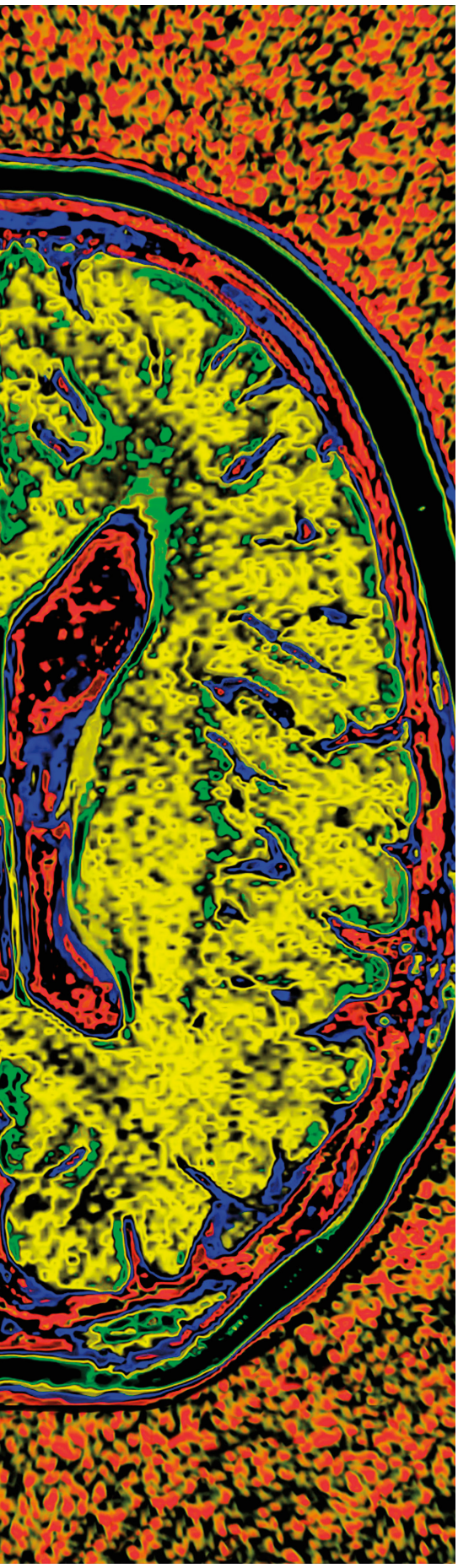


Stanford | MEDICINE

Stanford Experimental Therapeutics Hub

TRANSFORMING THE FUTURE OF PSYCHIATRIC CARE

In 2021, the U.S. surgeon general issued a rare public advisory calling attention to the mental health of our nation's youth. Citing an alarming upswing in rates of anxiety, depression, and suicidal ideation, Vivek H. Murthy, MD, MBA, called for systemic change in supporting the mental health of children, adolescents, and young adults throughout the United States.

Yet our youth aren't the only ones suffering from a mental health crisis: So are people of all ages. Whether it's due to a lack of access to mental health services; residual stress from the COVID-19 pandemic; substance abuse issues; financial, safety, or global worries; or myriad other causes, the United States is facing a mental health crisis of untold proportions. And the problem is getting worse.

In 2014, approximately 18.1% of adults aged 18 or older—43.6 million—had experienced mental illness during the previous year, the Substance Abuse and Mental Health Services Administration reports. By 2021, that number had risen to 22.8%, or 57.8 million people. Perhaps even more telling: In 2021, 57.2 million visits to physician offices resulted in a primary diagnosis of a mental disorder, according to the U.S. Centers for Disease Control and Prevention. And there were 48,183 deaths by suicide nationwide.

Unfortunately, despite the best efforts of clinicians and researchers, the available treatments for mental health disorders often prove inadequate, with many people facing the ongoing, debilitating effects of anxiety, depression, and other conditions when treatment fails.

That's something that a new research initiative being developed at Stanford aims to change.

◀ *Coloured axial magnetic resonance imaging (MRI) scan of the human brain. This view shows the brain's ventricles and the folds of the brain's cerebral cortex.*

"The Experimental Therapeutics Hub is driven by a relentless pursuit of answers. Our goal is to transform the therapeutic landscape of mental health by studying the intricate complexities of the brain and offering tailored solutions that provide relief to those who have suffered far too long."

—**NOLAN WILLIAMS, MD**
Associate Professor of Psychiatry and Behavioral Sciences; Director, Stanford Experimental Therapeutics Hub

Revolutionizing the Treatment of Mental Health Disorders—Led by noted psychiatrist and neurologist Nolan Williams, MD, the Stanford Experimental Therapeutics Hub is being established following the success of a groundbreaking therapy for treatment-resistant depression Dr. Williams developed at the Brain Stimulation Lab. Called the Stanford Accelerated Intelligent Neuromodulation Therapy system, or SAINT, this treatment has led to dramatic improvements in patients with severe depression and ushered in new hope for millions of people suffering from the condition.

Building on the unprecedented success of SAINT and the revolutionary research taking place at the Brain Stimulation Lab, the Experimental Therapeutics Hub will be a place where investigators can have the freedom to expand scientific avenues beyond traditional psychiatric research. The Hub will house the existing Brain Stimulation Lab, in addition to a sister lab, the Stanford Psychedelics and Consciousness Lab, and will create a robust clinical trial enterprise; explore more precise targets for existing and new therapeutics; and investigate the therapeutic potential of psychedelic substances, among other endeavors. The intent of this new effort is to provide relief to the millions of people suffering from depression and other life-limiting mental health issues.

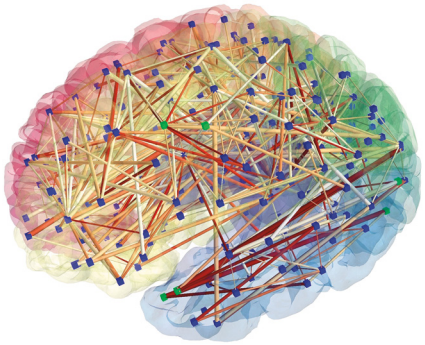
At the helm of this enterprise, Dr. Williams, an associate professor of psychiatry and behavioral sciences, is assembling a team from a broad range of disciplines to join the Hub and advance the field of brain research. Visionaries from neurology, anesthesia, neurosurgery, psychiatry, and neuroimaging are signing on to be part of this accelerated discovery effort.

"Patients struggle with what I call brain emergencies—when the brain is essentially attacking itself to the point that individuals can't function, reaching the point of despair and hopelessness," he says. "We need to meet these critical emergencies with really significant interventions, which we hope the Experimental Therapeutics Hub will be able to provide."

Hallmarks of the Stanford Experimental Therapeutics Hub will include:

The diligent pursuit of answers: Because the underlying biology and physiology of many mental disorders are not well understood, the Hub aims to develop new brain imaging tools, identify biomarkers, and build algorithms to help clinicians properly diagnose and optimally treat disorders. Their goal is to establish guidelines so patients can be quickly and accurately assessed to predict the most effective treatment from the outset—a vast improvement from the traditional patient experience.

A drive for better diagnostic tools: Currently, there are no established physiological characteristics of various mental illnesses; psychiatrists rely on patients accurately relaying their symptoms to come to a diagnosis. And while that can point a provider down the right treatment path, it can be a bit of a guessing game as to what specific disorder a patient may have and which therapy will generate the most effective response. Dr. Williams and his fellow researchers will take a multipronged approach to address this challenge by harnessing the power of machine learning, exploring biological phenotyping, and pursuing advanced imaging techniques. The knowledge gained through these investigations will shed light on the mechanisms behind brain disorders and offer insights to develop highly personalized treatment plans for a vast range of conditions.



NEW HOPE FOR SEVERE DEPRESSION

Nolan Williams, MD, is revolutionizing the treatment of severe depression through his groundbreaking treatment protocol, SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy). An innovative form of repeated transcranial magnetic stimulation (TMS), SAINT uses functional MRI to target a specific region of the brain in each individual patient, then employs an accelerated stimulation regimen involving multiple short TMS sessions every day for five days (vs. once-daily sessions over a period of six weeks in traditional TMS protocols).

SAINT's results are unprecedented: Nearly 80% of those with treatment-resistant depression experience rapid, long-lasting remission, which typically happens within days and lasts for months.

In September 2022, the SAINT protocol was awarded the FDA's stamp of approval as a rapid-acting treatment for severe depression, making it the first commercially available rapid-acting neuromodlation therapy and the first to use functional MRI to map out an individual's brain connectivity to identify the optimal anatomic region for stimulation.

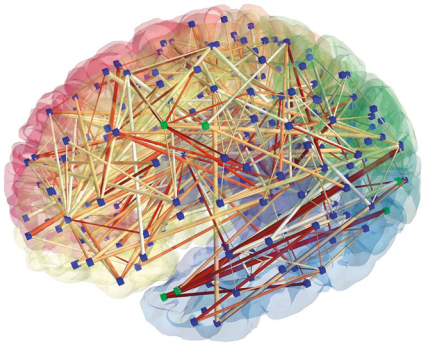
Research Areas Within the Stanford Experimental Therapeutics Hub—Dr. Williams and the dedicated researchers in the Brain Stimulation Lab and Stanford Psychedelics and Consciousness Lab are committed to exploring areas outside the traditional approaches to mental health treatment, including the following:

Refinement and expansion of SAINT's treatment capabilities: The Brain Stimulation Lab is using SAINT as a platform that can be modified for a variety of other difficult-to-treat brain disorders. The team is also refining treatment plans for the subset of patients who experience relief from SAINT applied through a TMS coil but for whom that relief is not durable. They know that these patients often can be successfully treated with repeated sessions, but that route is arduous and time-consuming. As a result, the team is turning its focus toward developing and evaluating a small, minimally invasive, implantable device offering the same benefit that patients would receive from repeated SAINT treatments. This implanted version of SAINT, coined "iSAINT," would deliver precisely targeted stimulation to the brain via electrodes implanted under the scalp—as often and for as long as the patient might require without the need for continued office visits (similar to how a cardiac pacemaker works). This would enable patients to receive effective treatment with minimal disruption to their work, social, and family lives, as well as at reduced long-term cost.

Biomarkers for treatment-resistant depression: Despite decades of functional neuroimaging research, the biological signatures of major depressive disorder (MDD) and other psychiatric disorders remain poorly understood. Conventional resting state functional magnetic resonance imaging (fMRI) analyses, which identify brain networks, have had difficulty reliably detecting psychiatric disorders. As such, Dr. Williams' team conducted a study using fMRI to investigate whether the flow of neural activity differs between patients with MDD and those without. They found that there is an abnormal flow of brain activity within the salience network—a brain network implicated in emotional processing—in many patients with MDD symptoms. Additionally, they showed that Dr. Williams' SAINT protocol restored typical brain activity patterns in the salience network, alleviating these symptoms. These exciting results offer a new pathway for identifying and treating mechanisms of neuropsychiatric diseases.

Stanford Hypnosis Integrated with Functional-Connectivity Targeted TMS (SHIFT): Hypnosis-based treatments offer an affordable, low-burden, nonpharmacological alternative to many neuropsychiatric conditions treated primarily with medication. However, not all people benefit equally from hypnosis. The Brain Stimulation Lab developed SHIFT—a noninvasive brain stimulation protocol designed to increase responsiveness to hypnosis-based treatments. Based on prior research from the labs of Dr. Williams and David Spiegel, MD, the Jack, Lulu, and Sam Willson Professor of Medicine, the Lab designed a neuroimaging-guided intervention using repeated transcranial magnetic stimulation. Results from an initial study showed that this approach increased responsiveness to hypnosis (also called "hypnotizability"). Future applications will test clinical modifications of SHIFT to enhance the effects of nonpharmacological treatments.

Magnesium-Ibogaine: the Stanford Traumatic Injury to the CNS (MISTIC) protocol: Psychedelics and other similar compounds (psilocybin, MDMA, ketamine, and ibogaine) are currently being studied to determine their mechanism



SAINT TARGETS NEURAL NETWORKS

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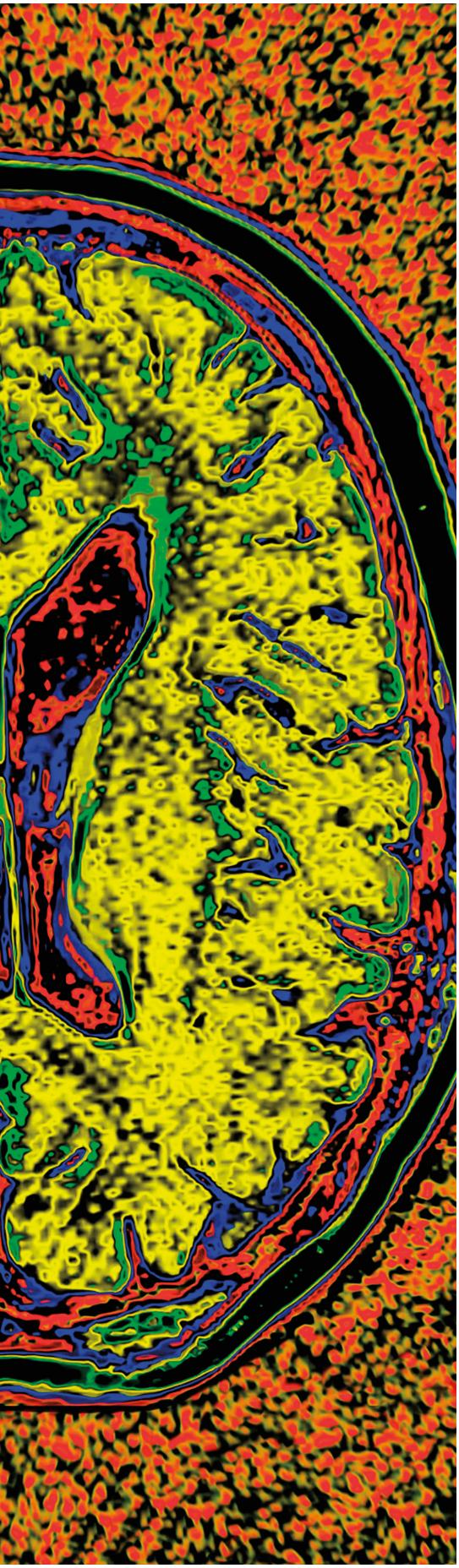

of action and potential therapeutic effects in humans. Initial research shows that many of these compounds offer psychiatric benefits by allowing the brain to enter a highly responsive state and reprocess traumatic memories. A recognized pioneer in studying the efficacy of psychedelics in treating psychiatric disorders, Dr. Williams is studying the use of ibogaine to treat post-traumatic stress disorder (PTSD) caused by traumatic brain injuries in veterans through his MISTIC protocol. In a study with 30 U.S. special operations veterans who exhibited moderate to severe symptoms of depression, anxiety, and PTSD, Dr. Williams' team found that MISTIC resulted in relief of traumatic brain injury-related mental illness and disability, with 80% of participants experiencing remission immediately following treatment. Perhaps even more promising: Researchers observed increased volume and strengthened connectivity of brain regions involved in cognitive function and emotion regulation. Preliminary evidence suggests that these improvements were sustained at six months follow-up. This could mark a turning point for countless people around the world suffering from PTSD and other psychiatric conditions.

Helping to Drive the Science Forward—Dr. Williams and his team are leading some of the most efficacious treatments in psychiatry today, and it is largely due to the unmatched generosity of philanthropic supporters. SAINT was entirely funded by philanthropy and is likely the first treatment approved by the FDA with that distinction.

The importance of philanthropic involvement in this work can't be overstated—it gives researchers greater flexibility to pursue high-risk, high-reward, novel investigations that can yield the most innovative solutions while fast-tracking academic discoveries to real-world therapeutics. We encourage you to continue that legacy of hope—to make a lasting difference in the lives of countless patients, their families, and loved ones, and the future of psychiatric care.

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