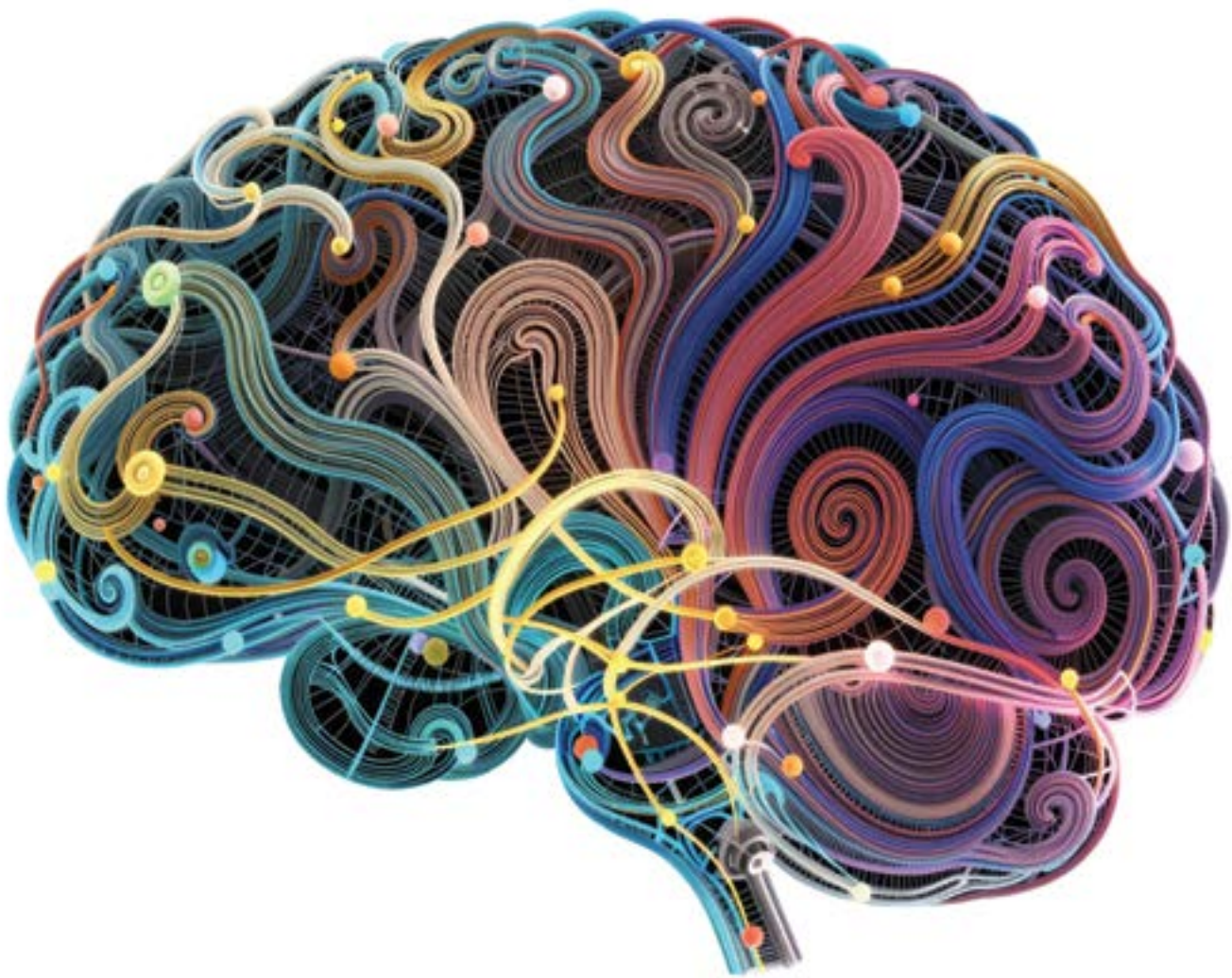
Restoring Dysfunctional Brain Circuits in Depression

BBRF Distinguished Investigators for 2026

Brain & Behavior MAGAZINE

FALL 2026



Putting Digital Technology to Work in Improving Mental Health

PRESIDENT'S LETTER

Welcome to our Fall 2026 issue of *Brain & Behavior Magazine*. Every advance in neuroscience research begins with a question—and the opportunity to pursue it.

In this issue we are proud to present the 2026 "class" of **BBRF DISTINGUISHED INVESTIGATORS**. These well-established scientists are each provided with $100,000 to pursue high-risk, high-reward research projects. These important grants are made possible through the generosity of the WoodNext Foundation, which has committed $5 million over 5 years to support the BBRF Distinguished Investigator grant program.

Our **PATHWAYS TO THE FUTURE** story provides several interesting examples of how Foundation grantees are putting a variety of digital technologies to use with the aim of improving the diagnosis and treatment of psychiatric disorders. Some of these technologies are built into the cellphones that nearly all of us carry; others are embedded in wearable devices like Fitbit ordinarily used to monitor exercise or vital health signs; and still others are incorporated in cellphone apps. In the psychiatric context, information derived from digital datastreams, sometimes in conjunction with textual replies that users are prompted to supply via apps like ChatGPT, is helping caregivers distinguish one diagnosis from another, or even make adjustments in real time to therapeutic regimens to reflect changes in a patient's condition.

In **A RESEARCHER'S PERSPECTIVE**, we capture the substance of a fascinating BBRF webinar presented earlier this year by Dr. Conor Liston, a past BBRF grantee and member of the Foundation's Scientific Council. In detailing findings made over recent years in his lab, Dr. Liston addresses how neural connections in the cortex are increased following ketamine treatment and how these new connections correspond with reduced depression symptoms. He considers whether this relationship applies in other depression treatments, and how specific depression symptoms such as anhedonia may be modified by treatment. Finally, he suggests how fMRI-based subtyping of depression patients may help predict their individual responses to TMS and other depression therapies.

We are also proud to present the winners of BBRF's prestigious annual **KLERMAN AND FREEDMAN PRIZES.** The six awardees and honorable mentions for 2026, all of whom have previously received BBRF Young Investigator grants, are recognized, respectively, for Exceptional Clinical and Basic Research.

As we do in each issue of *Brain & Behavior*, we also report news of treatment advances 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. Your support empowers researchers to explore promising ideas, deepen our understanding of the brain, and accelerate the search for better treatments, cures, and methods of prevention for neurological disorders.

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.

CONTENTS

PUBLICATION CREDITS

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Putting Digital Technology to Work In Improving Diagnosis and Treatment Of Brain & Behavior Disorders

IN BRIEF

A variety of mobile technologies and apps are making possible enhanced diagnosis and treatment of several brain and behavior disorders. Sensors built into smartphones, web-based tools powering special-purpose apps, and wearable sensors like Fitbit, respectively, are enabling doctors to fine-tune treatments for depression and anxiety, distinguish bipolar disorder (BD) from other diagnoses, and monitor and predict mood shifts in BD patients.

PAIRING SMARTPHONE SENSORS & ChatGPT TO TRACK ANHEDONIA IN DEPRESSED ADOLESCENTS

The ubiquity of smartphones and the rapid advance and widespread public adoption of AI tools like ChatGPT has raised the question of how such technologies can be harnessed to improve psychiatric assessment and treatment.

A recent pilot study directed by **Christian A. Webb, Ph.D.** a 2018 and 2015 BBRF Young Investigator at McLean Hospital and Harvard Medical School, tested one way in which mobile phones and the large language model (LLM)-based ChatGPT tool can together aid in the assessment of behavioral changes that are important for therapeutic improvement in a behavioral therapy for adolescents with depression.

Innovations of this kind could open doors to therapy adjustments made in real time based on indicators gleaned directly from patients. Also involved in the research were **Diego A. Pizzagalli, Ph.D.**, BBRF Scientific Council, 2017 BBRF Distinguished Investigator, 2008 Independent Investigator; and **Erika E. Forbes, Ph.D.**, 2014 BBRF Independent Investigator, 2006 Young Investigator.

Smartphones can passively collect rich behavioral data—in research like this, with users' consent—by tracking patterns of movement and activity. LLMs like ChatGPT can analyze text and language with impressive accuracy. Still, it has remained unclear whether these technologies can provide insight into the emotional or motivational aspects of an individual user's behavior.

This question helped to drive the team's study, which examined the two technologies in the context of a talk therapy called behavioral activation (BA), which aims to reduce the classic depression symptom of anhedonia (the loss of interest in pursuing rewards or pleasure) by targeting patterns of avoidance and withdrawal and increasing patients' engagement with rewarding activities.

A core assumption of BA is that increased activity in daily life leads to symptom change. "Tools that assess activation between [therapy] sessions could help therapists monitor treatment progress and make timely adjustments, an objective consistent with calls for data-informed psychotherapy," noted Dr. Webb and his team.

Their pilot study made use of smartphone-based passive sensing of patients' mobility patterns and LLM-derived ratings of daily text entries they provided during the 3-month therapy period. These data were examined in relation to daily assessments of positive and negative emotions, as well as weekly assessments of anhedonia, depressive symptoms, and a traditional self-report of activation.

The team recruited 38 adolescents, ages 13–18, to receive BA treatment targeting their anhedonia. Each was offered 12 weekly hour-long individual BA therapy sessions. Before each session, participants rated their anhedonia, depression, and "activation" (in essence, their engagement in daily activities and avoidance patterns), using self-report measures. A subset of 13 participants also contributed passive smartphone data—collected continuously via built-in cellphone acclerometers and GPS sensors.

Every other week during treatment all participants completed a "burst" of real-time assessments ("ecological momentary assessments") over 5 consecutive days via 2–3 surveys delivered each day via a smartphone app. Each time they were prompted by the app, participants were asked to rate their positive and negative affect (6 items, to be rated on a 5-point scale, generating data about being "happy," "interested," and "excited"; and "sad," "nervous," and "angry"). Next, they were asked to provide responses via unrestricted texting, "about what they were doing the night before, with whom they were interacting, and the most enjoyable and stressful events since the previous prompt."

The text responses were analyzed using OpenAI's GPT-4o model, as well as by a human "rater" for one-fourth of responses, to evaluate consistency between human and AI ratings. The team found "substantial agreement" between the two. As for the "silent" real-time monitoring made possible by the smartphone, this data was used to measure activity levels using the intensity of physical activity during the day; the percentage of time a participant spent at home; the distance and "mobility area" traveled each day relative to the home; and places visited each day.

The study produced interesting results. The most important, perhaps, was that "activation" among the depressed and anhedonic adolescents—as deduced from passive sensors in their smartphones—correlated positively with "activation ratings" generated by GPT analysis of their texts and patients' activation self-report score over the course of therapy.

On the GPS side, greater activation corresponded to more places visited and more time spent away from home, though not distance traveled. In addition, increases in GPT-rated activation were associated with higher daily positive and lower daily negative affect. The team also found that smartphone passive sensing features could be used to forecast weekly improvements in anhedonia and depressive symptoms.

The results led the researchers to suggest that LLMs such as GPT can extract psychologically meaningful information from unstructured text. "Importantly, our study shows that LLM-based assessments can also provide clinically relevant insights based on language generated outside the therapy room, offering scalable and unobtrusive ways to monitor therapeutic processes in patients' daily lives."

"Daily text assessments could help clinicians monitor" the response to behavioral activation therapy "in real time, while mobility patterns could indicate whether treatment is gradually translating into symptom improvement."

Christian A. Webb, Ph.D.

In another potential application of mobile technology to treatment of psychiatric disorders, **Dr. Webb** and colleagues, in a separate study, tested whether a freely available smartphone app featuring "mindfulness" exercises could be useful in helping adolescents ruminate less. Rumination refers to repetitive and negative self-focused thinking, often concerning stressful or negative past events. It is often seen in adolescents who are anxious or depressed, and studies have shown that it is a style of thinking that can predict the onset of both disorders.

The app used in the study, called CARE, was downloaded on each of the participants' phones and they were taught how to use it. Based on their inputs of sleep and wake times, users were prompted via random notifications within that time window to engage the app. Each time they used the app, they took a survey to assess whether they were ruminating and to what degree, and to indicate their current mood.

90% (72 of 80) of the adolescents completed a 3-week trial with the CARE app, with the typical user completing a total of 29 mindfulness training sessions, an average of 1.5 sessions per day. Reductions in rumination were assessed over two time intervals—"immediate" (i.e., pre- to post-mindfulness exercise) and "cumulative" (i.e., overall change in rumination over the course of the 3-week trial). Use of the app led to better immediate success among girls and older adolescents.

Those with higher levels of rumination at the beginning of the study, and those who suppressed their emotions less, had better cumulative outcomes. Levels of anxiety and depression symptoms prior to the trial did not predict who would most likely be helped.

AN APP TO DETECT LIKELIHOOD OF AUTISM AT 'WELL-CHILD' PEDIATRIC VISIT

Researchers have developed an app delivered on digital tablet devices that significantly improves upon currently existing tools to screen toddlers for a possible diagnosis of autism spectrum disorder (ASD). Early detection of ASD is widely regarded as critical, making it more likely a child will have prompt access to therapeutic interventions that can improve outcomes.

The app, called SenseToKnow, was deployed in a multi-clinic setting. In an initial test reported in *Nature Medicine*, it was administered in 475 cases during a routine "well-child visit," typically made when a child is 18–24 months of age.

Often, pediatricians give parents a questionnaire at the well-child visit called the Modified Checklist for Autism in Toddlers (M-CHAT). This tool has been shown to have higher accuracy in research settings than in the real world, especially in cases involving girls and children of color. Another important screening tool uses eye-tracking technology to measure children's attentional preferences for social vs. non-social stimuli. Autism is characterized by reduced spontaneous visual attention to social stimuli, and while machine-learning analysis of eye-tracking data has yielded encouraging results for its ability to distinguish autistic vs. neurotypical children, it does so on the basis of only one of autism's various behavioral signs, which also include facial expressions, head movements, response to name, and motor behaviors (including restricted or repetitive behaviors).

The SenseToKnow app involves the display on the tablet of brief movies; the child's behavioral responses are recorded via the tablet's frontal camera and are designed to elicit a wide range of autism-related behaviors including those just mentioned as well as social attention and eye-blink rate. It was developed by a team led by psychologist Geraldine Dawson, Ph.D., and electrical and computer engineer Guillermo Sapiro, Ph.D., of Duke University. The team that tested the app and analyzed the results included 2015 BBRF Young Investigator **Kimberly L. H. Carpenter, Ph.D.**, and 2001 BBRF Young Investigator **Scott N. Compton, Ph.D.**, both also at Duke.

The data collected by the app are quantified via computer vision analysis (CVA). Machine learning is used to integrate multiple digital data streams into a combined algorithm that classifies each child as either "autistic" or "nonautistic." It also automatically generates metrics reflecting a statistical

Kimberly L. H. Carpenter, Ph.D.

"confidence level" associated with the diagnostic assessment made in each case. If the app administration falls below a certain level, it can easily be re-administered to boost the confidence metric.

The app *does not determine* if a child has ASD. Screening tools like the app are designed to *predict the likelihood* of the presence or absence of a condition, but are not by themselves able to make a positive diagnosis. Expert clinical examination and various diagnostic methodologies are needed to make a "gold-standard" determination in each case.

In the group of 475 toddlers tested (they ranged in age from 17 to 36 months and included 269 boys and 206 girls), 49 were diagnosed with ASD and 98 were diagnosed with developmental delay without autism; 328 of the children were assessed as "neurotypical." The key question was: how well did the app identify children in each category?

Overall, its sensitivity was 88%; its specificity was 81%. By comparison, in a prior test of over 25,000 children, the M-CHAT questionnaire had an excellent sensitivity of 95%, but a specificity of only 39%. This means the parental questionnaire *didn't miss* very many cases of ASD, but it also generated a *high number of false positives.* The low false positive rate in the app suggests an important strength.

While the new app has the advantage of making its determination on the basis of entirely objective, computer-analyzed data, and captures features reflecting the variety of autism-related behaviors and early-warning signals, it remains imperfect. As the researchers note, some autistic toddlers will exhibit only a subset of ASD-related features. Conversely, some nonautistic children may exhibit behaviors typically associated with ASD.

Importantly, when results of SenseToKnow assessments were combined with those from the M-CHAT questionnaire, the "positive predictive value" of the result for each child increased substantially. Thus, one of the team's conclusions was that combining available screening methods, specifically the new app and M-CHAT, which are both highly accessible at no or negligible cost, would significantly enhance the accuracy of autism screening in the real-world setting of the pediatrician's office at the time of the "well-child" exam.

Efforts to improve SenseToKnow are under way, as are larger clinical tests that assess broader samples of the population with more typical rates of ASD and developmental delay.

WEARABLE SENSORS HELPED TO DISTINGUISH ADOLESCENT BIPOLAR DISORDER FROM ADHD AND OTHER DISORDERS

Diagnosing bipolar disorder (BD) can be difficult. To make a positive diagnosis, an individual must experience at least one major depressive episode and at least one manic or hypomanic episode. (Mania is characterized by significantly elevated and/or irritable mood as well as notably increased energy and activity; hypomania is a less intense version, but with equally important mental health implications).

When an initial depressive episode *precedes* an initial manic/hypomanic one, it is impossible with current diagnostic tools to predict *at that point* that a given individual will or will not at some future time experience a manic or hypomanic episode. A diagnosis of major depressive disorder can be made, but not a BD diagnosis.

In some depressed people, a subsequent manic episode will occur, making a BD diagnosis possible. But even then, it is possible to confuse symptoms of other psychiatric conditions for changes in energy and activity that also occur in mania/hypomania. In ADHD, for example, hyperactivity can in some cases be mistaken for mania/hypomania. In view of this, a person with depressive symptoms and hyperactivity could conceivably have unipolar depression (e.g., major depressive disorder) and co-occurring ADHD—or, perhaps, bipolar disorder without ADHD.

Distinguishing people with overlapping symptoms involving both depressive mood and significantly elevated levels of energy and activity can result in delays of positive diagnosis (whether for BD or other disorders) that can be measured, in some cases, in years. Misdiagnosis or a long time-lag before a correct diagnosis is made can translate into missed opportunities for matching the

patient with the therapies most likely to help them, which in turn can lead to less satisfactory long-term outcomes.

Researchers at the University of Pittsburgh are among those who have been working to discover objective markers—biological and/or behavioral—that might enable doctors to predict at an early stage that an individual has BD *or* one or more other disorders, or BD *and* one or more other disorders.

Michele A. Bertocci, Ph.D.

Michele A. Bertocci, Ph.D., a 2019 BBRF Young Investigator, and Rasim S. Diler M.D., led a team that also included **Boris Birmaher, M.D.**, 2022 BBRF Ruane Prize winner and 2013 BBRF Colvin Prize winner, in utilizing actigraphy and artificial intelligence (AI) to test models that might be used in the clinic to help differentiate BD in adolescents from other conditions. Actigraphy is an objective method of measuring an individual's rest and activity cycles, via a device worn on the wrist that contains a digital accelerometer akin to those incorporated into smartphones and sleep- and exercise-monitoring devices.

Actigraphy has helped other researchers better understand disturbances in daily circadian rhythms in BD patients. The new study uses the technology to examine the relationships between daytime activity and BD, excluding nightly periods of sleep. This focus on daily activity follows in part from past research showing that in adults, a decrease in daily activity has been seen in patients experiencing a depressive episode, relative to activity in manic/hypomanic episodes.

The team studied data from 389 adolescents, average age 15, who had been admitted to the specialized Child and Adolescent Bipolar Spectrum Services unit in Pittsburgh's Western Psychiatric Hospital. The cohort studied included patients with BD but not ADHD (61); BD with ADHD (86); ADHD without BD (115); and a variety of other psychiatric disorders (127). All of these youths were inpatients at the time of data collection, and each had at least 4 days of actigraphy data.

Two AI programs were used to search for patterns in data that for each participant was broken down into non-overlapping hour-long periods during the day (between 7 am and 8 pm) characterized by comparative levels of activity. This yielded analytical units that registered intervals of minimum and maximum activity throughout the day. These 60-minute intervals were regarded by the team as "objective markers of clinical self-reports of elevated and reduced daily activity levels." They aligned with DSM diagnostic thresholds such as the 4-hour daily criterion for elevated activity associated with hypo/mania.

A large set of what computer modelers call "features" was built into the algorithms used by the two AI programs to train themselves to parse the data and discover useful patterns. Both AI programs were highly effective in this task. With an accuracy of 90% or more, both programs used data on individual maximum and minimum daily activity along with patient age to classify the four diagnostic subsets within the total cohort.

"Actigraphy data, collected during inpatient stays," succeeded in "differentiating between difficult-to-distinguish psychopathologies of BD without ADHD, BD with ADHD, ADHD without BD, and other illnesses," the team reported in *Psychiatry Research Communications*.

"Each diagnostic group [in the cohort] shows behavioral trends toward elevations and reductions in daily activity differently," they noted.

The team suggested that its findings, if replicated and extended, "strongly support" using actigraphy to provide objective and quantifiable measures to assess inpatient activity and classify diagnoses. This, they said, "can complement clinical observations, especially by identifying subtle differences in activity patterns that may not be visually apparent."

FITBIT DATA STREAMS HELP PREDICT MOOD SHIFTS IN PATIENTS WITH BIPOLAR DISORDER

In addition to efforts to use digital technologies to help make accurate diagnoses of bipolar disorder, there are also applications that seek to address the mood shifts that characterize BD—an objective akin to efforts decribed earlier to track anhedonia and rumination symptoms in depressed and anxious young people.

A team led by 2019 BBRF Young Investigator **Jessica M. Lipschitz, Ph.D.**, of Brigham and Women's Hospital, recently tested whether data from wearable Fitbit devices (worn like a watch) could generate predictions about shifts in mood that are accurate enough to "meaningfully inform treatment" in BD patients. **Katherine E. Burdick, Ph.D.**, winner of the BBRF Colvin Prize in 2021 and a two-time BBRF grantee, was senior member of the team.

In recent years, 2022 BBRF Young Investigator **Sarah Sperry, Ph.D.**, and

colleagues, have published evidence calling into question the commonplace assumption in clinical medicine that periods between low and high mood in bipolar disorder are ones of "normal" mood. Their finding of considerable "mood instability" in many patients between episodes of depression and mania/hypomania has the potential to improve care and quality of life by directing attention to these periods "between" major mood episodes.

The new research by Drs. Lipschitz, Burden, and colleagues suggests one way to track patients in real time. Called "digital phenotyping," the moment-by-moment measurement of data such as sleep patterns, daily activity, and heart rate, collected by wearable digital devices, offers a potential avenue for early detection of major mood episodes in BD patients.

Jessica M. Lipschitz, Ph.D.

The team selected the Fitbit device because of its commercial availability and low cost, and most importantly because it is entirely passive: users do not input data of any kind. The devices have also proven over the years to be quite accurate and consistent in registering user data.

Participants in the Fitbit study had been diagnosed with Bipolar I (depression and at least one manic episode) or Bipolar II (depression and at least one hypomanic episode). Those included in the statistical analysis had to have completed at least 24 weeks of a 9-month Fitbit data monitoring period.

Although the Fitbit data is acquired passively, those in the final cohort of 54 also completed a self-report questionnaire given every 2 weeks during the 9 months, indicating any depression and/or manic/hypomanic symptoms. Data from these questionnaires were used to determine the accuracy of machine learning algorithms used to predict mood symptoms, not as input for the algorithms. The team identified one algorithm among the several tested that generated superior predictive results.

Data collected on each user by Fitbit devices covered such facets as number of daily steps taken; number of minutes spent in non-active or "sedentary" mode; heart rate (daily average and resting average); total sleep time; amounts of time and number of nightly intervals spent in deep sleep and REM sleep; number and duration of nightly awakenings; and bedtime.

After filtering out data from 11 of the original 65 participants (17%) who either dropped out or were not sufficiently compliant with the protocol, the team was able to use the Fitbit data to accurately predict clinically significant depression with 80.1% accuracy, and clinically significant manic/hypomanic symptoms with 89.1% accuracy. One other past test of Fitbit for this purpose yielded similar accuracy, but only after filtering out 46% of the data, meaning that it served its predictive purpose mainly in participants who were highly compliant with the protocol, and may not work as well in a general sample of BD patients seeking treatment. The accuracy numbers for this trial were calculated after the fact, looking back on all the data.

"Our findings are particularly noteworthy," the team wrote, "because all input was passively collected; none of the metrics utilized were invasive in terms of privacy; we used mainstream consumer devices; and our methods did not demand high levels of Fitbit compliance." For these reasons, the team suggests its results and methods "are an important next step toward a digital phenotyping approach that could be feasibly and broadly implemented across BD patients in routine care."

❖ **PETER TARR**

BBRF Names Ten 2026 Distinguished Investigators Funded by WoodNext Foundation

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: bipolar disorder, autism genetics, traumatic memory, cocaine-use disorder, psychosis, and depression. The awards are made possible by the WoodNext Foundation. This is year three 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 much remains unknown about their underlying biology," said Jeffrey Borenstein, M.D., President and CEO of the Brain & Behavior Research Foundation. "Our Distinguished Investigator Grants support bold research that could lead to breakthroughs in prevention, diagnosis, and treatment. We are deeply grateful to the WoodNext Foundation for making these pioneering studies possible."

"Advancing mental health requires bold, high-impact scientific research," said Nancy Chan, Executive Director of the WoodNext Foundation, a fund of a donor-advised fund program. "We are honored to support BBRF's Distinguished Investigator Grants and the researchers driving new discoveries."

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 191 leading experts in brain and behavior research, who review grant applications and select the most promising projects.

Here are the recipients of the 2026 BBRF Distinguished Investigator grants:

Ravi Allada, M.D.

Professor of Neurosciences

Executive Director, Michigan Neuroscience Institute

University of Michigan

Dr. Allada suggests that understanding the biological connection between bipolar disorder, sleep, and circadian rhythms could transform how we diagnose, monitor, and treat this condition. His project seeks to connect risk genes for bipolar disorder to biological mechanisms and clinical outcomes. This could identify new biomarkers for diagnosing and monitoring the illness, such as blood-based tests of circadian rhythm strength. They may also point to new treatment strategies.

Basic Research
Bipolar Disorder

"Sleep and daily rhythms play a powerful role in mood, yet we still don't fully understand how they are disrupted in bipolar disorder. Support from BBRF allows us to connect genetics to these rhythms, with the goal of developing better ways to predict symptoms and personalize treatment for patients."

Paola Arlotta, Ph.D.

Chair, Harvard Department of Stem Cell & Regenerative Biology

Professor, Stem Cell & Regenerative Biology, Harvard University

Harvard University

Dr. Arlotta has used human brain organoids—stem cell-derived cell-culture models of human brain tissue—to show that when mutated, multiple genes associated with autism spectrum disorder (ASD) risk share an early developmental pattern in which inhibitory neurons develop out of step with the excitatory neurons they wire with. She hypothesizes this type of early asynchronous development of inhibitory neurons leads to later abnormalities that may be shared across many ASD risk genes. This project seeks to directly test this hypothesis.

Basic Research
Autism Specrum Disorder

"With BBRF's support, we will be able to pilot critical work aimed at understanding whether early neurodevelopmental divergencies in autism result in specific neural circuit-level dysfunctions observable after birth. It is very exciting work to me, as the results could help inform the development of targeted therapeutic interventions based on pharmacological modulation of circuit behavior."

Christopher W. Cowan, Ph.D.

Professor and Chair, Department of Neuroscience

Medical University of South Carolina

Dr. Cowan is interested in single-gene causes of ASD that account for a significant fraction of ASD cases. One such gene is MEF2C, which encodes a protein that regulates neurotypical brain development and function. Loss-of-function mutations or deletions in one copy of MEF2C cause a syndrome (MCHS) which is characterized by ASD, language deficits, seizures, intellectual disability, sleep disturbances, immune dysfunction, and motor and sensory system deficits. This project seeks advance an RNA-based therapeutic approach to treat MCHS.

Next-Generation Therapies:
Autism Spectrum Disorder

"What a tremendous honor! These critical research funds will enable us to advance a novel treatment for individuals with a genetically linked form of profound autism, and if successful, could open up a new approach for treating numerous neurodevelopmental disorders."

Aline Desmedt, Ph.D.

Professor

NeuroCenter Magendie U1215 (INSERM, France)

Dr. Desmedt has developed an animal model that reproduces in mice the two memory components of PTSD: traumatic hypermnesia—the intense, involuntary, and recurrent re-experiencing of traumatic memories; and contextual amnesia, i.e., remembering details or events but forgetting the surrounding circumstances. This project seeks to identify neural mechanisms underlying the switch to and from pathological to normative fear memories. The aim is to determine the extent to which a memory trace is transformed when (re)contextualized traumatic memory is normalized, shedding light on neurobiological mechanisms that could inform new treatments.

Basic Research:
PTSD

"I am pleased and honored to have received this grant, which will allow my team to identify the neural mechanisms underlying the switch from pathological PTSD-like fear memory to normative fear memory and vice-versa. We hope to shed light on mechanisms to promote innovative therapeutic and preventive strategies."

Karen D. Ersche, Ph.D.

Professor of Addiction Neuroscience, Addiction Research Group

University of Cambridge, UK

Dr. Ersche seeks to identify underlying mechanisms that drive maladaptive behavior in cocaine use disorder (CUD). One such mechanism may involve endocrine disruption. This project seeks to illuminate the behavioral relevance of hormonal imbalance in chronic cocaine users based on a cohort of 180 adults, investigating endocrine, behavioral, and neural markers of decision-making and emotion processing. It will explore, for example, how neuroendocrine dysfunction relates to risky and social decision-making in CUD. The hope is to uncover new targets for intervention, and ultimately to improve outcomes.

Basic Research
Addiction, Substance-Use Disorders

"With this funding enabling us to investigate neuroendocrine mechanisms we aim to identify clinically relevant biomarkers that could inform new therapeutic targets, improve physical health, and support behavioral change during recovery."

Stephen J. Glatt, Ph.D.

Professor of Psychiatry and Behavioral Sciences

Professor of Neuroscience and Physiology

The Research Foundation for the State University of New York, Upstate Medical University

Dr. Glatt is working to develop the ability to non-invasively profile the molecular dynamics of the living human brain. This project will validate an algorithm called the Brain Gene Expression and Network Imputation Engine (BrainGENIE+), which allows the team to register gene-expression levels and patterns in 10 distinct brain regions using just a blood sample. The goal is to uncover molecular states that underpin brain health and disease and establish an atlas of gene-expression features of the living brain in healthy individuals.

Basic Research
New Technology

"I am extremely grateful for continued support from BBRF. In times of uncertainty and changing priorities in federal funding, BBRF provides a solid, consistent, and vital source of research funding, enabling us to take chances and pursue novel ideas that challenge the status quo."

Alicia Izquierdo, Ph.D.

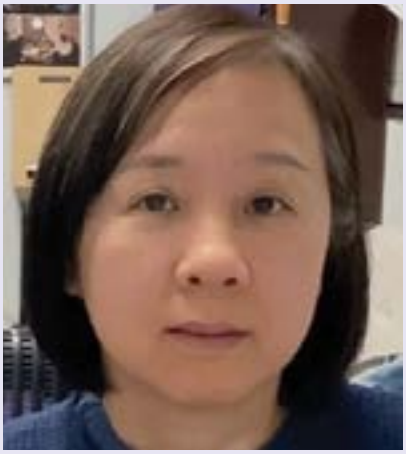
Professor, Behavioral Neuroscience

University of California, Los Angeles

Dr. Izquierdo notes that our brains often discern patterns in randomness. Adaptive behavior should take into account both moment-to-moment randomness, ("stochasticity"), as well as the speed of change ("volatility"). Dissociating these factors in the laboratory is computationally and neurobiologically challenging. In this project Dr. Izquierdo will use a novel behavioral paradigm and modern systems-neuroscience techniques to identify mechanisms underlying this dissociation in thalamo-frontocortical circuits. The team hopes to accelerate understanding of neural circuit modulation in psychosis.

Basic Research
Psychosis, Schizophrenia

"I am very grateful to BBRF for generously supporting our team in this bold research direction, providing us the freedom to pursue an ambitious project. This funding also makes possible a new research focus in addressing important translational questions highly relevant to schizophrenia."



Wei Jiang, M.D.

Professor, Pharmacology & Immunology

Medical University of South Carolina

Emerging evidence highlights the role of peripheral influences, including the gut–brain and oral–brain axes, in regulating emotion. Dr. Jiang's past work suggests chronic heavy cannabis use enriches oral *Actinomyces* microbes, which induce anxiety-like behavior, mitochondrial dysfunction, and impaired inhibitory neurotransmission. This study investigates the mechanisms by which chronic cannabis use drives anxiety through pathogenic oral microbiota and metabolites, and will explore targeted therapeutic approaches.

Basic Research,
Substance-Use Disorder

"I am deeply honored and grateful to BBRF. This support allows my team to pursue a new direction in understanding brain disorders by identifying immune- and microbiome-derived triggers that originate outside the brain. Being part of the BBRF community has been incredibly meaningful to my career, and I sincerely thank the Foundation and its visionary supporters."

Loren L. Looger, Ph.D.

Principal Investigator & Professor of Neurosciences

University of California, San Diego

This project involves exploration of a novel pharmacological mechanism that may be exploited to ameliorate depression: the upregulation of serotonin synthesis inside of cells. Dr. Looger proposes such upregulation would address the extracellular pathways addressed by SSRIs and also intracellular pathways. The team will use a high-throughput drug screen to identify modulators of serotonin synthesis. Compounds discovered from this screen may illuminate molecular pathways involved in serotonin synthesis and trafficking and may serve as lead molecules for the development of new medicines.

Basic Research,
Next-Generation Therapies
Depression

"These BBRF funds will allow us to perform an incredibly exciting set of experiments looking for drugs that modulate serotonin production, destruction, and trafficking in several key cell types. These experiments could help us uncover unknown pathways through which serotonin is acting and which could be modulated in disease. We can't wait to share our findings."

Jamie L. Maguire, Ph.D.

Professor, Neuroscience

Tufts University

Dr. Maguire's goal is to further the development of a novel, evidence-based treatment with transdiagnostic potential for psychiatry. The project focuses on impaired neurosteroid synthesis, implicated in numerous psychiatric illnesses. The team has developed a potential treatment which enhances the synthesis of these endogenous compounds with well-established anxiolytic and antidepressant effects. They have already identified small molecules and now will take next steps to develop a novel treatment with transdiagnostic potential for psychiatric illnesses.

Next-Generation Therapies
Depression, Anxiety

"Translating preclinical findings into novel evidence-based treatments is challenging. BBRF's commitment to support innovative projects to understand and treat severe mental illness helps close the gap and enables this potentially impactful work to move forward. I am deeply honored and grateful."

Restoring Dysfunctional Brain Circuits in Depression

By Conor Liston, M.D., Ph.D.

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BBRF Scientific Council member
2013 BBRF Young Investigator

[Editor: This text is adapted from a BBRF webinar given by Dr. Liston on April 12, 2026, which can be viewed on the BBRF website and YouTube channel]

IN BRIEF
Describing research results from his lab, Dr. Liston addresses how neural connections are increased following ketamine treatment and how these new connections correspond with reduced depression symptoms; whether this relationship applies in other depression treatments; how symptoms such as anhedonia may be modified by treatment; and how fMRI-based subtyping of depression patients may help predict response to TMS and other therapies.

I'm a neuroscientist and a psychiatrist, and much of the work in my group has been oriented around answering an important unanswered question in depression neuroscience: What are the mechanisms that control the changes in mood over time that are the defining feature of depression?

Depression, by definition, is fundamentally episodic: it is defined by periods of low mood interposed between periods of wellness.

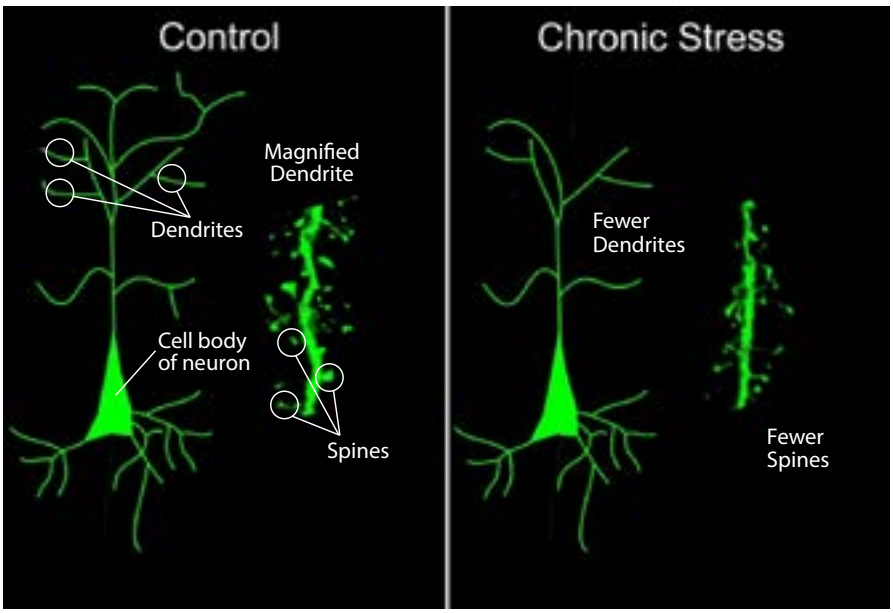
To date, most research has tended to focus on comparing groups of depressed people with groups of never-depressed people—i.e., "healthy controls"—and doing so at a single point in time.

We've learned a lot from this work. But it remains unclear why a person gets depressed today as opposed to last week or next month, and what determines how long they stay depressed. It's also unclear, when depressed patients are treated and get better, what mechanisms initiate that recovery. We also don't yet understand whether there may be other mechanisms involved in sustaining that recovery over time.

If we can advance our understanding of these questions, we can perhaps develop better ways of treating people and achieving more durable recoveries for our patients. The research I'm going to discuss here pertains directly to these questions.

HOW NEURAL CONNECTIONS ARE MODIFIED BY KETAMINE TREATMENT

My lab has been following people with depression and repeatedly getting functional MRI (fMRI) brain scans from them as they cycle in and out of depressed mood states, and then doing analogous studies in mice, whose brains we are able to study closely with sophisticated microscopes—something we obviously can't do in people living with depression. The imaging technique we use for mouse brains allows us to look at how microcircuits in the brain change in response to chronic stress and in response to antidepressants. It's likely that many mechanisms are involved in mood changes, but we (and others) think an important one involves the remodeling of tiny structures called postsynaptic dendritic spines. We often refer to them by the shorthand, "spines."



As you can see **in the image above**, spines are thorny protrusions from the branches (called dendrites) of neurons. You can think of each spine as a structural marker of a synapse—that is, a point of connection between brain cells.

We know that chronic stress, which can trigger depressive episodes in vulnerable people, reduces the number of these spines and therefore the number of of brain connections. Conversely, we know that drugs like ketamine, which act as antidepressants, do the opposite. They lead to the formation of new connections between brain cells.

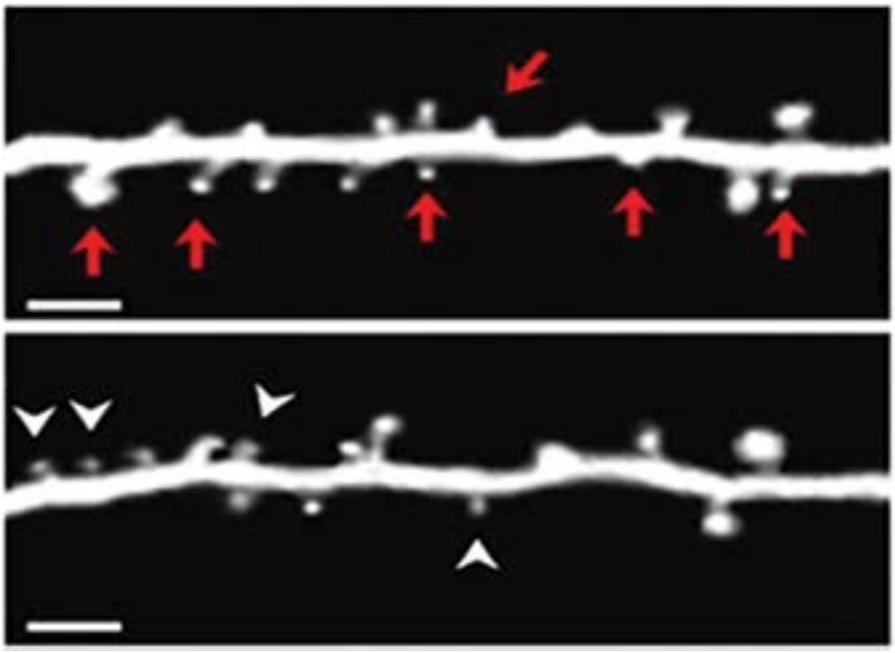
Knowing this, it's been tempting to speculate that the formation of new connections is required for initiating the mood improvement that many paitents experience when treated with antidepressants. Proving this would be an important advance. What is the evidence? In a first series of studies I'm going to describe, we set out to test this hypothesis.

Are the new connections we see in the depressed mouse brain after treatment with ketamine required to drive changes in mood and changes in behavior that we see shortly after the animals are treated? We found that they were required, but not in the way we expected. I'm going to try to explain what this means for depression treatment.

In depression, what neural mechanisms are engaged in recovery? Are different mechanisms at work in sustaining that recovery?

We use a technology called two-photon microscopy to observe the brain in great detail in living mice, including those exposed to stress, which can trigger depressive episodes in vulnerable people. This enables us to visualize in real-time the remodeling of dendritic spines, these points of connection between brain cells. The technology is amazing: we can return again and again to the exact same position in the brain with micrometer precision (millionths of a meter). And then we can ask what impact stress and antidepressants have on the remodeling of these brain cell connections.

One experiment involved imaging the brain before and after various chronic stressors. We asked what impact these stressors have on remodeling brain cell connections.



You don't need to be an expert to see the result—you can appreciate it by eye. **In the pair of images above**, the top image is a view of spines before an animal was injected with stress hormone, which mimics the impact of stress. **In the bottom image**, the same dendritic segment in the same animal 10 days later.

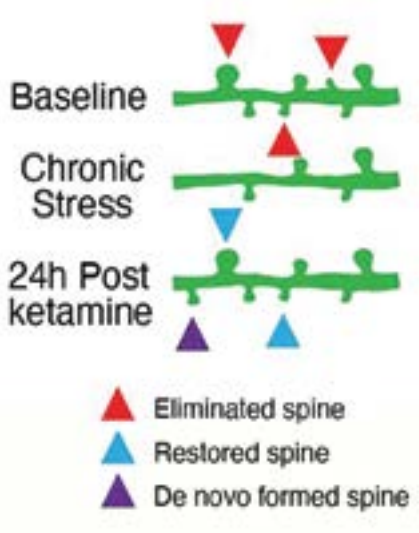
The **red arrows** in the top image above denote spines that were eliminated after the animal was stressed. You see them in that image, but not in the bottom one, after the equivalent of chronic stress. Conversely, **the white arrowheads** in the bottom image point to newly formed spines that weren't present in the pre-stress (top) image.

We found that stress enhanced the rate of both spine elimination and new spine formation in multiple cortical areas. (New spines are routinely being created, especially early in the life of a mouse—or human being—as the brain is developing). But importantly, we found that chronic exposure to stress led to a *net loss* of spines.

It was interesting to us that the loss of connections didn't occur randomly. They occurred in specific positions in the neuron, which tend to cluster together in particular locations. This suggested to us that specific connections to the cortical cells we were looking at—specific projections from other brain regions—might be targeted for pruning by chronic stress, in a guided way. This led us to wonder if perhaps antidepressants were doing the opposite.

We treated the same group of stressed animals with ketamine or a placebo and then imaged them a day later. We chose that time point because, as anyone who has experience with ketamine treatment knows, after a single day, many patients report feeling that their mood is much improved after only one treatment. We found that in the ketamine-treated animals, there was a significant growth of synapses, a growth of spines, a *net increase* in connections between brain cells, that occurs after treatment.

This is consistent with the idea that ketamine (and possibly other antidepressants) might be acting to reverse the effects of stress. But this is something that needs to be tested.



As shown **in the schematic above**, we classified each connection that formed after ketamine treatment. A "restored spine" [blue arrowheads] was one that formed in a position where a

spine used to exist, pre-stress, and then disappeared with chronic stress. We also labeled brand new spines, which we call "de novo spines" [purple arrowhead]. These are spines that formed after ketamine treatment in a position where we didn't observe a spine before.

Ketmaine is restoring many connections that were lost after stress: We noted that about half of the connections that formed after ketamine treatment were restored spines. But at the same time, about half of the new connections we saw post-treatment were forming in new, random positions. This enables us to estimate that ketamine is partially rescuing the loss of connections that occurs after stress, but not fully rescuing it.

We think this might be relevant for patients' clinical experiences in a way that I'm going to describe next. Please keep in mind that one of the major challenges associated with ketamine is sustaining recovery from depression after the initial treatment.

AN UNEXPECTED FINDING ABOUT KETAMINE'S IMPACT ON CONNECTIONS

What we learned about the role of new connections that form after ketamine treatment was really interesting and not what we expected. We did two experiments. First, we imaged the mice before and after chronic stress, and then again in the hours and days, up to a week, after ketamine treatment. We asked which comes first: changes in the spines and their connections, or changes in the animals' behavior?

We found that the changes in behavior—ketamine's rapid antidepressant effect—occurs very quickly, just three hours after treatment. In fact, we now know that they occur even faster than that.

Whereas the formation of new connections didn't begin until 12 hours after ketamine treatment, and peaked about a day later. This means that the formation of these new connections couldn't be required for *initiating* ketamine's antidepressant behavioral effects—because the improvement in behavior comes before the new connections form.

Another bit of data helped us understand more. It told us that the restoration of lost connections was tightly correlated with the maintenance of ketamine's antidepressant-like behavioral effect when we tested it two days or one week later. This enabled us to hypothesize that the new connections after ketamine are required for *sustaining* the antidepressant effects over time, even if they are not required for intiating these effects.

To test this, we teamed up with a group at the University of Tokyo that developed a technology that can be used to delete newly formed connections in the brains of animals in a very selective way. We used it to delete the newly restored connections after ketamine treatment and asked what impact it had on behavior. We found that if you delete those new connections, ketamine's antidepressant behavioral effect wears off within a day or two.

We conclude from this and related experiments that after treatment with ketamine, the formation of new connections in this brain circuit isn't required for initiating an antidepressant effect, but it is required for sustaining it over a period of days.

This is important because we know that if you treat depressed patients with ketamine, many or most of them will report feeling a lot better the next day. But if you don't do anything else to help them and you just wait a week or two, almost all of those people will get depressed again. The impact that the new connections have, post-treatment, in sustaining the antidepressant effect wears off. That's why in clinical practice, ketamine is often delivered multiple times.

CAN WE EXTEND KETAMINE'S ANTIDEPRESSANT IMPACT?

Other research has shown that repeated ketamine dosing can be beneficial for boosting the formation of new connections, compared with a single treatment. In a clinic, ketamine may be administered twice a week for a few weeks. We know that with repeated dosing a larger proportion of those new connections will get integrated into circuits and, at least in mice, they can persist for the lifetime of the organism.

There might be other ways of maintaining the new connections that are forged after an initial ketamine treatment—ways that don't involve repeated ketamine dosing. Exercise is known to boost the formation of new connections in the brain, and can assist with learning and memory. You can imagine that pairing exercise, at least in some individuals, with ketamine treatments (not at the same time, but perhaps in sequence on different days during the course of treatment) could be useful. We have preliminary data in animals suggesting this might be the case and it requires further study.

Pairing ketamine with psychotherapy is another possibility. The formation of new connections after ketamine treatment might render the brain more plastic, more responsive to the learning that takes place during psychotherapy, including the learning of new skills for promoting stress resilience. In treatment-resistant patients, we might further consider pairing ketamine with other treatments that spur connections, like TMS (transcranial magnetic stimulation), which stimulates the brain non-invasively through the scalp using magnetic-field pulses. It will be interesting to test if this gives rise to a synergy—benefits that one doesn't get with either treatment given by itself.

DO OTHER ANTIDEPRESSANT TREATMENTS SPUR NEW CONNECTIONS?

Do other antidepressant treatments work as ketamine does to promote formation of new connections? We have evidence that at least some do. For example, new research from our lab shows that TMS treatments in mouse models of depression also spur new connections. TMS does so in a very specific subtype of cell, which is interesting. There's a lot of interest in psilocybin and other psychedelic compounds. Preliminary clinical trial data looks very promising. More research on psilocybin needs to be done, but there's evidence that psilocybin also promotes the formation of new connections.

What we don't know yet is whether first-line, slower-acting antidepressant drugs like the SSRI medicines induce new connections in the way I've described here in the case of ketamine. Some researchers think this may be the case, but suspect they do so via different mechanisms and on a slower time course. Overall, I think there is good reason to think that new connections are a common pathway that is important across a range of antidepressants for maintaining antidepressant effects.

You might be wondering: What *initates* the antidepressant behavioral effects of ketmaine—the lifting of depression symptoms, sometimes within minutes? This has long eluded us. In recent months, our team has published results of experiments that we think demonstrates the mechanism behind the drug's rapid action. This research has potentially important implications for improving the treatment of depression, including the development of new rapid-acting antidepressants with fewer side effects than ketmaine. *[Editor: full details of this important new research will be the subject of a story in our next issue.]*

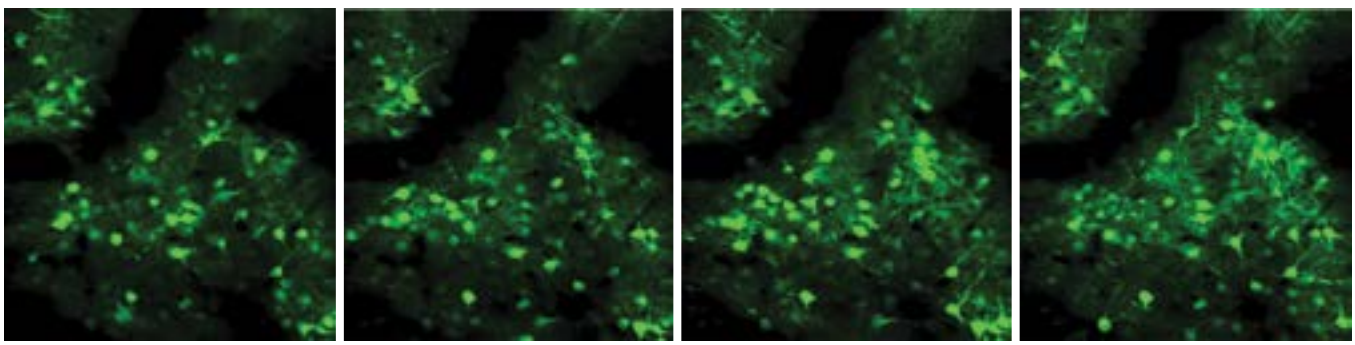
HOW NEURAL CIRCUIT FUNCTION IS MODIFIED BY KETAMINE

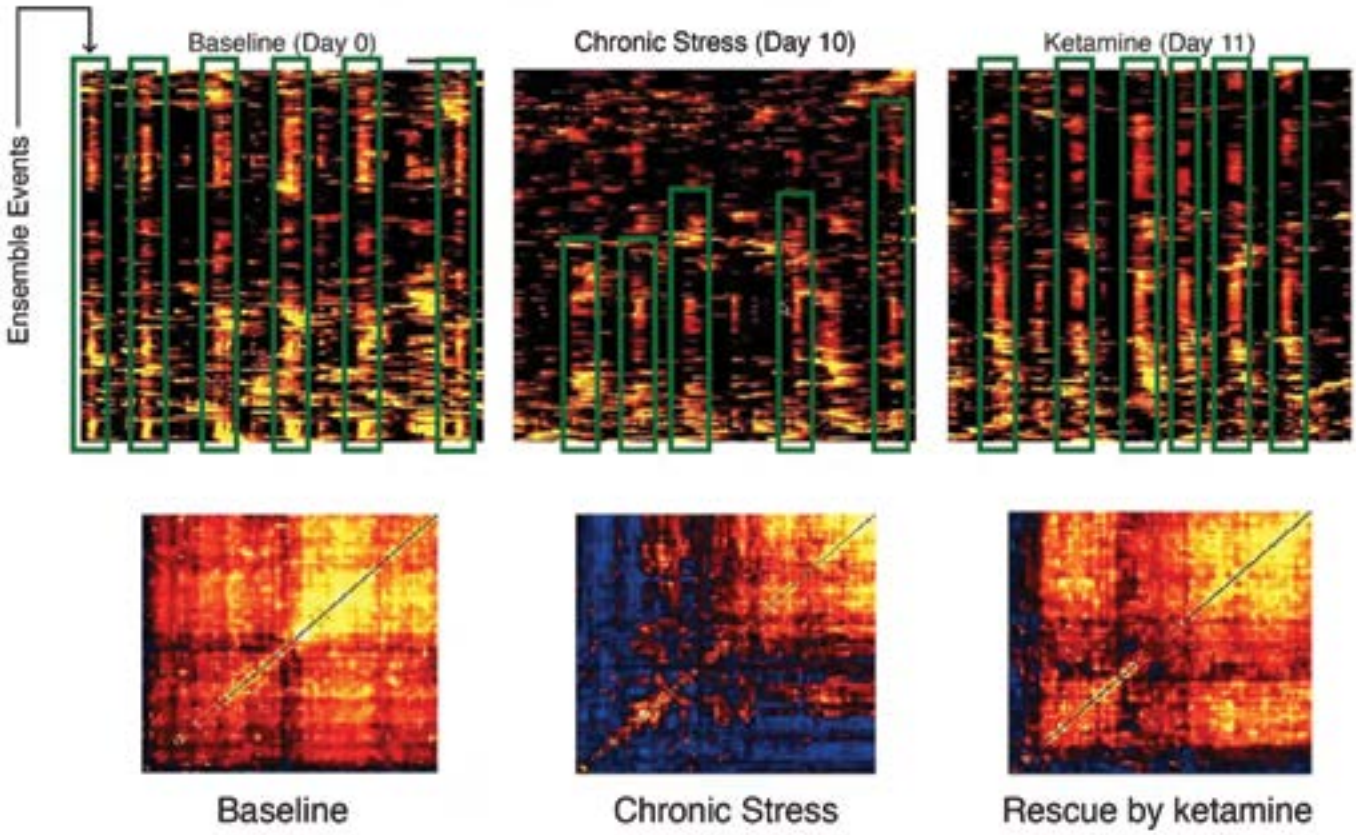
I'd like to talk a bit about experiments we did in parallel with the research on new connections I've already discussed, focusing on what we see in terms of circuit function in animals undergoing antidepressant treatments. To test this, we use a method very similar to the one I have described: live, 2-photon imaging of mouse brain circuits through a cortical window. But instead of imaging the structural markers of connections between brain cells, the dendritic spines, in these experiments we're imaging the cells' functional properties—not how they're connected but rather what they are doing.

In the series of images below, which are actually individual frames of a movie we made, cortical neurons have been genetically engineered to glow green when they become active. In the movie, you get these beautiful images that look like Van Gogh's "Starry Night," where neurons are lighting up and then disappearing and lighting up again. We try to suggest this in the row of individual frames from the movie, below.

This visual readout serves as a marker of how active the brain cells are. We predicted that if many connections between neurons were being lost after chronic stress and restored after ketamine treatment, then we might see changes in what we call **functional connectivity**—the degree to which the activity in connected pairs of cells is correlated. We would expect to see activity levels change after chronic stress and then go back to normal after ketamine treatment. And that's indeed what we did observe.

Using color-coding, we were able to see and compare activity in cells that are strongly connected functionally, and in cells that are not strongly connected functionally.





In the "heat-map" images above, warm colors denote pairs of cells that are strongly functionally connected, and cool colors denote pairs of cells that don't have a strong functional connection. The baseline, prior to stress, is seen in the lower left panel. In the lower middle panel, after chronic stress in this animal, there's a loss of warm colors (lower middle panel), which means a loss of functional coupling between neurons. When we treat the animals with ketamine, those warm colors come back (lower right panel).

The reason we see these changes has to do with what we call "ensemble events." **These are visualaized in the 3 corresponding images on top,** in which you read the data in columns, from top to bottom. A lot of the activity we captured occurs when these ensembles of cells become active at about the same time. And you can see that chronic stress (top center panel) significantly disrupts the occurrence of these ensemble events (and when they do occur, they tend to involve fewer cells). In the top right image, you can see that after ketamine treatment, the ensemble activity we saw before stress is restored.

We think these ensemble events are behaviorally relevant in various ways. We think they impact fear learning, cognitive flexibility, the perception of social hierarchies, and reinforcing social interaction behaviors. But next, I'm going to focus on another behavioral impact, pertaining to neural activity related to seeking rewards, which is highly relevant in depression.

REWARD CIRCUITS, ANHEDONIA, AND KETMAINE

How do you respond when you're motivated to obtain a reward? You make an effort to obtain it. We know from past experiments that a particular circuit in the brain, which projects from the anterior cingulate cortex (ACC) to an area involved in reward processing called the nucleus accumbens (NAc), is important for encoding a predictive signal of reward—our expectation of receiving a reward, given various levels of effort. The ACC→NAc circuit integrates information about effort to gain a reward. Its signal is required for reinforcing future decisions to expend effort to obtain rewards.

The signal in this circuit scales with effort. We think this is really relevant in depression, because we know that patients often experience anhedonia, a loss of interest or pleasure in things or activities that they used to enjoy.

You can imagine if you're depressed that even getting out of bed, getting dressed, walking to your favorite restaurant to spend time with friends, these things might feel very effortful and you might just choose never to engage in them. But we also know that if you encourage a depressed person to actually engage in the enjoyable activity, they often do enjoy it—the problem often lies in willingness to expend effort to obtain the reward.

We think that the ACC→NAc circuit I mentioned is very important for those kinds of decisions. It turns out that in animal experiments, after chronic stress, the animals very consistently stop choosing high reward/high effort options in favor of a low reward/lower effort option.

We're currently looking at how antidepressants like ketamine influence the function of this circuit.

DO NEURAL NETWORKS CHANGE AS PATIENTS' DEPRESSION SYMPTOMS CHANGE?

Next, I'd like to tell you about our work in people with depression. We're very grateful to them for making this work possible. Very dedicated reseachers in my lab tracked a small number of people 40, 60, up to 120 times, over a period of 1–2 years as the patients cycled in and out of depression.

They collected brain scans from these participants over and over again, along with detailed clinical assessments that allowed us to map what is changing in the brain as a person's symptoms change.

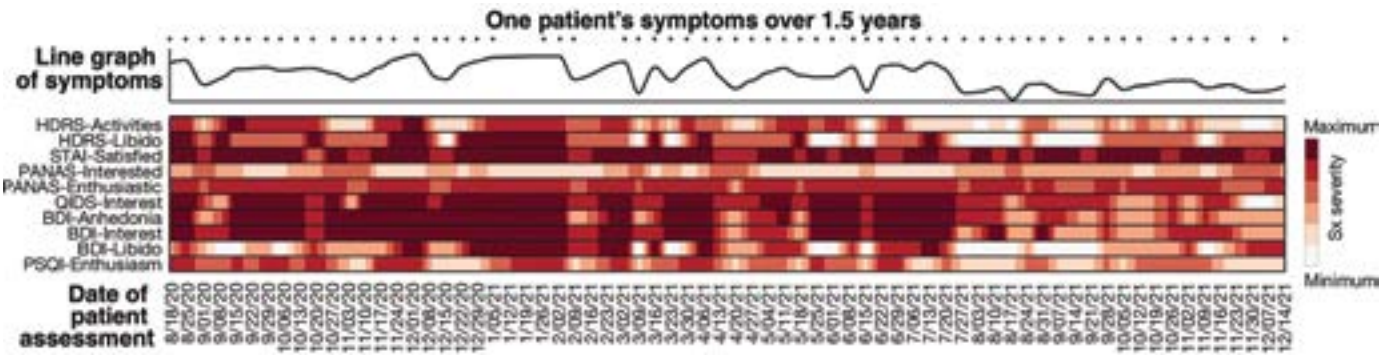
You can see **in the illustration below**—again, data rendered in the form of a "heat map"—that there are a number of symptoms displayed in rows; they're related to anhedonia, loss of interest in pursuing pleasurable activities. The darker colors depict times when this particular person was more anhedonic. The lighter colors denote times when this person didn't really have much anhedonia at all.

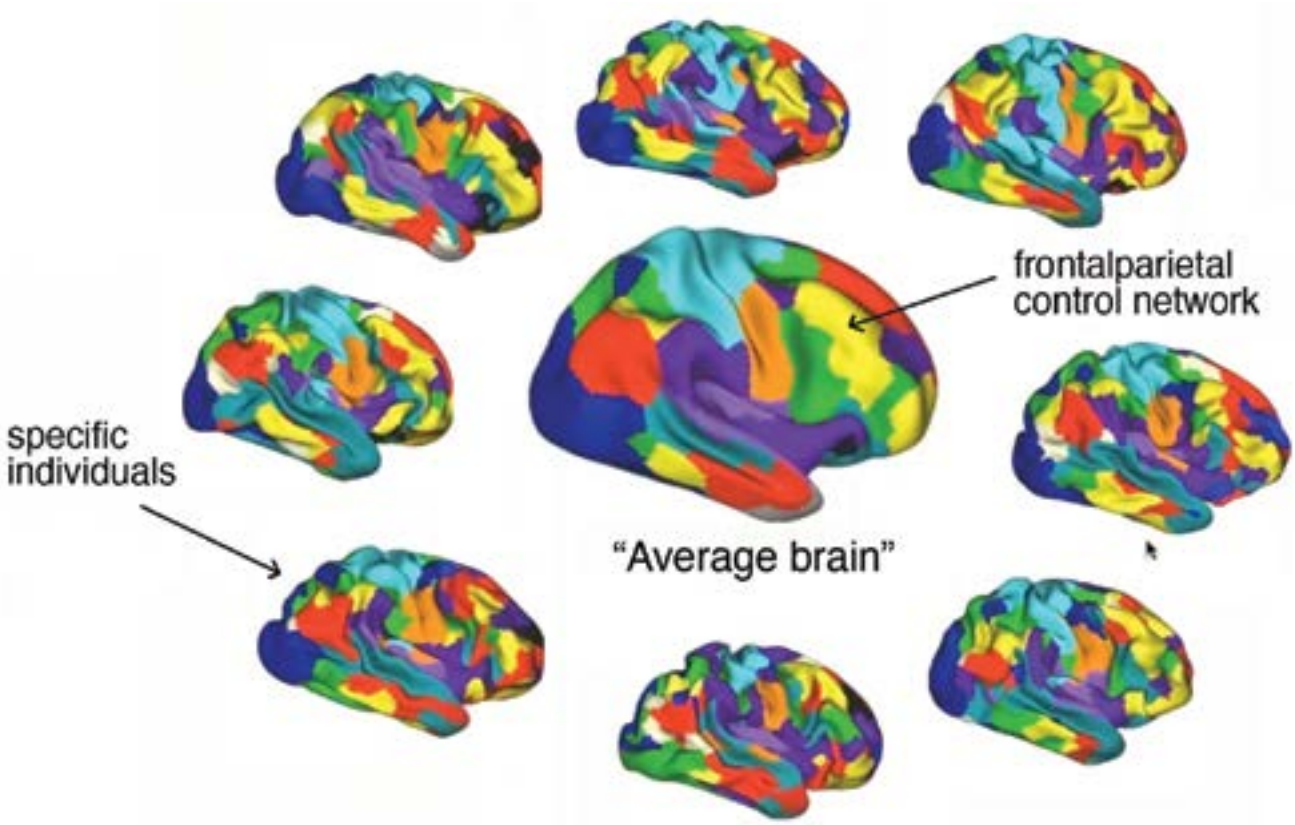
What you can see by glancing at the line graph just above the heat map, summarizing the data, is that there were a lot of fluctuations. Sometimes this person reported very severe anhedonia, but sometimes had essentially no anhedonia. Because we're doing this sampling repeatedly over time, we realized that we'd be able to study how these changes relate to changes in **network topography**—the boundaries of neural networks—as they change over time, as revealed in fMRI scans.

We've known for some time that the brain is organized into functional networks, which are **depicted in the brains rendered on the top of the facing page** by different colors. Recently, scientists have discovered that the boundaries of these networks are actually quite different in different individuals, kind of like a fingerprint or even like a face.

You can see that everyone whose brain is depicted in this graphic has a network we've colored yellow [see arrow] called **the frontoparietal control network.** Everyone has it in about the same position, but the boundaries are dramatically different across these different individuals. In some people, it's very small, in some people it's much larger.

Now think of this in the context of using an antidepressant treatment like TMS, which targets a particular area of the





brain based on positioning a magnetic coil over a certain place on the scalp. In different patients this would potentially affect dramatically different networks, based on the network topography of their brains as shown in this graphic. We wanted to ask whether these networks are systematically different in the brains of depressed people compared to people who've never been depressed.

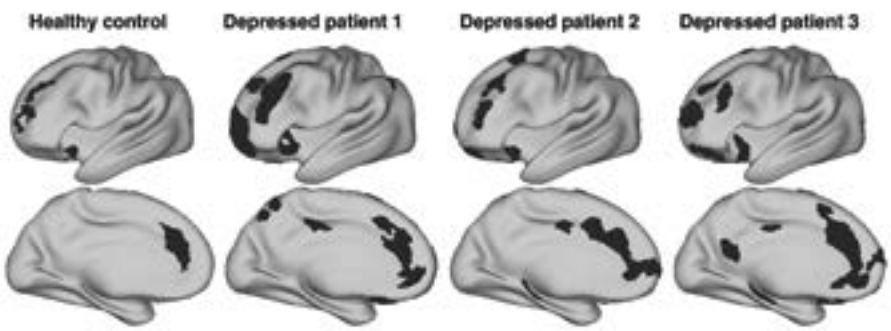
ENLARGEMENT OF THE SALIENCE NETWORK IN DEPRESSION

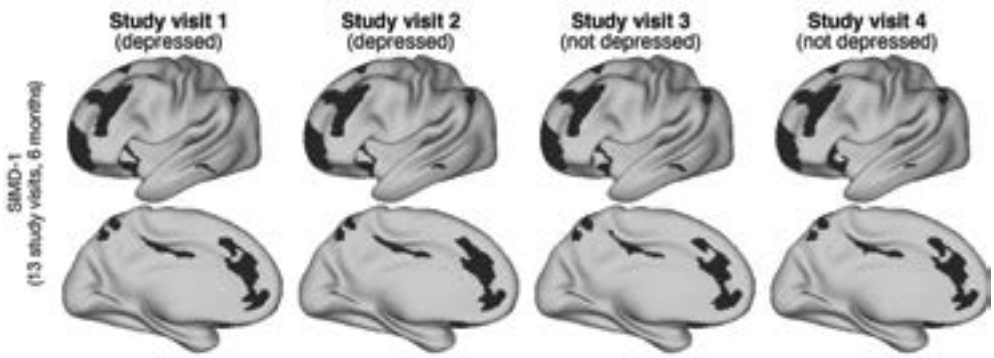
What we found was really striking: one network and only one network is dramatically expanded in the brains of people who suffer from depression. This network is called the frontostriatal salience network. **The "salience network,"** as we refer to it, is important in orienting attention to emotionally important or relevant stimuli in the environment.

We find that this network is dramatically expanded in depressed people. Again, you don't need fancy statistics, you can just see it. **In the set of brain images below**, the salience network (shaded in black) is much larger in three individuals with depression compared to a never-depressed person. We see this very consistently across many people with depression.

One question we asked was about how the expansion of the salience network affects orienting our attention to emotionally salient stimuli, and why this might be important—what it might do to contribute to depression.

Perhaps it's the case that this network expands as a person gets depressed and then contracts as a person gets well again. We were well positioned to test this hypothesis because as I've noted, we have imaging data as people became depressed and not depressed and depressed again. What this showed us was just the opposite of what we predicted.





The graphic above shows the boundaries of the salience network (in black) in one individual, over four representative study visits. In the two early visits, shown on the left, the person is depressed. In two subsequent visits (right), the person is not depressed. You can see that the boundaries of this network hardly change over time. We see this in all the patients we scan: the network topography, the size of the salience network, really does not change. It's unrelated to how depressed they are currently at the moment. This led us to rethink our hypothesis.

We next had the idea that perhaps this salience network isn't expanding and contracting as a person gets depressed and not depressed, but instead that it somehow is conferring *risk* for depression.

How might we test this? We reasoned that if that were the case, we should find that the network is expanded in individuals who have never been depressed but later go on to become depressed. This, in comparison to the network's size in individuals who were never depressed and don't become depressed later on.

We turned to data in a unique resource called the ABCD study, which has been going on for years. Over 10,000 kids have been enrolled and then followed from ages as young as 7 up through their teen years. Among those 10,000 kids, we selected 60 who were never depressed at ages 10 and 12 and then went on to become depressed in their teenage years. Because of their participation in the ABCD study these children had brain scans at both of these time points.

We did indeed find that the salience network was expanded in the children who went on to become depressed a few years later—this, compared to the nework's size over time in those who did not become depressed. We're currently investigating how an enlarged salience network might contribute to risk.

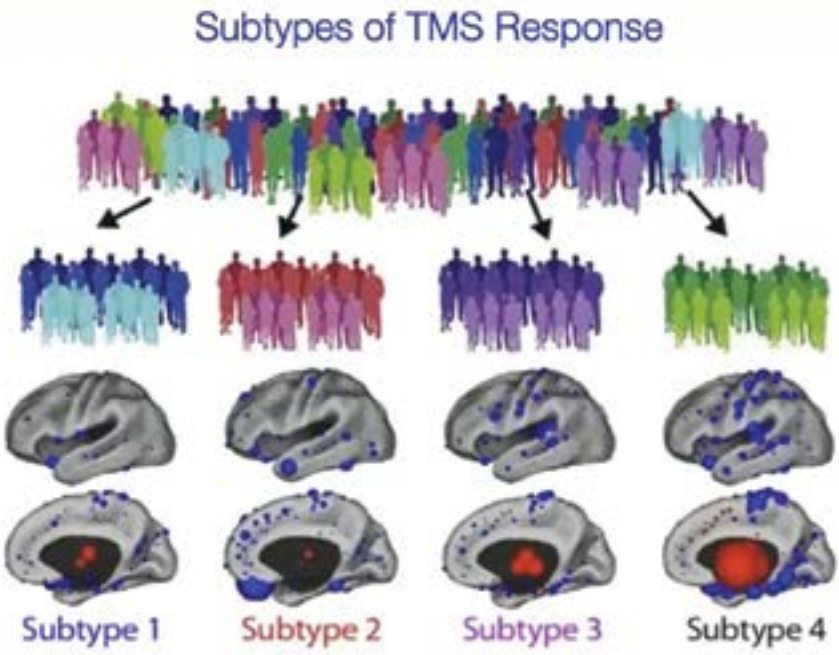
Importantly, we also found that the expansion of this network occurred differently in different individuals. When this network expands, it encroaches on the territory of its neighbors in different ways. You can cluster the people in the sample and identify at least three subgroups of patients based on which neighboring networks are being encroached upon.

We think that the increased risk conferred for depression may be related either to the expansion of the salience network or to how it encroaches on its neighbors, or some combination of the two.

We're currently incorporating our data into tools we've developed for subtyping patients with depression based on fMRI data. We already know that these fMRI-

derived subtypes are associated with different kinds of responses to TMS treatment for depression. This relates to what I mentioned earlier: people with different patterns of functional connectivity might be expected to respond differently to brain stimulation at a given site.

Functional brain scans may enable prediction of patient response to specific depression treatments.



To give an example of how such information might be used, we found that one of the subtypes we identified, Subtype 1 **(see graphic above)** is highly responsive to TMS. Subtypes 2 and 4 are not at all responsive and subtype 3 shows an intermediate level of responsiveness. We now know that you can use a similar approach to model individual differences in response to SSRI antidepressant medciations.

We hope to be able to combine these findings into a pipeline that might be used, first, to identify people who are likely to respond to first-line SSRI medications for depression, and then, second, give them the medication that we think will work.

If we think that they're not very likely to respond to this medication, we could perhaps consider prioritizing second-line treatments like TMS and using this subtyping approach to identify what is the optimal target for treatment. We're currently testing this strategy to see exactly how well it works. ❖

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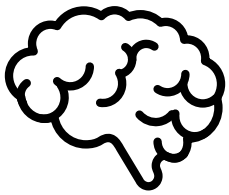

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Stan B. Floresco, Ph.D.
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Robert Freedman, M.D.
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David Goldman, M.D.
Andrea Beth Goldschmidt, Ph.D.
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Raquel E. Gur, M.D., Ph.D.
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Sheena Josselyn, Ph.D.
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Atsushi Kamiya, M.D., Ph.D.
Eric R. Kandel, M.D.
Thomas L. Kash, Ph.D.
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Richard S.E. Keefe, Ph.D.
Christoph Kellendonk, Ph.D.
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James L. Kennedy, M.D.
Robert M. Kessler, M.D.
Mazen Kheirbek, Ph.D.
Mary-Claire King, Ph.D.
Arnold Kriegstein, M.D., Ph.D.
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Francis S. Lee, M.D., Ph.D.
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Vikaas S. Sohal, M.D., Ph.D.
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Rita J. Valentino, Ph.D.
Jeremy M. Veenstra-VanderWeele, M.D.
Susan M. Voglmaier, M.D., Ph.D.
Aristotle N. Voineskos, M.D., Ph.D.
Nora D. Volkow, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Daniel R. Weinberger, M.D.
Myrna M. Weissman, Ph.D.
Rachel Yehuda, Ph.D.
Jared W. Young, Ph.D.
L. Trevor Young, M.D., Ph.D., F.R.C.P.C., F.C.A.H.S.
Carlos A. Zarate, Jr., M.D.

2026 Klerman & Freedman Prizes for Exceptional Research by BBRF Young Investigator Grantees

Six Young Investigators received the annual BBRF Klerman and Freedman Prizes on Friday, July 24th in New York City, in recognition of their exceptional research.

These prizes pay tribute to Gerald L. Klerman, M.D. and Daniel X. Freedman, M.D., whose legacies as researchers, teachers, physicians, and administrators have indelibly influenced neuropsychiatry.

The prizes recognize exceptional clinical and basic research by young scientists who have been supported with BBRF Young Investigator Grants—our hallmark program which enables aspiring young scientists with innovative ideas to garner the pilot data needed to go on to receive further funding once they have "proof of concept" for their work.

The prize winners are selected by committees of the Foundation's Scientific Council, an all-volunteer group of 191 distinguished scientists across brain and behavior research disciplines. This early recognition of their work by the Foundation's Scientific Council often serves as a precursor to further accomplishments, awards, and prizes as well as to their establishment as independent investigators at their institutions.

Gerald L. Klerman, M.D.

Dr. Klerman, who held important academic positions at Yale and Harvard, made substantial contributions to psychiatric diagnosis and classification during a time of great change. He understood and appreciated the importance of descriptive, biological, psychoanalytic, social, interpersonal, and behavioral approaches, and was uniquely able to integrate them cogently. He demanded that theories and hypotheses be tested empirically, and spearheaded many key scientific research programs. He headed the Alcohol, Drug Abuse and Mental Health Administration under President Carter, and, with Dr. Myrna Weissman, co-developed interpersonal Psychotherapy (IPT).

Daniel X. Freedman, M.D.

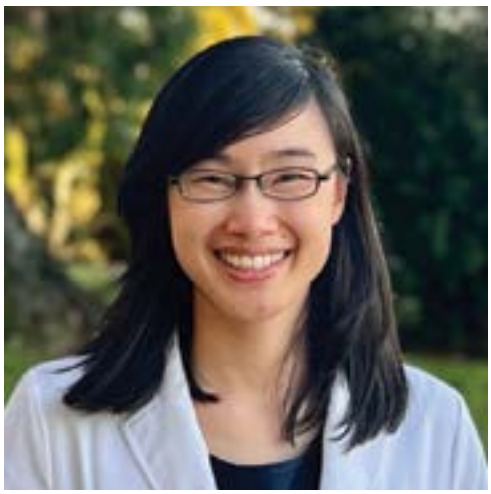
Dr. Freedman was one of the most important American academic psychiatrists of the postwar period. He was an innovator in bringing the biological sciences to psychiatry. Over the years, he, and successive waves of students who were attracted to work with him, continued to explore and develop ideas regarding neurotransmitters in the brain. He profoundly impacted the academic structure of the field through his leadership roles at Yale University, the University of Chicago, and UCLA.

The 2026 Klerman Prize

The Klerman Prize was established in 1994 by BBRF Scientific Council Member Myrna Weissman, Ph.D., in memory of her late husband, Gerald Klerman, M.D.

The Selection Committee for the Prize was chaired by **Carolyn Rodriguez, M.D., Ph.D.** The co-chair was **Anissa Abi-Dargham, M.D.** Other members included: Carmen Andreescu, M.D., Zafiris J. Daskalakis, M.D., Ph.D., Cecile D. Ladouceur, Ph.D., Diego Pizzagalli, Ph.D. and David Silbersweig, M.D.

2026 Klerman Prizewinner for Exceptional Clinical Research



Joline M. Fan, M.D.

University of California, San Francisco

2022 BBRF Young Investigator

Dr. Joline Fan was honored for her work on "Mapping Corticolimbic Circuitry of Arousal Using Human Intracranial Electrophysiology in Individuals with Severe Depression."

Dr. Fan's research focuses on understanding overlapping brain circuitry underlying mood, sleep, and epilepsy, and on advancing personalized neuromodulation strategies for psychiatric and neurologic disorders. Her work investigates how deep-brain networks regulate mood, arousal, and pathological excitability.

Utilizing intracranial recordings from an ongoing clinical trial at UCSF involving individuals with treatment-resistant depression, Dr. Fan has demonstrated that corticolimbic and arousal networks are interconnected and that targeted stimulation of these circuits can modulate both mood and wakefulness. Her studies have helped identify neural biomarkers that may guide more personalized therapeutic interventions. More recently, she has advanced the use of low-intensity focused ultrasound as a non-invasive tool for stimulation mapping and modulation of deep brain networks involved in mood and related symptoms.

"The Klerman Prize is deeply meaningful to me because it recognizes work we are doing to understand brain circuits underlying mood and sleep and to translate these findings to personalized neuromodulation therapies. I am deeply honored and humbled to acknowledge that these types of efforts require a huge team of support, including from mentors, collaborators, and patients."

2026 Klerman Prize Honorable Mentions

Erica Berlin Baller, M.D.
University of Pennsylvania

2023 BBRF Young Investigator

Dr. Erica Baller was honored for her work on "Anxiety as A Disease of Network Disruption: Learning from Multiple Sclerosis."

Dr. Baller cares for hospitalized individuals with both medical and psychiatric disorders and leads a research program that uses multiple sclerosis as a model to understand how white matter disease in the brain contributes to mood, anxiety, and cognitive disorders. To do this, she combines advanced brain imaging, medical record research, and targeted clinical patient evaluations to map how injury location and burden relates to symptom profiles and clinical trajectories. Her work aims to enable early, targeted treatment for the general psychiatric population, as well as patients most vulnerable to psychiatric complications of neurological diseases.

"Consultation-liaison psychiatry sits at a complicated intersection—close to patients, but historically distant from basic and translational science that drives the field forward. When I committed to a research program anchored in the psychiatric care of medically ill patients, it felt like a risk. This recognition means so much to me because it affirms that rigorous, translational approaches to the psychiatry of medical illness are not only feasible but valued."

Nili Solomonov, Ph.D.
Weill Cornell Medicine

2022 BBRF Young Investigator

Dr. Nili Solomonov was honored for her work on "Precision Functional Mapping: A Novel Approach for Target Engagement During Psychotherapy for Late-Life Depression."

Dr. Solomonov focuses on developing scalable, neuroscience-informed psychotherapies for depression. She applies computational modeling, artificial intelligence, and neuroimaging to identify mechanisms of treatment response and design targeted interventions. Her lab conducts clinical studies in mid- and late-life depression, suicidality, and postpartum depression, leveraging multimodal longitudinal data to uncover illness heterogeneity. A central focus of her work is social reward processing as a mechanism of action, which has informed the development of interventions such as Engage & Connect and machine learning–based approaches for precision treatment assignment. Her program emphasizes translation of scientific insights into scalable interventions, delivered to underserved populations in community settings.

"I am deeply honored to receive the Klerman Prize Honorable Mention. BBRF's early support was instrumental in launching my independent research program. I am humbled to be part of the community of accomplished, innovative, and inspiring BBRF-supported scientists."

The 2026 Freedman Prize

The Freedman Prize was established in 1998 in honor of the late Daniel X. Freedman, M.D., a founding member of BBRF's Scientific Council.

The Selection Committee for the Prize was chaired by **Marina Picciotto, Ph.D.** The co-chair was **Cecilia Flores, Ph.D.** Other members included: Ted Abel, Ph.D., Mazen Kheirbek, Ph.D., Keri Martinowich, Ph.D., Colleen McClung, Ph.D., and Bita Moghaddam, Ph.D.

2026 Freedman Prizewinner for Exceptional Basic Research

Vineet Augustine, Ph.D.

University of California, San Diego

2023 BBRF Young Investigator

Dr. Vineet Augustine was honored for his work on "Cardiac Interoceptive Neural Networks Modulating Mental States in Health and Disease."

Dr. Augustine's laboratory studies how signals from the body's internal organs are sensed, transmitted to the brain, and translated into physiological responses and behavioral states. His central focus is cardioception, the neural encoding and central representation of cardiac signals, a research domain his laboratory has established and defined. His team asks a fundamental question: does the heart actively shape how the brain works, or is it merely regulated by the brain?

His most recent work demonstrates that myocardial infarction (heart attack) is not a condition confined to the heart, but a distributed neurobiological disorder orchestrated by a defined three-node circuit linking specialized pain-sensing neurons in the vagus nerve, hypothalamic brain circuits, and sympathetic ganglia in the neck, and it actively drives disease progression after a heart attack. When any node of this circuit is blocked, heart damage is substantially reduced, electrical stability is restored, and cardiac function improves. This work opens new avenues for circuit-based therapeutics targeting heart disease through the nervous system.

"Receiving the Freedman Prize is a profound honor. To be recognized by BBRF for research that started with a simple question and grew into a new exciting area is something I will carry with me throughout my career. I am deeply grateful to BBRF and to the scientific community that has supported this work."

2026 Freedman Prize Honorable Mentions

Xiaoting Wu, Ph.D.
Icahn School of Medicine at Mount Sinai

2023 BBRF Young Investigator

Dr. Xiaoting Wu was honored for her work on "Neural Mechanism Underlying Valence-Associated Social Memory."

Dr. Wu's research aims to understand how neural circuits and brain activity support social cognition in both health and disease. Her lab focuses on social memory, social decision-making, and related aspects of social behavior, with a particular interest in how molecules and neuromodulators shape the function of brain circuits. To achieve this, her lab combines cellular, circuit, and systems-level approaches to map how the composition of neural circuits gives rise to brain activity and subsequently social behavior. Dr. Wu hopes to use these insights to advance the development of therapies for the social deficits common in autism, schizophrenia, and mood disorders.

"Receiving the Freedman Prize Honorable Mention is a deeply meaningful recognition of my lab's work. This acknowledgment motivates us to keep pushing forward in our efforts to understand the neural basis of social cognition, and to move closer to our ultimate goal of improving treatments for mental health disorders."

Wendy Xin, Ph.D.
University of Toronto

2023 BBRF Young Investigator

Dr. Wendy Xin was honored for her work on "Unraveling Fear: Investigating The Role of Parvalbumin Interneuron Myelination in the Formation and Preservation of Fear Memories."

Dr. Xin studies how neurons interact with oligodendrocytes, the cells that make myelin in the central nervous system. Disruptions in myelin lead to significant motor and cognitive impairment and are also linked to a range of neurodevelopmental and psychiatric conditions, including schizophrenia, autism spectrum disorders, and mood disorders. Dr. Xin is exploring how oligodendrocytes and myelin influence brain development, activity, and plasticity. Her work aims to deepen our fundamental understanding of the brain and pave the way for new therapeutic approaches targeting myelination to treat neurodevelopmental and psychiatric disorders.

"I'm deeply honored to receive the Freedman Prize Honorable Mention just as I launch into my independent career. This recognition is incredibly affirming and strengthens my commitment to uncovering how myelin contributes to neurodevelopmental and psychiatric disorders."

Workplace Matching Gifts

Are you passionate about supporting research? Interested in having your employer match your donation to BBRF? It's very easy. Check with your company to see if they match charitable donations. If they do, whatever gift you make to BBRF, they may match it, doubling the impact of your gift! If BBRF isn't on your employer's matching gift list, you can request BBRF be placed on their list and ask that they match your gift to BBRF.

To learn how to make a workplace matching gift, contact 646.681.4889 or development@bbrfoundation.org.

Recent Research Discoveries

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

Stress Vulnerability Differs in Males and Females, Revealing Circuit That Might Be Targeted to Protect Against Stress, Especially in Females

A new study has provided what is likely the most detailed account to date of biological changes that take place in the brain when someone has post-traumatic stress disorder (PTSD). The findings shed light on PTSD pathology, identify specific and potentially targetable genetic, cell-type, and functional alterations, and also shed light on factors distinguishing brain changes in PTSD vs. major depressive disorder (MDD).

When we are subjected to stress, the body responds by producing stress hormones, the most pervasive of which in humans is cortisol. A continuing subject of research is precisely how the proliferation of stress hormones acts upon the body and brain to initiate and/or accelerate pathological processes that contribute to illnesses such as anxiety disorders, depression, and PTSD.

A new study in *Molecular Psychiatry*, whose first author is 2020 BBRF Young Investigator **Brian F. Corbett, Ph.D.**, of Rutgers University, does precisely this kind of work. It explains the mechanism by which cellular receptors for cortisol and other stress hormones (glucocorticoids) act to regulate the expression of a specific gene that tends to protect us from the harmful impacts of chronic stress. Interestingly, the team, led by **Seema Bhatnagar, Ph.D.**, also shows how this mechanism has an important protective role in females even in the absence of stress. Dr. Bhatnagar, who is affiliated with the Children's Hospital of Philadelphia and University of Pennsylvania, was the recipient of BBRF Young Investigator grants in 2000 and 1998.

Past research has shown that cortisol and other glucocorticoids counter inflammation caused by stress when these hormones activate the body's stress response system organized around the so-called "HPA axis" (formed by the hypothalamus, pituitary and adrenal glands). Newly generated stress hormones bind to glucocorticoid receptors (GRs) found in cells throughout the body and brain. Once bound, something remarkable happens: the entire complex moves into the cell nucleus, where DNA of the genome resides. There, the complex binds to specific locations, or loci, in the genome. These genome binding sites are called GREs, or glucocorticoid response elements.

Once bound to GREs, GRs act as "transcription factors," meaning that they have the ability to regulate gene expression—when and how much a particular gene or genes are activated. Activated GREs can suppress or reduce the activation of genes that are involved in generating inflammation; their effect is anti-inflammatory. But this process can go awry and the pro-inflammatory effects of stress can go unchecked. This is called glucocorticoid resistance, typically caused by chronic activation of GRs. This is one way in which stress generates inflammation in body and brain, which in turn can cause illness—in the case of brain, inflammation that can promote anxiety, depression, or PTSD.

Drs. Corbett and Bhatnagar have created a breed of rats that has enabled them to learn much more about exactly how stress hormone-activated GREs alter gene expression to reduce stress-related inflammation and behavioral changes that this can cause—notably, social withdrawal when an animal is subjected to intense, chronic stress.

The rats they use in these experiments have a specific GRE deleted from the genome. The team used the genome-editing tool called CRISPR/Cas9 to cut out this tiny element from among the billions of DNA elements that comprise the rat genome. Rats are used as a proxy for humans, as their genomes and brains are very similar to those of people due to our common evolutionary history as mammals.

There are thousands of GREs in the genome (in both rats and people), but the one deleted by the team was in a specific location: very close to a gene called S1PR3. Why this

particular GRE? In past experiments, they had noticed that expression of the S1PR3 gene was significantly higher in the medial prefrontal cortex (mPFC) of rats that were resilient to stress. Expression of the equivalent human gene is known to be reduced in veterans with PTSD and is negatively correlated with symptom severity.

Like people, some rats are unusually vulnerable to stress while others are highly resistant to its negative impacts. The team subjected both kinds of rats as well as "average" stress responders to intense social stress, caused when one animal dominates and bullies another repeatedly. "When stress-vulnerable rats are stressed in these experiments," Dr. Corbett explains, "they show reduced sociability and depression-like behavior. On the other hand, resilient rats, when stressed, behave like non-stressed controls." Propelling the research forward was the realization that "we didn't know why S1PR3 [expression] was high in resilient rats. Then we had the idea

that maybe it isn't naturally high, but is actually increased by stress."

The team's prior experiments established that elevated S1PR3 expression was linked with protection from the ill effects of chronic stress. They showed that when stress hormones dock at GR receptors and activate GREs in the nucleus, this raises the expression of S1PR3—specifically, in the mPFC of resilient rats. This, in turn, promotes active coping and sociability "by mitigating stress-induced inflammatory processes in the mPFC." Elevated mPFC levels of S1PR3 were not seen in stress-vulnerable rats.

In the new experiments, the team tested rats whose GRE near the S1PR3 gene had been deleted and compared them with typical or "wild-type" animals. The aim was to test whether this GRE locus, in particular, was the one responsible for the protection from stress seen in resilient animals. Males with the missing GRE after being subjected to "social defeat stress"—as expected—had elevated markers of inflammation and exhibited social withdrawal. What was most interesting was the fact that female rats with deleted GREs showed the same inflammatory and behavioral response, but, importantly, even when they had not been subjected to social-defeat stress.

This is a potentially powerful fact pertaining to differences in stress response long observed in males and females (rodents and people). Average, healthy adult female rats have 5 to 10 times more stress hormone in circulation than males—a level similar to that seen in males only when they are under stress. The team suggests that their naturally higher stress hormone levels make females especially dependent upon the "protective" impact generated when the S1PR3 gene is activated. This was seen in their experiments: more than males, females depend upon the activation of this particular GRE by stress hormones to boost S1PR3 expression and the protection it provides.

Regarding that protection, in animals with deleted GREs, the team noted elevated levels of a type of neutral activity between the brain's locus coeruleus (LC) and mPFC in males subjected to social defeat stress, but also in non-stressed females. Might this be a pathway be involved in protection against stress? Evidence in support of this theory was obtained by the team in a final set of experiments, in which they inhibited this LC-mPFC circuit. In stressed male rats that had the critical GRE deleted, the circuit was hyperactive, but inhibiting it during social defeat had the effect of increasing the animals' social interactions. In effect, they became resilient to the stress.

In addition to confirming results of prior experiments about mechanisms involved in resilience and vulnerability to chronic stress, the team, in noting the different responses to GRE deletion in males and females, may have discovered something with powerful implications for treating stress in females. It may make sense, they suggest, to try to treat such stress in people by finding a way to inhibit the LC-mPFC pathway whose activation is associated, at least in rodents, with stress resilience. This possibility can now be pursued in future studies. ❖

Genetic Analysis Across 14 Psychiatric Disorders Suggests the Degree to Which Different Disorders Are Driven by Shared Biological Processes

A newly published study in the journal *Nature* involving dozens of past and present BBRF grantees, Scientific Council members and prize winners, among hundreds of co-authors, takes an important step forward in the effort to better understand what various psychiatric illnesses have in common and what makes them distinctive—specifically, at the level of genetics, but also, perhaps, underlying biology.

Comparing illnesses that have separate diagnostic criteria (as comprehensively captured, for instance, in the DSM-V manual used by psychiatrists) is trickier than it may sound. First, many patients with one disorder are ultimately diagnosed with other, ostensibly distinct disorders—for example, those who suffer from depression and anxiety; or from PTSD and anxiety and depression. Some (but by no means all) people with bipolar disorder experience psychotic episodes, which are typically associated with schizophrenia. Many people diagnosed with eating disorders also suffer from anxiety disorders and/or OCD. The list goes on. In such cases, are the comorbid illnesses in any way related? Or wholly distinct in their biological causation and underlying mechanisms?

Even from the genetic point of view, distinguishing among different diagnoses can be more complex than might be assumed. Researchers have learned over the last 2 decades that there are many overlaps in genetic vulnerabilities for various disorders, in some cases extensive.

Dr. Andrew Grotzinger, of the University of Colorado, one of the lead authors of the new paper trying to "map the genetic landscape across 14 psychiatric disorders," explains: "Right now, we diagnose psychiatric disorders based on what we [doctors] see in the [examining] room, and many people will be diagnosed with multiple disorders. That can be hard to treat, and disheartening for patients." The team's new research, he says, "provides the best evidence yet that there may be things that we are currently giving different names to that are actually driven by the same biological processes."

As noted by another team leader, **Jordan W. Smoller, M.D., Sc.D.**, a 2002 BBRF Young Investigator, the new findings, among other things, provide key insights into the biological pathways and gene expression patterns of specific brain-cell types that are implicated in various illnesses. "These findings provide valuable clues for advancing our understanding and treatment of mental illness with greater precision," he said.

The team noted in its paper that "the full scope of shared and disorder-specific genetic influences [upon mental illnesses] remains poorly defined." The large international team, which included members from 10 Working Groups of the influential Psychiatric Genomics Consortium (PGC), addressed the problem by "triangulating across a suite of cutting-edge statistical and functional genomic analyses" which were applied to 14 childhood- and adult-onset psychiatric disorders. Data from genome-wide association studies (GWAS) and related studies involving over 1 million patients and 5 million healthy controls were used.

The 14 illnesses were: ADHD, alcohol-use disorder, anorexia nervosa, anxiety disorders, autism spectrum disorder, bipolar disorder, cannabis-use disorder, major depression, nicotine dependence, OCD, opioid-use disorder, PTSD, schizophrenia, and Tourette syndrome.

Analyses of the combined dataset revealed that five underlying "genomic factors" accounted for 66% of the genetic differences between those with any of the 14 disorders and those without them. In addition, the researchers identified 238 genetic variants associated with shared risk pathways across disorders.

The five "factors" referred to by the team are actually five groupings of the 14 disorders, each of which has a "shared genetic architecture," i.e., genetic features that are common to all disorders in the factor. In one of the five categories, dubbed "SB" because it consists solely of schizophrenia and bipolar disorder, more than 70% of the genetic "signal" for one disorder is part of the signal for the other disorder. At the level of "signs and symptoms" as observed by doctors, these two illnesses have long been viewed as quite distinct. And yet, at the level of genetics, most of the commonly occurring DNA variations associated with elevated risk in both illnesses are the same.

This suggests underlying biological pathway and gene-expression irregularities in cells that may be impacted by some of the genetic variants that the two illnesses share. In some cases, and in certain combinations, where present, these gene variations may generate similar symptoms in a subset of patients, such as mood swings, or psychosis, or certain cognitive impairments. Because of pleiotropy (one gene having a role in multiple symptoms), this is very hard to untangle—but the data in the new study speaks to the importance and potential treatment benefits, for patients, of trying to do so.

The four other groupings of the 14 disorders based on genetic architecture are: disorders with compulsive features (eating disorders, Tourette syndrome, OCD, for example); "internalizing conditions" in which symptoms are directed inward (major depression, anxiety, PTSD); substance-use disorders; and neurodevelopmental disorders (autism, ADHD, for example).

In each of the groups, "we saw that the included disorders are more similar than unique," at the level of genetics, Dr. Grotzinger says. Ideally, this knowledge might lead, he suggested, to "strategies to target them in a different way, one that doesn't require, say, four separate pills or four separate psychotherapy interventions." ❖

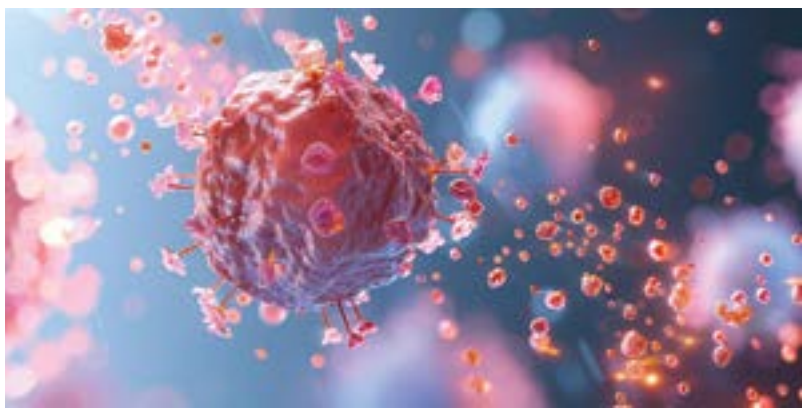
Major Depression Shares Immune Signature With Inflammatory Skin Ailments, Suggesting Novel Therapeutic Possibilities, Study Indicates

A growing body of evidence suggests the immune system is dysregulated in some patients with major depressive disorder (MDD). Past studies have shown that 20% to 30% of patients have low-grade systemic inflammation. Now, newly published research co-led by BBRF grantees shows one way in which links between the immune system and depression may be exploited to develop new therapeutics to reduce depression symptoms.

Two of the co-first authors of the paper reporting the new research in *Molecular Psychiatry*, **Flurin Cathomas, M.D.**, and **Lyonna Parise, Ph.D.,** and two of its senior authors, **Scott J. Russo Ph.D.**, and **James W. Murrough, M.D.,** were involved in a study published in 2024 that explained how a protein called MMP8, released during chronic social stress by circulating immune cells, can invade the brain and induce changes that in animal models correlate with behavioral changes such as social avoidance that are seen in depression and other mood disorders.

Dr. Cathomas received a BBRF Young Investigator grant in 2020 and Dr. Parise in 2022. Dr. Russo is a BBRF Scientific Council member and 2008 and 2006 Young Investigator. Dr. Murrough, also a Scientific Council member, received a Young Investigator grant in 2009.

The new research explores the concept of whether drugs like those approved for use in inflammatory skin conditions such as atopic dermatitis (AD) and psoriasis might potentially benefit major depression patients.



"Despite the large number of studies describing immune changes in MDD, few clinical studies have tested the efficacy of anti-inflammatory drugs in reducing depression symptoms," the team noted. This, they said, "stands in stark contrast to primary immune-inflammatory disorders like AD and psoriasis." AD is the most common inflammatory skin disorder, affecting up to 10% of adults; psoriasis affects another 3%. Dysregulation of T-helper cells plays a key role in both conditions.

T-helper cells (also called CD4+ lymphocytes) are key players in the adaptive immune system. They activate other immune cells, including B cells, macrophages, and cytotoxic T cells, to combat infections. They recognize specific pathogens and differentiate into specialized subtypes to tailor immune responses against intracellular bacteria, parasites, or viruses.

Pathways involving one of the subtypes of T-helper cells, called Th2 (T-helper 2), are inhibited by a drug called dupilumab (Dupixent) that has been approved for long-term treatment of moderate-to-severe AD. Delivered via injection, this monoclonal antibody therapeutic targets a site on a receptor called IL-4, a cellular regulator of the immune response.

A first step taken by the team in exploring the possibility of using a drug like dupilumab in depression was to compare the immune signature of MDD patients with those of people with AD and psoriasis. Were there similarities? They analyzed blood samples from 25 people with MDD, 30 with AD, 21 with psoriasis, and 32 healthy controls who were neither depressed nor suffered from any inflammatory conditions. Levels of 353 proteins in the blood were assessed.

This revealed that MDD shares certain aspects of the inflammatory signature seen in AD, specifically elevated Th2 pathway activation as well as several other immune and neurovascular abnormalities. In MDD patients, the Th1 pathway also showed elevated activation, although less prominently than the Th2 pathway. In AD, Th2 "skewing" results in activation of particular T-helper cells and up-regulation of certain proteins whose levels correspond with activation of specific immune cell types.

A computer-driven analysis suggested to the team that dupilumab, which, in targeting the IL-4 receptor, inhibits the Th2 pathway, might help to reverse the immune signature seen in the MDD patients. To test this possibility, they used mice and a behavioral paradigm called social-defeat stress. Animals dominated by aggressive cagemates develop behaviors analogous to those seen in depression. In stress-naïve animals, they used a drug to inhibit the portion of the IL-4 receptor (the IL-4-alpha subunit) targeted by dupilumab. The animals were then subjected to social-defeat stress, but did not develop social-avoidance behavior that is the usual result.

The study demonstrated that the serum of patients with MDD "contains unique up-regulation of neuroinflammatory and vascular inflammation or cardiovascular risk proteins, but also shares immune abnormalities with inflammatory skin diseases, most notably the Th2 skewing in AD." These abnormalities appear to be modifiable by inhibiting IL-4 receptors. Before a drug like dupilumab would be tested in human patients, human studies and clinical trials are needed, the researchers said, to determine the precise role of the Th2 pathway in major depression.

While the study doesn't indicate any overlap in pathology between MDD and AD or psoriasis, the results do indicate that systemic inflammation is common to all three "and generally hastens disease progression." The hope, the team said, is that in MDD, as in AD, therapeutic targeting of proinflammatory pathways that all three disorders share would result in a significant reduction in depression symptoms and reduction of the chance of disease progression via inflammatory pathways. ❖

Therapy Update

Recent news on treatments for psychiatric conditions

PILOT TRIAL COMBINING COGNITIVE BEHAVIORAL THERAPY (CBT) WITH PSILOCYBIN YIELDS RAPID, SUSTAINED RELIEF OF MAJOR DEPRESSION

Marc J. Weintraub, Ph.D.

David J. Miklowitz, Ph.D.

A research team led by BBRF grantees has published positive results of a small pilot trial that combined several months of cognitive behavioral therapy (CBT) for major depressive disorder (MDD) with two administrations of psilocybin, the psychedelic drug found in certain species of mushrooms.

A number of clinical trials in depression have tested psilocybin combined with various forms of psychotherapy or psychological support. Those experiencing positive outcomes have sometimes experienced pronounced effects. But there has been a lack of standardization in psychotherapy procedure in these trials, which has made results difficult to compare, including analysis of the relative contributions to outcomes of the drug and the co-administered psychotherapy.

In the *Journal of Affective Disorders* reporting results of the new study, the authors note: "Ultimately, it has been difficult to know what psychotherapies have been used with psilocybin, and what these adjunctive treatments are doing." The team was led by **Marc J. Weintraub, Ph.D.**, a 2023 BBRF Young Investigator at UCLA; its senior member, also at UCLA, was **David J. Miklowitz, Ph.D.**, 2011 winner of the BBRF's Colvin Prize, 2001 BBRF Distinguished Investigator and 1987 Young Investigator.

The researchers set out to pair psilocybin with CBT, a standardized, evidence-based therapy that has been consistently associated with antidepressant effects in people with MDD. The "most profound effects" of CBT, they note, are in preventing or delaying depressive relapses. Among CBT's virtues, in addition to its broad usage and carefully vetted impacts in depression and other mood disorders, is the fact that it is "manualized": therapists who offer it can adhere to published procedures that reflect many years of practice and refinement.

For this pilot trial, 16 participants were recruited, with current major depression symptoms that were rated as moderate in severity. There were no controls; all knew that they were receiving combined psilocybin and CBT therapy. The typical participant was in their early 40s. Three-fourths were White, 44% were female, and about two-thirds were college graduates.

Psilocybin-assisted CBT was given over a 4-month period and included 12 one-hour sessions (9 weekly then 3 biweekly). Psilocybin, in capsule form, was administered after psychotherapy sessions 3 and 6—first at a dose of 10 mg and then at 25 mg in the second session if the patient did not have adverse reactions (none did). After assessment following completion of the 12 sessions, a follow-up assessment was made 3 months later.

Though the cohort was small, results were impressive. "Following weeks of psychotherapeutic preparation, psilocybin provided immediate and significant relief from mood and anxiety symptoms," the team reported. The combined treatment "was rated as highly acceptable by participants and study clinicians, with no serious adverse events reported."

Independent assessments indicated that 13 of the 16 participants showed at least moderate improvement in depressive symptoms (25% improvement or greater) by the

end of treatment, by which time 9 had fully remitted from depression. Improvements in depression symptoms and in tests measuring psychosocial functioning after psilocybin was administered were maintained at the 3-month follow-up. The team found that changes in depression severity were correlated with improvements in emotion regulation and what they call "positive and negative cognitive schemas," by which they mean the patient's ability to think positively and to deemphasize negative self-conceptions. This suggests one possible way in which the psychedelic drug may have synergistic effects when administered in concert with CBT.

These results, in the team's view, justify larger, randomized and placebo-controlled trials in which psilocybin is combined with CBT and other forms of standardized, evidence-based psychotherapy. It would make sense, they said, to try to more precisely account for psilocybin-specific antidepressant effects in subsequent tests. The team is currently taking this approach in a randomized trial that compares psilocybin-assisted CBT to psilocybin treatment with minimal psychotherapy. They also note it would be worth testing psilocybin with some of the patient groups excluded from this test, including people who are not physically healthy, those who are taking medicines that affect the serotonin system, and those who experience major depressive episodes in the context of bipolar disorder. ❖

PERSONALIZED ACCELERATED TMS THERAPY TARGETING BRAIN'S THREAT CIRCUITY SIGNIFICANTLY REDUCED PTSD SYMPTOMS

Sanne J.H. van Rooij, Ph.D.

A clinical trial led by BBRF grantees has demonstrated for the first time that personalized targeting of non-invasive TMS brain stimulation therapy can reduce the brain's reactivity to threat in patients with PTSD.

Noting robust reductions in PTSD symptoms after a follow up period of 3 to 6 months in those who received the therapy, the researchers said that TMS as they administered it "may induce a brain state where approaching trauma-related memories and triggers is more acceptable" to patients, and that over time following the treatments, this may lead "naturally to reduced PTSD symptoms as patients take their lives back."

It's a potentially important development in PTSD therapy, since many who receive standard evidence-based psychotherapy (e.g., "exposure therapy") or drug therapy (only two medicines, paroxetine and sertraline, are approved for PTSD) either do not respond, drop out of treatment, or relapse over time.

The trial, recently reported in the *American Journal of Psychiatry*, involved 7 BBRF grantees and was led by **Sanne J.H. van Rooij, Ph.D.**, a 2021 and 2018 BBRF Young Investigator. Among the paper's senior authors were **William M. McDonald, M.D.**, a 1999 BBRF Young Investigator, and **Kerry J. Ressler M.D., Ph.D.**, a BBRF Scientific Council member, 2017 BBRF Distinguished Investigator, 2009 BBRF Freedman Prize winner, and 2005 and 2002 BBRF Young Investigator.

This was the first clinical trial seeking to demonstrate the impact of personalized TMS targeting a specific portion of the amygdala that has been shown to mediate reactivity to perceived threat. "Dysregulation within the brain's threat neurocircuitry, particularly hyperactivity of the amygdala, is a central mechanism underlying clinical symptoms in PTSD" as well as the related condition called hyperarousal, the researchers noted. Hyperarousal is a state of chronic, heightened physiological and emotional alertness that can lead to severe anxiety, irritability, hypervigilance, insomnia, and intense reactivity to triggers—all features of PTSD.

In neuroimaging studies, greater reactivity of the amygdala to perceived threat has been associated with nonresponse to trauma-focused therapy. In addition, when the right portion of the amygdala has been deactivated in surgeries addressing treatment-resistant epilepsy, doctors have noted the amelioration of PTSD in patients who suffered PTSD symptoms in addition to epilepsy. These and other observations have led to the theory that over-engagement of the right amygdala is a main driver of PTSD symptoms.

TMS cannot reach far enough into the brain to directly alter neural activity in the amygdala. But in the newly reported clinical trial, the team wanted TMS, which directs magnetic pulses into the brain, to be focused on an area of the cortex (the dorsolateral prefrontal cortex, or DLPFC) lying a little less than one inch below the scalp—specifically, a spot that is most robustly connected, functionally, with the right amygdala. Their premise was that low-frequency TMS—known to reduce cortical excitability—would also have the effect of reducing right amygdala reactivity to perceived threat, provided it were focused on that functionally connected spot in the cortex.

The trial was double-blinded and randomized. The patient cohort consisted of 50 people, average age about 40, 86% of whom were female and 60% were White. The average score on a scale called PCL-5 to measure PTSD symptoms was 37.7 prior to treatments. (Scores of 31-33 indicate probable PTSD.) All received a pre-treatment fMRI scan, which enabled precise targeting in each patient of the spot in the DLPFC most robustly connected, functionally, to the right amygdala.

Twenty-six randomly selected participants received active low-frequency TMS treatments, at 1-Hz, in twice-daily sessions given over 10 consecutive weekdays. The two daily sessions, separated by 10 minutes, delivered a total of 1,800 magnetic pulses to the cortex (36,000 total pulses over the 10 treatment days.) This is considered "accelerated" TMS, as opposed to the much slower schedule of treatments, with similar numbers of pulses delivered over 4-6 weeks, in standard TMS. Twenty-four participants received a placebo treatment, using the same treatment schedule and procedure over 10 days, albeit delivering no active brain stimulation.

The primary outcome measured in the trial was right amygdala reactivity, measured before and immediately after 10 days of TMS/placebo treatments. In those receiving active TMS therapy, the hypothesis was validated: after 10 days of treatment, the right amygdala became less reactive when participants were scanned while being asked to view a series of faces with expressions ranging from fearful to neutral.

The team reported that clinical PTSD symptoms were also "significantly" reduced with active TMS. Hyperarousal symptoms "significantly decreased" in the active TMS group from pre-TMS to the assessment made immediately following the treatment course ("post-TMS"), but not in the group receiving placebo. Total PTSD symptoms "significantly decreased" in the active TMS group from pre-TMS to post-TMS, and from pre-TMS to the assessment made at follow-up. Importantly, the continued improvement at long-term follow-up was not observed in the placebo group.

At the 3- to 6-month follow-up, "a clear separation [in results] was observed" between those who had received active TMS and those who had received placebo. Starting from a pre-TMS PCL-5 score of 39.9, the active treatment group had a 19.5-point reduction, on average (to about 20). Scores below the high 20s indicate symptoms that are below the threshold of clinical PTSD. In the placebo group, after an initial decline in total symptoms (a score decrease from about 37 to about 30, possibly due to the placebo effect seen in most clinical trials), there was no further reduction in the long follow-up period. Hyperarousal symptoms were also markedly lower in the active TMS group at 3-6 months post-therapy, compared with those in the placebo group.

"We think that the full behavioral effects of active stimulation may take some time to emerge," Dr. van Rooij commented, "as many PTSD symptoms reflect learned or adaptive behaviors, such as avoidance, and behavioral change takes time." The team also noted that a delayed or continued therapeutic clinical response in the period following TMS and other forms of brain stimulation for PTSD as well as depression has been previously noted.

It is in the light of this data that the team suggested that targeted treatment with accelerated TMS like that delivered in the trial may, over time, change the brain in ways that render trauma-related memories less likely to result in hyperarousal, and more likely that trauma memories can be accepted and lived with, resulting in an ability of patients to "take their lives back." Larger trials are needed to confirm the findings in this trial, the team said. ❖

GLP-1 DRUG SEMAGLUTIDE SUBSTANTIALLY REDUCED HEAVY ALCOHOL CONSUMPTION AND WEIGHT IN PATIENTS WITH ALCOHOL USE DISORDER + OBESITY

Nora Volkow, M.D.

George F. Koob, Ph.D.

Researchers have reported positive results in the first clinical trial testing the diabetes and weight-loss medicine semaglutide (Ozempic, Wegovy) in treatment-seeking patents with alcohol use disorder (AUD) who were also obese.

Over the years, the FDA has approved three medicines for AUD: disulfiram, acamprosate, and naltrexone, which are only utilized by an estimated 2% to 4% of adults with AUD. These drugs work by reducing cravings or causing severe nausea when alcohol is consumed, but they are seldom prescribed for a variety of reasons. Researchers have been testing a range of alternatives.

There has been considerable interest in adapting semaglutide and other drugs in its class, which have a novel mechanism of action, targeting cellular receptors for a peptide called GLP-1. Stimulators ("agonists") of the GLP-1 receptor have gained widespread attention for their effects on brain pathways involved in appetite regulation and reward. The GLP-1 peptide (a short chain of amino acids) is secreted by cells in the small intestine, but it is also synthesized in the brain. GLP-1 receptors are localized in brain areas involved in reward and addiction.

Several GLP-1 receptor agonists have shown significant reductions in alcohol consumption in animal models of alcohol addiction. In humans, one trial involved 48 patients with AUD, but they were not "treatment-seeking" individuals—they had no particular desire or motivation to reduce or cease their consumption of alcohol. Despite this, low-dose semaglutide was associated with a significant reduction in alcohol consumption over 2 months. In the only reported trial to date involving people with AUD who actively wished to reduce or cease drinking, a once-weekly GLP-1 agonist called exenatide did not result, in the overall group, in a reduction of the number of heavy drinking days, but the drug did enable those with AUD and obesity to do so.

This result became the starting point for the newly reported trial, which was conducted by a team led by Anders Fink-Jensen, M.D., DMSci, of Mental Health Centre Copenhagen and Copenhagen University in Denmark. The team included BBRF Scientific Council member **Nora Volkow, M.D.**, a leading expert on addiction who is director of the NIH's National Institute on Drug Abuse (NIDA); and **George F. Koob, Ph.D.**, a 1999 BBRF Distinguished Investigator. Results were published in *The Lancet*.

The trial, which was randomized, double-blinded, and placebo-controlled, was conducted at the Mental Health Center Copenhagen. All of the 108 participants, evenly divided among men and women, with an average age of about 50 and nearly all White, were seeking to obtain professional help to reduce, control or stop alcohol abuse. All had a body/mass index, or BMI, of 30 or higher (30 is the lower limit of obesity), and were diagnosed (using DSM-V criteria) with alcohol use disorder. Participants had a minimum of 6 heavy drinking days during the 30 before the beginning of the trial (the average number was 17), and 85% met criteria for severe AUD.

They were randomized into two groups of 54, one receiving 26 weekly injections of semaglutide (2.4/mg per dose), the other receiving placebo injections. Up to 10 sessions of cognitive behavioral therapy (CBT) focusing on motivation and craving strategies as well as relapse prevention were available to every participant over the 26 weeks.

Participants who received semaglutide had greater reductions in the number of heavy drinking days (41% fewer, on average) compared to those receiving placebo (26%). The amount of alcohol consumed over the prior 30 days dropped by over 70% in the semaglutide group (from 78 ounces of 100% alcohol at baseline—the equivalent of 130 shots of 80-proof spirits over 30 days—to 23 ounces, or about 39 shots). In the placebo group, typical total consumption over 30 days declined by 46%, much less but still a substantial amount, reflecting the

placebo effect, the desire to reduce drinking, and the fact that participants received CBT therapy over the course of the trial.

Mean number of drinks per drinking day also fell markedly in the semaglutide group, declining by 3.5 (vs. 2.1 in the placebo group). Biomarkers and metabolic measures also showed much greater improvement in the semaglutide group vs. the placebo group. The greatest benefit of semaglutide was seen in the subset of the cohort who reported 12–17 heavy drinking days per 30 days at baseline, as well as in the subset diagnosed with severe AUD. Risk levels for drinking established by the WHO, which are now used in FDA clinical trials for AUD therapies, were also noted to decline by two levels in the semaglutide group after 26 weeks of therapy. The most common adverse effects reported were gastrointestinal, and were more frequent in the semaglutide group, but most were short-lived, and none were severe.

In this trial, mean weight loss was comparable to that of individuals with obesity treated with semaglutide. Those receiving the drug lost about 25 pounds on average, vs. 5 pounds in the placebo group. Importantly, reduction in alcohol consumption was closely related to weight loss in the semaglutide group, although not in the placebo group. This is consistent, the team said, with the "prevailing hypothesis suggesting that [semaglutide's] therapeutic effects arise from overlapping neurobiological mechanisms that modulate both metabolic regulation and reward-related pathways shared between obesity and alcohol use disorder."

The team concluded: "Findings from this trial provide support for broadening the indication for semaglutide to [include] AUD in patients with a BMI of 30 or greater, which could benefit millions." About 890 million adults globally have a BMI over 30, and in the U.S., 8 million adults are estimated to have obesity and high alcohol consumption.

Future studies will need to replicate and expand their results, the team said. Larger and more diverse patient cohorts are needed, lower dosages of semaglutide have to be tested, and follow-ups need to be conducted beyond 26 weeks. ❖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GLOSSARY

BEHAVIORAL ACTIVATION THERAPY (p. 5) aims to reduce the classic depression symptom of anhedonia (loss of interest in pursuing rewards or pleasure) by targeting patterns of avoidance and withdrawal and increasing patients' engagement with rewarding activities. It assumes that increased activity in daily life leads to symptom change. Digital tools that assess activation between therapy sessions are helping therapists monitor treatment progress and make timely adjustments—"data-informed psychotherapy."

DIAGNOSTIC "SENSITIVITY" vs. "SPECIFICITY" (p. 8) Two key ways of gauging the utility of diagnostic tests. Diagnostic sensitivity is a test's ability to correctly identify those with the disease, minimizing false negatives. Diagnostic specificity is its ability to correctly identify those without the disease, minimizing false positives. A test with, for example, a sensitivity of 95%, but a specificity of only 30% identifies nearly everyone with a given illness, but also generates many false positives, limiting its utility.

DIGITAL PHENOTYPING (p. 9) A way to track patients in real time via digital technologies. One example is a passive wearable device that provides moment-by-moment measurement of sleep patterns, daily activity, and heart rate, that is being used for for early detection of major mood episodes in bipolar disorder patients.

DENDRITIC SPINES (p. 15) Commonly called "spines," these tiny knob-like structures protrude from the branches (called dendrites) of neurons. Each spine can be thought of as a structural marker of a synapse—that is, a point of connection between brain cells. Chronic stress associated with depression has the effect of modifying both spines and dendrites, reducing their number relative to a pre-stress condition. Successful antidepressant therapy, conversely, results in a restoration of some (but not all) spines lost to stress, and can spur the growth of new spines. Dr. Conor Liston and colleagues have found that such recovery is required to sustain antidepressant effects over time, but not necessarily to initiate improvements in mood.

ENSEMBLE EVENTS (p. 19) Functional neuroimaging (e.g., fMRI) can reveal patterns of activity among brain cells that share connections. Research shows that ensembles of cells that become active at about the same time—"ensemble events"—can be disrupted by chronic stress, reducing the number of such events and the number of cells involved when they do occur. In animal experiments, treatment with ketamine can "rescue" ensemble activity to levels approaching those seen prior to stress.

NETWORK TOPOGRAPHY (p. 20) The boundaries of neural networks provide information about brain organization and the ways in which information flows among cells and brain areas. The shape of networks changes over time in response to a variety of factors among which are those which give rise to symptoms in psychiatric illness, such as depression. Such changes can be mapped in fMRI scans.

SALIENCE NETWORK (p. 21) One brain network has been observed by Dr. Conor Liston and colleagues to expand dramatically in the brains of people who suffer from depression. This network is called the frontostriatal salience network. The "salience network," as it is often called, is important in orienting attention to emotionally important or relevant stimuli in the environment. Experiments revealed that the network's topography, including its size, is in fact unrelated to how depressed someone is, or even whether they are depressed or in remission. Rather, it may be the case that an enlarged salience network confers *risk* for depression, a theory which, if confirmed, could help identify early in life those who are particularly vulnerable to the illness.

Image credits: p. 15: *Frontiers in Behavioral Neuroscience* (adapted); p. 16 top: *PNAS* (adapted); p. 16 (bottom), p. 19: *Science* (adapted); p. 20, p. 21 (bottom), p. 22 (top): *Nature* (adapted); p. 18, p 21 (top), p. 23: Liston Lab (adapted).

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