance prompted experiments in the laboratory, which in turn have culminated in discoveries that may have translational value for precision medicine.

## MYSTERY 1: How to explain conflicting signals from the immune system in schizophrenia?

In 2022 Dr. Sawa and his team published a study in the journal *Nature* that addressed a potentially important clinical inconsistency. For years, they and others had been interested in whether or how the body's immune response—and the inflammation it can cause—plays a role in schizophrenia.

It was logical to routinely collect and analyze cerebrospinal fluid (CSF) from patients—a clear liquid bathing the brain and spinal cord that helps to keep the central nervous system healthy, in part by providing it with the protection of the immune system. It had been well established that in the CSF of schizophrenia patients, levels of tiny signaling proteins called pro-inflammatory cytokines were elevated, compared with levels in the CSF of healthy people. Why would this be the case?

Since these cytokines are released when the immune system has been activated, this observation supported the idea that immune activation might play a role in schizophrenia pathology. The problem with this idea was conflicting evidence also coming from schizophrenia patients. Imaging studies with patients with

## How can an injury or insult to the fetus—caused, for example, by a mother's stress during pregnancy—translate into greatly increased risk for psychiatric illness years after birth?

pro-inflammatory cytokine elevation in their CSF offered evidence of no consistent increase in the activation of immune cells in the brain.

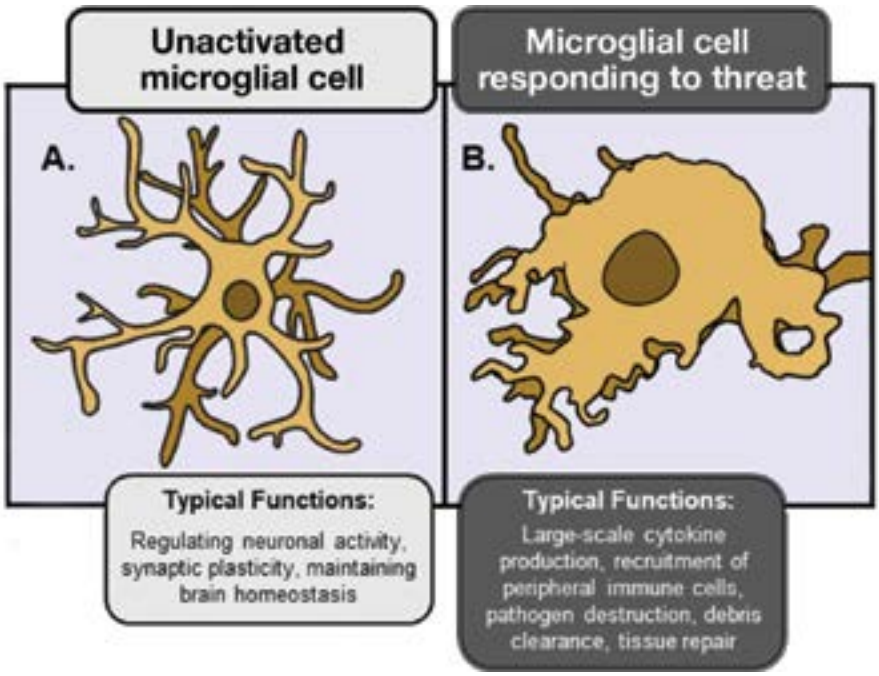
The team led by Dr. Sawa observed this discrepancy in his clinical cohorts, and other groups acknowledged it. The inconsistency is potentially important because many studies have shown that the primary immune cells of the brain, called microglia, can affect brain circuit connectivity and the way neurons function. Their main function is to protect the brain, but it had been proposed that microglia might not be functioning properly under conditions of immune challenge spurred by environmental stress. Perhaps, the team reasoned, this would help to explain schizophrenia pathology in at least some fraction of cases.

Dr. Sawa's team hoped to shed light on the immune activation mystery in schizophrenia patients by going into the lab and performing a series of sophisticated experiments, some in test tubes but most of them in mice, examining what happens to young microglia in the fetal brain after the mother, during pregnancy, has been subjected to stress. "Maternal immune activation" or MIA, during pregnancy, was a promising way to study schizophrenia pathology given that prenatal immune stress and perinatal implications are regarded major risk factors for the illness. Dr. Sawa wanted to know: what happened to microglia in the offspring of mouse mothers that had been stressed during pregnancy?

The team compared the responsiveness of microglia from adult MIA offspring with that from offspring of mice that had not experienced stress during pregnancy. They could see that the activation patterns of many genes in the two sets of microglia differed; 76% of genes that had different activation patterns in adult MIA offspring were downregulated—their expression levels were lower. This was traced, in other experiments, to alterations in a process called epigenetic regulation that helps maintain expression patterns—when and how often particular genes are activated in the cell nucleus (in this case, in microglial cells).

Importantly, many of the "downregulated" genes were recognized to be involved in immune response pathways, whose function was also found, in subsequent experiments, to be altered, in the same animals. Consistent with the epigenetic finding, the team concluded that the alteration in immune response pathways was acquired in response to MIA before birth—it was a result of the activation of the maternal immune system—and was maintained postnatally, into adulthood after these animals were born.

Reflecting molecular changes, these results appeared to relate back to the original mystery in schizophrenia patients that set all of this research in motion. Dr. Sawa's team found that "blunted" activity of microglia in the fetal period (following maternal




The brain's microglia normally undergo a change once an immune or other threat is detected. Dr. Sawa's experiments showed this response is blunted in the fetal brain when a pregnant mother is subjected to stress, and that this blunted response continues postnatally.

stress) corresponded, once the same animals matured, into bunted microglial reactivity to immune challenges in adulthood. The experiments provided an example of how an injury or insult suffered by individuals prior to birth affected brain biology in a lasting way.

How did this relate to schizophrenia patients and the puzzling data Dr. Sawa's team had collected from them? Cytokines or other proteins carrying the signal of immune threat may be generated in adults with schizophrenia, but in the brain, their microglia seem unable to respond properly—as suggested by the brain imaging data the team had previously collected. This lack of cellular response explains, at least in principle, how a vulnerability or pathology incurred in the fetal period might play out many years later, after birth—perhaps in people, as the Sawa lab's experiments showed that it can in mice.

In a final round of experiments, the team administered a drug to pregnant mice that had been subjected to immune-activating stress. The drug, as the team intended, had the effect of deleting the population of microglia in their fetuses that had been impacted by the mother's stress. Also as expected, a natural process ensued: the fetal brain was repopulated with microglia. But these new cells had not been exposed to the mother's earlier immune challenge and did not show blunted reactivity. The same animals, after birth, grew into adults showing none of the immune activation deficits seen in the adults whose microglia and immune pathways had been impaired prenatally by maternal stress.

This research has not yet led all the way back to the clinic, although it may help us understand what happens to the immune response in the brain—and why—in at least some schizophrenia patients. The team, says Dr. Sawa, is extending this line of research by investigating, among other things, how

**Effects of "maternal immune activation" (MIA):** Pregnancy is a particularly vulnerable time for expectant mothers who contract a virus or come down with the flu. Dr. Sawa's team performed experiments in pregnant mice, showing that when they were subjected to stress that activated their immune system, immune-signaling proteins called cytokines were released into their circulatory system. Some cytokines were transferred to the developing fetus through the placenta, which in turn led to prenatal immune stress in the fetus/offspring.

the timing of maternal stress during pregnancy impacts microglia prior to birth and also once the animals reach adulthood, as well as how such changes affect behavior. Among the translational possibilities, this research might lead to efforts aimed at modifying the emerging fetal immune response, a strategy, if it proves feasible, that could conceivably prevent pathology that culminates years later in schizophrenia or perhaps other psychiatric illnesses.

## MYSTERY 2: How does early-life stress increase risk for postpartum depression?

A second set of experiments that exemplify the Sawa team's "reverse-translation" approach also concerns how events that occur early in life—in this case, adolescence—can result in important threats to mental health many years later.

The team's point of departure was epidemiological evidence indicating that girls who experience significant stress during adolescence appear to be at elevated risk for suffering postpartum depression (PPD) after giving birth. Dr. Sawa, in collaboration with his colleagues with an expertise in postpartum depression, has confirmed this observation. But why would it be so? How is an environmental exposure translated into a biological vulnerability—and one that may not manifest for many years? It's a grand-challenge question that neuroscientists and psychiatrists have asked for many years about this and other early-life insults to the developing brain.

PPD is defined as a major depressive episode affecting women in the period following childbirth. It is the most common complication of childbirth, affecting approximately 10% to 15% of women who give birth in the United States. An estimated 5% to 10% of women who experience PPD have a severe form of the disorder, posing a direct threat to the life of the mother, and, of course, the welfare of her newborn. Both severe and less severe forms of PPD have been linked with abrupt changes in hormone levels after childbirth, and can be addressed today with rapid-acting medicines (brexanolone and zuranolone) whose development has been influenced by research performed by BBRF grantees.

Genetic variations are likely involved in elevated individual risk for PPD, but

Epidemiological evidence indicates that girls who experience significant stress during adolescence appear to be at elevated risk for suffering postpartum depression (PPD) many years later, after giving birth.

environmental exposures to trauma, stress, and other factors are also probably involved in many instances. For Dr. Sawa, research his team performed culminating in a 2013 paper in *Science* provided a starting point for new experiments a few years ago examining one potential mechanism involved in connecting early-life exposures into elevated risk for PPD. "In our paper from 2013, we made observations about how stress can be converted into long-term effects," Dr. Sawa says. "We found how adolescent stress may cause long-term changes in gene expression via epigenetic mechanisms, specifically involving the glucocorticoid system and dysregulation of the HPA axis."

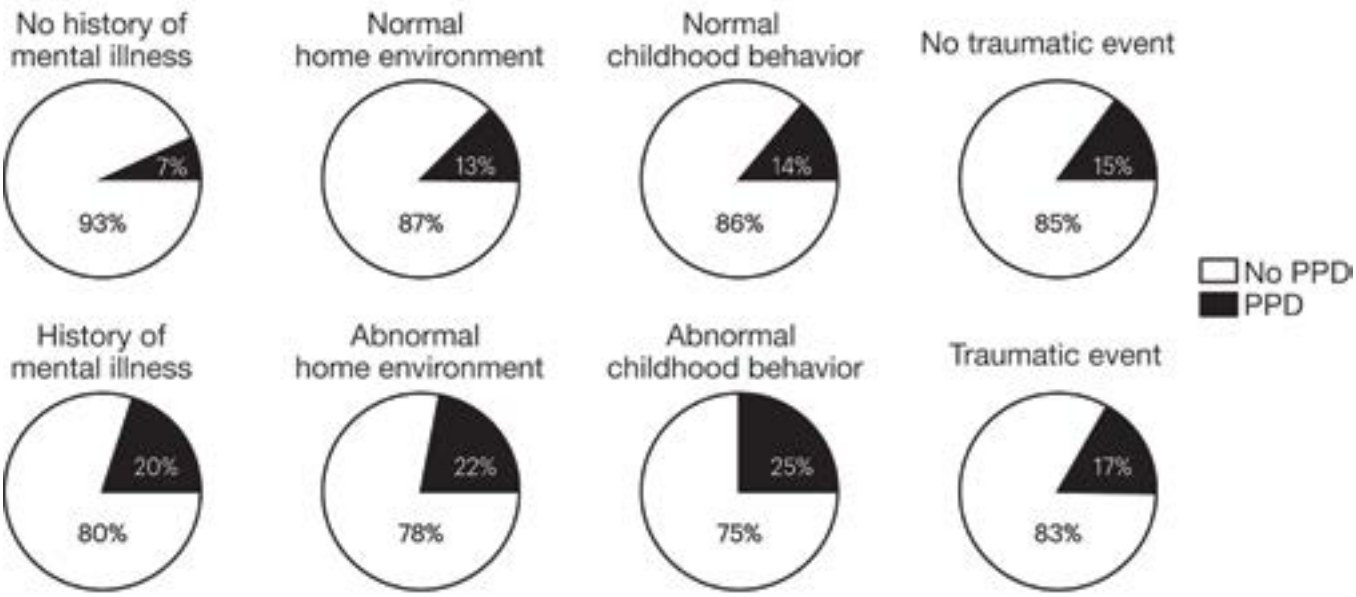
**The HPA axis** is a communication system involving the hypothalamus, pituitary, and adrenal glands, which form the body's main stress response network. This network uses hormones to link perceptions of threat or danger with the body's physiological reaction to such threats—the stress response.

**Glucocorticoids** are hormones found in almost every human and animal cell, which, when they bind at glucocorticoid receptors in cells, generate a response that is generally anti-inflammatory. They upregulate, or increase, the activity of immune-suppressing proteins, while downregulating, or decreasing, the activity of immune-stimulating proteins.

Women who have experienced adverse life events are three times more likely to have PPD than women who did not experience any adverse life events, Dr. Sawa and colleagues noted in a 2024 paper in *Nature Mental Health* carrying forward the 2013 research to specifically address how early exposure to trauma may affect PPD risk much later in life. The team knew that patients with depression who have experienced adverse life events tend to be treatment-resistant. For this reason, they investigated the longitudinal effects—the effects over time—of adolescent stress on the HPA axis and postpartum behaviors in mice and people. In mice they observed that social isolation during adolescence caused prolonged elevation in glucocorticoid levels, and dysregulation of the HPA axis.

"Many studies have reported alterations in plasma hormone levels in [human] patients with PPD and a correlation between hormonal changes and onset of PPD symptoms. Thus, we examined the plasma levels of estradiol, progesterone, prolactin, oxytocin, and corticosterone in our animal model," the team said in their paper.

Among mice that had given birth, the team found that levels of the stress hormone corticosterone, both in animals that had been stressed and unstressed in adolescence, was increased after late pregnancy and the early postnatal period in comparison to adult mice that were not pregnant and had not given birth. To some extent, this elevation is a normal part of pregnancy and childbirth. Corticosterone levels in previously




Women who have experienced adverse life events are significantly more likely to have PPD than women who did not experience any adverse life events. Some specific comparisons of PPD rates are given in this chart.

unstressed mothers did begin to decrease after delivery, but importantly, corticosterone levels in mothers that had been stressed in adolescence were found to be consistently higher than those in unstressed controls, both one week and three weeks postpartum.

To the team, these data suggested that a change in the control of the HPA axis might have occurred in the animals that had experienced early-life stress, and that this resulted in a prolonged elevation of corticosterone levels—an elevation that continued into adulthood and affected some animals in pregnancy and postpartum.

To Dr. Sawa's team, the mechanism tentatively identified in their model mouse system may help explain "an important subset of patients with PPD who experience adverse life events and resultant changes in the HPA axis."

Half of patients with PPD are known to be resistant to treatment with SSRI antidepressants (like Zoloft or Prozac) and these treatment-resistant cases are likely to be associated with adverse life events. The team used their adolescent stress paradigm to model such clinically difficult cases. In mouse mothers that had adolescent exposure to stress, the researchers tested the postpartum therapeutic impact, if any, of SSRIs; a brexanolone-like drug; and an FDA-approved drug that blocks glucocorticoid signaling (a glucocorticoid receptor antagonist). After one week, only the drug that inhibited the glucocorticoid receptor showed evidence of reducing PPD-like symptoms in the model mice. For this reason, the team suggested that repurposing glucocorticoid receptor antagonists for some cases of treatment-resistant PPD may be a therapeutic approach worthy of testing more in animals and eventually in people.

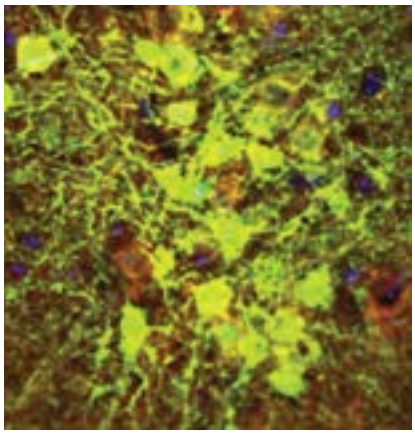
"What I really want people to appreciate about this work is about connecting the idea of reverse-translation with precision medicine," Dr. Sawa says. The idea of a brief course of a glucocorticoid receptor-blocking medicine right after delivery is potentially applicable for a subset

Experiments by Dr. Sawa and colleagues confirmed in animal models that chronic adolescent stress can perturb the HPA axis and stress response in a way that significantly raises the risk, later in life, of postpartum depression.

of patients. The team regards its approach in this work to be strictly "complementary." Current medications are very supportive of women post-delivery, but there are still a significant number of patients who don't respond even to recently approved rapid-acting treatments. That is who this work may specifically address—an example, if the approach works, of precision medicine.

## MYSTERY 3: Can shared 'risk' genes account for symptoms shared across illnesses?

"Remember," Dr. Sawa stresses, "in what we do, we try always to start from the clinic—from patients. This includes psychiatric genetics. In genetic studies of psychiatric illness, there is always a gap, between genetic risk factors that are identified in these studies and biological mechanisms through which they exert their effects. There is always a gap, and what we are trying to do is fill this gap."



The Sawa lab showed that overexpression of a regulatory microRNA molecule called miR-124, identified in this image in excitatory neurons of the mouse prefrontal cortex, causes behavioral and synaptic deficits. These are traced to overproliferation of excitatory AMPA receptors in the affected neurons. This discovery can now be taken back to patients, perhaps in the form of future therapies to "downregulate" these AMPA receptors in key brain areas and possibly impacting shared symptoms across schizophrenia and bipolar disorder.

A third example of reverse-translational research in the Sawa lab concerns the results of genome studies that have found genetic risk factors that are shared in bipolar disorder and schizophrenia. Standard treatment of these illnesses has tended to be based entirely on diagnosis, and treatments for schizophrenia are usually different from those for bipolar disorder (schizophrenia treatments focusing mainly on psychosis symptoms, and bipolar treatments focusing on mood symptoms). But it has long been known that these two illnesses, despite their differences, can share some important and often debilitating symptoms. Some patients with bipolar disorder experience psychosis, which is seen, albeit much more often, in schizophrenia. Both disorders also show neurocognitive impairments in areas including executive functioning and memory.

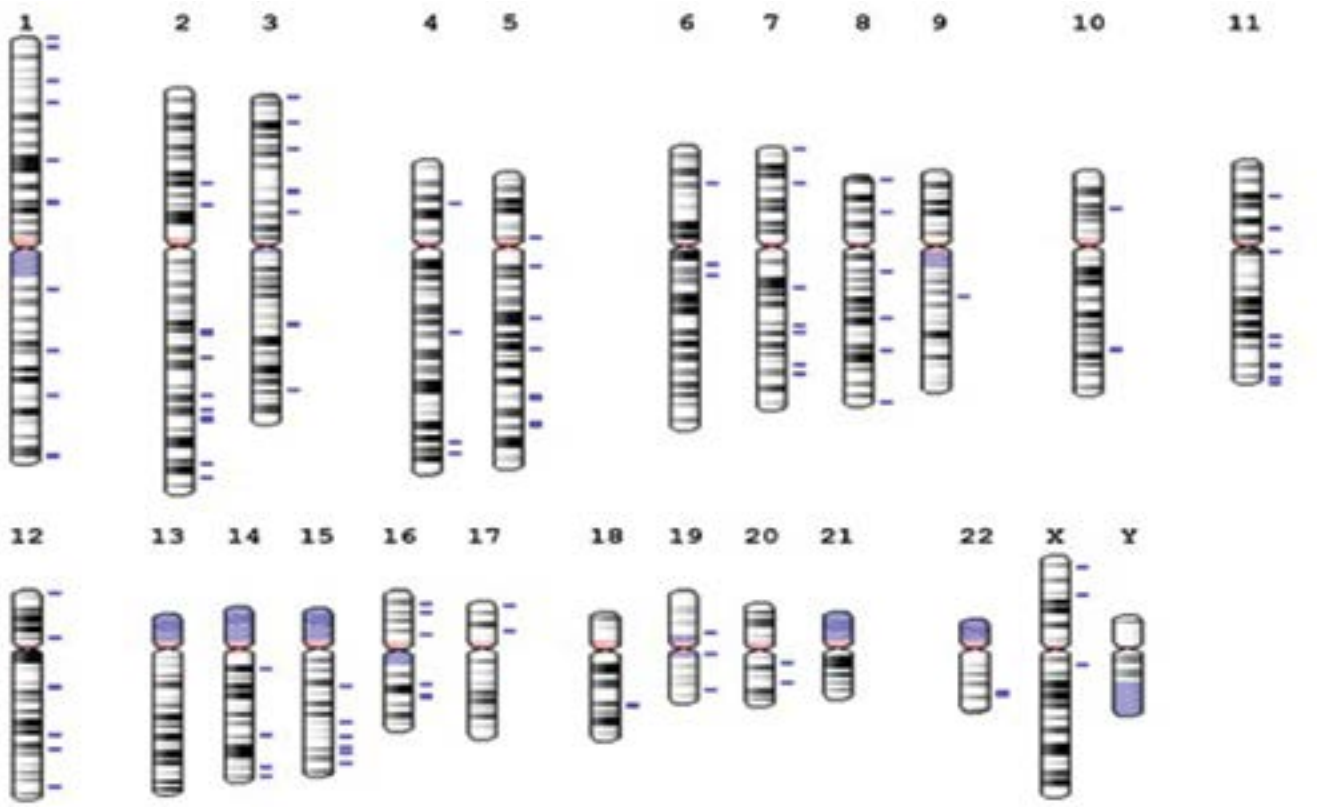
This sharing of certain symptoms has an intriguing echo in data from genome studies of each illness, which have indicated significant genetic overlaps. That is, in studies comparing genomes of large numbers of individuals, commonly occurring variations in DNA that are consistently seen in people with schizophrenia (compared with people who do not have the illness) are in many instances also seen in people with bipolar disorder, and vice-versa.

Do shared genetic risk factors have anything to do with biological changes that give rise to pathologies in both illnesses, and particularly those which may affect symptoms that are shared across the two conditions?

In 2023, Dr. Sawa and his team published a paper in *Neuron* presenting what they call "a novel research framework in which human and animal studies are combined to address a disease mechanism that bridges across pathogenesis [causation], pathophysiology [how disease causes functional changes in biology], and clinical manifestations."

The paper reporting the results of this effort is complex, but its main thrust concerns the impact of one of the common genetic variations linked specifically with both schizophrenia and bipolar disorder. The team showed that this shared DNA variation, in neuronal cells, causes an "upregulation," i.e., increased levels, of a small RNA molecule (a microRNA) called miR-124.

Dr. Sawa and colleagues discovered an upregulation of miR-124 in neuronal cells biopsied from living patients with schizophrenia and bipolar disorder in the clinical cohorts that Dr. Sawa has established. This upregulation of the microRNA was found to be associated with DNA variations shared across the two illnesses. The next step represents the team's "reverse-translational" move back into the laboratory, where they created a mouse model to study how the genome variation becomes manifest, mechanistically, in cells, and ultimately is able to have an impact on behavior.




Large genome studies involving hundreds of thousands of people have found genetic risk factors—"risk locations" in the genome—that are shared across multiple disorders. In this graphic, risk locations for schizophrenia across the 24 human chromosomes are indicated by tiny blue tick-marks along the right edge of each chromosome. Some of these same risk locations are seen in some people with bipolar disorder. Can this information be linked to symptoms shared across the two illnesses?

In the model mice created by Dr. Sawa's team, miR-124 was upregulated in neurons of the medial portion of the prefrontal cortex. The researchers observed that this, in turn, led to an increase in the number of excitatory cellular receptors (called AMPA receptors) in the affected neurons. This proliferation of excitatory receptors perturbed the transmission of signals at synapses, the tiny gaps across which neurons communicate. It was this synaptic dysregulation that the team, in a final step, was able to directly connect (in mouse models) with behavioral deficits seen in both schizophrenia and bipolar disorder—"shared deficits" affecting social behavior and hyperstimulation or hyperactivity. In other words, this research, which began with genome and symptom data from affected patients, led, via experiments in the lab, back to the symptoms that patients actually experience and live with.

The results, Dr. Sawa suggests, can now be integrated into large clinical studies focusing on "revisiting" the train of causation that the team established in their animal model, but this time in the context of actual patients. It might lead, for example, to new biomarker-based diagnostic methods—here, as in the research on PPD, perhaps for a subset of patients—in this case, with the specific vulnerability involving miR-124 and its pathway, who may be diagnosed either with schizophrenia or bipolar disorder. It is also possible that a future treatment involving selective downregulation of AMPA receptors in affected brain areas might be useful in either or both illnesses.

"In the bigger picture," Dr. Sawa and colleagues concluded in the 2023 *Neuron* paper, "our new intellectual framework that focuses on the neurobiological mechanism(s) underlying specific behavioral dimension(s)—rather than classical diagnostic categories (e.g., schizophrenia and bipolar disorder) may open new avenues for the discovery of additional key biological pathways" that bridge causation, functional changes in biology, and clinical symptoms in "a wide range of neuropsychiatric conditions, hopefully invigorating drug development pipelines."

Many people—not least patients and their loved ones—are impatient for new treatments for common and often devastating illnesses such as schizophrenia, bipolar disorder, and depression. The reverse-translation approach being pursued by Dr. Sawa and his team suggests one specific approach that talented researchers have employed to expand the area of what is known in order to provide the eagerly awaited and sorely needed next generation of therapies.

❖ **PETER TARR**

# BBRF Names Ten 2025 Distinguished Investigators Funded by WoodNext

In March, the Brain & Behavior Research Foundation announced the award of Distinguished Investigator grants totaling $1 million to 10 senior-level scientists conducting groundbreaking research in neurobiological and behavioral science. These $100,000, one-year grants support projects exploring critical areas of mental health, including opioid use disorder, depression in pregnant women, schizophrenia, bipolar disorder, and the effects of psychedelics on perception and consciousness. The awards are made possible by the WoodNext Foundation. This is year two of their overall grant commitment of $5 million over 5 years to support the BBRF Distinguished Investigator grants program.

"Mental illnesses affect millions of individuals and families, yet there is still so much to learn about the underlying biology and potential treatments," said Jeffrey Borenstein, M.D., BBRF's President and CEO. "By supporting bold, high-risk research, our Distinguished Investigator grants empower leading scientists to pursue innovative ideas that could pave the way for major breakthroughs in preventing, diagnosing, and treating psychiatric illnesses. We are deeply grateful to the WoodNext Foundation for their generous support, which makes it possible to fund these pioneering studies."

"At the WoodNext Foundation, we believe that bold, high-impact scientific research is essential to advancing our understanding of mental health and improving lives," said Nancy Chan, WoodNext's Executive Director. The WoodNext Foundation is a component fund administered by Greater Houston Community Foundation. "We are honored to support BBRF's Distinguished Investigator grants, which empower leading researchers to push the boundaries of knowledge and develop innovative approaches to mental illness."

Recipients of the Distinguished Investigator grants are professors at research institutions in the U.S. and internationally. They were selected by a committee of the BBRF Scientific Council, comprising 192 leading experts in brain and behavior research, who review grant applications and select the most promising projects.

**Here are the recipients of the 2025 BBRF Distinguished Investigator grants:**

**Eva S. Anton, Ph.D.**

*Professor, Cell Biology & Physiology*

***University of North Carolina at Chapel Hill***

Dr. Anton will investigate signaling molecules and processes (the "signalome") engaged when the primary cilium of neurons is activated, including how it might be harnessed in the service of neural circuit modulation and correction. The hope is to establish how deregulated primary cilia signaling interferes with neural circuit dynamics and contributes to circuit malfunction.

Basic Research
**Biology of the Brain: Neural circuit modulation**

***"I am honored and fortunate to have received this award. This support from BBRF will enable us to embark on a new research initiative. We are immensely grateful to BBRF for giving us the opportunity to explore the unconventional mechanisms of inter- and intra-neuronal communication that are at the crossroads of normal brain function and neuropsychiatric disorders."***

## Flavio Frohlich, Ph.D.

*Professor of Psychiatry, Cell Biology & Physiology, and Biomedical Engineering*

*Director, Carolina Centre for Neurostimulation*

***University of North Carolina at Chapel Hill***

Dr. Frohlich will develop and test a novel non-invasive neurostimulation approach (aperiodic tACS) designed to rapidly reduce depression symptoms in women who are pregnant. tACS, or transcranial alternating current stimulation, has been shown to be safe and effective in major depressive disorder in several pilot trials.

Next-Generation Therapies
**Depression**

***"I am honored and thrilled to receive this award. It helps us launch a new research program of non-invasive brain stimulation for psychiatric symptoms during pregnancy. The award has the potential to bend the history of non-invasive brain stimulation for pregnant people who struggle with depression. I am grateful to the Foundation and its visionary supporters for enabling us to tackle a big challenge in peripartum mental health."***

## Rita Goldstein, Ph.D.

*Professor in Neuroimaging of Addiction*

***Icahn School of Medicine at Mount Sinai***

Dr. Goldstein seeks to identify reliable behavioral markers of brain function that change with treatment and predict outcomes in individuals with opioid use disorder (OUD). The team will employ a naturalistic approach targeting spontaneous speech, which will serve as a behavioral marker of neural plasticity with treatment.

Diagnostic Tools/Early Intervention
**Addiction/Substance Use Disorders**

***"Receiving this grant is a great honor that I deeply cherish. Belonging to the BBRF community has been one of the most meaningful experiences in my career, reinforcing my dedication to the use of neuroscience in the treatment of people with drug addiction and other mental health disorders. I feel grateful for the BBRF's generous support of my journey."***

## Marek Kubicki, M.D., Ph.D.

*Professor of Psychiatry*

***Brigham and Women's Hospital, Inc.***

Dr. Kubicki focuses on matrix metalloproteinase-9 (MMP-9), a protein involved in conveying pro-inflammatory molecules from the periphery into the brain via the blood-brain barrier. MMP-9 blood levels are elevated in all stages of schizophrenia, The team will employ PET scanning to test a recently developed MMP-9 brain marker called [18F] MMPi in 12 individuals.

Diagnostic Tools/Early Intervention
**Biology of the Brain: Markers of brain inflammation**

***"It's an honor to be called 'Distinguished Investigator'! I have been conducting research in the schizophrenia field for over 25 years, and had received two BBRF Young Investigator awards early on. Both of those awards had major impact on the trajectory of my research career! This one is a highlight of my accomplishments, and I hope to put it into good use."***

## Christopher J. Pittenger, M.D., Ph.D.

*Mears & Jameson Professor and Deputy Chair for Translational Research, Dept. of Psychiatry*

***Yale University***

Dr. Pittenger investigates rare, potentially causal mutations in OCD. The team recently identified the first such mutation, in a gene called Scube1. Recapitulating this mutation in a mouse leads to repetitive behaviors and cognitive inflexibility. This project will further characterize the model, seeking insights into consequences of the mutation that can then be investigated in patients.

Basic Research
**Obsessive-Compulsive Disorder**

***"I am very excited to receive this award. BBRF has been critical to my career from the very beginning, supporting early-stage work that has allowed my research to grow in new directions. This grant will allow us to characterize a novel mouse from which we hope to gain insights that will shed new light on the molecular and circuit-level pathophysiology of OCD, paving the way for new, generalizable insights and in time, we hope, for new treatment strategies."***

## Sagiv Shifman, Ph.D.

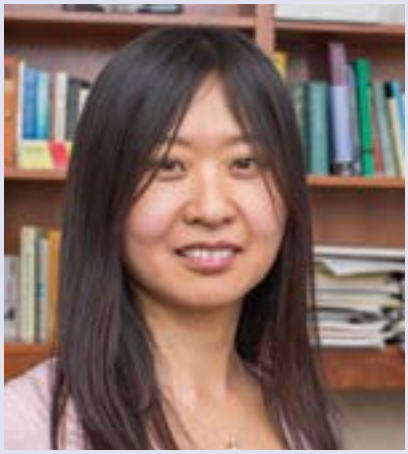
*Professor, Department of Genetics*

***The Hebrew University of Jerusalem, Israel***

Dr. Shifman hypothesizes that a brain "protection factor" provides resistance for neurodevelopmental disorders in females, and aims to identify its neurobiological origin. The team will use mouse models of ASD that show social behavior problems in males. They will also use a mouse model to assess how sex chromosomes and sex hormones affect gene activity in the brain and determine what factors contribute to the protective effect in female mice.

Basic Research
**Autism Spectrum Disorders**

***"I am deeply honored to receive this support, which will enable us to investigate the mechanisms underlying the increased risk of autism among boys. We are hopeful that our findings will contribute to a deeper understanding of autism risk factors and pave the way for the development of new treatment strategies."***



## Doris Tsao, Ph.D.

*Professor of Neuroscience, HHMI Investigator*

***University of California, Berkeley***

Dr. Tsao aims to uncover neural mechanisms behind the effects of psychedelics on perception and consciousness. She will study these effects using macaque monkeys. By comparing how the brain represents expectations in facial perception with and without the influence of psychedelics, she hopes to be able to observe how these substances alter perception at the neural level.

Basic Research
**Biology of the Brain: Psychedelics and perception**

***"This grant allows my lab to explore an entirely new frontier—how psychedelics affect cortical processing—a topic we know surprisingly little about despite the immense excitement surrounding their potential to treat psychiatric disorders such as depression and PTSD. It's incredibly exciting to build a bridge from fundamental neuroscience to research that could have direct translational relevance for mental health."***

## Jared W. Young, Ph.D.

*Professor, Department of Psychiatry*

***University of California, San Diego***

Dr. Young seeks to develop therapeutics to address cognitive deficits in bipolar disorder patients. The team will target presynaptic mechanisms related to very high dopamine levels (hyperdopamienrgia), specifically, the trace amine associated receptor-1 (TAAR1), which can catabolize dopamine at the presynaptic level. The receptor will be specifically targeted (with an agonist) in the mouse anterior cingulate cortex, on the hypothesis that it will remediate ACC hyperdopaminergia in the mice.

Basic Research,
Next-Generation Therapies
**Bipolar Disorder**

***"I am very excited that our group has received the opportunity to pursue this research, which builds on our long interest in attenuating risk-taking in people with bipolar disorder, deficits which have been associated with suicide attempts and drug-seeking behavior. This award continues my long-standing appreciation of BBRF from which I was fortunate to receive two Young Investigator awards that really launched my independent career. I thank BBRF and look forward to our continued affiliation."***

## Venetia Zachariou, Ph.D.

*Edward Avedisian Professor and Chair of Pharmacology, Physiology & Biophysics*

***Boston University***

Dr. Zachariou aims to understand the neurochemical and molecular mechanisms underlying the actions of opioids, in order to make interventions that promote analgesia while minimizing the risk of addiction. This project identify seeks to identify novel G protein signaling cascades that control gene expression maladaptation associated with undesired action of opioids and risk for the development of substance use disorders.

Basic Research
**Addiction/Substance Use Disorders**

***"This award will support research on understudied G protein signaling complexes that regulate transcriptional activity within brain regions involved in pain perception and analgesia. These signaling complexes also affect the activity of neuronal projections that mediate the rewarding effects of opioids. By targeting these multiprotein complexes, we aim to block the addiction-related effects of opioids while enhancing their analgesic properties."***

## Stanislav S. Zakharenko, M.D., Ph.D.

*Faculty Director, Division of Neural Circuits and Behavior, Developmental Neurobiology*

***St. Jude Children's Research Hospital***

Dr. Zakharenko will elucidate cellular manifestations of auditory hallucinations in mouse models of the two strongest genetic predictors of schizophrenia, 22q11.2 microdeletion syndrome (22q11DS) and 3q29 microdeletion syndrome (3q29DS). He proceeds from the team's identification of abnormal sound-associated neuronal ensembles that appear during periods of silence (SNEADS) in the auditory cortex, investigating the possibility that SNEADS might be a pathogenic event that is a cellular correlate of auditory hallucinations.

Basic Research
**Schizophrenia**

***"This award will enable my team to explore how neuronal activities are organized into pathogenic ensembles in the auditory cortex of animal models of 22q11.2 deletion syndrome, one of the strongest risk factors for schizophrenia. It will be instrumental in exploring how these abnormal neuronal activities may cause auditory hallucinations. This may provide us with a better understanding of this enigmatic symptom of schizophrenia."***

# ADHD: What You Need to Know

## A Q&A for parents, teachers, and families by Dr. Jeffrey Borenstein with Dr. Stephen Hinshaw

**Stephen P. Hinshaw, Ph.D.**, is Distinguished Professor of Psychiatry and Professor of Psychiatry and Behavioral Sciences, University of California, Berkeley. The 2019 winner of BBRF's Ruane Prize for Outstanding Achievement in Child & Adolescent Psychiatry Research, his research on ADHD focuses on assessment and treatment with special attention to the interplay of neurobiological vulnerability and environmental contexts (especially parenting practices and peer relationships), and the long-term impacts of deficits in executive function. Dr. Hinshaw is the author of hundreds of papers and books, including *The ADHD Explosion*, and is a pioneer in investigating ADHD in girls and women.

**Jeffrey Borenstein, M.D.,** is a psychiatrist, President & CEO of BBRF, and host of the PBS television series *Healthy Minds*.

**IN BRIEF**

A world expert in ADHD, Dr. Stephen Hinshaw advises parents and teachers that ADHD is not an attention deficit per se, but rather, more of a regulatory disorder, often reflected in an inability to shift gears between tasks and to stay focused when that is appropriate. Ultimately, ADHD is a family affair, he says, and a child-school-parent affair. "Everybody needs to work together."

**Dr. Hinshaw, what exactly is ADHD?**

The stereotype about ADHD is that it's all about fidgeting, squirming, and running around the classroom; not following multipart directions, not seeming to listen, making careless mistakes.

In fact, ADHD is extreme levels of two types of behaviors or symptoms. The first type has to do with inattention, distractibility, not following directions. These are the quieter symptoms. All of us have some of them, but if you are on the high end of the spectrum, we say that you're in the realm of the "inattentive" form of ADHD.

The other domain is about hyperactivity and impulsivity. "Hyperactive-impulsive" symptoms do include fidgeting, squirming, or running when you're not supposed to be running. Also, acting too far ahead of what the consequences of something would be.

Hyperactive-impulsive symptoms are somewhat more prominent in boys, and inattentive symptoms are somewhat more prominent in girls, but most kids who get referred to a doctor have a high degree of both the inattentive and the hyperactive-impulsive symptoms. Learning and behavior, including classroom deportment, are compromised.

**Acting out is very commonplace in young people. How can you distinguish ADHD from normal behavior?**

It's true that many people say, "Well, a lot of young kids are like that." But while a child typically gets older and develops better self-control, there are some kids who are really on the far end of the continuum.

Kids who get a diagnosis of ADHD are way too likely to experience accidental injuries. In fact, young kids with ADHD have a higher risk of death than young kids without ADHD under the age of 6. Failure in school is also more likely, not necessarily because of a learning disorder but because of the inability to pay attention and follow directions. They're way too likely to get picked on, bullied by, or rejected by their peers. That's because they may not read facial cues very well, and may fight back in ways that make them unpopular. And then, later in life—as my group has shown in several longitudinal studies from childhood through adulthood—those affected are too often at risk for substance use disorders and for aggression, particularly boys, and for depression, particularly girls.

There are other issues. As our "Berkeley Girls with ADHD Longitudinal Study" (BGALS) has shown, far too many girls with low self-esteem and depression get involved relatively early in adolescence in what we call self-harm: non-suicidal self-injury, cutting, burning, self-mutilating. And rates of attempted suicide by those in their late teens or early twenties are much higher than in other girls.

Now, many kids with ADHD—in the right conditions and the right settings, and when you find their strengths—can thrive later on. But it's a serious condition, and an equal-opportunity one. More boys than girls have ADHD, but girls have it too. It's across all racial and ethnic groups, and all socioeconomic levels.

**So, this is serious and needs to be attended to. In the classroom, what would teachers see? What should raise the alarm?**

Let's start with preschool. More often in boys than girls, they're going to see a child who is running around, can't sit at circle time, pokes at other kids, disrupts the story that's being read. Some girls with ADHD at that age are just as disruptive and just as hyperactive, but they are more likely to lapse in their attention and not follow what the story is.

In grade school, these kids are often bright. The bell curve of intelligence scores for kids with ADHD follows pretty much

the national norms. But it becomes an issue if the kid hasn't heard the teacher say, "Open your books to page 12, look at the second paragraph, and answer question two." They're thinking, "Wait a minute. Question two? What did she say before that?"

Just as much as these behavioral patterns, ADHD also involves problems with executive function: maintaining your attention for a long period of time, planning what you're going to do rather than just jumping into it willy-nilly. Also, it affects working memory: holding a string of information together, like the parts of a multipart direction. Early on, that could be going from math to reading, and in middle school, from algebra to history.

ADHD is not really an attention deficit, per se. Many people, especially people with ADHD, can get highly engaged in something they really love. So, if you think of hyperfocus as a symptom, ADHD is more of a regulatory disorder. It's the inability to do well at shifting gears between tasks, particularly those that are highly engaging vs. those that are rote. This problem with shifting "set" is a hallmark of ADHD. It takes a long time for kids with ADHD to learn self-regulation, partly because levels of dopamine functioning in their brains often don't do the same things they do in neurotypical brains.

**When it comes to treatment, what are some behavioral interventions?**

The treatments of choice are really engaged in more by parents and teachers than by the kids themselves. Kids with ADHD struggle to get intrinsically motivated because they're not hearing the direction and they're slower to remember the parts of the task they're supposed to do. Their bodies and brains are going to require smaller steps for success, and very specific rewards in the early part of their learning to motivate that success.

Reward charts can help, but the other kids in the class, or their siblings, don't need to have one. So, part of the treatment plan for ADHD is to do some psychoeducation about what ADHD really is. What people need to understand is that these kids are not willfully lazy or unmotivated: there are some biological differences that produce these behaviors.

What we need to do is be very positive. Build behavioral goals and academic goals into small, doable steps. Then, you can use things like a reward chart. If a kid isn't sitting at the dinner table the full time she's supposed to, and her average—you've used a clock—is three minutes, you build it to five minutes and then she gets her check on her chart. Or, if in reading circle, the boy with ADHD can't last 15 minutes but can last five, then you move to seven and then to nine.

The small steps build in success. They build a good self-esteem. And they do something that's really important for parents and teachers. All too commonly, adults working with kids with ADHD interact with them by saying things like, "Don't do that, you shouldn't be doing that." It's negative, and often emotionally loaded. What we try to do is change the ratio of positives to negatives. Where there's three or four negative comments for every positive, just flip it. For every negative comment, there should be three, four, or five positive comments.

So it helps if you have a reward program. It helps if you build skills into small steps. And it helps if you stop the bickering and arguing that only lead to more misbehavior.

**It seems that for professionals who work with ADHD kids, it's key to coach parents and teachers about what a diagnosis means and what can be done.**

Exactly. That's called PMT, Parent Management Training. Parents learn how to set up a reward chart. They tailor the rewards to the kids, improving success in small steps. Maybe they need a timeout program if the kid's misbehavior is severe, but they still want many more positive interactions and points than negative ones. If their home chart is in deficit, the parents are doing it wrong. "Billy's 1,000 points in the hole." No! They've got to have a positive total, so he's got something to continue to work toward.

With Parent Management Training, the parent says: "Let's have the meeting with the teacher, and let's have the therapist (with the parent or parents as well as the teacher) sit down and figure out what some school goals are." Very behavioral, small steps of improvement from where the child is right now. The teacher can either electronically, or on an index card, make a check: "Yes, Sarah today did this and that," or, "No, she didn't live up to that." That report is shared with the parents, and checks are added to the reward chart at home. This puts parents and teachers on a level playing field. They're working toward parallel goals and reinforcing one another to be positive.

**What about the use of medication to help treat ADHD in kids?**

Medications are used more often in the United States than other countries for ADHD, but the rest of the world is gradually catching up. Primary treatments for ADHD are called stimulants, or SDRIs: selective dopamine reuptake inhibitors. They keep dopamine in the synapse a little

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"Too often, adults working with kids with ADHD interact with them by saying things like, 'Don't do that, you shouldn't be doing that.' It's negative, and often emotionally loaded. What we try to do is change the ratio of positives to negatives. Where there's three or four negative comments for every positive, just flip it. For every negative comment, there should be three, four, or five positive comments."

bit longer to help regulate the five or so pathways in the brain that carry dopamine as a neurotransmitter. Most of those pathways have to do with executive functions, focus, sustained attention, and controlling motor behavior. There is the methylphenidate/Ritalin class and the amphetamine/Adderall class.

We can't predict ahead of time who's going to respond to which of those types of stimulant meds, or what dose. The stimulant meds are in and out of your bloodstream in a day and night cycle. So, with a good doctor and with a willing teacher, parents can fill out some ratings and change the dose once or twice a week, over a couple of weeks, and find the best dosage. It doesn't take month after month to assess, the way it does for many medications for other psychiatric conditions in kids.

There are also non-stimulant alternatives, which work on the neurotransmitter norepinephrine, sometimes called noradrenaline. They don't work quite as quickly as the SDRIs do, but over several weeks they can help reduce impulsivity and improve behavior. They probably, on average, don't have the same attentional boost that you get with the traditional SDRI medications.

A lot of families that I've worked with say, "Why would you medicate a child for behavior problems? Wouldn't you do therapy with them?" If parents are in doubt, depending on the severity of the child's behaviors, they can do a trial. Parents and teachers really need to collaborate on this trial, to avoid a situation where the teacher doesn't know when the dose is switched but still fills out the ratings. You can empirically determine, for example, that a low dose of a Ritalin-type compound didn't work but a medium dose of an Adderall-type compound did work.

About 15% of kids with ADHD don't respond well to any form of medication. It's important to know that, too.

**So, you're saying parents don't have to commit to a specific medication or dosage for their children, they can do a trial first. What about ADHD and genetics?**

Genes play a very strong role. But it's not one gene or 20 or 100—it's many hundreds, if not thousands operating together. Also, about 35% to 45% of the biological parents of kids with ADHD have a moderate-to-severe degree of ADHD themselves, whether they've been diagnosed or know it or not.

If you as a parent maybe aren't as on top of your checkbook as you

**"Calm, warm, reasonable, democratic parenting—but parenting with real demands and limits—is probably the optimal approach for families…When parents change their style to a more authoritative stance, and are warm and limit-setting, their kids improve."**

should be, and if you've got anger management issues, parenting a kid who provides challenges in attention and impulse control is going to be especially challenging. Research shows that—before starting Parent Management Training—if you help parents with their own ADHD symptoms through cognitive behavioral therapy or through medication, or you help parents with their own moderate to severe depression, their engagement in Parent Management Training goes up appreciably and they do it more reliably and consistently.

Ultimately, ADHD is a family affair, and it's a child-school-parent affair. Everybody needs to work together.

**What is the best approach for teachers to take in their discussions with parents?**

The best approach is not to be a psychologist, psychiatrist, or expert, and "know" automatically that the kid has ADHD. Rather, have a parent-teacher conference and discuss what you're seeing. This allows parents to non-defensively describe some of the issues previous teachers may have mentioned. And, where relevant, it might enable the parent to say, "I was like that as a kid, too." You're building familiarity with the topic. You're building a commitment to work together.

It's also important to talk about individual differences. Some kids are good artists, and some kids are really good at sports. Some kids can sit calmly, and other kids need to move around a bit more. Different kids have different learning styles and thrive in different kinds of environments.

Another teaching strategy is to have classrooms that are project-based, that allow some parts of the day where you can stand and work at a workstation—not sit with hands folded from 8:30 until 3:30. This approach may allow some energy to get out—and may even help kids without ADHD.

In a flexible classroom, there are real expectations. It's not the same as an open classroom where everyone's working at her or his own pace. There are standing periods and there are periods where kids can work in groups. So, structure and some flexibility seem to be, for many kids with ADHD, an ideal combination to get the most out of the native smarts they have.

This is similar to the way in which calm, warm, reasonable, democratic parenting—but parenting with real demands and limits—is probably the optimal approach for families. When parents set limits and stick to them using the positive, reward-based approach I mentioned earlier, that is called authoritative parenting. It's helpful for a lot of kids, but especially kids with ADHD.

As for resources for parents, they can consult their local mental health center, or maybe their pediatrician is in a group of developmental behavioral pediatricians with a lot of expertise in ADHD. It may also be possible

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as a family and a school to have accommodations made—under Section 504, for example. You're going to give your child a fighting chance of not feeling like a failure every year, and it's never too early. [Editor's Note: Section 504 of the Rehabilitation Act of 1973 prohibits discrimination on the basis of disability in programs or activities receiving federal financial assistance, ensuring equal access to services and opportunities for individuals with disabilities.]

**You also recommend looking for the child's strengths and interests.**

All parents have some expectations or ideals for their kids—what they will be when they grow up and what they're going to be good at. But then they find out that their child or teen has a diagnosis of ADHD. Maybe it comes out in preschool, especially for a boy. For a girl, it's going to take longer because she's more likely to have these exclusively inattentive symptoms that may not show up until late in grade school or middle school, or even high school. As genetically based as ADHD is, we know from very good data that when parents change their style to a more authoritative stance, and are warm and limit-setting, their kids improve. Biology is not destiny.

The same thing is true for classrooms and kids with ADHD. Especially in girls but also in boys, you need to radically accept that your kid may not be the kid you expected—or maybe you did because you know about your own ADHD, if you have it. At the same time, though, you can take the blame off yourself. Maybe it was just the genes you passed along. But you also have to radically commit to getting Parent Management Training, getting the teacher involved, and doing a medication trial.

So, it's cutting a little slack. This kid may not be exactly whom I expected, but you ask, "What are they really good at?" Maybe it's sample collecting, maybe it's animal husbandry, maybe it's a sport that's not a traditional team sport. If your kid likes something and gets good at it, A, that's a good reward for the reward program to build at home. And B, maybe that's going to foster a somewhat non-traditional career that they're going to thrive at years later. This "strengths" approach gets everybody focusing on the positive, not the negative.

**Say parents have spoken to their child's teacher, and then to their pediatrician. The pediatrician is going to send them to a specialist. What should they look for in that person? And what about the importance of a careful evaluation?**

ADHD takes some real time and effort to evaluate well, but not maybe in the way many people think. It's a low-tech diagnosis. Sure, there are brain scans now—MRIs, fMRIs, etc. That research is progressing. We see some differences in neurotransmission patterns in the brains of kids with ADHD on average compared to neurotypical kids on average. But

It's very important to be positive. If, in a reading exercise, the girl with ADHD can't last 15 minutes but can last five, then you move to seven and then to nine.

**"What you should look for in a treating professional is someone who doesn't just write a prescription and say, 'Go home and come back in three months,' but someone who also includes the behavioral component and other interventions. It's both medication and a behavioral approach, together."**

none of those is good enough yet to say, "You've got ADHD and I don't," or vice versa. What you're looking for is the kid's behavioral and emotional patterns in their everyday world, in that classroom. That's why teacher ratings and a teacher interview are essential. That's why parent ratings and an interview with them are essential.

Also, with parents, you want to get a good developmental history. What about early milestones? Maybe there is a speech and language delay. Does the child have a subtle seizure disorder? Because seizure disorders can look like ADHD. Has the child been traumatized? Again, we know from the Berkeley Girls with ADHD Longitudinal Study that one of the very difficult long-term outcomes for too many girls with ADHD is low self-esteem. Another outcome is depression in adolescents, and cutting and self-mutilation, around that time, and then actually attempting their own lives by late adolescence or the early twenties. That risk goes up by about 300% if a girl with ADHD has also experienced physical or sexual abuse and neglect early in life.

ADHD is a really biological thing. We call it a neurodevelopmental disorder. It starts early in life. But trauma on top of that is especially triggering of terribly low self-esteem and self-destructive behavior later in life. So, an evaluation even of younger kids is important. The average girl in our country who starts non-suicidal self-injury, self-harm, starts it now before the age of 11. So, we need pediatricians and specialists to screen for depression, and to screen for learning disorders, and to screen for early self-injury—in addition to getting this deep look at the ADHD symptoms.

"With Parent Management Training, the parent says: 'Let's have the meeting with the teacher, and let's have the therapist (with the parents and teacher) sit down and figure out what some school goals are.' Very behavioral, small steps of improvement from where the child is right now."

The final part of an evaluation is computerized tests of attention, objective tests. They can be helpful, but they're not definitive. One-on-one in front of a computer screen, many kids with ADHD can pull it together for a short while, but then you put them in a classroom or in their family and things fall apart pretty quickly.

So, what you should look for in a treating professional is someone who doesn't just write a prescription and say, "go home and come back in three months," but someone who also includes the behavioral component and other interventions.

**I think that's very important, Steve. And that's what we need to do much more in our country. The research is clear: kids with moderate to severe ADHD on average do best on the right dose of medication, along with Parent Management Training, teacher consultation, and helping these kids with their social skills. It's both medication and a behavioral approach together. Medications may re-sculpt the brain a bit to be more receptive to input, but they don't teach a child academic skills or social skills. As you say, they've got to learn those skills from the behavioral treatments.** ❖

# Recent Research Discoveries

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

## Vulnerability to Acute Stress-Related Suicide Risk is Linked in Study to Expression of an Immune-Related Brain Protein

There is new evidence in the continuing effort by researchers to probe how depression, stress, and inflammation affect the risk of suicide and suicidal behavior. Results of the new research, published in *JAMA Psychiatry*, "align with a growing body of literature supporting an association between suicide risk and various manifestations of cerebral neuroinflammation."

The researchers, co-led led by BBRF Scientific Council member **J. John Mann, M.D.**, and first author Sarah Herzog, Ph.D., both of Columbia University, note that decades of study have made clear that suicide risk is "multifactorial," reflecting complex interactions between predisposing vulnerabilities such as genetics or family history and more immediate stressors such as major depressive episodes, acute or chronic stress, or other environmental conditions.

Dr. Mann, a renowned expert in the study of suicide, is the 2022 BBRF Colvin Prize winner and a 2008 BBRF Distinguished Investigator. The team also included **Nadine Melhem, Ph.D.**, a 2013 and 2004 BBRF Young Investigator, and **M. Elizabeth Sublette, M.D., Ph.D.**, a 2007 BBRF Young Investigator.

There is already considerable evidence of a relation between inflammation and suicide risk. Elevated inflammation levels in both the brain and the body's periphery have been linked with risk. Postmortem examination has revealed structural alterations in brain cells called microglia in individuals who have died by suicide. Microglia are immune cells unique to the brain and central nervous system, and elevation in their numbers is usually taken to indicate immune system activation. Other postmortem studies have shown elevated expression of cytokines (specifically IL-4 and IL-13) in a part of the cortex in such individuals. Cytokines are chemical messengers whose numbers also increase when the immune system is active. Postmortem results have also shown that in other parts of the body—outside the central nervous system and brain—inflammatory markers including IL-6, TNA-alpha, and C-reactive protein are elevated in people who have died by suicide.

Despite this important evidence, it remains unclear precisely how inflammation, in the brain or in the body's periphery, might affect suicide risk or a propensity for suicidal behavior. It has been proposed that neuroinflammation "may reflect a stress-sensitized brain state that confers risk for suicide by heightening an individual's negative reactions to stress." This stress reaction might take the form, for instance, of suicidal ideation and/or negative mood.

It is understood that life stressors are the most common intermediate event appearing to precipitate suicidal behavior, the team notes. Their study sought to determine whether pro-inflammatory processes in the central nervous system (including the brain) are associated with the acute emergence of suicidal ideation and negative mood specifically when stressors are present.

Hoping to shed light on the question, the team recruited 53 individuals (70% female; average age 30) with a diagnosis of current major depressive disorder. Nearly half had a co-morbid personality disorder, and 37% had a past history of substance

use disorder. Importantly, 38 of the 53 had no past history of suicide attempt, while 15 did have such a history. Also important: of those who had a history, an average of 5 years had elapsed since the last suicide attempt.

Participants' diagnoses were confirmed at the start of the study and suicide attempt history was taken. Participants also completed self-report measures of current suicidal ideation and depression severity. These assessments took place within about 3 weeks of a PET scan made of each participant's brain.

Just before the scan, each was given an intravenous injection containing an imaging-sensitive radiotracer that enabled the team to detect a protein called TSPO over a 90-minute scan period. This protein is found throughout the body and performs various functions; in the brain, TSPO is found in the outer membrane of microglia cells, and evidence of its binding (which the PET scan detects) is regarded an excellent indicator of immune system activation. Participants also gave arterial blood samples to detect levels of TSPO binding in the body's periphery during the PET scan.

A subgroup of 21 study participants completed 7 days of ecological momentary assessment (EMA), delivered via a smartphone or other electronic device. Each was asked to report 6 times daily on levels of suicidal ideation, negative affect, and stressors.

Results in the subgroup that provided EMA assessments indicated that elevated TSPO binding in the brain was associated with greater suicidal ideation and negative affect during EMA sessions in which a stressor was reported (compared with sessions in which no stress was reported).

The team interpreted this as meaning that while TSPO might still be associated with both depression and negative affect, its association with suicidal ideation in the specific context of stress "is independent of mood symptoms." The same conclusion was supported by looking at data from participants in the current study who did and did not have suicidal ideation. They found "significantly higher TSPO binding" in those with depression who reported suicidal ideation compared with those who reported no suicidal ideation.

In sum, the study suggests to the team that elevated TSPO binding in the brain "is associated with the propensity to experience more severe depressive symptoms" when stress is present. Put another way: elevated TSPO binding in people with depression may be an indicator of vulnerability to acute stress-related increases in suicidal ideation, and thus, risk of suicide.

As for the biology that might explain their observations, the team noted that elevations in TSPO binding in the brain may reflect a range of pro-inflammatory alterations not only in microglia, but also astrocytes and other cell types expressing the TSPO protein. Overall, the team said the study results support the broad concept of an association between suicide risk and manifestations of neuroinflammation in the brain and central nervous system. ❖

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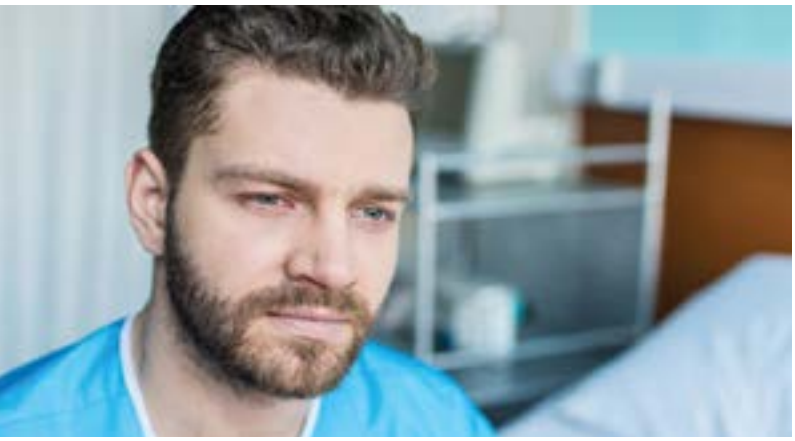
# Researchers Report Clozapine Reduced Risk of Second Psychosis Relapse by 34% in Study of 3,000 Young Schizophrenia Patients

What is the most effective way to prevent psychosis relapses in people who have been hospitalized for a first episode of schizophrenia? Results of a population-based study recently published in *Lancet Psychiatry* suggest a treatment strategy that is at variance from current standard practice. It involves quickly placing schizophrenia patients suffering a first psychosis relapse on the atypical antipsychotic medicine clozapine.

As noted by the research team that published the new evidence about preventing relapses, "a large proportion of patients have a good response" to antipsychotic medications following their first episode of schizophrenia-related psychosis. About 80% have reductions in total symptoms of at least 20%, and about half have a 50% or greater reduction. Still, about 70% of newly diagnosed schizophrenia patients will have at least one psychosis relapse within 5 to 7 years.

This is crucial, the researchers say, because the effectiveness of antipsychotic medicines declines after a first psychosis relapse, and notably so after a second relapse. Led by two researchers from Finland, Drs. Heidi Taipale and Jari Tilhonen, the team noted the paucity of robust data about preventing psychosis relapses in young schizophrenia patients, and sought to determine, using Finnish national medical databases, whether the initial choice of an antipsychotic medication after a first episode or of switching from one medicine to another following a first relapse would affect the risk of a given patient having a second relapse within two years. **Oliver Howes, M.D., Ph.D.**, a 2013 BBRF Independent Investigator, and **Christoph U. Correll, M.D.,** a 2007 BBRF Young Investigator, were members of the team and co-authors on the new paper.



"There is no established treatment protocol for patients who have relapsed despite ongoing antipsychotic treatment," the team writes. There are several possible options: continuing with the same medicine that was used before a first relapse; switching to another antipsychotic, whether oral or a longer-lasting injectable; or prescribing several antipsychotic medicines in concert. Importantly, they add, "clozapine is the most efficacious antipsychotic, but due to safety problems treatment guidelines state that at least two other antipsychotics should be tried before switching to clozapine." Even when clozapine is selected, there are obstacles: patients must regularly have their blood monitored, since a rare side effect of clozapine is agranulocytosis, a serious condition marked by dangerously low white cell counts. This often serves to steer patients away from clozapine.

To assess the full spectrum of second-relapse risk probabilities in young schizophrenia patients, the team mined Finland's comprehensive national health database. Included in their analysis were individuals 45 years old or younger who were hospitalized for first-episode schizophrenia and subsequently were hospitalized for a psychosis relapse between 1996 and 2014. The study included only patients who had not been taking antipsychotic medicines within the year prior to their initial hospitalization for schizophrenia and whose relapse occurred within 5 years of their first-episode discharge.

Thanks to the Finnish records, the team could analyze how each of the patients in the study cohort of 3,000 first-episode schizophrenia patients were treated, specifically in the 30 days prior to hospitalization for a first psychosis relapse and in the 30 days following discharge. The possible treatments included: clozapine; non-clozapine oral antipsychotic monotherapy or multiple antipsychotic agents; long-lasting antipsychotic injectable; or no use at all of an antipsychotic.

The question addressed was: in each of the various approaches, what was the risk of the patient having a second relapse within two years of discharge after the first relapse? The cohort was 30 years old, on average, and 64% were male. Soberingly—although no surprise to the researchers—71% of the cohort had a second relapse within 2 years of discharge for their first relapse. But there were large differences within the total cohort that corresponded with what kind of treatment they received just before and just after the first relapse.

One eye-opening finding was that after being hospitalized for a first episode of schizophrenia but before a first psychosis relapse, 45% of the cohort were not taking any antipsychotic medicine. About 32% were taking a single non-clozapine oral antipsychotic. About 10% were taking clozapine. About 4% were taking a long-lasting injectable antipsychotic (typically receiving injections once a month).

The fact that such a large portion of the cohort were not taking any antipsychotic medicine at the time of a first relapse suggested to the team that in the "real world," many patients choose to stop treatment—and, in terms of preventing relapses, this is harmful to patients.

Perhaps the most striking finding had to do with clozapine: 973 participants used non-clozapine oral antipsychotic monotherapy prior to their first psychosis relapse, 71% of whom (695) had a second relapse within 2 years. But those who switched to clozapine within 30 days of discharge following first relapse had a significantly lower risk of a second relapse: their relapse risk was reduced, said the team, by 34%.

"Compared with continuing the same treatment strategy used before the first relapse, switching to clozapine was always associated with the lowest risk of a second relapse," the team reported. Those switching from a non-clozapine antipsychotic monotherapy to clozapine had a 34% lower risk of second relapse. Those switching from no use of an antipsychotic at all prior to the first relapse to clozapine after it had a 48% reduction in second- relapse risk.

The team interpreted their results this way: "Our findings challenge the current treatment guidelines recommending clozapine as a 3rd-line treatment," a practice which results "in long delays to clozapine initiation" even when a switch to clozapine is made. Also they noted: "When a person with first-episode schizophrenia has a first psychosis relapse, continuation with the same non-clozapine antipsychotic or a switch to another non-clozapine oral antipsychotic is not beneficial in suicide prevention." They therefore concluded: "Clozapine initiation should be considered as a part of shared decision-making with the person with schizophrenia and care-givers." ❖

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# Evidence That Endocannabinoid Activity May Protect Brain Vasculature, Leading to Stress Resilience

While stress is a well-validated causal factor in anxiety disorders and depression, understanding the mechanisms that confer susceptibility to stress in some people and resilience in others is an active focus of research. Such factors may be key in developing the next generation of therapies to treat anxiety, depression, and other mood disorders.

In a new paper appearing in *Nature Neuroscience*, a team led by 2016 BBRF Young Investigator **Caroline Menard, Ph.D.**, of Université Laval, Quebec, Canada, report results of experiments that identify new mechanisms involving the endocannabinoid system in brain cells that appear to contribute to stress resilience.

In past research, Dr. Menard and colleagues have shown that levels of the key protein called Claudin-5 (Cldn5) were low in mice susceptible to becoming depressed after exposure to chronic social stress. Cldn5 is one of the proteins found in cells lining the inside of blood vessels in the brain which are responsible for integrity of the blood-brain barrier (BBB). This barrier normally protects the brain from toxins, viruses and pro-inflammatory molecules circulating in the bloodstream. In stress-vulnerable mice, the team documented blockage of the regulatory mechanism that causes the gene for Cldn5 to become active, a factor perhaps involved in loss of BBB integrity.

In their new paper, Dr. Menard and team focus on a particular involvement of the endocannabinoid system in stress resilience. Endocannabinoids are naturally occurring co-regulators of the stress response throughout the body (among various other functions). The two main receptors for endocannabinoids are called CB1 and CB2, with the former being more plentiful and important in the brain. Dysfunction of the endocannabinoid system has been linked to depressive behaviors in both animals and people.

The researchers knew from past studies that chronic severe social stress not only can cause mice to manifest depression-like behaviors; they also knew that such stress leads to disruptions in the BBB, specifically a leakage in its tight junctions (forged by proteins like Cldn5) that normally prevent pro-inflammatory molecules circulating in the blood from reaching brain tissue.

The brain has its own unique immune cells, called astrocytes. Astrocytes play a mediating role between the neurovascular system and brain cells. Threadlike projections from astrocytes connect them with neurons and other brain cells including glial "helper" cells. At the same time, they also send robust projections to blood vessels in the brain. These astrocytic projections culminate in oblong surfaces that attach to the exterior wall of brain blood vessels. They are called "astrocytic endfeet," and in the words of the researchers, "they are perfectly positioned" to modulate properties of the BBB during stress exposure.

The team used super-resolution microscopy and gene-expression technology to look closely at astrocytes in two brain areas in mice subjected to chronic social stress: the prefrontal cortex (PFC) and the nucleus accumbens (NAc). The PFC is involved in social behaviors, executive function, and decision-making. The NAc has key roles in reward and mood regulation.

They found that in a portion of the NAc called the nucleus accumbens shell, CB1 receptors for endocannabinoids were highly expressed in male animals that were resilient in the face of chronic social stress. This elevated expression of the CB1 receptor was particularly evident in the endfeet of astrocytes in the NAc shell—the portion of the astrocyte that comes in direct contact with brain vasculature.

Separate experiments showed that overexpression of the gene (called Cnr1) that encodes the CB1 receptor in astrocytes within the NAc shell dampened anxiety- and depression-like behaviors in male mice. Analysis indicated that this overexpression of the Cnr1 gene promoted the expression of genes in the astrocytes involved in vascular regulation.

The team reported two other related experiments of note. In one, both physical exercise and antidepressant treatment increased the expression of astrocytic Cnr1 around blood vessels in the NAc of male mice. In the other, performed in postmortem tissue from people who had been diagnosed with major depressive disorder, the team confirmed a loss of the human gene that encodes the CB1 receptor in astrocytes within the NAc.

These results are consistent with the finding in this study of increased expression of endocannabinoid receptors in astrocytes in the NAc of stress-resilient animals. More broadly, the study suggests one specific way in which the endocannabinoid system may be involved in moderating stress, not only in mice but possibly also in people. Increasing numbers of CB1 receptors in NAc astrocytes appears to promote resilience to stress by dampening alterations of the BBB normally induced by chronic stress exposure.

Endocannabinoid activity in astrocytes appears "to promote vascular remodeling and attenuates inflammation contributing to biological adaptation underlying stress resilience," the team wrote. Identifying such beneficial adaptations related to endocannabinoid-associated changes within the BBB "can represent a promising approach to development of innovative therapies," they said.

The team also included **Gustavo Turecki, M.D., Ph.D.**, a 2016 BBRF Distinguished Investigator, 2008 BBRF Independent Investigator, and 2000 BBRF Young Investigator. ❖


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# Therapy Update

Recent news on treatments for psychiatric conditions

## EXPERIMENTS POINT TO POSSIBLE NEXT-GEN DRUG THERAPIES FOR BIPOLAR DISORDER, INCLUDING FOR LITHIUM NON-RESPONDERS

Anouar Khayachi, Ph.D.

Long-term use of mood-stabilizing drugs has long been a cornerstone of clinical treatment for bipolar disorder (BD). Lithium, which has been in use longer than any other, can be highly effective. In particular it can prevent or reduce the intensity of episodes of mania. Symptoms of mania include hyperactivity, euphoria or highly elevated mood, rushed speech, poor judgment, reduced need for sleep, aggression, and anger.

But lithium doesn't help every patient; in fact, only about 1 patient in 3 responds to it. Among those who do, an important added benefit is that suicide and overall mortality rates are significantly reduced. But toxicity has been associated with lithium administration over the long-term, and its use has been replaced in some patients with drugs not originally approved to treat bipolar disorder, including anticonvulsants such as valproate and lamotrigine.

Given lithium's well-documented ability to be of great benefit to a sizeable subset of BD patients, researchers have taken great pains to discover why it works for them: how the drug affects the central nervous system, at the level of cells, networks, and circuits. The answer has remained elusive, but new research co-led by BBRF grantees and published in the journal *Lancet* not only sheds light on the drug's mechanism of action, but also points to novel therapeutic approaches for patients, including those who do not respond to lithium.

2022 BBRF Young Investigator **Anouar Khayachi, Ph.D.**, of McGill University, Canada, is first author of the new paper, and part of a Canadian team that includes co-leaders **Guy A. Rouleau, M.D., Ph.D.**, a 2010 BBRF Distinguished Investigator, Austen J. Milnerwood, Ph.D., and **Martin Alda, M.D., FRCPC**, 2020 BBRF Colvin Prize winner and a 2003 and 1999 BBRF Independent Investigator.

The team used a stem cell-based technology called iPSC (induced pluripotent stem cell). Cells—in this case, blood cells—are harmlessly sampled from individuals both with the illness under study as well as healthy controls. In the lab, these cells are gown in culture and brought back to a stem cell-like state, then re-programmed to re-develop as neurons. The team grew cultures of this kind from 5 BD patients who were responsive to lithium, 4 who were not responders, and 5 age and sex-matched healthy controls (all participants in the study were male).

The point of such research is to discover processes in cells from patients that differ from those in cells from controls. In this case, the BD patient-derived neurons enabled further comparison—between cells derived from patients who were lithium responders and those who weren't.

One important observation made in prior work by the team as well as other researchers was replicated in this work: all of the patient-derived neurons, regardless of the donors' lithium response status, displayed hyperexcitability. When these cells were treated with lithium over 7 days, the hyperactivity was reversed in cells derived from lithium responders, but, as expected, it was not reversed in cells from lithium non-responders.

The next step was to conduct many different kinds of tests on these three sets of neurons grown in culture dishes. Many things were revealed. First: In cells grown from lithium responders—in which hyperactivity was reversed with lithium treatment—the team noted changes in the ability of positively charged sodium ions to flow into and out of the cells, relative to cells grown from lithium non-responders.

Additional experiments that included analyses of protein activity and gene expression revealed that the potentially therapeutic effect of lithium on neurons derived from lithium responders was associated with a specific intracellular signaling pathway, called the Akt signaling pathway. Neurons (and other cells) regulate their survival and growth, in part, via this important pathway.

Other experiments demonstrated that a compound that activates the Akt pathway mimicked the effect that lithium has on neurons—it reverses their hyperexcitability—but only in neurons grown from patients who responded to lithium, not in those from non-responders. Among the implications is that it may make sense to develop and test Akt pathway activators to treat mania in bipolar patients. If the activity of such an agent was as therapeutically beneficial as that of lithium, and the agent was found to be less toxic or have fewer long-term side effects, it might be considered as a replacement for lithium.

Another key finding from the team's experiments also has therapeutic implications. In all BD patient-derived neurons grown in culture—neurons from both lithium responders and non-responders—activation of a protein complex called AMPK (AMP-activated protein kinase) reduced heightened neural network activity that seems to be characteristic in BD. AMPK is an energy sensor inside of cells, a major cellular regulator of lipid and glucose metabolism. Targeting AMPK in neurons might be a strategy to address neuropathology in lithium non-responders and responders alike.

One approved AMPK activator, metformin, is taken by millions of people. People with BD have a 2-fold increased risk of type II diabetes, and insulin resistance is present, the team notes, in about 50% of patients, "which might correlate with disease severity/progression." There has been some suggestion that lithium exerts therapeutic effects in BD via its impact on insulin signaling. Akt and AMPK are both also involved in insulin signaling and the development of insulin resistance. One study has found that metformin improved clinical outcomes in BD patients, not only lowering insulin resistance but improving mood symptoms as well. This preliminary finding "and the results of our work here support use of AMPK activation for BD," the team said, although, of course, this will remain a hypothesis until considerable additional research is performed. ❖

## CLINICAL TRIAL ASSESSED ACUPUNCTURE FOR SEVERE COMBAT-RELATED PTSD

Tanja Jovanovic, Ph.D.

Seth D. Norrholm, Ph.D.

For several thousand years, acupuncture has been used in China to address a wide variety of medical complaints and conditions, as well as mental and spiritual ones. Involving the insertion of small, thin needles—typically, between a half-dozen and 20—at various positions or "points" on the surface of the body over the course of up to an hour per session, acupuncture has been explained by traditional practitioners as a way of accessing and manipulating a "life-force energy" called *qi* that they believe to be flowing through the body.

Over the last half-century, practitioners of Western medical science have attempted to analyze acupuncture's effects on the body, its impact on the brain, as well as its efficacy in relieving pain, stress, depression, and other conditions. Findings have been highly varied, for a range of reasons. Among these: there are many ways of administering acupuncture, making it difficult to compare results across different applications.

There is another important difficulty for Western science in trying to assess acupuncture (which also affects research on psychedelics). It's very difficult to devise a "placebo" version of the treatments that is not readily distinguished from the real thing. Also, in many clinical tests, high rates of withdrawal by participants have limited the statistical power of collected data.

A team of researchers led by Michael Hollifield, M.D., of the VA Medical Center in Long Beach, California has been working on these issues for some years. In a paper recently published in *JAMA Psychiatry,* he and colleagues compared a standardized protocol for administering acupuncture with a "sham" version of acupuncture that they believe satisfies the requirements of an effective placebo, in the treatment of group of combat veterans diagnosed with PTSD. Members of the research team included **Tanja Jovanovic, Ph.D.**, a 2015 BBRF Independent Investigator and 2010 Young Investigator; and **Seth D. Norrholm, Ph.D.**, a 2008 BBRF Young Investigator.

Over a period of 4 years the team recruited 93 individuals. Of these, 85 were male; a majority were in their mid- or late-30s. A majority had had at least some college education; more than half were not currently employed; about half identified as Hispanic. Over 60% had either "moderate" or "moderate to heavy" combat experience. The PTSD-triggering event for each participant occurred during the time of their combat deployment. Three-fourths of the triggering events were combat-related (others included other violence or loss, sexual assault, or accident).

Each participant had received a PTSD diagnosis consistent with DSM-5 criteria. Each also had PTSD severity measured prior to the trial, at its midpoint, and after its conclusion. The gold-standard assessment tool called CAPS-5 was used; the group averaged about 36 on entry to the trial—considered "severe."

Participants had 15 weeks to receive 24 sessions, each involving 30 minutes of either active acupuncture or sham. Those in the active group had needles placed (sequentially) at a series of points on the front and back of the body that were standardized by Dr. Hollifield and colleagues in earlier research—the insertion points corresponding to places deemed important in traditional Chinese medicine. Those receiving the sham treatments had sessions that were the same in time, frequency, and duration as the active treatment group. The sham procedure was called by the team "minimal needling," and did involve the insertion of needles into the body. Thus, like those receiving active treatment, those receiving "sham" therapy, too, experienced a distinct sensation produced by insertion of the needles.

Assessments were made in the participants' PTSD scores before, at the midpoint and after the trial. Active acupuncture resulted in a larger reduction in PTSD symptom severity than sham, the team reported. The CAPS-5 score in the acupuncture group declined from over 36, on average, to 18.6 ("threshold to moderate" symptoms); in the sham group, it declined from 36 to 26.7 (middle of the moderate range). The benefit received by those in the sham group was attributed to the classic placebo effect, which is thought to be due to the regular attention participants receive as well as the excellence of the facility where the sessions were given (the Long Beach VA Hospital, in this case).

The advantage of having active acupuncture was described by the team as "statistically significant and clinically meaningful." Advantages in symptom reduction were seen in the active treatment group following the midpoint of the treatment course, but not before.

Another measurement made during the trial suggested the advantage and possible viability of acupuncture for PTSD. Each participant was tested before, during and after the trial for their fear-potentiated startle response—their involuntary reaction to a loud sound paired with an unpleasant stimulus. A key component of this test involves the ability to control the fear response after the aversive stimulus ceases, a process called "extinction," which has been shown to be altered in PTSD. Results of this data indicated to the team that in those who received active acupuncture there was an enhanced extinction of learned fear—thought to be an important component in successful treatment of PTSD.

Various drug therapies for PTSD as well as talk therapies including cognitive behavior therapy are available for those suffering from PTSD. These do help a portion of patients, but are not effective for many others. Results of this trial, in the team's view, suggest acupuncture "should be considered a rational choice" for treating PTSD "at least in combat veterans," in view of the "moderate to large clinical and biological effects" it showed in the trial (i.e., respectively, reduction in symptom severity scores and enhanced extinction of learned fear).

Future trials are needed, among other things, to directly compare active acupuncture treatments with CBT and drug therapy approaches for PTSD, the team said. ❖

William P. Horan, Ph.D.

## NEW SCHIZOPHRENIA DRUG COBENFY ALSO APPEARS TO REDUCE COGNITIVE SYMPTOMS IN PATIENTS WHO EXPERIENCE THEM

Researchers have published evidence indicating that Cobenfy, a new drug for schizophrenia approved by the FDA in September 2024, may help reduce cognitive impairments in some patients, in addition to its previously documented effect of reducing both positive and negative symptoms of the illness.

Cobenfy, developed under the name KarXT, combines two compounds called xanomeline and trospium chloride. It is the first-ever drug approved for schizophrenia that does not target the D2 dopamine receptor in brain cells. Xanomeline targets two specific receptors in brain cells, called M1 and M4, that are part of the muscarinic acetylcholine system. Trospium chloride prevents xanomeline from affecting receptors in the body's peripheral nervous system, i.e., outside the central nervous system, in order to minimize side effects that could arise if peripheral receptors were activated.

The drug was approved for the treatment of schizophrenia in adults after two pivotal phase 3 clinical trials reported in 2024. Both trials were 5 weeks in duration, and tested the new drug in a combined sample of over 500 participants with acute schizophrenia (the subjects had been hospitalized). Those who received the drug had significant reductions in both positive and negative symptoms, compared with those receiving placebo. Neither first- nor second-generation antipsychotics, while often very effective in reducing positive symptoms such as hallucinations and delusions, have appreciable therapeutic impact on negative symptoms, which include flat affect, reduced motivation, and social withdrawal.

A team of investigators led by **William P. Horan, Ph.D.**, wanted to follow up on preliminary evidence from a phase 2 trial of the new drug suggesting that it might also improve cognitive performance in at least some patients. Dr. Horan is a 2016 BBRF Maltz Prize winner and 2008 and 2004 BBRF Young Investigator. The team also included **Steven M. Paul, M.D.**, an emeritus member of the BBRF Scientific Council, who played an important role in the drug's development; **Richard S.E. Keefe, Ph.D.**, 2003 BBRF Independent Investigator and 1995 and 1991 Young Investigator; and **Philip D. Harvey, Ph.D.**, BBRF Scientific Council member and 2023 BBRF Lieber Prize winner.

As the team noted in their paper appearing in the *American Journal of Psychiatry*, considerable pharmacologic and genetic evidence from non-human studies indicates that the M1 and M4 muscarinic receptors "are key modulators of neural networks underlying cognitive function." These receptors are concentrated in brain regions crucial for cognition, including the hippocampus and prefrontal cortex. Xanomeline, which activates these two receptors, has shown promising effects on cognitive functioning in animal models. It has also been explored as a potential therapeutic in Alzheimer's disease, based on findings that it may improve memory impairments. However, these earlier studies did not involve the recently approved version of the new drug which combines xanomeline with trospium chloride.

The phase 3 clinical trials for Cobenfy included baseline cognitive assessments of participants before the trial began, with most also undergoing additional assessments after 3 and 5 weeks, the latter marking the conclusion of each trial. This cognitive data was not a factor in the drug's approval, but is of great interest since no existing "monotherapy" for schizophrenia, i.e., no single-drug treatment such as antipsychotics, effectively addresses the cognitive impairments associated with the illness. These include deficits (relative to unaffected individuals) in executive function, visual and spatial memory, the ability to pay attention in a sustained manner, and verbal recall and recognition. During the phase 3 trials, these cognitive domains were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB), a brief assessment delivered via a tablet device.

The new study of the phase 3 results was sponsored by Karuna Therapeutics, the company that developed Cobenfy, which has been acquired by Bristol Myers Squibb.

The new study retrospectively analyzed the phase 3 trial results, building on observations from the earlier phase 2 trial. It found that participants who took Cobenfy (rather than placebo) performed better on the CANTAB battery—but this benefit applied only to those who had moderate or more severe cognitive impairment prior to the beginning of the trial.

In the overall group that combined the participants in the two phase 3 trials who received Cobenfy for 5 weeks, the drug was not associated with cognitive improvement in any of the domains tested. But a subset of the whole had significant preexisting ("baseline") cognitive issues (about 38% of the total group of 357); of these 71 received Cobenfy and 66 received placebo. Those who received Cobenfy had improvements in their composite CANTAB score, with the largest improvements seen in verbal memory, involving both recall and recognition. The size of the effect is described by the team as "moderate."

Such benefits are deemed significant by the researchers, since, as Dr. Horan points out, it was "the first time a monotherapy for the treatment of schizophrenia has shown a replicable cognitive benefit."

The team also found that cognitive effects of Cobenfy had no correlation with the drug's therapeutic impact on schizophrenia's positive and negative symptoms. Participants receiving the drug had improvements in those symptoms compared with those receiving placebo, whether or not they also had cognitive improvement.

As a next step, the team suggested the current results warrant "a well-controlled trial in clinically stable patients," i.e., unlike those in the phase 3 trials, who were experiencing acute episodes. The new trial might specifically seek to recruit patients known to have cognitive impairments, they suggested. It has been estimated that a majority of schizophrenia patients have such impairments, although the impacts of these impairments on function vary widely, from case to case. ❖

# GLOSSARY

**REVERSE TRANSLATION** (p. 5) A research approach that seeks to discover how clinical observations (for example, of patients with psychiatric disorders) can be understood in a biological context. This portion of the inquiry is conducted in the lab, often in animal experiments. The aim is to translate newly obtained insights back to the clinic—in the form of biomarkers to aid diagnosis, or new targets for better treatments.

**MICROGLIA** (p. 6) Immune cells unique to the brain whose main function is to protect the brain. Research suggests they may be perturbed under conditions of immune challenge spurred by environmental stress. Dr. Akira Sawa has studied this in the context of stress experienced by females during pregnancy (see "MIA," below) and the impact this has upon microglial reactivity in the fetus and postnatal brain.

**MATERNAL IMMUNE ACTIVATION /"MIA"** (p. 6) The immune system can become active under many conditions of potential threat, including when an individual is exposed to acute or chronic stress. This can have both protective and harmful impacts, depending on the context and the intensity of the response, but potentially risks inflammation. Maternal immune activation during pregnancy can have impacts upon the immune response in the developing fetal brain, which in turn can cause a blunting of the postnatal immune response. This may explain one path of dysfunction in individuals who have disorders with neurodevelopmental roots, including schizophrenia.

**HPA AXIS** (p. 8) A communication system involving the hypothalamus, pituitary, and adrenal glands, which form the body's main stress response network. This network uses hormones to link perceptions of threat or danger with the body's physiological reaction to such threats—the stress response.

**GLUCOCORTICOIDS** (p. 8) Hormones released by the adrenal gland that are found in almost every cell. When they bind at glucocorticoid receptors, they generate a response that is generally anti-inflammatory. This response can be dysregulated by many factors, including significant exposure to environmental stressors. This dysregulation can have impacts years or even decades following the precipitating stress—including heightened risk for postpartum depression.

**mircoRNAs** (p. 10) Small RNA molecules that play a plethora of regulatory roles in cells.

**'RISK GENES'** (p. 10) Locations ("loci") along the 3 billion-letter human genome where specific variations in DNA sequence occur much more often in people diagnosed with particular human illnesses, e.g., bipolar disorder or schizophrenia. Those two conditions, despite their dissimilarities, share some symptoms and also have a number of shared risk genes. Research has explored whether the shared risk locations help explain shared symptoms.

**PARENT MANAGEMENT TRAINING – PMT** (p. 19) A therapeutic strategy stressing positive reinforcement that is used in various childhood disorders, including ADHD. It focuses on changing parent-child interactions to foster positive behaviors and reduce challenging ones, e.g., by setting up a "reward chart" that encourages incremental improvements toward desired objectives.

**Image credits:** p. 6: *J. of Neuroinflammation* (adapted); p. 9: Sawa Lab/*Nature Mental Health*; p. 10: Sawa Lab/*Neuron*; p. 11: *Translational Psychiatry.*

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