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special report

PSYCHIATRY’S NEW FRONTIERS
Hope amid crisis

Is this the defining moment?
A surge in mental health care discovery is underway

Prying open the conversation
Chipping away at stigma

Cultural challenges
Busting the barriers

New wave psychiatry
Delivering quick depression relief through electromagnetism

Beyond the psychiatrist’s office
Mental health solutions for kids in crisis

plus

Choosing optimism
Chelsea Clinton on health equity

A school within the hospital
Connecting children to ordinary life
The term “trauma” is often misused to refer to any form of stress — from physical abuse to test anxiety. Trauma is the focus of my research, and I know as well as anyone how harmful trauma can be. Yet, not every stressful experience is traumatic; and not all stress is bad.

As a culture, we’ve pathologized stress, casting it as a villain — a threat to our mental health that must be avoided, rooted out and vanquished. Too much stress is harmful, but I’ve seen in my patients that some stress is crucial to healthy development. Without it we grow weaker, more vulnerable and less resilient, as individuals and as a society.

So, while trauma and other forms of distress deserve our attention, they’re not the entire story. The rest of the story — capacity for strength, resilience and adaptability — is getting short shrift in our clinics, labs and broader society. For this reason, I’m calling for a reset and reframe, shifting to an approach centering on resilience, strength and adaptability — not pathology.

Research by the Stanford Early Life Stress and Resilience Program, which I direct, has found that strengthening self-confidence and awareness of one’s coping abilities improves the function of the brain’s frontal lobe. In other words, triumphing over challenges can bolster frontal lobe function, which means improved decision-making, focus, emotional self-control and social skills. Our evidence-based, longitudinal studies have also demonstrated that children who practice mindfulness meditation — engaging in appreciation of the moment, regardless of how stressful life might be — get better sleep, which supports their psychological well-being.

The approach I’m advocating is attentive to the entire patient, their medical, personal and psychiatric histories, bringing together expertise on different areas of life, including nutrition, exercise and sleep.

Toward this vision, I encourage patients to employ stress to build confidence, competence and self-determination — not to wholly eliminate it from their lives. Consider, for example, the hypothetical case of Chris, a 10-year-old with acute social anxiety who was getting into fights at his new school. Chris had recently begun splitting time between his newly divorced parents’ apartments, which were in a new school district. It was during transitions from his mom’s to his dad’s that Chris became most upset.

Together, we decided that rather than avoid or eliminate the stressors that triggered Chris’ anxiety — transitions between homes and school — we would anchor on his strengths, which included his ability to bike and his reliable and caring relationships with his parents, his older sister and his dog. When it was time for the siblings to move to their dad’s each Wednesday, rather than getting a ride from their father, they would walk or bike with their dog the 3 miles to his place. These trips became fun adventures that bolstered Chris’ self-confidence. He settled into his new school and began to build friendships, his anxiety became manageable and violent incidents tapered off. Chris learned that he was more than a diagnosis and that by anchoring on his strengths and capabilities he could meet future challenges as they arise.

By shifting from a pathology-centered model into a strength- and competency-based one, we not only better support individuals to help themselves but also to help others. Resilient individuals live more fulfilled lives and are better equipped to help each other and contribute to a more resilient society.

— VICTOR CARRIÓN is the Endowed John A. Turner, MD, Professor for Child and Adolescent Psychiatry.

Victor Carrión proposes that mental health care prioritize building resilience — not avoiding stress.
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A CONVERSATION WITH CHELSEA CLINTON
Given the dire state of mental health and of mental health care in our country, it is easy to feel overwhelmed. The crisis is well-documented, and the situation, especially for teens and children, people of color, LGBTQ+ individuals, and non-English speakers, is untenable. Yet, I believe there is reason to hope. As you’ll find in this issue, we’re seeing promising results and progress in medical research, patient care and education. Stanford Medicine teams bring together experts from diverse disciplines — from psychology and psychiatry to bioinformatics and bioengineering — to advance our fundamental understanding of how the human brain functions and what leads to emotional, social and behavioral problems.

The Stanford Center for Precision Mental Health and Wellness has been at the forefront of this work since it launched in 2018. Its faculty and researchers are transforming the way we detect, define, diagnose and tailor treatments for mental disorders.

The diversity of projects underway across Stanford Medicine is breathtaking. Research seeking to better understand how the brain works using AI-powered imaging techniques, optogenetics (which was founded here at Stanford), and lab-grown clumps of brain tissue known as organoids. Treatments that explore the efficacy of magnetic currents and of psychedelic drugs. Studies linking brain function with the gut microbiome.

The Human Neural Circuitry program, which opened late last year, combines high-touch care and high-tech tools in an inpatient research center to study conditions such as depression and obsessive-compulsive behavior and discover how to better treat them.

Stanford Medicine faculty are leading efforts to address the mental health crisis affecting our young people. The Stanford Parenting Center opened in early 2020 to ensure that parents had easy access to evidence-based mental health information to support their children. It now offers a wide variety of resources online and through webinars and virtual classes. And a suicide prevention toolkit co-authored by Stanford Medicine mental health experts is being used nationwide.

Finally, and possibly most importantly, society today recognizes that mental health is an integral facet of public health — and that a mental health crisis needs to be acted on with the same urgency as any other public health crisis. We are recognizing that we must develop the skills and habits to support our own resiliency and mental fitness. Across any number of metrics — from the growing percentage of Americans seeking information about it online to the heartening increase of related telehealth visits — we are beginning to give our mental health the attention it deserves.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of Stanford School of Medicine
Vice President for Medical Affairs at Stanford University
Professor of Otolaryngology-Head & Neck Surgery
Reviving cognition

IN 2001, Gina Arata was in her final semester of college, planning to apply to law school, when she suffered a traumatic brain injury in a car accident. The injury so compromised her ability to focus that she struggled in a job sorting mail.

“I couldn’t remember anything,” Arata said. “My left foot dropped, so I’d trip over things all the time. I was always in car accidents.”

In 2018, Jaimie Henderson, MD, professor of neurosurgery at Stanford Medicine, implanted a device deep inside Arata’s brain to electrically stimulate the central lateral nucleus, which regulates many aspects of consciousness.

Arata noticed a difference immediately. When asked to list items in a grocery store’s produce aisle, she could rattle off fruits and vegetables. Then a researcher turned the device off, and she couldn’t name any.

“Since the implant, I haven’t had any speeding tickets.” Arata said. “I don’t trip anymore. I can remember how much money is in my bank account. I wasn’t able to read, but after the implant I bought a book. Where the Crawdads Sing, and loved it and remembered it.”

Four others with traumatic brain injuries have benefited from the experimental procedure developed by researchers at Stanford Medicine and several other institutions. The results are described in the Dec. 4, 2023, issue of Nature Medicine.

A need for TBI treatment

More than 5 million Americans live with the effects of traumatic brain injury — difficulty focusing, remembering and making decisions. Though many recover enough to live independently, their impairments prevent them from returning to school or work and from resuming their social lives.

“In general, there’s very little in the way of treatment for these patients,” said Henderson, the John and Jene Blume-Robert and Ruth Halperin Professor of neurosurgery, who shared senior authorship of the paper with Nicholas Schiff, MD, a professor at Weill Cornell Medicine.

The post-surgery progress of Arata and the other participants was measured by a standard test of mental processing speed called the trail making test. At the end of the 90-day treatment period, they had improved their speeds on the test by 32% on average.

“Our goal now is to try to take the systematic steps to make this a therapy,” Schiff said.
Alexa, manage my diabetes
A NEW ARTIFICIAL INTELLIGENCE application for monitoring Type 2 diabetes runs on a device already familiar to tens of millions of Americans: a smart speaker, commonly used to play music and check the weather.

Stanford Medicine researchers developed the voice-activated app, which tells patients the correct insulin dose without requiring them to contact their doctor’s office or wait for an appointment.

“People simply don’t have that much access to care,” said Ashwin Nayak, MD, clinical assistant professor of medicine. “We want to empower patients to do it themselves.”

A paper about the app was published Dec. 1, 2023, in JAMA Network Open. Nayak shares lead authorship with Sharif Vakili, MD, clinical assistant professor of medicine. The senior author is Kevin Schulman, MD, professor of medicine and co-director of the Clinical Excellence Research Center at Stanford Medicine.

The study followed 32 individuals with Type 2 diabetes who were taking insulin and struggling to achieve healthy blood-glucose levels. Half of them received a speaker preloaded with the voice-based AI software. Each participant’s insulin protocol — including starting insulin dose, goal for fasting blood glucose, and insulin-dose instructions — was included in the software on their device.

Though the trial sample size was small, the impact was dramatic. Over the eight-week study period, 81% of patients in the group who used the AI-enabled device achieved glycemic control of their diabetes compared with 25% of patients who received traditional care. Patients using the device had their insulin dose adjusted more frequently and needed far fewer doctor’s appointments to get their diabetes under control.

Autoimmunity’s XX factor
THAT SECOND X chromosome is the reason women are more susceptible than men to autoimmune disorders, according to a study published Feb. 1, 2024, in Cell.

In mammals, male sex is typically determined by the presence of single X and Y chromosomes in every cell. Female sex is determined by the presence of two X chromosomes — but that arrangement risks generating twice the number of X-coded proteins per cell, which would be toxic. So, nature devised a clever workaround: X-chromosome inactivation.

Yet, as the researchers found, X-chromosome inactivation, which is achieved by a molecule called Xist, can lead to autoimmune disorders. The gene for Xist is present on all X chromosomes, but Xist is produced only in cells with an XX pair.

Xist, in cahoots with other proteins it recruits, coats the genes of one of the female cell’s two X chromosomes, drastically cutting its output. But, they found, the oddball complexes of proteins and genetic material formed in the inactivation process can trigger a strong immune response.

This could account for why as many as 4 out of 5 people in the U.S. with autoimmune disease are women, according to lead author, basic life research scientist Diana Dou, PhD, and senior author, genetics professor Howard Chang, MD, PhD.

Eating disorder admissions rise
IN THE PAST decade, physicians have taken a broader view of adolescent eating disorders, thanks to greater recognition of eating patterns that can harm patients’ health, especially their heart function.

As a result, hospitalization rates for the disorders have climbed six- to seven-fold since 2010, according to a Stanford Medicine-led study of admissions at 12 U.S. hospitals published Dec. 21, 2023, in Hospital Pediatrics.

Much of the increase includes patients who might not have been diagnosed with disordered eating in the past. These individuals are not underweight when diagnosed but have undergone dangerously rapid weight loss.

More teens are also being diagnosed with a condition called avoidant/restrictive food intake disorder, which was formally recognized in 2013 for patients who struggle to eat enough food for reasons that aren’t related to body image.

“Eating disorders have the highest mortality rate of any psychiatric disorder,” said the study’s senior author, Megan Vo, MD, medical director of the Eating Disorders Outpatient Clinic at Stanford Medicine. “We have an opportunity here to save lives.”
Telomeres’ obesity connection

A GENETIC MARKER linked to premature aging — shortened telomeres — reversed in obese children during a diet and exercise program, according to a study published Oct. 23, 2023, in Pediatric Obesity.

Like the solid segment at the end of a shoelace, telomeres are protective caps that prevent a chromosome’s ends from fraying. They tend to gradually shorten with aging, but various conditions, including obesity, cause them to shorten prematurely.

In the study, the researchers followed 158 children, all of whom were 8 to 12 years old and obese. From baseline to the end of the weight-management program, the children’s average telomere length increased significantly. It shortened again in the year after the program ended.

The study’s results may help explain the basis of the biological benefits of losing weight, eating healthier and being more physically active.

“We saw that the recommended behaviors everyone knows about — eating fewer high-fat or high-sugar foods and fewer calories, increasing physical activity, and reducing screen time — can slow down biological aging associated with obesity in children,” said the study’s senior author, Thomas Robinson, MD, who is the Irving Schulman, MD, Professor in Child Health.

Lab-grown heart tissue yields insights

RESEARCHERS HAVE ENGINEERED heart tissue out of stem cells to study what makes our body’s engine tick. A team led by Joseph Wu, MD, PhD, the Simon H. Stertzer, MD, professor of medicine and of radiology, created the tissue and is using it to study how an abnormally fast heartbeat — tachycardia — can cause the heart to lose its ability to pump blood sufficiently, a condition known as tachycardia-induced cardiomyopathy.

“Tachycardia is probably more common than we think,” said postdoctoral scholar Chengyi Tu, PhD.

To study the condition, Wu and his collaborators conducted a 10-day experiment using the engineered heart cells: Over the first five days, they induced tachycardia by stimulating the tissue with electricity. Over the next five days, the tissue made a full recovery.

The outcome tracks with what doctors already know about tachycardia-induced cardiomyopathy — that the condition is mostly reversible.

In another experiment, the researchers used electricity to induce tachycardia in a different group of engineered heart cells. The team supplemented some of the cells with NAD — a molecule that supports energy reactions. On the day after electrical stimulation ended, the treated cells recovered 83% of their original function, whereas the untreated cells showed little improvement.

By giving patients NAD through an off-the-shelf supplement or by IV injection, the researchers believe they can restore the chemical balance and accelerate a patient’s recovery from tachycardia-induced cardiomyopathy.

The results of the experiments were reported Nov. 27, 2023, in Nature Biomedical Engineering. Tu is the lead author, and Wu is the senior author.

Equalizing cancer screening

NATIONAL guidelines that rely on age and smoking exposure to recommend people for lung cancer screening are disproportionately failing minority populations, according to a new study.

A method incorporating additional information, including family history and health problems, more successfully eliminates racial disparities, the study found.

The findings, published Oct. 26, 2023 in JAMA Oncology, are based on data on a group of 105,261 U.S. residents with a history of smoking.

To compare the national guidelines with the alternative method, the researchers looked at the eligibility-to-incidence rate — the number of people in a group eligible for screening compared with the number of lung cancer cases found in that group over a certain time. Higher ratios imply adequate screening; lower ratios imply that some lung cancer cases are occurring in people who were not deemed eligible for screening.

Based on the national guidelines, white people had a ratio of 20.3, while African Americans had a ratio of 9.5. The alternative method did better at cutting disparities, resulting in a ratio of 18.4 for white people and 15.9 for African Americans.

The researchers hope that their findings will spur dialogue about how to devise more equitable guidelines for lung cancer screening.

Summer Han, PhD, associate professor of neurosurgery and of biomedical informatics is the study’s senior author.
PSYCHIATRY’S NEW FRONTIERS
Hope amid crisis

Reasons for hope

SOLUTIONS FOR THE MENTAL HEALTH CRISIS EMERGE THROUGH INNOVATIVE RESEARCH, DIAGNOSTICS AND TREATMENTS
By Nina Bai
PHOTO ILLUSTRATION BY JULES JULIEN

IT’S THE SPRING OF HOPE FOR MENTAL HEALTH, astir with novel discoveries, life-changing therapies and more openness than ever before — yet, for many, it feels like the winter of despair. The pandemic years, that crucible of stress, isolation and uncertainty, fueled and exposed mental health problems. In 2022, nearly 1 in 4 American adults (about 59 million people) said they experienced a mental illness in the previous year, but only half of those afflicted reported receiving any mental health treatment.
Among children and adolescents, the prevalence of mental illness, which had been steadily creeping upward, jumped during the pandemic, according to the U.S. Substance Abuse and Mental Health Services Administration. In 2019, 15.7% of American adolescents aged 12-17 reported experiencing a major depressive episode in the past year. In 2022, that number was 19.5%. That same year, 13.4% of adolescents — just over 1 in 8 — seriously thought about killing themselves.

And even as the pandemic has stoked demand for mental health care, it also has worn down the mental health workforce, already short-handed, with early retirements and widespread burnout. Access to affordable, effective interventions remains a daunting barrier. People face long waiting lists and lack of insurance coverage. Many treatable conditions remain undiagnosed because people lack a way to obtain assessments.

Yet, below this perfect storm of mental health crisis, there is a strong undercurrent of hope that begins in the lab. Research is leading the way toward treatments that are more effective, more personalized and more accessible.

“The manner in which we know the brain now, compared with what we knew in previous decades, is incredibly different,” said Victor Carrión, MD, the John A. Turner, MD, Endowed Professor for Child and Adolescent Psychiatry and vice chair of the department of psychiatry and behavioral sciences.

Collaboration is vital for translation, and our departmental awards and programs promote and emphasize synergy between research and clinical practice,” said Laura Roberts, MD, the Katharine Dexter McCormick and Stanley McCormick Memorial Professor and chair of the department of psychiatry and behavioral sciences. “Our bench scientists doing tremendous research also work alongside our clinicians to make sure that new knowledge translates to the clinical setting and has a direct impact on patient care.”

Researchers developing transcranial magnetic stimulation, for example, work with clinicians who treat patients with severe depression to design clinical trials, and their techniques are informed by teams inventing new ways to measure the flow of brain signals and those building virtual reality models of the brain.

A clearer understanding of the biology of mental health disorders not only leads to breakthrough treatments — but just as powerfully, helps dissipate stigma.

“There’s been a large shift in stigma in the past 25 years,” said Heather Gotham, PhD, clinical professor of psychiatry and behavioral sciences, who leads the coordination of a nationwide network of centers dedicated to implementing evidence-based mental health care.

The Mental Health Technology Transfer Center Network, funded by the Substance Abuse and Mental Health Services Administration, offers training in preventing school violence, substance use in the workplace, adolescent depression and more, and it offers support for mental health providers seeing refugees and asylum seekers.
“One thing that’s made a difference is the greater understanding that mental health disorders and substance use disorders are chronic, relapsing disorders of the body, just like diabetes and heart disease,” Gotham said.

With this new awareness, more people want to be mental health literate. In the past few years, Gotham has seen a surge of interest, from a broader community, in the network’s online courses — from teachers, for example, who want to be more responsive to the needs of students and reduce stigma in the classroom.

Less stigma also means more money for research and mental health services. Funding for mental health has become a rare bipartisan issue. In 2022, Congress passed the Bipartisan Safer Communities Act, which has provided $245 million to fund mental health services like training for school personnel, first responders and law enforcement and expanding the 988 suicide and crisis lifeline.

Stanford Medicine researchers know that to make the most impact with their discoveries they must reach those who need help the most — through online symptom screenings, virtual therapy, group therapy, inclusive clinical trials and community interventions.

They are training mental health professionals locally and globally in new evidence-based techniques. Providers in more than 38 countries, for example, have been trained in cue-centered therapy, a 15-week treatment program developed at Stanford Medicine to help children and teens recover from chronic trauma. Recently, pro bono training in cue-centered therapy was provided to clinicians in Ukraine.

What gives Roberts hope is that a more open conversation on mental health is drawing together experts from different fields with a shared purpose. “It used to be that clinicians would stay in their clinical practice and refer to journals for new research, and researchers would stay in the lab and never see a patient — and we don’t have that now,” she said. “I see more openness and more flexibility from the current generation of researchers and clinicians.”

Read on in this issue of Stanford Medicine to learn about some of the ways Stanford Medicine researchers and clinicians are advancing the understanding of mental health and sharing that knowledge. SM — Contact Nina Bai at nina.bai@stanford.edu
Crammed elbow to elbow around a table in a tiny basement-level Clark Center conference room, a multidisciplinary cross-section of scientists, physicians, engineers and students convened to scarf sandwiches and compare notes.

They were there that fateful Friday in 2019 because Karl Deisseroth, MD, PhD — one of Stanford Medicine’s most forward-thinking researcher-clinicians — had invited them. And lunch was on him.

“We needed a lot of sandwiches in that jam-packed little room,” recalled the D. H. Chen Professor and a professor of bioengineering and of psychiatry and behavioral sciences.

He referred to the every-few-months gatherings that typically occurred on Fridays as “clinical subgroup meetings,” but most who were invited knew them simply as “Karl’s lunches.” And for the med school’s most inquisitive minds, they were hot-ticket invitations.

Deisseroth began putting these lunches together more than a decade ago not to feed bored, hungry medical folks but to feed fires in them, foster communication and create the kind of alchemy he believed necessary for quicker medical science advances. Turns out, it worked.

In November 2023, Deisseroth and his team of collaborators introduced a major byproduct of that bread breaking: the Human Neural Circuitry program. Stationed at a corner suite partitioned from a wing on Stanford Hospital’s fifth floor, the recently launched program pools the expertise of disparate brain specialists — psychiatrists, neurologists, neurosurgeons, anesthesiologists and bioengineers.

At the team’s disposal: cutting-edge tools to measure cognitive function, a high-powered data-gathering infrastructure to process and study brain activity in real time, and experienced hospital
staff to care for patients from within and outside the Stanford Health Care system.

What makes the program unique? There is the supercharged network speed and computational power: Data goes from the patient’s brain, transmitted by electrodes placed inside the skull or detectors on the surface, to a server across campus and back to the researchers in half a millisecond, Deisseroth said.

And there is the hybrid hospital room/research setting that includes a small bio lab where living cells coming straight from a patient’s brain can be instantly analyzed, with full consent of the participants. The cells come from clinically useful electrodes that were placed for medical care and would otherwise have been discarded. A graduate student in Deisseroth’s lab at the time — Sam Vesuna, MD, PhD, currently a resident in Stanford’s psychiatry program — heads up that bio lab analysis.

“This area of the hospital is set up for medical care of patients who have just had brain surgery and have electrodes implanted deep in their brains,” Deisseroth said. “It’s state-of-the-art medicine, but it also provides an amazing source of real-time data from the brain of a human being.”

Another asset this setup offers: human communication. Alongside the electrophysiological and cellular analyses, people provide real feedback — whether prompted by an artful psychiatric interview or just natural conversation. Mice and other animals have aided neuroscience understanding, but the limitations are obvious.

“There’s nothing like the real-time verbal feedback we can get from our fellow human beings,” Deisseroth said.

**IF YOU BUILD IT**

Deisseroth, the program’s creator and director, is both a practicing psychiatrist, mostly treating patients with depression and autism, and one of the world’s leading neuroscientists and bioengineers. With a foothold in the research and clinical worlds, he was an ideal person to broker the launch of the program.

The goal? To study the human brain in a fashion previously attempted only in animal models. In time, the collaborators believe, discoveries made through the program will lead to new therapies for all manner of neuropsychiatric disorders — conditions ranging from depression and anxiety to epilepsy and Parkinson’s to obsessive-compulsive disorder and autism to eating disorders and schizophrenia.

The Human Neural Circuitry program is an extension of the lunches where the silo-busting began. Those helping Deisseroth run it — Paul Nuyujukian, MD, PhD, assistant professor of bioengineering and of neurosurgery; Carolyn Rodriguez, MD, PhD, professor of psychiatry and behavioral sciences; and Vivek Buch, MD, assistant professor of neurosurgery and the Christina and Hamid Moghadam Faculty Scholar — represent historically disparate fields of brain science but gathered for many meetings a week over the past two years to build the program.

A FLASH OF LIGHT

Deisseroth caught a glimpse of this future at that standing-room-only lunch in 2019 that sparked the program’s creation. During the discussion, a member of Deisseroth’s team (graduate student Isaac Kauvar, who was working with Vesuna) shared results of their mouse study of dissociation — a mental disconnection of emotion from sensations of the body. A neurosurgeon (professor of neurosurgery Jaimie Henderson, MD) chimed in that he had performed surgery on an epilepsy patient experiencing spontaneous dissociation.

Eyebrows immediately raised around the table; intrigued smiles formed. Why couldn’t those two studies be synergized, with resulting insights made many more times powerful?

Then, Deisseroth, Kauvar, Vesuna and several colleagues launched their study: Using comparative data from laboratory mice and a patient at the Stanford Comprehensive Epilepsy Program suffering from a severe seizure disorder, the team was able to implicate a particular kind of activity of certain sets of cells in dissociation — in human and mouse. The team — which also included Henderson, the John and Jene Blume-Robert and Ruth Halperin Professor; Nuyujukian; and Josef Parvizi, MD, PhD, professor of neurology, who had treated the initial patient with Henderson — published their results in 2020 in *Nature*.

Their reveal of this physical underpinning for a previously unexplainable mind state became the crucial proof of concept for a collaborative program combining brain studies in animals and humans.

After the success of this effort, Deisseroth began rallying stakeholders to create the broader program, meeting with hospital and medical school leaders, space planners, nurses, physicians, clinical trial staff, and research protocol committees, along with Nuyujukian, Rodriguez and Buch.

Many years — and many conversations — later, the Human Neural Circuitry program was born. Several studies have been launched through the program, with more on the way — all using the powerful tools of modern science inside a clinical setting with real patients: a dream come true for those seeking to understand the inner workings of the brain.

“This program makes clear,” Deisseroth said, “the irreplaceable value of just getting together and talking over lunch.”

**SM**

— Contact Mark Conley at mjconley@stanford.edu
‘It’s state-of-the-art medicine, but it also provides an amazing source of real-time data from the brain of a human being.’

DATA GOES FROM THE PATIENT’S BRAIN, TRANSMITTED BY ELECTRODES PLACED INSIDE THE SKULL OR — AS MODELED HERE, BY HIGH DENSITY EEG DETECTORS ON THE SKULL’S SURFACE — TO A SERVER ACROSS CAMPUS AND BACK TO THE RESEARCHERS IN HALF A MILLISECOND.
Going beyond ‘How often do you feel blue?’

AI emotional assessments are aimed at diagnosing mental illness more accurately and quickly

By Nina Bai
Illustration by Juan Bernabeu

One way to find out how someone is feeling is to ask them. “In the past two weeks, how often have you felt little interest or pleasure in doing things?” begins a standard questionnaire for depression. “How often have you felt afraid, as if something awful might happen?” inquires one questionnaire for anxiety. “Several days? Nearly every day?”

Self-reporting is how most psychiatric disorders are diagnosed and monitored today, but it’s far from perfectly reliable. In a sense, these are subjective impressions at brief
points of time, usually recorded in environments outside a person’s daily life, such as a psychiatrist’s office.

Researchers at Stanford Medicine are developing artificial intelligence tools to not only provide a more accurate picture of a person’s mental well-being but also to flag those in need of help and guide providers in choosing treatments. Certainly the stakes are high — with concerns for privacy, safety and bias — but AI is opening up unprecedented possibilities in psychiatry.

One AI tool being developed would evaluate the details of speech to predict a patient’s anxiety and depression severity, said Betsy Stade, PhD, a postdoctoral fellow at the Stanford Institute for Human-Centered Artificial Intelligence, who has built machine learning models that can do just that.

“These new tools will give us some objective, reproducible measures, instead of being based on what the person is thinking of themselves at the very moment they are filling out the questionnaire,” said Ehsan Adeli, PhD, assistant professor of psychiatry and behavioral sciences.

In speech, for example, people with depression tend to use more first-person singular pronouns: I, me, my, mine. “This effect is so subtle that you might not notice it in conversation, but despite being small, it’s quite robust,” Stade said.

In another study, Stade found that people with depression tend to talk specifically about sadness, while those with anxiety talk about a wider range of emotions.

Therapist offices of the future may be equipped with AI assistants that listen and analyze in the background — suggesting the best medications, therapy techniques and even specific phrases a therapist might use in responding to a patient.

Adeli is developing so-called ambient intelligence — technology integrated into buildings that can sense how the people inside are doing. In addition to audio analysis, pressure sensors on the floor could measure walking gait, thermal sensors could track physiological changes, and the same visual systems that help self-driving cars navigate roads could detect unusual behavior.

Using ambient intelligence in hospitals or senior care facilities, for example, could identify an occupant who is hallucinating, at risk of suicide or showing early signs of cognitive decline.

Outside clinical settings, AI is already serving as a first-line screener for people in crisis. Recently, Stanford Medicine researchers worked with a telehealth company to develop Crisis-Message Detector 1, which could quickly and accurately identify patient messages suggesting that the patient was having thoughts of suicide, self-harm or violence to others. These messages were flagged and prioritized for review by crisis specialists, reducing wait times for people experiencing mental health crises from nine hours to less than 13 minutes.

AI systems like Crisis-Message Detector 1, intelligent buildings and speech analyzers are designed to alert and assist humans, who ultimately choose next steps and provide care.

“I don’t think AI is ready to be the sole decision-maker, nor should it be in the future,” Adeli said.

SOME PREFER AI THERAPY

But autonomous AI therapists are on the horizon. Companies are creating AI that can offer cognitive behavioral therapy and empathetic support, initially through text, but they eventually could incorporate audio and video to read a client’s facial expressions and body language.

Whether patients will engage with a nonhuman therapist remains to be seen, but one recent survey found that 55% of respondents would prefer AI-based psychotherapy — citing convenience and the ability to talk more openly about embarrassing experiences.
The concept of an artificially intelligent therapist isn’t new. In fact, one of the earliest conversational programs, named ELIZA, developed in the 1960s at the Massachusetts Institute of Technology, was designed to mimic a Rogerian psychotherapist. Its creator, Joseph Weizenbaum, meant to show AI’s inferiority to human conversationalists but, to his dismay, many people found ELIZA compelling, even compassionate.

(A few years later, a computer science professor at Stanford University created a chatbot in the opposite role. PARRY was designed to mimic a person with paranoid schizophrenia — often expressing fear, anger and mistrust — and to serve as a practice patient for students.)

These days, with the rapid advance of large language models, people are “hacking” ChatGPT for mental health support — by prompting it to act like a therapist, or even Sigmund Freud.

**MORE WAYS AI COULD HELP**

Training an AI therapist might require reams of real therapy transcripts, which are not readily available because of patient privacy concerns. But new research suggests that giving an AI model fewer transcripts of good quality and then “tuning” its responses — to be more empathetic, for example — could work just as well. Generative AI could even generate more training data.

Ever since ELIZA was developed, people have pondered AI’s potential to make mental health care available to the masses.

At first, AI could deliver more prescriptive kinds of therapy, Stade said — such as cognitive behavioral therapy for insomnia, or support in between sessions with a human therapist. She is part of a Stanford team developing an AI “companion” to help people practice the skills they learn in cognitive behavioral therapy, such as identifying and reframing negative thoughts.

“When I think about the promise of fully AI psychotherapists, I think of the possibility that you could be getting huge numbers of patients really high-quality treatment at very low cost,” she said.

In 1975, the scientist Carl Sagan, PhD, imagined “computer psychotherapeutic terminals,” like telephone booths, that could be available to the public for a few dollars per session.

“No such computer program is adequate for psychiatric use today, but the same can be remarked about some human psychotherapists,” he said.

Ironically, our attempts to create an AI therapist could help us identify exactly what it is that makes a good human therapist.

Psychotherapy works — about as well as medications in many cases — but how it works is not well understood. We don’t know why some therapists are consistently more effective than others who offer the same treatments, or why some patients improve while others do not.

Most research into therapy looks at outcomes over weeks of treatment, not what happens between therapist and patient minute to minute. Features that make therapy successful are difficult to capture without fine-grained analysis of the therapy experience. This is where AI could be extremely useful.

“There are all these nuanced and very detailed decision points that therapists face, probably hundreds of them, within any given therapy session,” Stade said. “We just don’t have enough information about if some of those decisions are crucial, if they’re really the drivers of people getting better.”

Instead of replacing humans, perhaps AI’s real potential is to show us how to better help ourselves.

— Contact Nina Bai at nina.bai@stanford.edu
WHEN HE HELPED LAUNCH the course PSYC 215: Introduction to Psychedelic Medicine in the fall of 2019, Gianni Glick knew there was a resurgent wave of interest in medical research devoted to the use of psilocybin and MDMA for tough-to-treat disorders like anxiety, depression and post-traumatic stress disorder.

As a psychiatrist involved in clinical trials, he had watched firsthand as these illicit drugs, cleared for research purposes, worked seeming miracles on stuck brains that
hadn’t budged on more conventional interventions.

One thing he didn’t know while fine-tuning the syllabus for the course, among the first of its kind in a major medical school setting: The 100 available seats wouldn’t be nearly enough. “Every year the class fills up within 15 minutes of the start of the enrollment period,” said Glick, MD, assistant professor of psychiatry and behavioral sciences. “Sometimes we have people packed in, standing along the wall, just to listen.”

The popularity of the course — co-taught with Trisha Suppes, MD, PhD, professor of psychiatry and behavioral sciences, and Boris Heifets, MD, PhD, assistant professor of anesthesiology, perioperative and pain medicine — reflects a skyrocketing global interest in psychedelic therapies since COVID-19 magnified the dire need for better mental health treatments.

It’s mirrored by Stanford Medicine psychedelics research, past, present and in the pipeline. It’s also indicative of a once-flourishing psychiatric movement that might just be rising from the ashes to meet the moment of need.

“There is such hope and hunger for this to work because there hasn’t been much mental health innovation the past four decades,” Heifets said. “We don’t yet understand these drugs well enough, so we need to tread forward and study them cautiously.”

FLY SAFE

THERE IS ONE THING SCIENCE has concluded with conviction about psychedelic therapy for mental health conditions: A well-trained copilot — a therapist, psychiatrist or psychologist — is essential to a trip’s successful therapeutic outcome.

“These drugs allow you to do things you can’t do with waking consciousness,” Williams said. “But they really shouldn’t be recreational substances — they’re too powerful.”

Psilocybin — the psychoactive ingredient in magic mushrooms — and MDMA — the synthetic drug known as ecstasy or “molly” — are the primary substances gaining scientific traction. Both are illegal under U.S. federal law, but exceptions are made for their use in medical research.

The anesthetic ketamine — also known as the party drug Special K — is considered “psychedelic adjacent” because its dissociative effects can feel similarly mind-altering — more of a stepping-outside-one’s-body experience than a full-on technicolor Alice in Wonderland-style kaleidoscope trip. Ketamine is also much easier to study because of its longtime legal status within medicine.

Suppes is organizing the core group of Stanford Medicine investigators, among the thousands worldwide, who are aggressively studying how these compounds work on neural pathways. Suppes; Heifets; Williams; Karl Deisseroth, MD, PhD; Carolyn Rodriguez, MD, PhD; Leanne Williams, PhD; and Charles DeBattista, MD — all senior faculty in the Department of Psychiatry and Behavioral Sciences investigating the drugs’ effects on cognition or specific disorders — have formed a working group to share ideas and find collaborative research opportunities.

In the 1950s and ’60s, before they became known as illicit drugs used for recreation, psychedelics were widely researched around the world for psychiatric use — 40,000 subjects tested led to 1,000 papers written. But as they leaked from the lab into

‘He described feeling more alive, more connected to the world, safe in his own body again — and not just then, but for months afterward.’
the counterculture party scene, President Richard Nixon passed the Controlled Substances Act as part of his War on Drugs initiative in 1971 — essentially grinding all medical research on the drugs to a halt.

Now, as government regulation loosens, studies are coming fast and furious at places like Johns Hopkins and Yale universities; University of California, San Francisco; and Stanford Medicine. Bolstered by this growing body of science, the U.S. psychedelic medicine market is expected to bloom into a $12 billion industry by 2029. A scan of the global database for ongoing clinical trials shows more than 1,800 that involve psilocybin, MDMA or ketamine. Add in LSD and that total soars higher.

As the number of Americans facing mental health challenges has skyrocketed, the U.S. government has gotten on board. In December 2023, Congress passed legislation that included funding for clinical trials of psychedelic-assisted therapy for active-duty service members. This January, the Department of Veterans Affairs announced that it will also begin funding psychedelic-assisted therapy to treat veterans with PTSD and depression. Beyond the use by veterans, the FDA is expected to approve MDMA for treating anxiety with PTSD by this fall. Australia has moved even more swiftly: In July 2023 it joined Switzerland as the only countries to make medicinal psychedelics a reality.

**IS MIND EXPANSION THE POINT?**

Stanford Medicine is uniquely contributing to psychedelic research, Heifets believes, in its mechanistic approach to studies: the attempts to understand how the drug, the setting, the guidance, the “trip” and the expectation all factor into the outcomes.

“We’ve done some very creative science to get at issues such as, ‘What is the experience of dissociation like? What is the neurophysiology of tripping? How does hope factor into the equation?’” he said. “That’s where I see our Stanford collaborative group really setting itself apart and bringing something unique to the study of psychedelics.” For instance, Heifets and collaborators found a way to get around psychedelics’ placebo-controlling limitations — how do you fake a psychoactive experience? — by administering ketamine to depressed patients who were already under anesthesia. The result: Depression levels remitted even for those who didn’t receive ketamine.

“We’re seeing signs that nondrug factors, such as giving patients hope, drive this process,” Heifets said. Some of that research tells Heifets that efforts underway elsewhere that focus on removing the psychedelic effects of psychedelics might be missing the point. “There is a growing body of evidence,” he said, “that the experience matters.” Heifets and collaborators think they’ve identified multiple reasons. MDMA and psilocybin both appear to have the ability to dissolve one’s sense of self to a point where formerly rigid thought pathways can be altered. Psilocybin seems to enhance the brain’s capacity for change — known as neuroplasticity — something that mental illness frequently stifles.

The consciousness-expanding ability of these substances is just one factor. Working with a professional who sets expectations before the trip, provides supervision in a safe environment and helps process the material that arises is an equally important part of the equation, the science is showing.

Suppes and collaborators are close to publishing a study on the effects of psilocybin used by veterans with treatment-resistant depression. “What we’ve seen so far has been pretty astounding — we just need to do more,” said Suppes, noting that pilot studies have not always found the strength of the psychedelic experience to be key to response. She and co-investigators have embarked on a follow-up psilocybin dosing with most of the veterans in her original study and are set to launch another comparing the effects of MDMA and cognitive behavioral therapy.

Stanford Medicine’s most talked-about peer-reviewed research on psychedelics involved the drug ibogaine, which has not to date received authorization from the U.S. Food and Drug Administration. That’s why the compound, made from the root of a shrub native to Central Africa, was administered to study participants outside the country, in Mexico. The research looked at the impact of a single dose of ibogaine on 30 special operations veterans with traumatic brain injuries.

The improvements in mental health were “the most dramatic I’ve ever captured from a pharmaceutical compound in an early-stage trial,” said Nolan Williams. Symptoms of depression, anxiety and PTSD were dramatically reduced.

As a practicing psychiatrist, Glick was drawn to the therapeutic potential of psychedelics based largely on seeing a unique type of healing during clinical trials. He vividly recalls an anxious middle-aged patient who was scared of human interaction. When he arrived for his first-ever psilocybin dose, he had been holding in years of trauma, feeling uncomfortable in his own skin.

“He had sealed away whole pieces of his personality, and I remember watching him recover entire parts of himself right there,” he said. The session was intense — at times “painful and frightening” — but Glick said the patient persevered and came out on the other side with a renewed sense of vitality. “He described feeling more alive, more connected to the world, safe in his own body again — and not just then, but for months afterward,” Glick said. “To see someone on the path of becoming whole again after a single dose, that told me there was something significant going on there.”

— Contact Mark Conley at mjconley@stanford.edu
Organoid brain models yield insights into resilience

Genes influence our ability to bounce back from stress

By Krista Conger

Photograph by Timothy Archibald

In a world in which it can sometimes feel that bad news lurks around every corner, it can be tough just to get out of bed. But some people seem uniquely able to weather even particularly traumatic or challenging experiences — abuse, natural disasters, war or even a yearslong global pandemic — that leave others with life-altering scars. Psychiatrist Victor Carrión, MD, wants to know why.

Carrión, the John A. Turner, MD, Endowed Professor for Child and Adolescent Psychiatry, studies psychological resilience, which helps people withstand stress and trauma.
without lasting damage to their mental health. Resilience is a dynamic trait molded by the intersection of one’s personality, social and family connections, physical health, and — intriguingly — Carrión suggests, genetics.

“Over the past decades, I and others have done research to elucidate the impact of stress on brain structure and function,” Carrión said. “One potential mechanism is the neurotoxic effects of the stress hormone cortisol. But we still don’t know much about the biological basis of resilience.”

Carrión has teamed up with Alexander Urban, PhD, an associate professor of psychiatry and behavioral sciences and of genetics, to use what are called neural organoids — small balls of cells grown in the laboratory that mimic the three-dimensional structure of the human brain — to ferret out the molecular foundations that help some people bounce back when others, despite their best efforts, fall flat.

The researchers are combining their laboratory research with a population study of schoolchildren in Puerto Rico, which has experienced multiple natural disasters including hurricanes, earthquakes and floods during the past decade. The stress has left many students struggling with anxiety, depression, poor sleep and, in some cases, post-traumatic stress disorder. Is it possible to help these children become more resilient?

Obviously, there’s only so much (or so little) experimentation that can be done on living human brains. Few people would volunteer a chunk of their gray matter so researchers can probe their specific genetic makeup. But because neural organoids are made from easily obtained skin or blood cells, they share the DNA sequences of the person from whom they are derived.

RESUMABLY, ANY QUIRKS and foibles in that DNA sequence that may cause a glitch in a person’s mental makeup will be reflected in the way cells in the organoid communicate (or don’t), organize themselves into functional (or dysfunctional) neighborhoods, or decorate their DNA with chemical tags that activate or deactivate gene expression in response to environmental cues — a level of regulation called epigenetics. During the past two decades, genetic sequencing technology has advanced to the point that researchers can easily ascertain not just DNA sequences but also gene activity and the presence or absence of epigenetic tags. Urban and his laboratory have been exploring the frontiers of this technology, called high-throughput sequencing, to study the human brain. Now they’ve coupled it with the study of neural organoids to understand behaviors and emotions at the molecular level.

The promise of an up-close-and-personal peek under our psychological hoods has rocked the world of mental health research since neural organoids were developed for widespread use nearly a decade ago in the laboratory of Sergiu Pasca, MD, the Kenneth T. Norris, Jr. Professor II of Psychiatry and Behavioral Sciences.

“I wanted to push the boundaries and make the human brain accessible so that we can transform psychiatry through molecular biology,” Pasca said. “My dream is to ultimately find cures for some of the most devastating neuropsychiatric disorders and to understand what makes the human brain unique and, perhaps, uniquely susceptible to disease.”

Since his 2015 publication detailing the efficient generation of neural organoids and his later creation of more complex structures called assembloids to study human neural circuits outside the body, Pasca and his lab have shared their technique with hundreds of laboratories and even provided make-your-own-organoid kits to those unfamiliar with working with stem cells. “Ten to 15 years ago, we would not have been able to predict the types of experiments we are doing today,” Pasca said.

As their suffix suggests, organoids resemble, but don’t completely recapitulate, aspects of a naturally formed organ like a liver or, in this case, a brain. But they are more than just poorly made replicas. Think of them more as swanky, hard-to-identify forgeries of pricey designer bags rather than bargain-bin knockoffs of some once-trendy sunglasses. That’s because, despite their similarity to a small boba tea bubble, neural organoids pack a big punch in a tiny package. They include many of the cell types found in a mature human brain, including neurons and support cells called glia, and they self-organize into a structure that roughly mirrors our cerebral cortex, where memories and emotions reside and thinking and learning occur.

Urban and Carrión are using the easily manipulated organoids to identify key genes involved in resilience and mental health as well as the environmentally influenced epigenetic tags that tune those genes’ activity.

“Cortisol exposure allows us to model the effects of stress on these cells,” Carrión said. “What innate characteristics in a person’s brain confer resilience, and are there ways to intervene to help people struggling with post-traumatic stress or anxiety? The cortisol model allows us to study genes that are activated or deactivated when the cells are ‘stressed.’”

Epigenetic tags act as an additional blanket of control between the DNA sequences we inherit from our parents and the actions of the genes that are encoded in those DNA sequences, and as mediators between the DNA sequence and the information gleaned from a cell’s environment.
‘My dream is to ultimately find cures for some of the most devastating neuropsychiatric disorders and to understand what makes the human brain unique and, perhaps, uniquely susceptible to disease.’

“Next, we will expose organoids made from the cells of resilient and less-resilient people to increasing levels of cortisol and then analyze them with the high-throughput sequencing machines to determine which genes are activated or inactivated differently in response,” Urban said. “We don’t have to artificially stress out a human in order to pin down pressure points in the genome and identify genetic variants or specific biochemical markers associated with resilience.”

Preliminary work in Urban’s lab has identified dozens of genes that change in their activity levels when organoids are exposed to increasing cortisol levels. More than one-third of these genes have been associated with stress response in humans, which strongly suggests the model accurately reflects at least part of what goes on in human brains. Urban has also partnered with Laramie Duncan, PhD, an assistant professor of psychiatry and behavioral sciences. Duncan uses large genome-wide association studies to improve our understanding of the cellular roles played by genes associated with conditions such as schizophrenia and post-traumatic stress disorder. Overlaps between her datasets and Urban’s organoid studies further indicate the researchers are on the right track.

“It’s clear that these organoids respond to cortisol in ways that are quite similar to human brains, even on the molecular level,” Urban said. “That’s very exciting.”

Their preliminary findings also suggest a role for genes involved in collagen production, which influences atherosclerosis formation. “Some children under stress experience accelerated aging, including heart disease, so this is particularly interesting,” Carrión said.

He wants to find out if the right kinds of external intervention, including a preventive mindfulness and yoga curriculum he has studied extensively and a treatment approach he’s developed called cue-centered therapy, might help the Puerto Rican schoolchildren. If mind-body training affects how and when epigenetic tags associated with stress are applied, it may help a less resilient child become more resilient through mind-body training.

“Resilience and non-resilience aren’t binary states,” Carrión said. “They exist along a continuum of possible responses to environmental stress and trauma. Also, you can be resilient at certain times or in certain situations or parts of your life and less resilient in other situations.”

“Resilience is not just a hard-wired phenotype,” Urban said.

Examining differences between organoids from children more or less affected by stress, and their responses to intervention, should help Urban and Carrión further home in on genes involved in our collective stress responses.

“When we make stem cells and organoids from people who we know have a certain psychiatric diagnosis, we can pinpoint differences that become our key candidate genes for therapy or diagnosis,” Urban said. “This goes beyond resilience and can include other conditions including schizophrenia or autism. That’s why this approach is so powerful.”

Carrión agrees: “Most of us know about genes and our environment. Finally, we are beginning to understand how stress directly impacts our genetic code and whether we can intervene to help people be more resilient.”

— Contact Krista Conger at kristac@stanford.edu
We could be changing lives’

THE IMPORTANCE OF GETTING PRECISE WITH MENTAL HEALTH TREATING IT AS HEALTH

By Mark Conley

ILLUSTRATION BY JOAN BERNABEU
Imagine a world where, as a matter of course, your doctor asks you as much about your brain as your body. You talk about memory, mood and sleep. You go over family history of serious mental illness, neu-rodervent disorders, depression and anxiety. And then your doc can order a detailed scan of your brain, called a functional MRI, to help map out its specific circuitry and look for signs of disruption.

Combined with details about your genetic makeup and responses you provide to specific questions or cues, it could help inform a personalized path for therapy. Which of the standard antidepressants are likely to be most effective? What regions of the brain are best to target with transcranial magnetic stimulation? Might one of the emerging psychedelic interventions play well with your circuitry — or a specific version of talk therapy?

Welcome to the world — still under construction — of precision mental health. It is a future envisioned and engineered by Stanford Medicine researchers, and it is fueled by the imperfect present where 1 in 5 U.S. adults deal with a mental health condition, yet only half of those seek treatment and roughly 30% of these patients experience no remission with any of the available treatments.

In a nutshell, precision mental health is the idea that measuring the biochemistry and circuitry of the brain, with all available tools and data, is as important as gathering evidence about the rest of the body — or more so given the high percentage of brain dysfunctions that can manifest life-threatening disorders. It is viewing what we now call mental health as brain health. Or, more succinctly, just health.

“There is such a sense of urgency with these conditions that if we could get this into practice, we could be changing lives,” said Leanne Williams, PhD, the inaugural Vincent V.C. Woo Professor of psychiatry and behavioral sciences. And perhaps saving them. Williams lost her partner, who suffered from untreated major depression, to suicide in 2015.

She and her Stanford Medicine colleagues at the Stanford Center for Precision Mental Health and Wellness, which Williams directs, are among a small segment of the psychiatry field aiming to show how this could work clinically. Though the medical establishment is slow to change, the movement is growing here and abroad, particularly in a post-pandemic world where recognition of mental health’s insufficient resourcing and one-size-fits-some approach is ubiquitous.

“For too long people have said, ‘The brain’s just too complicated.’ But we have enough of an understanding of brain architecture — of its main superhighways — to know what gets disrupted in all sorts of conditions,” said Williams, who recently secured her largest-ever grant, $18 million from the National Institute of Mental Health to study the cognitive biotype, a hard-to-treat type of depression her research team identified through brain imaging. “There is a clear consensus in the research world: ‘Why aren’t we moving this into the clinical world?’”

**IMAGING AND BIOTYPING**

As Williams was beginning her career as a clinical psychologist in her native Australia, she recalls witnessing a patient diagnosed with schizophrenia hold a staticky transistor radio up to his ear, trying to blunt the voices in his head. “I thought to myself, ‘This is a circuit-level problem,’” she said.

Moments like that made her certain the clues to understanding psychiatric conditions lived in the world of neuroscience where the hows and whys of brain circuitry are investigated.

At the University of Sydney she helped establish one of the earliest labs connecting psychiatry and neuroscience. By the time she was recruited to Stanford, in 2012, she was convinced that brain circuitry’s contributions to psychiatric suffering were not trivial, nor was understanding that role out of reach.
“Leanne was determined this could be done — and she is showing the world how,” said Ruth O’Hara, PhD, senior associate dean for research, the Lowell W. and Josephine Q. Berry Professor of Psychiatry and Behavioral Sciences, and co-director of the Stanford Center for Precision Mental Health and Wellness.

Brain imaging is the primary tool used at the center. Functional magnetic resonance imaging has aided the identification of six large-scale circuits — those “superhighways.” Williams, O’Hara and colleagues have found that certain patterns of dysfunctions in these circuits — which they’ve named “biotypes” — correlate with specific variations of depression or anxiety and can help determine their best treatment options. Or at least rule some out.

A 2023 Williams-led study of 1,008 people with previously unmedicated depression, published in *JAMA Network Open*, found that individuals whose brain’s cognitive control circuit showed decreased activity in two particular regions were less likely than others to respond to traditional antidepressants. The team labeled this group — which made up 27% of those in the study — the cognitive biotype. They are an example of the people who are likely to benefit from less commonly used medications or treatments like transcranial magnetic stimulation, or TMS.

When Williams’ partner died by suicide, she hadn’t yet associated specific quirks in neural circuits with specific symptom profiles. But she suspects now that his form of depression was consistent with the cognitive biotype, meaning he might have benefited from non-pharmacological treatments such as TMS.

“Depression is very heterogenous, yet we start with the same treatments for everyone,” said Laura Hack, MD, PhD, the lead author of the study, an assistant professor of psychiatry and behavioral sciences and director of the Stanford Translational Precision Mental Health Clinic, which puts Williams’ research into clinical use.

People with treatment-resistant forms of anxiety and depression who are referred there undergo a comprehensive battery of evaluations. The clinicians assess symptoms and neurocognitive ability, test blood for telltale proteins, analyze genetics to determine the ability to metabolize certain drugs, and look at functional MRI data gathered from patients at rest and while performing tasks. Patients and their referring doctors receive a report with a thorough explanation and the implications for treatment recommendations.

So far, Stanford Medicine is among a small cadre of institutions around the world putting these methods into clinical use in psychiatry. Williams is also working with the U.S. Department of Veterans Affairs to apply precision techniques with vets who struggle with depression and PTSD. But she firmly believes primary care physicians of the future will also see these as essential tools for caring for their patients over a lifespan.

“I hear from many primary care providers who want this now,” Williams said. “It’s just a matter of making it available and getting them the proper training.”

Equally important, Williams believes, is making the unexplainable explainable to people suffering from little-understood — and therefore highly self-stigmatized — conditions. “When people can see, ‘Oh, this is what’s happening inside my brain,’ they can understand what’s making them ill, stop placing any blame on themselves and embrace treatment.”

Perhaps most importantly, the oftentimes agonizing gap between symptom onset and relief can be shrunk. “In mental health, we have a tendency to move slowly to adopt our findings — unlike fields such as cardiology or oncology,” O’Hara said. “This gives us a chance to speed things up in very important ways.”
Culture in care

STANFORD MEDICINE MENTAL HEALTH PROFESSIONALS SPEAK TO INEQUITIES

By Emily Moskal

Reducing socioeconomic barriers to care.
Integrating cultural nuance and religious understanding.
Advocating for public policy changes to support patients' mental health.

These are a few of the actions Stanford Medicine therapists who work with marginalized communities say are keys to effectively caring for patients who face societal discrimination.

“Most of our systems of care are tailored to support individuals from the majority population,” said Christina Khan, MD, PhD, a clinical professor of psychiatry and behavioral sciences and co-chief of the psychiatry department’s Diversity and Cultural Mental Health Section. “This bias perpetuates mental health care disparities among marginalized groups. If we hope to move toward greater equity and justice in mental health care, we must support individuals from marginalized backgrounds in a way that considers their culture.”

To understand the challenges to providing support for these groups, Stanford Medicine asked five therapists from the Department of Psychiatry and Behavioral Sciences with expertise in culturally informed care to envision mental health support tailored to their needs.

Here’s what we asked:
What are special factors affecting the mental health of the communities you serve?

What tops your wish list of changes that would promote equity and justice in mental health care?

What inspires you about your work?
The most significant challenges for improving mental health care are socioeconomic. When I first started working in Oakland, I was surprised to find that stigma toward mental health, though a barrier, was rarely the limiting factor in finding treatment. Instead, the major barrier was a lack of affordable, culturally responsive providers. This left patients on long waitlists and fed mistrust of the health care system.

The change I would recommend is to improve reimbursement rates for public insurance and expand creative incentive programs such as loan forgiveness for psychiatrists working in underserved communities. Hopefully, this would relieve the dire shortage of psychiatric providers who take insurance and reduce wait times for patients.

The most inspiring aspect of my work has been following up with patients whose lives have changed after our clinic’s interventions. It’s incredible that even brief interventions with a mental health specialist can have profound changes on people’s lives.

**STACY LIN, PHD,**
clinical assistant professor and director of psychotherapy for the Stanford Mental Health for Asians Research and Treatment Clinic

Racism and violence against Asian American and Pacific Islander folks, which has increased in the COVID-19 era, affect Asians’ mental health, as does the model minority myth that perpetuates stereotypes of Asians being unilaterally successful and not needing help.

My patients’ mental health experiences are heterogenous. I wish their health care integrated their cultural values and acknowledged systems-level factors such as racism that are not addressed in most of our interventions, which tend to focus on the individual. Having a more expansive definition of psychotherapy — that includes individual-level change and advocacy that targets systemic discrimination — promotes healing.

Being alongside people as they find meaning from even the most painful experiences of their lives is an honor. Watching patients grow more rooted in themselves and develop agency over shaping their own futures reminds me to show up for them fully every day.

**AXEL VALLE, PSYD,**
clinical assistant professor and co-director of La Clínica Latina, focused on mental health care for people who identify as Latino or Hispanic

Latinos in the U.S. encounter significant barriers to accessing high-quality mental health care. Most commonly, those are language and cultural barriers between them and health care providers. Encouraging providers to appreciate, learn and navigate cultural nuances is crucial for dismantling health care disparities.

To cultivate change by selectively hiring clinicians, it’s essential to consider language to bridge existing gaps in mental health inequities. Having providers who are fluent in the patient’s language not only broadens their access to care but also substantially improves patient outcomes.

As a clinical psychologist, I find inspiration in the resilience and adaptability of Latinos facing mental health challenges.

Witnessing patients progress through therapy with willingness, gratitude and humility is a testament to the potential impact of culturally sensitive care.

**RANIA AWAAD, MD,**
clinical professor and director of the Muslim Mental Health and Islamic Psychology Lab, co-founder of Maristan, a Muslim mental health nonprofit dedicated to providing culturally sensitive and accessible mental health services and educational resources, director of centerspace, a clinic that provides culturally contextualized mental health care, and co-chief of the psychiatry department’s Diversity and Cultural Mental Health Section

One of the most difficult issues for the American Muslim community is Islamophobia and other forms of discrimination that make this community feel marginalized. Suicide attempts among this population of people are twice the national average. Religiously congruent mental health services are few and far between.

I want people to know that this group has a rich heritage and tradition. Anyone who’s going to work within the Muslim community needs to know how integral faith, religion and spirituality are to this community.

When patients are able to bring their faith into the story, they find relief because their coping mechanisms are aligned with their spiritual and faith practices.

I have a dream to revive the concept of the maristans — institutions from the eighth century onward that were dedicated to healing psychological illnesses — that have spiritual symbolism within their architecture.

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I have a dream to revive the concept of the maristans — institutions from the eighth century onward that were dedicated to healing psychological illnesses — that have spiritual symbolism within their architecture.
The coldness hanging in the air is what Leanne Williams remembers most about that morning nearly a decade ago. She was walking through the doorway of her seventh-floor San Francisco condo when an abnormal chill immediately assaulted her senses. Something was very wrong.

Williams’ worst possible suspicions were confirmed moments later. Her partner, Jack, had taken his life at age 49 after a decades-long battle with depression. For many months afterward, that singular detail — the raw, frigid coldness — haunted Williams every time she stepped outside into the swirling bay breezes.

“It’s strange how those visceral things stick with you and reemerge,” said Williams, PhD, the Vincent V.C. Woo Professor of psychiatry and behavioral sciences. “I walked around in shock for a long while after that —
the feeling that stuck with me was the coldness of that room."

Eventually the numbness gave way to other roadblocks that emerge when a serious mental health condition turns lethal. How do you adjust to such a tectonic change in your daily life? How do you open the door to talk to others about this situation, both personally and professionally? How do you tell your story in a way that doesn’t make it feel about you — but instead conveys that if this can happen to someone like you, it can happen to anyone?

“It took me a long time to figure out what to say and how to say it,” Williams said.

There is a common denominator that prevents people like Jack, a physician, from getting the kind of help that might have saved his life and that prevented Williams — one of the world’s foremost researchers of treatment for depression — from incorporating her personal story into her professional narrative for five years.

“Even in medicine, stigma is very much a real thing,” Williams said.

Yet, the more Williams shares the personal nature of her mission — to her colleagues at Stanford Medicine, to the wider world of neuropsychiatric science at the dozens of conferences where she speaks annually — the more she believes the openness and truthfulness of storytelling will change how people perceive maladies of the brain. Perhaps it can help diminish the murky mythology of mental health stigma.

The term stigma originated in ancient Greece. It refers to symbols burned into the skin of enslaved people that branded them as criminals or traitors to be shunned. Then in 1963, sociologist Erving Goffman, PhD, imbued it with its modern meaning: any negative attitude, prejudice or false belief associated with specific traits, circumstances or signs of illness.

It’s estimated that half the American population will face a mental health condition at some point in their lifetimes, and studies have shown that stigma and discrimination can sometimes be worse than the mental health condition.

According to a 2022 *Lancet* commission on ending stigma and discrimination in mental health, half of people with treatable psychiatric conditions don’t seek treatment. And those people die 10 to 20 years sooner from preventable physical diseases than those in the general population.

A 2021 study by researchers at Penn State and Indiana University published in *JAMA Network Open* attempted to ascertain whether stigma had improved in recent decades. It found that there had been “a decrease in the stigma regarding depression” but that more generally “prejudice and discrimination attached to mental illness has been persistent, interfering with help-seeking, recovery, treatment resources, workforce development and societal productivity in individuals with mental illness.”

People conducting research in the world of medicine will tell you it also has a serious effect on where funding dollars end up. That’s why they are motivated to change the stigmatized narrative around brain science. Major scientific advancements have followed funding in physical conditions such as cancer and heart disease.

Stigma represents a tangled web of multi-directional unkind judgments — to oneself or from others — and it’s typically rooted in a lack of understanding that often is caused by the condition’s complex nature and the fragmented language used to explain it.

That lack of clear answers about the pathophysiology of psychiatric diseases leads to the stigmatization of mental health disorders. There can also be subconscious stigma that a person places on themself while enduring a crisis or tragedy. There’s also the larger stamp of stigma imposed by a society struggling to understand — without assigning blame — the complexities of neuropsychiatric disorders.

“People forget that cancer and heart disease weren’t always talked about openly either. I had an uncle who died young from cancer that no one wanted to mention,” Williams said, adding that his Hodgkin lymphoma would’ve been easily treatable today. “It took a lot of stories being told for people to better understand, for that stigma to be broken.”

But the brain’s connection to behavior gives it a tougher road to hoe — and stigma assigning blame to cognitive dysfunction runs deep: in families; in institutions like school, church and the workplace; in Hollywood scripts; and in media reporting.

Even in the elite halls of medicine — where novel approaches to mental health interventions are bustling — stigma remains a surprisingly formidable barrier.

“Many people get into psychiatry and neuroscience because they have a personal connection to brain disorders — they’ve felt it, it’s touched them,” said Williams, a leader of the movement to leverage discoveries in neuroscience to tailor treatments for psychiatric conditions. “Yet you don’t hear those stories very often.”

That’s why she continues to grow more comfortable telling her own. She also supports many others who approach her with heartfelt expressions of thanks, offer versions of their personal narrative and ask for tips on how to start sharing their experiences more broadly.

“More and more,” she said, “we’re starting to realize the importance of making our stories part of the bigger story.”
Jack was an emergency room doctor and supervisor at a Bay Area hospital who had quietly suffered from depression for years. Despite Williams’ constant pleas, he refused to seek treatment out of fear that any paper trail involving a mental health condition could jeopardize his career as a physician.

“The guilt that I felt was overwhelming,” Williams said. “You just wonder how you couldn’t have known that it had gotten to that point.”

Jack exhibited signs of a specific high-functioning form of depression that Williams has since identified as the cognitive biotype. It is one of seven specific classifications of depression and anxiety that Williams has classified as the baseline forms — each requiring different treatment game plans. That classification system is the basis of her specialty known as precision mental health.

Because he wasn’t willing to be prescribed antidepressants, the longtime first-line approach to depression, Williams recommended to Jack that he try one of the newer forms of treatment that could be done in a clinical trial setting — and might leave less of a medical paper trail. But even that seemed riskier to him than doing nothing. In the end, she believes, he was a victim of self-stigma as much as a victim of depression.

“Rationally, he knew his depression was nothing to be ashamed of,” she said. “But there was also a part of him that believed he should be able to cope.”

Rather than take time off from work to process her loss after he died, Williams threw herself headlong into the war on depression that had suddenly grown more personal. She sought counsel from a few close friends and colleagues who helped her process the guilt. They assured her she had done everything she could to help Jack, who never shared any thoughts of self-harm with her.

Williams decided to pull light from the darkness in symbolic ways. She put together a small memorial for Jack held on a bright, sunny day “out in nature, amidst the flowers.” She dyed her blond hair bright white. “I wanted to crystallize the focus on light,” she said. “It was important for me to focus on the celebration of life and to channel all that energy into positive change.”

At first, she felt uncomfortable talking about her situation openly. She was afraid talking about it would be perceived as self-indulgent: more about her own grief than the loss of her loved one. But, as she spoke publicly about her work and the need to find fast implementations for precision mental health interventions, she began feeling a different pang of internal distress.

“I felt like such a hypocrite,” she said. “Here I was, standing before audiences of my peers at conferences, starting off...”
Hope amid crisis

The rise of mental illness among young people is as daunting as it is undeniable. The rate of adolescents aged 12-17 in the U.S. who suffered a major depressive episode nearly doubled from 8% in 2007 (according to Pew Research Center) to 15.1% in 2018-19 (according to the Centers for Disease Control and Prevention).

Yes, 2007 is the year that the iPhone debuted, and we’ll save the debate of correlation versus causation for another time. However, the deleterious effects of social media — online bullying and the displays of curated perfection, to name two — on maturing psyches are well established.

And yes, the CDC report occurred before the isolation of the pandemic curbed the socialization that teens not only crave but also need on the road to adulthood. More recent information — a 2022 U.S. Substance Abuse and Mental Health Admin-

Beyond the psychiatrist’s office

EMPOWERING COMMUNITY-BASED MENTAL HEALTH SOLUTIONS FOR YOUNG PEOPLE

By Ivan Maisel and Kimberlee D’Ardenne

PHOTO ILLUSTRATION BY JULES JULIEN
receives a phone call from the Palo Alto, California, police that a local teenager has died by suicide, the news arrives with the surges of emotion common to grief: sadness over learning someone had been in such pain, anger that society had failed the student.

But Gloner, the chief executive officer of Project Safety Net, also allows herself to focus on hope — hope that one suicide will not beget another — and implements a plan she has prepared for responding to just such a tragedy.

During the past 15 years, Palo Alto has experienced two suicide “clusters,” in which several local young people ended their lives in a matter of months. Project Safety Net was created after the first cluster, in the 2009-10 academic year, to coordinate the efforts of local schools, government and the mental health community to curtail the contagion of suicide and to promote youth mental health and well-being.

The nonprofit exists, in part, because of the work of Stanford Medicine professionals such as Shashank Joshi, MD, and Sherri Sager. Joshi is a professor of psychiatry and behavioral sciences who helped establish the organization and served as a founding board member. Sager, recently retired as senior vice president and chief governmental relations officer at Stanford Medicine Children's Health, secured critical financial support from Lucile Packard Children’s Hospital Stanford.

“It’s like an emergency preparedness response,” said Gloner,
After a suicide, the organization activates the crisis response team — assisting local schools with expertise, promoting grief support meetings and serving as a communications hub.

Community conversation and action are crucial after a suicide, King said but, in the aftermath of a tragedy, that doesn’t come easily.

“There was a lot of pain,” Gloner said of a recent death. “There was stigma. There was conflict. There are people who did not want to talk about suicide but to focus more on well-being. And there were some who said, ‘No, we need to talk about suicide.’”

Project Safety Net’s staff members talk about suicide because the kids are talking about it. “The goal,” Joshi said, is to “help to empower the youth voice in thinking about how we can support their mental health. We’re asking, ‘What is it that will help you really feel like you’re a part of this community?’ And we’re saying, ‘Your voice matters, we care about you and we care about you thriving.’”

Striking the right balance between listening to children and leading them is the tricky part, Gloner said. “You want to take care of children, and you want to keep them safe. There are some adults who say, ‘Children are not Buddha. We know better.’ I leave that be. I try to think of it this way: You are the coach and the mentor — the caring adult to guide them.”

Another outcome of the all-hands-on-deck response of parents, educators and doctors after the first cluster of deaths was the launch of the Bay Area-based HEARD Alliance in 2009, a collaboration of health care and education professionals to assemble best-practice resources on a website and develop strategies to promote mental health and prevent suicide. Funded by Stanford Medicine Children’s Health and other groups, the organization has produced a 300-page document — co-written by Joshi — to meet those goals. This toolkit, which has been accessed more than 200,000 times on the organization’s website, is a guide for implementing suicide prevention policies required of all California schools serving students in kindergarten through 12th grade.

Now on sabbatical, Joshi is directing some of his energy to working with professionals across the country who are interested in forming similar collaborations in their communities. And he’s advocating for curtailing pedestrian access to the site of many of the tragedies in Palo Alto, the local train tracks, by gathering data on costs, meeting with city officials and talking with administrators from the rail system. He and his team are also researching what other communities have done to prevent access to train tracks — and the success of their efforts.

“It’s starting with a literature review, which systematically examines the world literature on safety at train tracks of every kind of train — commuter trains, freight trains, bullet trains. What is the standard of prevention? What’s the state of the art according to the science?”

The eruption of the second suicide cluster in 2014-15 illustrates the elusive quality of progress in treating mental illness. Depression among young people has increased. So has anxiety. Yet so has outreach and destigmatization and increased awareness of the importance of good mental health. “Talking about mental health as part of overall health is common, expected, everyday,” Joshi said. “Mental illness is much less stigmatized because young people have been able to tell their stories and feel seen and heard. Our community has also found out how common mental health challenges are, a part of everyday life.”

Awareness in and of itself is not a solution. But it is a start, a quickening of pace, toward solving any societal ill, be it smoking tobacco, climate change or mental illness.
RYAN MATLOW, PHD, grew up south of Palo Alto in Watsonville, California, an agricultural community where many speak Spanish and no English. Matlow’s background is not Latino, and his first language is English, but childhood friends spoke Spanish so he learned the language. His exposure to cultural, financial and language gaps led him to a career in child clinical psychology, specializing in addressing traumatic stress in children, especially where immigration plays a role. A clinical associate professor of psychiatry and behavioral sciences, he has served as an advocate for children separated from their families at the U.S.-Mexico border and held in immigration custody.

Now, living in Half Moon Bay, California, where about a quarter of the population is Latino, Matlow and other Stanford Medicine health care providers are working with the community organization ALAS (for Ayudando Latinos a Soñar, which means Helping Latinos Dream). The nonprofit aims to promote mental health and social wellness within the area’s largely Latino farmworker community through arts and cultural practices originating in Mexico and Central America, such as playing mariachi music and performing folklorico dance.

Starting in 2011, the organization has grown to provide mental and physical health care and social work case management. In 2023, ALAS received a Stanford Medicine Outstanding Community Partner Award and is supported in part through funding from Stanford University — including a Stanford Impact Labs seed grant and a research grant from the Stanford Office of Community Engagement.

Speaking at a Stanford Medicine Community Health Symposium last year, the founder of ALAS, Belinda Hernandez-Arriaga, PhD, told of an experience that spurred her to create the organization. Hernandez-Arriaga, a social worker, said one of her cases involved the young daughter of an immigrant farmworker who suffered recurrent abdominal pain. Doctors conducted tests and found no physical cause — and suggested the pain might have an emotional source. They recommended mental health support, which Hernandez-Arriaga provided.

“These months into our treatment, she drew for me a picture of a mama cat and a baby cat with tears streaming down their faces. She x-ed out the mama cat, and on the top she put, ‘No Papers,’ and on the baby cat she put ‘Papers.’ That began the story of realizing the immigration trauma that so many have,” said Hernandez-Arriaga, an assistant professor of clinical psychology at the University of San Francisco.

The shootings in Half Moon Bay last year that killed seven farmworkers — five Latino and two Chinese immigrants — compounded that trauma for many, Matlow said.

Before the shootings Matlow and his graduate students had begun helping ALAS evaluate the efficacy of its cultural programs.

“Obviously, for immigrant families there is bias or discrimination, threats to social identity, loss of culture,” Matlow said. “These cultural arts programs are designed to counter that, design a space where kids can build community and connect with their cultural assets. We wanted to capture the impact. This sort of research drives funding. It helps provide validity and legitimacy to the approach ALAS is taking in their offerings.”

Stanford Medicine physicians work with ALAS to provide care as well. For example, Christina Buysse, MD, a developmental behavior pediatrician, and Anne Berens, MD, a postdoctoral medical fellow, are building evaluation programs for children in the community with developmental disabilities.

After the 2023 shootings, ALAS stood on the front lines of survivor assistance, with Stanford Medicine physicians among those providing mental health care support. Rona Hu, MD, a clinical professor of psychiatry and behavioral sciences, provided...
emergency assistance and crisis support for survivors who speak Mandarin. Matlow and Nancy Ewen Wang, MD, a professor of emergency medicine, collaborate with ALAS to support the Spanish-speaking community.

“We’re thinking about how we can organize and mobilize a system for providing longer-term care to complement what ALAS provides, anticipating that there will be ongoing stress,” Matlow said. “Sometimes the trauma sets in later. It’s a gradual recovery process.”

JUST FOR YOUTH: ALLCOVE

STEVEN ADELSHEIM, MD, has been working for decades to increase access to mental health care for youth and is a driving force behind allcove, a network of low-cost mental health care centers geared toward people aged 12-25 years that is now expanding across California.

“Opening the first allcove center and knowing we were finally able to give young people the support they need was a tearful moment for me,” said Adelsheim, a clinical professor of psychiatry and behavioral sciences. “It is amazing that there is so much interest in allcove and that the model it’s based on is expanding internationally, but there is still so much to do to overcome barriers to accessing care.”

These barriers include the stigma still associated with mental illness and a strained behavioral health workforce. The result is that though half of all mental health disorders start by age 14, a majority go untreated. Trained as a child psychiatrist, Adelsheim knows the importance of diagnosing mental health disorders as soon as possible.

“Early intervention is critical for mental health; we know it works for mental illness as well as it does for other conditions such as obesity, childhood asthma and HIV/AIDS,” said Adelsheim. “allcove provides an opportunity for us to both normalize mental health care and to make care accessible.”

Adelsheim’s efforts began in schools, but when he learned about a mental health care clinic system for youth in Australia called headspace, he jumped at the chance to bring the model to the U.S. The model embeds mental health care centers throughout the community, making them accessible even when schools are closed, and all are run in partnership with young people. Adelsheim secured funding from the Robert Wood Johnson Foundation to explore the feasibility of bringing the model that became allcove to the U.S., and the network launched in 2021.

There are allcove centers in the California cities of Palo Alto, Redondo Beach and San Mateo, with centers in development in South Orange County and Sacramento. New funding from the state Department of Health Care Services will bring allcove to six more locations. Each center works with a consortium of local agencies and nonprofits. The Santa Clara County Behavioral Health Services Department, for example, runs allcove Palo Alto, with Stanford Medicine Children’s Health providing adolescent medicine services. Financial support for allcove comes from many organizations, including Stanford Medicine Children’s Health, the California Mental Health Services Oversight and Accountability Commission, and the Lucile Packard Foundation for Children’s Health.

The allcove model involves youth in all aspects of what happens inside the centers. Each site has its own advisory group made up of 16- to 25-year-olds, many of whom have lived experience with mental health challenges. These groups work to make sure anyone who walks into an allcove center feels welcome, whether they are enjoying the colorful, comfortable seating in the lobby or are completing intake forms that have been rewritten to use inclusive language. The approach is effective: Young people logged more than 4,000 visits to allcove Beach Cities in Redondo Beach in the year and a half after it opened.

“Valuing youth input also lets allcove constantly evolve to quickly meet the needs of the community,” said Nina N., who served as a youth adviser for four years starting when she was in high school. Because of that experience, Nina is now working toward a career in health policy so she can continue to break down barriers to care. (Nina’s surname has not been used to protect her privacy.)

Clinicians and staff collaborate with youth advisers to create workshops based on community needs, on topics such as the importance of sleep or how to manage stress. The centers also offer programs to build community and a sense of belonging — for example, game nights at allcove Beach Cities and “hooked on crochet” classes at allcove Palo Alto.

At no or low cost to them, visitors to allcove can receive individual, group and family therapy in addition to medication therapy. Each center also offers drop-in appointments and a menu of additional services that all reinforce mental health, including substance use treatment, physical health services, peer and family support, and education and employment support.

“When researchers study the effectiveness of models like allcove, a common question they ask youth is, ‘If you hadn’t come here today, where would you have gone?’ and usually the answer is, ‘Nowhere,’” Adelsheim said. “It is so important that youth have a place to go, and the allcove model is creating access where there wasn’t any before.”

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— Contact Ivan Maisel and Kimberlee D’Ardenne at medmag@stanford.edu
How moms and dads can provide mental health care

CENTER HELPS PARENTS GUIDE THEIR CHILDREN THROUGH PSYCHOLOGICAL CHALLENGES

By Erin Digitale

PHOTOGRAPH BY LESLIE WILLIAMSON

NATIONALLY, THERE ARE 5 psychiatrists for every 10,000 children who need one. About 80% of children in the U.S. who need mental health care do not receive it.

In 2019, two Stanford Medicine mental health experts started brainstorming concrete ways to address this crisis in kids’ access to care, which they had seen expanding for years.

“Our waitlists were just growing and growing,” said child psychologist Elizabeth Reichert, PhD, clinical associate professor of psychiatry and behavioral sciences. Children with mental health problems waited six months to a year for treatment; by the time of their first appointment, some kids’ problems had eased, while others’ had severely worsened. “Talking to colleagues across the country, it was the same.”

Reichert and child psychiatrist Mari Kurahashi, MD, clinical associate professor of psychiatry and behavioral sciences, developed a way to help kids get faster care for common pediatric mental health problems that is now serving as a model for other institutions across the country: the Stanford Parenting Center.

They co-direct the center, which provides evidence-based parenting techniques via free webinars, low-cost online classes and practical resources shared on social media.

The center’s materials give parents of struggling kids easy access to information a psychologist or psychiatrist would typically share in early appointments, such as what to try at home to help ease a child’s anxiety, depression, attention-deficit/hyperactivity disorder or addictive behaviors. Essentially, the center helps parents learn how to deliver research-backed mental health care themselves.

“Our mission really is to target the pediatric mental health crisis on multiple levels: prevention, decreasing risk factors, intervening before things are full-blown, and then also offering treatments for full-blown psychiatric disorders,” Kurahashi said.

ADAPTING TO THE UNEXPECTED

KURAHASHI AND REICHERT became friends soon after they were both hired at Stanford Medicine in 2014, bonding over the challenges of working with patients and discussing how their mental health expertise influenced their own experiences of parenting young children. (They each have two kids.)
DURING THE PAST CENTURY, psychiatry has been stuck in a rut. In the beginning, there was talk therapy to help patients recognize internal conflicts that generated negative thoughts and behaviors. Then there was psychopharmacology, the use of mood-altering drugs. While these approaches worked for some, they left many patients without hope.

Enter a new wave of psychiatric treatments based on an ancient approach to healing the brain — electricity.

Back in A.D. 46, Roman physician Scribonius Largus treated migraines by placing a live electric torpedo fish “on the place which is in pain, until the pain ceases and the part grows numb.” Over the millennia, there have been variations on this theme — shock therapy and deep brain stimulation, to name a few. But none of these treatments have been practical or safe enough to use in mainstream psychiatry — especially the torpedo fish.

Now, a Stanford Medicine research team is developing a noninvasive, more targeted electromagnetic treatment that can improve mental disorders like depression in a week or
less with long-lasting relief. Called Stanford neuromodulation therapy, or SNT, it uses a magnetic paddle placed on the scalp to deliver gentle electrical pulses that reset brain circuits that have gone awry. This next generation in transcranial magnetic stimulation is successfully treating severe depression in people for whom other approaches have failed. In a small double-blind, randomized clinical trial, nearly 80% of the 14 participants went into remission after five days. Follow-up studies have shown similar results, with about half of the participants remaining depression-free four weeks after treatment.

The Stanford University Brain Stimulation Lab has led the charge to refine this technology, incorporating new knowledge about functional brain circuits and learning theory to recalibrate misbehaving brain networks for conditions that include bipolar disorder, addiction, borderline personality disorder and obsessive-compulsive disorder.

**Brain training**

The Brain Stimulation Lab director, Nolan Williams, MD, didn’t have a roadmap for a career in psychiatry and neurology growing up in Charleston, South Carolina. Both parents were blue-collar workers without college degrees. Though he met some medical professionals while attending the Academic Magnet High School in North Charleston, he attributes most of his success in medicine to early training in martial arts.

“I started taekwondo when I was 8 and was granted a black belt at 15. I won two world championships in college,” said Williams, 41, whose laid-back demeanor and shoulder-length auburn hair project more of a surfer vibe than that of a psychiatrist. (He also kitesurfs.)

Taekwondo taught him that success in life boils down to five principles: courtesy, integrity, perseverance, self-control and indomitable spirit. He believes in the repetitive mind-body drills that both taekwondo and medicine require to build skills and perform at a high level.

“When you step into the ring, you know there’s going to be a fight,” he said. “You have to be fully present in that moment, not thinking about the future or the past.”

Today, Williams is an associate professor of psychiatry and behavioral sciences focused on building better tools for treating mental illness. His research spans a wide range of solutions, from rapid-acting psychedelics to retraining misfiring brain circuits.

Williams entered the nascent field of electrical brain stimulation in 2006 as a medical student under the mentorship of Mark George, MD, a professor of psychiatry, radiology and neurosciences at the Medical University of South Carolina. George pioneered the use of transcranial magnetic stimulation, TMS, for mapping mood-regulating brain circuits and was the first to identify the cingulate cortex as a brain region that plays a role in depression. He conducted some of the first clinical trials of TMS for treating persistent depression, and his six-week protocol was approved by the U.S. Food and Drug Administration in 2008.

After completing dual residencies in psychiatry and neurology and a research fellowship with George, Williams came to Stanford Medicine as an instructor. It seemed like an excellent place to take TMS to the next level. The chair of the Department of Psychiatry and Behavioral Sciences, Laura Roberts, MD, was supportive of the new frontier of interventional psychiatry and breaking down walls between neurology and psychiatry. Stanford Medicine’s academic ecosystem fostered collaborations between medicine and engineering, leading to discoveries in brain-circuit mapping, genetics and the use of light to influence brain activity. Another advantage: The campus is located at the epicenter of a thriving biotech community and venture capitalists willing to invest in paradigm-busting ideas. So, Williams stepped into the ring and began building a team to tackle depression — one of the most disabling and costly medical conditions worldwide.

**Dream machine**

Sergio “Checo” Gonzales left his home in rural Northern New Mexico in 2010 to pursue undergraduate and medical degrees at the University of New Mexico. His driving passion is to improve the health care disparities that he witnessed as a child. His research is focused on mathematical modeling of complex social systems in resource-poor communities. He loves academic research, and he’s had visiting scholar stints at Harvard, Wharton and Washington University School of Medicine. He even learned Diné Bizaad, the Navajo language, so he could form deeper connections with members of the Navajo Nation for whom he was providing health care. In this culture, he would be called an azee’iltii’í, one who makes Western medicine.

Today, this work is on hold, as he struggles with depression, specifically anhedonia, a lack of interest, enjoyment or pleasure from life’s experiences.

“The most challenging aspect of it is my inability to feel any kind of emotion,” Gonzales said. “I can intellectualize the importance of my research, my fiancée, my dogs and my family, but I am often paralyzed with the idea that I’m a worthless person who doesn’t want to be on this earth.”

While he thinks he may have suffered from undiagnosed depression since childhood, severe symptoms emerged during the first year of medical school, when he realized that he needed to find an environment more supportive of all his talents and academic interests. He also faced significant barriers to finding
psychotherapy and pharmacotherapy that worked for him.

“I was contemplating taking my own life and really struggling to complete daily tasks needed to make progress in my academic career.”

To survive, he took a leave of absence from medical school and began work toward a PhD in biomedical data science at Stanford Medicine. After a couple of rough years during the COVID-19 shutdown, his psychiatrist enrolled him in the SNT clinical trial, which was transformative.

“It was like magic,” Gonzales said. “Over two days, I went from feeling like death was the only way to end my suffering to my normal self, excited to live the rest of my life. The only side effect was that I felt great.”

The remission enabled him to return to his studies and pick up the pieces of his life. Nearly all his symptoms disappeared. But over the following three months, symptoms crept back. Now he’s in a holding pattern, back in intensive psychotherapy and finding no relief with multiple trials of pharmacotherapy, waiting until he can resume the “magic” SNT treatments when they become available to the public.

The discovery process

SNT, a type of accelerated TMS, can improve depressive symptoms in less than a week.

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The discovery process

One in 5 people suffer from depression in the United States, 322 million worldwide. The economic burden of major depressive disorder among U.S. adults is immense, estimated at $326 billion in 2018 (in 2020 dollars).

But some of the most devastating impacts of depression are immeasurable — broken families, abandoned jobs, hospitalizations and suicides. More than 700,000 adults in the U.S. die by suicide annually, and it is the fourth-leading cause of death among 15- to 29-year-olds.

Before SNT, there were no quick fixes for people who sink into life-threatening despair. Talk therapy takes months to years to be effective. Antidepressant drugs must be taken for four to six weeks before benefits are felt — if those medications work. TMS requires at least six weeks of treatments. But SNT, a type of accelerated TMS, can improve depressive symptoms in less than a week.

Breakthroughs with SNT were twofold. The first was the discovery that electricity flows backward in the sadness-control brain circuit of many people with depression. The second was that dysregulated circuits could be retrained more quickly by administering a more intense pattern of magnetic pulses over a shorter period.

Anish Mitra, MD, PhD, now an assistant professor of psychiatry and behavioral sciences, was instrumental in the lab’s discovery of the backward circuit problem. As a graduate student at Washington University in Saint Louis, Missouri, he developed a mathematical tool to identify active areas of the brain through analysis of brain scans. His tool could measure tiny timing differences in the blood flow to various brain circuits, which, in turn, revealed the direction of electrical flow through these circuits.

When they used this tool to analyze severely depressed patients, they noticed that electricity flowed through the emotion control brain circuit, the left dorsolateral prefrontal cortex, in the wrong direction from healthy controls. Moreover, if they sent electrical pulses against this current, they could fix it, much as a pacemaker resynchronizes an irregularly beating heart.

Williams thought about this new finding in the context of his martial arts training and new research on optimal learning. He knew that the six-week, low-intensity TMS treatments weren’t fast enough for patients in crisis situations. His hypothesis was that more repetitive, high-intensity bursts would be more effective, using the same learning strategies that people use to study for exams or prepare for a taekwondo competition. After some trial-and-error studies, he found an optimal pulse pattern for treating major depressive disorder. Next, his team designed a clinical study to assess the efficacy of this approach, and he became the first to treat real-world patients with SNT, targeting the depression brain network of neurons originally discovered by Michael Fox, MD, PhD, at Harvard Medical School.

In 2021, the FDA designated SNT as a “breakthrough therapy,” which put it on a fast track through the regulatory approval process, because of its potential to treat a serious condition much more effectively than existing therapies. Then in 2022, the FDA cleared the SAINT neuromodulation system as a Class II medical device, which combines SNT stimulator hardware and software with a neuronavigation tool for identifying a personalized brain target. It is the first noninvasive, rapid-acting neuromodulation approach to treatment-resistant depression.
Treatments are delivered in 10 50-minute sessions per day, over five consecutive days. It’s painless and noninvasive. Patients can watch movies or read during the sessions. The most common side effect is a headache that dissipates in a few hours.

**How it works**

SNT magnetically induces electrical flow through the “wiring” of a brain, the neurons, with gamma frequency bursts overlayed on theta waves. Theta waves are natural brainwave oscillations of 4 to 8 hertz (cycles per second) that are believed to be involved in the creative flow state and implicit learning. Gamma brain waves are the fastest brain waves, oscillating at a frequency of 30 to 90 hertz, and have been found to foster receptivity, happiness and the ability to concentrate.

The treatment begins with a resting-state functional magnetic resonance imaging (fMRI) brain scan that determines the exact location of an individual’s emotion-controller center. Next, a wand containing wire-wrapped magnetic rings, called toroids, is precisely positioned on the scalp just above the left side of the forehead. The coils deliver a shallow field of waves that harmlessly travel through the skull and induce a gentle flow of electricity through the brain’s emotional-control network. The objective is to strengthen the dorsolateral cortex’s role in suppressing the sadness region of the brain.

During the first double-blind, randomized clinical trial of SNT, 29 people with treatment-resistant depression were enrolled. Half received the new treatment, and the rest were given a sham treatment to rule out placebo effects. After five days, 78.6% of the treated group were no longer depressed, and some felt their depression lift after only a few days. Within two weeks, thoughts of suicide improved dramatically in this group. Remission rates in this trial and follow-up studies have yielded similar results, with 46% to 57% of treated participants reporting sustained depression relief four weeks after treatment. Some patients report being in remission for a year.

The study also showed that SNT doesn’t work for everyone with depression, only for those with a malfunctioning sadness-control brain circuit — and researchers discovered that the more severe the depression, the more signals were traveling the wrong way. This observation has opened a tantalizing possibility: Maybe they could use fMRI brain scan flow patterns to help diagnose mental conditions, adding another tool to the psychiatric toolbox.

**Fighting the system**

Designing innovative new medical hardware is hard. Getting it through the regulatory gauntlet and into clinics is even harder.

Williams’ ally in this effort is Brandon Bentzley, MD, PhD, a psychiatrist, technologist and neuroscientist who first met Williams at the Medical University of South Carolina.

“We were both molded in the incredible neuroscience community at MUSC, a community that framed brain function in terms of circuits,” Bentzley said. “In meeting Nolan, I was struck by our parallel ambitions to create new treatments for mental health based on a mechanistic understanding of the human brain.”

A year after he graduated, Bentzley followed Williams to Stanford Medicine for his psychiatry residency, and they began talking about the potential of TMS and how to get this promising new technology into the medical system.

In the past, treatments for mental illness were almost always the result of accidental findings. Antidepressants were discovered by observing the mood-altering effects of drugs being tested to treat tuberculosis. Antipsychotics were discovered while testing new types of anesthesia. Bentzley and Williams, on the other hand, set out from the beginning to design a treatment for depression rooted in an understanding of the underlying neurocircuity of the brain.

“Based on the efficacy and speed of the SNT treatment protocol, my hope is that we can use this technology as a generalizable platform where brain mapping is married to neuromodulation to provide effective treatments for many brain illnesses,” Bentzley said.

In 2020, Bentzley co-founded Magnus Medical Inc. to commercialize a system for SNT treatment — the SAINT neuromodulation system — while Williams continues his research on refining neuromodulation and applying it to other disorders. (Williams has equity and stock options in Magnus Medical.)

“Implementing technologies like this requires a shift in health care,” Bentzley said. “Reimbursements for mental health hospitalization haven’t changed in 20 years, and there is no easy way for these institutions to adopt new interventions.”

Mainstreaming SNT requires mental health care providers to have access to fMRI services, to purchase expensive new equipment and to train staff to operate it. To justify these expenditures, the company will have to educate the psychiatric community of its effectiveness and gather enough cost/benefit data to convince the federal Centers for Medicare & Medicaid Services (CMS) and more than 1,000 medical health insurers to reimburse institutions for prescribing these treatments.

Earlier this year, SAINT secured CMS reimbursement approval for treating major depressive disorder under “new technology add-on payments.” Historically, once a treatment receives CMS approval, other medical insurance plans add it to their list of reimbursable procedures. Bentzley’s strategy is to launch in large institutions for the most urgent cases of major depressive disorder, then move their systems into smaller clin-
ies. Ongoing work will focus on making the integrated software-hardware system easier for staff to learn and use. The company will add protocols for other mental conditions as soon as they receive FDA approval.

**What’s next**

**Williams’ Brain Stimulation Lab** has about 15 faculty and postdocs working on fast-acting therapies for psychiatric disorders. Targets include treatment-resistant depression, obsessive-compulsive disorder, mania, addiction, chronic pain, borderline personality disorder, depression associated with Parkinson’s disease and persistent tic disorders. Recently, the researchers in the lab identified a brain circuit that makes people more susceptible to hypnosis, which could be leveraged to make it easier for patients to overcome addictions such as smoking.

Williams’ peers and collaborators said they believe that SNT is the start of something big, though there’s still a lot of work to be done before it is fully implemented into clinical care at scale.

Claudia Padula, PhD, an assistant professor of psychiatry and behavioral sciences and addiction researcher at the Sierra Pacific Mental Illness Research, Education and Clinical Center at the VA Palo Alto Health Care System, thinks TMS and SNT are still in their infancy for treating alcohol abuse disorder: “We have a lot to figure out, in terms of mechanisms of action, optimal sites, and the number of sessions and pulses ... but the trajectory is looking really promising.”

Corey Keller, MD, PhD, an assistant professor of psychiatry and behavioral sciences, has been using TMS for years. As a researcher who runs a lab focused on personalized brain stimulation treatments, he is excited about having an FDA-cleared protocol as a launching point for next-generation technologies.

“For the past 15 years, TMS treatments have been largely nonpersonalized and one-size-fits-all,” Keller said. “TMS can apply millions of different patterns of stimulus. We can personalize the treatment target and intensity of stimulation, as is done in SNT. We are also close to being able to update stimulation patterns in real time, or after every treatment, to measure how much of the brain we’re changing and have that guide treatment. SNT represents an exciting next step in moving in this direction of personalized TMS.”

While Keller is enthusiastic about SNT, he also sees some challenges. It is unclear how this new treatment protocol will be adopted in clinics. The fMRI and neuronavigation equipment required to precisely position the magnetic coils may limit uptake in clinics due to the cost and extra staff needed — though Magnus Medical has streamlined the training and brain-targeting processes. And many clinics will have to make adjustments to handle the 10 consecutive hours needed to accommodate the 10 treatments-per-day protocol.

In the meantime, Williams is casting a wide net in looking for new psychiatric tools, some unconventional. For example, in 2022 his lab ran a study to assess the use of ibogaine, a psychoactive drug, to treat 30 special operations veterans who have traumatic brain injuries and post-traumatic stress syndrome. (Ibogaine is derived from root bark and has been used for centuries by Africans in spiritual and healing ceremonies.)

Surprisingly, participants experienced average reductions in anxiety, depression and PTSD symptoms of 81%, 87% and 88%, respectively, with results that lasted throughout the monthlong study that was published in January 2024 in *Nature Medicine*. According to Williams, to date about 1,000 veterans have traveled to Mexico for this treatment — because this drug is illegal in the United States.

Williams sums up the history of psychiatry in this way: Psychiatry 1.0 focuses on your thinking, behavior and past trauma in a way that might keep you in therapy for the rest of your life. Psychiatry 2.0 affects neurotransmitter levels in your brain that might require you to take drugs forever. Psychiatry 3.0 refocuses the story on recalibrating your brain circuits, an approach that’s correctable with negligible side effects.

“I’m an agnostic psychiatric tool builder. If it’s safe for the patient and the risk-benefit ratio is right, we’ll look at it. My job is to find tools that can help people feel more like themselves.”

**‘My job is to find tools that can help people feel more like themselves.’**

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**‘My job is to find tools that can help people feel more like themselves.’**

Where to get SNT treatments

**The Saint System** for the treatment of major depressive disorder became available in April 2024. This integrated hardware/software system will enable medical clinics

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At most schools, the two students would never have met.

One boy was a teenager in high school, the other a child in early elementary school. Because they were attending the school at Lucile Packard Children’s Hospital Stanford, in one big classroom for grades K-12, they became buddies.

They shared similar, life-threatening cancer diagnoses and were enduring many of the same treatments. But they also wanted to have fun and feel like regular kids. They bonded over the challenges of hospitalization and cooked up goofy hijinks. In an old photo, they’re grinning wildly as they show off matching chemotherapy ports.

Although it’s been more than 20 years since she worked with the two in the photo, Kathy Ho, who has taught high school at the Packard Children’s hospital school for 27 years, remembers their friendship fondly.

Watching the growth of such unusual, deep bonds has cemented her commitment to her job.

“It could easily go and work in a regular school, but there are things about being in a hospital school that you just don’t get elsewhere,” Ho said. “One of them is the camaraderie and mentorship that you’re not going to find anywhere else.”

Ho shared the story during a celebration for a big milestone: The hospital school at Packard Children’s is now 100 years old. The school, part of the Palo Alto Unified School District, educates students inside the hospital walls as they receive medical care.

Many children’s hospitals have such a school to help patients keep up with their studies. Hospital schools typically offer in-person instruction — in a classroom, at the bedside or both — to inpatients in kindergarten through grade 12. At some hospitals, including Packard Children’s, they are part of the Child Life and Creative Arts team, which works in many different ways to help kids feel like kids while they’re hospitalized.

The school now at Packard Children’s was founded in January 1924 in the Stanford Convalescent Home, the earliest precursor to today’s children’s hospital. The Con Home, as it was called, was open from 1919 to 1969. There, kids could recover from such conditions as malnutrition, tuberculosis and polio.

Although the capabilities of medical science have changed almost unimaginably in the past 100 years, the core mission of the school has remained: While children are sick, the school gives them a place to connect to ordinary life, where they can make friends, engage with their studies and get a break from medical procedures.
“We treat every kid as though they’re about to go back to regular school,” Ho said. “We want them to have as normal a childhood experience as possible.”

Sunbaths, sleep — and school

IN THE 1920S, the Stanford Convalescent Home was the only medical institution located at the university’s campus, as Stanford’s medical school and hospital were then 40 miles away in San Francisco. However, sunny, then-semi-rural Palo Alto, California, was considered an ideal place for children to recover from serious illness.

Soon after its founding, the Con Home moved into the one-time residence of Leland and Jane Stanford on Sand Hill Road. Jane Stanford died in 1905, and the building sustained severe damage in the 1906 earthquake. The original structure was converted into a 15-bed facility for children recovering from serious illnesses. In late 1923, a second building — called the McLaughlin Unit — was constructed next door, bringing capacity to 40 beds and leaving space for a classroom. The unit housed bed-bound children, while the original building, thereafter called the Stanford Unit, housed “runabout” patients.

Children received the best available treatments for the era: fresh air, sunbaths, plenty of sleep and nutritious food. With the expansion, the Con Home’s leaders began collaborating with the Palo Alto school district to equip and staff a classroom. As the home’s 1923-24 annual report described:

“The former dining room of the Stanford Unit has been converted into a delightful school room …. The school is especially adapted to its convalescent pupils and does not interfere with the rest periods or sun treatments. The sessions are shorter than usual, with frequent recess; and especial attention paid to recreation,” wrote Jessie Treat, chairman of the home.

The opportunity to attend school was important to children’s recoveries, Treat wrote: “Mental development is secondary to physical welfare, but to some degree they may be worked out simultaneously even among convalescents.”

The school’s first students dealt with a variety of medical conditions. Medical director Harold K. Faber reported that for the period from Oct. 31, 1923, when
the McLaughlin Unit opened, to Jan. 1, 1925, 240 children were admitted to the Con Home for, on average, 46 days each. The most common diagnoses reflect the challenges of pediatric medicine in the pre-antibiotic era: severe respiratory infections, including bronchitis and pneumonia; malnutrition; tuberculosis; cardiac disease, chiefly endocarditis; and chorea minor, a movement disorder. The mix of patients also reflected what was then the cutting edge of medical science: One child was being treated for diabetes, which was often fatal before mass production of insulin began in late 1923. All of these children had the opportunity to benefit from the school. Teachers visited bed-bound patients in the McLaughlin Unit, while Stanford Unit patients came to the classroom.

“I have been much impressed with the importance both physically and mentally of the school work which is done in the Stanford Unit and on a smaller scale in the McLaughlin Unit,” Faber wrote in the annual report. “The older children, without this work, would worry a good deal at the loss of time and probably of promotion in school. It is important, too, for their minds to be profitably occupied and for their physical activities to be somewhat limited during the convalescent period.”

Patients came and went from the Con Home and its school as the decades progressed and medical science improved. There were children like 8-year-old Mary Ann Lee, now Mary Ann Sing, who came to the Con Home for about a year in 1947 to recover from severe asthma.

“My father was a dentist, and my mother was a nurse by education,” said Sing, now 84. Sing’s asthma had caused her to lose a lot of weight. Her worried parents consulted their family doctor, who suggested that a temporary move from the cold, damp climate of San Francisco, where they lived, would improve Sing’s health. (Asthma medications like albuterol, a bronchodilator that can be delivered by inhaler, were still decades away.)

Some of what Sing recalls about the classroom — such as the students sitting at individual desks in straight rows — differ from the school’s current setup, where children work at large tables. But much is similar. A third-grader at the time, Sing enjoyed making friends with other pupils of all ages.

“It was good that they did not separate people by age or grade,” she said. “We had one teacher, and there was camaraderie.” She paused for a moment and chuckled.

“Especially when — you know how kids are — when you have a substitute, we treat that person differently. We did the same thing then, and I had a good time, I participated in that. I wasn’t a goody-two-shoes.”

The kids’ shenanigans were silly, “nothing really bad,” Sing said, adding that she later experienced similar treatment at the hands of mildly naughty students when she became a teacher.

Sing’s parents came to see her every Sunday for the Con Home’s weekly visiting day. Patients and families were separated by a rope and not supposed to interact.
“At first, I recall that my mother tried to run over and hug me, and I told her, ‘You can’t do that!’” Sing said, adding that she doesn’t recall being particularly homesick.

Sing has good memories of Stanford student volunteers helping her with everyday tasks (washing her hair, for example); of a woman who read bedtime stories to the patients — “she was excellent”; of her favorite food from the Con Home menu (turkey a la king with rice); and of the home’s Christmas celebrations, which included a party, gifts and a visit from carolers.

After about a year, having regained weight and with her asthma in remission, Sing returned home. Thanks to instruction at the Con Home school, she had kept up with her classmates back home, she found. She graduated from Lowell High School in 1957, then from the San Francisco College for Women (later incorporated into the University of San Francisco) with a major in history and political science. Eventually she married, had three children, obtained a teaching credential, and became a high school social studies and English teacher.

**Connecting with students**

In 1969, the Con Home was replaced by the $5 million, 60-bed Children’s Hospital at Stanford. This was where young patients received care until the present-day hospital's current West Building opened as Lucile Salter Packard Children’s Hospital at Stanford in 1991.

Kevin Danie began working at the hospital in 1988 and ended up teaching every grade level in the school for a total of about 20 years, interspersed with intervals of teaching in other schools in Palo Alto.

He enjoyed the connections he developed with children whose chronic medical conditions required repeated hospitalizations. Getting to know the students helped him make lessons fun. For one student, he would always say, “Correct” in an exaggerated, silly voice when she got an answer right.

“She just loved that and called me ‘Mr. Correct,’” Danie said. “I did that with her for about six or seven years. Then she got to high school and when I tried it, she said, ‘You’re a little extra, aren’t you?’” He laughed and remembered thinking, “My audience has changed.”

“Being silly and individual for them, I loved,” he said. “It was the ability to provide that normalcy and just give kids an opportunity to not think about their reason for being in the hospital.”

But the structure of the classroom — with its environment of teachers, classmates and lessons — held an even stronger message about normalcy for hospital school students, regardless of whether they were expected to make a full recovery or had lifelong conditions.

“Normal for them is to go to school. If there was no school, it’s sort of saying, well, we don’t value your normal life,” Danie said. “And being in school is a chance to let them know they’re not alone and share the experience of hospitalization with other kids.”

**Continuity and growth**

Today, Lucile Packard Children’s Hospital Stanford includes the 1991 building (now called the West Building) and the adjacent main building, which opened in 2017. The facility has 361 beds.

Through every expansion, the school has helped young hospital patients keep up with their studies. The school is now located in a classroom inside Packard Children’s, where Ho and two other teachers instruct around 450 students per year. The Ronald McDonald House at Stanford, which provides accommodations near the hospital to patients and their families, houses a second classroom, founded in 2017. It serves another approximately 50 students a year.

The COVID-19 pandemic’s effects on schools across the country had ripple effects on the hospital school, Ho said. Most schools now offer online portals for students to access their lessons when they are ill, for example. As a result, hospital teachers now frequently guide children through lessons from their home classrooms.

But hospital teachers still have plenty of work to ensure that their students can gain as wide an educational experience as possible. They figure out how to offer art lessons, science experiments, ways to learn about the natural world — all from the confines of the hospital. For many years, they hosted an annual prom each spring. It was on hold during the pandemic, but the team is bringing it back this year.

“I’m pleased when I read about things that happened in our school 100 years ago. I’m proud to be part of the tradition,” Ho said. “Creating a positive, joyful community for hospitalized children — the sort of place where you might make friends with a much younger kid who shares your diagnosis or join pals in mischievously teasing the substitute teacher — is just as important as it was a century ago.” SM — Contact Erin Digitale at digitale@stanford.edu
Yet she’s upbeat — in part because, for her, optimism is a moral choice, she told Lloyd Minor, MD, dean of the Stanford School of Medicine and vice president for medical affairs at Stanford University.

During a recent fireside chat at a Stanford Medicine leadership retreat, the two spoke about how Clinton’s Stanford undergraduate experience sparked her advocacy for health equity and child development, the power of building relationships, and how humility and optimism keeps her focused in challenging times.

Her interest in public health was first inspired by a junior-year reading: Infections and Inequalities, the autobiography of renowned physician and medical anthropologist Paul Farmer, MD, PhD, she said. The book tells how Farmer co-founded Partners in Health, a global nonprofit dedicated to bringing quality health care to impoverished people.

Clinton went on to earn a master’s in public health and a doctorate in international relations. One of her priorities today is promoting early child development through the Clinton Foundation’s Too Small to Fail initiative, providing parents with early language learning resources so they can talk, read and sing with their children from birth to prepare them for educational success.

This Q&A, based on the conversation between Clinton and Minor, has been condensed and edited for clarity.

MINOR: You’ve spoken and written about being at Stanford. What was it about the environment and your experiences here that helped guide your future education and leadership roles?

CLINTON: I was a little kid in the South and attended high school in Washington, D.C. I wanted to have a different experience ... a different adventure in life. I certainly found that here and have extraordinarily rich memories of my time as a student and as a person here.

I also made very strong friendships. I was a junior when I read Infections and Inequalities. I cold-emailed Paul Farmer three pages of thoughts, questions and critiques. He wrote me back and we started this pen pal relationship.

I didn’t know at the time that my mother knew Paul because she recruited him and Partners in Health to provide
medical and public health support to former Soviet Union countries.

Fast-forward to my dad asking me and others what he should do in his post-presidential life. I said, “I think you did a lot of great things while you were president ... but you haven’t done enough on AIDS. You need to do more, and you should start by talking to Paul Farmer.”

Thus began a profoundly important relationship between my dad and Paul over the next 20-plus years working to understand the HIV/AIDS crisis, and catalyzing what would become the Clinton HIV/AIDS initiative, then, in 2002, the Clinton Health Access Initiative.

MINOR: What are top issues you feel the Clinton Health Initiative and those of us in the academic community can impact through our work?

CLINTON: At Too Small to Fail, we’re trying to better convey concerns about the impact of climate change on pregnant people, infants and toddlers. In our research, practice and advocacy, we focus on helping parents better understand why, for example, extreme heat is a danger for them, but also what they can do about it.

Climate change often seems to be the pornography of despair. Everything feels so extreme and overwhelming, and I worry, consequently, of pushing people into cynicism. We’re trying to understand what helps parents and other caregivers best feel as if the science is informative and activating and not disempowering and disorienting.

I also worry that, because of the intensity of the past few years for many of our physicians or nurses or physician scientists, there will be this receding from the public sphere. But we need people to be even more engaged. We are always learning more about how to best protect and promote health. It’s only better communication — at a policy level but also directly to communities, to families, even to kids — that will start to rebuild the trust that I think all of us recognize we desperately need in our country.

MINOR: You’ve written about global health systems and think a lot about how impact scales — how we take discoveries and advances and get them into parts of the world that traditionally haven’t benefited. What are the take-home messages from scaling? Are there principles we should keep in mind as we look at our work here?

CLINTON: At the foundation, we try to always hold ourselves accountable.

We try to meet parents and caregivers where they are with resources they need to be effective first teachers for their children on early language, math and numeracy, and on social-emotional development.

We’ve built more than 600 libraries in laundromats, turning wash time into play time because low-income families spend two to four hours a week in laundromats. We also have more than 1,300 playgrounds across the country that are equipped with engaging educational signage to prompt parents and caregivers to turn play time into learning time and engage their children in language-rich conversations. And we’ve distributed more than a million books through partnerships with diaper banks.
All of these have rigorous evaluations alongside them. It’s something we’re highly focused on.

We are also doing more in New York City, where much of the core foundation team works and where, candidly, we hadn’t tried to do anything. Now we’re a core partner for the New York City birth health equity initiative the mayor and local health commissioner started.

While on a national average, a Black mother is three times as likely to die as a white mother giving birth, in New York City, it’s nine times. We like to think of ourselves as this bastion of liberal progressive policies. Yet, we have terrible — on an absolute and relative basis — maternal mortality rates.

We’ve partnered with the city to bring together this large set of different organizations who either could be or should be working on these challenges.

I share that because we are trying to have the humility of learning what has worked around the world that can and should be urgently put into practice here at home ... in our own ZIP codes.

**MINOR:** That’s such an important message ... a focus on looking forward, on optimism, and on the key concepts of humility and empathy. How do you think about those attributes in a fairly polarized world today?

**CLINTON:** I’ve heard Jim Kim, one of Paul Farmer’s partners in starting Partners in Health, say that optimism is a moral choice. And I believe that deeply — that it is a more moral place to be, to think about how we can always be building a more equitable, more sustainable, more inclusive, more joyous world than just accepting the status quo.

Whenever I feel the edges of despair, I think, “Is this productive? Do I want to just be depressed?” Or do I want to think, “What can I do with my experience, what I know, the people I know, the platforms that I am lucky and humbled to have, the sense that we can always be doing more?”

Being a parent of three kids makes it easier for me to be optimistic. I want to be able to tell them what I did today that, hopefully, was generative and positive and productive. **SM**

Let’s talk about it

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order for two decades. After his death, Sheline retrieved his journal writings, which described in vivid detail what it’s like to yo-yo between the manic-depressive swings of a serious mood disorder. She is piecing the journals together as a book in hopes of bringing greater understanding to serious mental health struggles.

“People have these tragedies happen in their families, and I think it’s important that they can talk about it,” Sheline said. “I’ve had a number of people who have known about my story and then have referred friends to me. When you’re struggling, it really helps to talk to someone who knows what the struggle is like.”

This is particularly true, she said, when people learn that a career psychiatrist who is studying the neuroscience behind serious disorders has faced the same systematic struggles they have in getting help for themselves or a loved one.

Like Williams, Sheline has thrown herself deeper into the hard work of developing treatments for neuropsychiatric disorders that bring relief more effectively and quickly. And she is embracing the strength of openness, of weaving her personal story into her professional narrative. She, too, feels like speaking out is an increasingly important part of her job description.

“How would you know about things like these unless you were exposed to them?” she said. “I think it’s important to shine a light on them for others.”

Williams not only agrees, she also sees signs of light all around.

She has seen it in the way people tend to discuss depression and anxiety more openly since those conditions became more universally understood and talked about during the COVID-19 lockdown.

She sees it in the growing support for precision mental health practices such as brain imaging, electroencephalogram (EEG) testing, depression phenotyping, magnetic brain stimulation and psychedelics — first-line therapies that transcend the pharmacological guessing game.

She sees it in her inbox when another scientist — or anyone — who has lost a loved one to suicide reaches out. She feels it in the level of trust shared by colleagues at the Stanford Center for Precision Mental Health and Wellness where, as director, she is cultivating a culture of openness around mental health that mirrors openness about physical health.

Within those small stories, Williams also sees a bigger one emerging.

“It’s early days for this level of openness about mental health, but we will get there,” she said. “We have to.” **SM**

— Contact Mark Conley at mjconley@stanford.edu

How moms and dads can provide mental health care

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“When I’m dealing with my own kids, my knowledge of research-supported methods helps me pivot, such as by being aware of my protective instinct and still fostering my kids’ ability to tolerate anxiety, rather than unintentionally maybe contributing to it,” Kurahashi said. Expert techniques — a parent helping their anxious child cope and build confidence in a new situation rather than allowing them to avoid the situation altogether, for instance — “can make a huge difference for families,” Kurahashi said.

Conversations about the interplay between their work and their parenting were part of what drove Kurahashi and Reichert to find new ways to put validated parenting information into the hands of other moms and dads.

The parenting center launched online on March 1, 2020. Just over a week later, the COVID-19 pandemic was declared by the World Health Organization.

Families were suddenly dealing with severe disruptions: curtailed extracurricular activities and social lives, unprecedented financial and professional stressors, and
Parents can fill out questionnaires about their class experiences, and their answers will form the basis of future scientific publications on the effectiveness of the center’s programming.

Though moms and dads are the experts on their own children, tested parenting techniques can help, Reichert said.

“What we know can help them guide their child’s trajectory in a healthy way,” she said. “I feel very grateful to be able to think on a larger scale about how to make that expert knowledge more accessible and expand the treatment paradigm beyond the one clinician-one child model.” SM

— Contact Kris Neeby at medmag@stanford.edu. Visit the Stanford Parenting Center at https://med.stanford.edu/childpsychiatry/parenting.html.
Ahab hunting down Moby Dick. Wile E. Coyote chasing the Road Runner. Walking over hot coals. Standing in a long line for boba tea or admission to a small, overpriced clothing store. Forking up for luxury nonsense.

These activities are all examples of the overvaluation of what economists call “sunk costs”: the price you’ve already irretrievably paid in time, money, effort, suffering or any combination of them for an item, an experience or a sense of self-esteem.

It’s a phenomenon we all recognize. It’s often irrational. But we do it. Ask me.

My ‘64 stick-shift red-white-and-glacial-blue Volvo station wagon was festooned with a phalanx of three small bowling trophies for hood ornaments (I called it “the Bowlvo”). It was falling apart like a piece of overcooked chicken. (One day as I sped down Interstate 25 in Colorado, the hood flew up in my face. Another time, as I was frantically downshifting into second gear while driving home at my usual unsafe speed on a winding mountain road, the shift lever came off in my hand.)

I would have gone to the ends of the earth, or at least the end of my rope, to keep it in running condition — or just to keep it.

Strangely, we’re hardwired to value something more if we’ve put a lot of sweat equity — what we had to do to get or keep that something — into it.

“It’s not just us,” said assistant professor of psychiatry and behavioral science Neir Eshel, MD, PhD. “This has been shown in animals across the animal kingdom.”

OK — all higher animals are hardwired to make doomed decisions. Why?

Blame dopamine, that much-talked-about “do it again, do it some more” brain chemical.

There’s a difference between wanting something and liking it, Eshel said. “You can want something very, very much even though you don’t even like it very much. Or vice versa.”

A few years ago, Eshel and Stanford Medicine colleagues began conducting experiments — described in a paper published in Neuron in November 2023 — to learn more about what, if any, role dopamine secretion in the brain plays in “liking” something versus “wanting” something.

The team thought of “liking” as how much mice will consume of a reward if getting it was cost-free and “wanting” as how much that animal’s consumption is affected by the cost of getting it.

In steps, starting at zero, the researchers increased the costs — in this case either the number of times mice had to poke their noses into a hole in a box, or the intensity of mild to moderate electric foot shocks mice had to endure — to get a reward: either sugar water or instant direct stimulation of dopamine release in two places in the brain known for their role in motivation and movement.

The researchers also varied the amounts of reward animals received for a given amount of persistence or discomfort.

Naturally, boosting the prize’s size increased dopamine release — but then again, so did raising its cost.

How does this wired sunk-cost hang-up make evolutionary sense? “In an environment with limited resources (as most are), when we typically get rewarded only after really hard work, we may need high dopamine secretion to get us to do it again,” Eshel suggested.

Maybe Eshel should have tested me. I know a thing or two about sunk costs.

I still miss the Bowlvo. BY BRUCE GOLDMAN
As anyone who’s getting on in years knows, some of our body parts show their age sooner than others. Aching knees and backs are hard to miss. What’s not so obvious is what’s going on with vital organs like hearts, lungs and brains.

New research led by Stanford Medicine investigators offers a path toward a blood test that would sort which organs remain sprightly and which are aging extra fast. “By monitoring the health of individual organs in apparently healthy people’s bodies, we might be able to find organs undergoing accelerated aging and to treat people before they get sick,” said the study’s senior author, Tony Wyss-Coray, PhD, the D. H. Chen Professor II of neurology.

According to the study of blood samples from 5,678 people, published in December 2023 in Nature, about 1 in every 5 reasonably healthy adults 50 or older is walking around with at least one organ aging much more quickly than its counterpart in others the same age. That person is at higher risk for diseases associated with that organ and for dying.

The silver lining: The results of a simple blood test might be able to guide treatments well before clinical symptoms manifest.

For this investigation, the researchers assessed the levels of thousands of proteins in people’s blood, found that nearly 1,000 of them originated within a single organ, and tied aberrant levels of those proteins to corresponding organs’ accelerated aging and susceptibility to disease and mortality.

The team next came up with an “age gap” for each organ: the difference between the organ’s actual age and its estimated age based on the protein levels specific to it. Having an accelerated-aging organ carried a 15% to 50% higher mortality risk in the next 15 years, depending on the organ affected.

Outwardly healthy people with accelerated heart aging incurred heart failure 2.5 times as often as people with normally aging hearts. Those with “older” brains were 1.8 times as likely to show cognitive decline over five years as those with “young” brains.

The organ-aging test will need several years of further refinement and clinical testing before it can be made commercially available. Wyss-Coray and colleagues have started a new company, Teal Omics, to expedite development of the test, and Stanford University’s Office of Technology Licensing has filed a patent application related to this work. — BRUCE GOLDMAN