PRECISION

HEALTH

BRAIN WAVES

How neuroscience could determine your mental health treatment

The elderly gentleman's screams echoed down the halls of the transitional home for the mentally ill, the voices in his head torturing him. His only relief came when he held a transistor radio, tuned into static, tightly clamped to his ear. • "The voices were not quieted by medication," says Leanne Williams, PhD, a Stanford neuroscientist who vividly remembers her patient from nearly three decades ago, when she was training to become a therapist in Australia. Many of the patients she cared for during those three years in her 20s had been institutionalized for years — some for decades. An older woman who believed she was constantly about to give birth, tortured daily by labor pains. A severely depressed young man whom Williams and her co-worker found one morning hanging lifeless from the back of a bathroom door, the depression finally too much for him to bear. • The experience was frustrating, Williams says. As a therapist, she believed that by understanding the psychology of human behavior she could treat these severely mentally ill patients. But she soon realized she simply didn't have enough tools to understand what was going on inside their brains. Instead, she began to learn from her patients. • "It struck me that the man who heard voices was using the sound frequencies on his radio to modulate his brain activity, yet we were bereft of treatments to do anything similar," she says. "I finished up these work experiences with 100 percent clarity that I needed next to go into research. I wanted to understand brain dynamics and how this understanding could be connected to the real-world experience of mental disorder. From then on, I was on a mission."

By Tracie White

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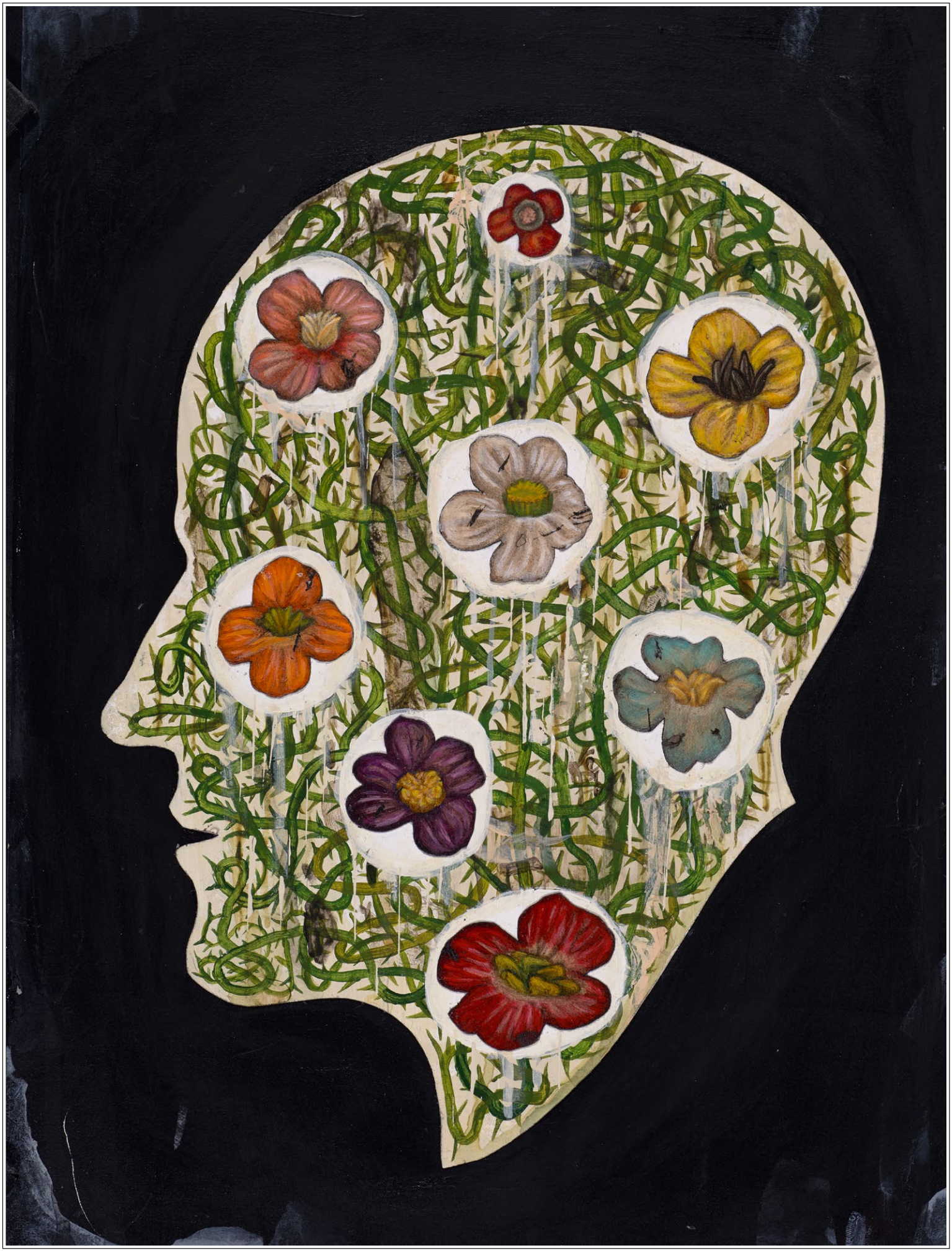

THE PAST QUARTER-CENTURY has seen a wealth of advances in neuroscience, from neuroimaging techniques that make it possible to see inside the live human brain to noninvasive electrical brain stimulation to selective activation of neurons using laser light for research in animals. The popularity of the field has exploded, with membership of the Society for Neuroscientists steadily climbing from its founding in 1969 to 40,000 members today. Yet little if any of this activity has resulted in improvements in clinical care for the mentally ill.

"We haven't yet seen the progress toward improved clinical care that we would have hoped," says Sarah Morris, PhD, acting director of the National Institute of Mental Health's Research Domain Criteria Initiative, a program begun five years ago to accelerate the translation of basic neuroscience research into new models for mental disorder and treatment. This gap, often caricatured as "mindless neuroscience versus brainless psychiatry," must be bridged if modern neuroscience is to bring help to the mentally ill, wrote Thomas Insel, MD, in May 2015 in *Director's Blog*, the blog he produced as director of NIMH.

The disconnect can, in part, be explained by the lack of a working biomedical model of mental illness, many in the field say. The current model of mental health treatment, in use since the days of Freud, is based solely on observation by clinicians and the reporting of symptoms by patients.

The new model combines these traditional methods of diagnosis and treatment with the biological concept of the brain as a network of circuits. The circuit, or network, approach focuses on how the billions of neurons in the brain communicate with one another via electrical signals. It cuts across the current broad diagnostic categories like anxiety or depression, with the hope of creating a new understanding of exactly what mental illness is.

The circuit approach, Williams says, provides a scientific path toward more accurate disease diagnosis and treatment while helping eliminate the stigma associated with mental illness as a personal failing or weakness.

"You boil it down to the superhighways of the brain, which are the routes where most of the neuronal traffic is going for the primary functions of the brain," Williams explains. "Imagine the road system. There are all these little hiking trails, then you've got the big superhighways where most of the traffic occurs. These brain circuits are explaining those main routes." Almost daily, new studies are published mapping these circuits and explaining what they do. Or what they don't, when altered or destroyed.

It's been nearly 30 years since Williams moved on from her career as a therapist and entered the world of brain research. And she's getting restless. Personalized neuroscience, a form of precision health that provides the best treatment for each individual patient, has the potential to change lives now, she maintains.

"I'm shocked so little of this research has bridged this gap," says Williams. She is running a clinical neuroscience study called the Research on Anxiety and Depression, or RAD, project. Funded by NIMH to develop the Research Domain Criteria Initiative approach, hers is one of the first studies to test a step-by-step process that combines neurobiological tests, such as brain scans, with measures of real-world function, such as occupational and social well being, to diagnose and treat patients. She describes it as a "pragmatic" research design that mirrors what would happen in an actual mental health clinic using this approach. By making it comfortable and practical for participants, she has designed a prototype for use in the real world.

'RIGHT NOW IN PSYCHIATRY we don't think about the brain at all when we are making a diagnosis or planning a treatment.'

The trial is an attempt to find an array of biological markers to classify anxiety and depression in new ways. It draws on the new model emerging from neuroscientists and psychiatrists — one that incorporates an examination of the brain as an organ much like a cardiologist examines the heart.

"We take it for granted in other areas of medicine that the organ is relevant," Williams says. "When you go to see the heart doctor with a heart problem, you would expect them to run tests. Right now in psychiatry we don't think about the brain at all when we are making a diagnosis or planning a treatment."

It's time we did, she says.

LEANNE WILLIAMS WANTS TO BRING PERSONALIZED NEUROSCIENCE INTO THE CLINIC.

Noreen Ford, a 59-year-old middle school teacher who lives in Belmont, California, is lying on her back inside a brain scanner — a functional magnetic resonance imaging machine — located in a lab in the university's Main Quad. A mechanical chunk-chunk-chunking noise startles her at irregular intervals. She's suffered mild depression on and off and had panic-like symptoms, but primarily she signed up for the RAD trial because, like many of the other participants, she was interested in "seeing inside my brain."

On a screen in front of her face flashes a series of photographs of smiling and terrified faces. She is supposed to push one of two buttons — one to indicate happy, the other to indicate fearful. This is one of several tests she will take during the hour or so spent inside the machine, each triggering a different brain circuit associated with depression and anxiety.

Williams sometimes seems as much a clinician as a brain scientist: Dressed more formally than the typical researcher, she drops by the lab regularly to check in and offers her lab assistants quiet encouragement. Williams describes the multiple fMRI tests that participants take as akin to "exercise for the brain."

Over the past two years, Ford and about 160 other participants with either anxiety or depression or a combination of the two have participated in RAD. They each spend a day on the Stanford campus for testing. They donate a swab of saliva for a genetic test that can help pinpoint antidepressant effectiveness and the influences of genetic variations on brain circuits, and they take a battery of "brain tests" while inside the fMRI machine for about an hour. After a walk across campus from the lab to the psychiatry building, meant to provide a relaxing break, participants eat lunch and then undergo a traditional symptom-based psychiatric evaluation.

Williams reads and interprets the resulting brain scans, searching for any abnormalities in those circuits. In an optional feedback session, Williams, the patient and the patient's therapist meet together in a comfortable therapy room to discuss how the patient's brain is functioning and possible treatment options, such as drugs, psychotherapy or brain stimulation. All participants also take a follow-up survey 12 weeks after the initial testing. The researchers plan to continue the trial through 2017.

"The results provide a lot more detailed information about what is going on with our clients," says clinical psychologist Nancy Haug, PhD, the research director at the Gronowski Center, a community mental health clinic and a collaborator with the RAD study. "A lot of times, the information confirms what our therapists already know and are already doing; other times it might suggest different treatment alternatives. Often the feedback sessions are very helpful."

Globally, 405 million people experience depression and 274 million experience anxiety disorder. These disorders are the main causes of disability and lost productivity, with an economic cost of about $50 billion per year, according to a study published in a 2013 issue of *The Lancet*.

The current treatment model relies on finding a treatment through a process of elimination.

"There is no objective way of saying which treatment will work best for which patient," Williams says. "Thirty percent of the time it will work. The other 70 percent of the time it fails. It can take a few years of trial and error. What is happening to your brain in the meantime is that it is becoming more and more unwell."

Patients grapple with new side effects each time they try a new drug, or withdrawals each time they change drugs. They jump from drugs to talk therapy to combined

AMIT ETKIN SAYS BRAIN SCANS SHOW PROMISE FOR PSYCHIATRY.

treatments and back again, searching for what works for them. Sometimes they never find it.

To get people better faster, or to get a higher percentage of people better, new drugs are crucial, says Amit Etkin, MD, PhD, assistant professor of psychiatry and behavioral sciences at Stanford Medicine. But the psychiatric drug pipeline has virtually dried up. "There is a huge concern about a lack of new drugs," says Etkin, who is also turning to neuroscience for improvements in mental health care.

RDoC, the NIMH project, has succeeded in increasing the pace of research bridging neuroscience and new clinical models, funding about 30 grants that each average $400,000 per year over four to five years. All of these are still in process, so they have not yet resulted in changes to clinical care.

Some neuroscience-based methods of treatment are close to cracking the clinical door, Etkin says. Brain stimulation methods such as transcranial magnetic stimulation or deep brain stimulation, which activate various brain circuits, have shown promising results as treatment for emotional disorders.

"It's a very active area of research right now," he says. He's also optimistic about the prospect of using brain scans for the early detection of mental illness and getting patients into treatment prior to the onset of symptoms.

"Think of it like a cancer screening test," he says. A routine fMRI scan would be part of a preventive-care treatment plan. "If you wait for symptoms, you've waited too long."

An ongoing national clinical trial called EMBARC is another effort to use the personalized approach. Launched three years ago by psychiatrists at the University of Texas Southwestern Medical Center, the trial — much like RAD and Williams' previous trial, iSPOT-D — is attempting to find biological markers that can better predict how people with depression will respond to medication. Helen Mayberg, MD, a professor of psychiatry at Emory University, made headlines recently with a study that identified a biomarker in the brain that predicts whether a depressed patient will respond better to psychotherapy or antidepressant medication.

Clinical trials are urgently needed to evaluate the efficacy of neuroscience-based treatments in clinical care, Mayberg says. She, like Williams, is an advocate for moving neuroscience research into the clinic now.

"Patients just can't wait for all the scientists to solve all the riddles of the brain," Mayberg says. "Every few months, there's another discovery of another tool to get at another aspect of how the brain is working. The hard part now becomes, how much do you need to know before you can do something practical with it?"

The trajectory of Williams' career has mirrored these developments in neuroscience. After studying behavioral psychology as an undergraduate and working as a clinical therapist for those three years in her 20s, she received a British Council scholarship to study for her PhD in cognitive neuroscience at Oxford University, which she earned in 1996, and began a career as a research scientist.

"I wanted to go to Oxford because of their history of innovative work linking clinical symptoms of mental illness to underlying physiology," Williams says. "This was before the days of brain imaging, and the measures we used included performance on behavioral tasks, physiological recordings and eye-movement recordings."

Understanding the brain as an organ became her new focus, and as technology advanced, functional magnetic resonance imaging became her new research tool.

"The more I wanted to understand what was really going on in the human brain, the more I knew I'd have to understand the neurobiology of the brain," she says. The advent of new imaging tools like positron emission tomography and functional magnetic resonance imaging has been key to advances in modern neuroscience. A PET scan uses radioactive tracers to look for disease in the body. An fMRI measures changes in blood oxygen levels, which can indicate brain activity. In 1999, Williams was recruited to the University of Sydney's psychology school and in 2004 to its medical school, where for 12 years she was the director of the Brain Dynamics Center, which aimed to help create a new neurobiological model of the brain for understanding mental illnesses.

For Williams, the RAD study is a benchmark in her career. Finally, findings from her years of brain research are being tested in clinical care. To design the study, she has drawn on data from the iSPOT-D trial, which included more than 1,000 people with depression and revealed biomarkers — brain circuit patterns and genetic profiles — that appear to predict treatment response. Williams was the lead academic researcher of the industry-sponsored trial from 2008 to 2013.

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For example, her report, published in the journal *Neuropsychopharmacology*, indicated that participants whose fMRIs showed low reactivity in the amygdala — a small structure in the brain that plays a key role in processing emotions — would respond better to the SSRI class of antidepressants like Prozac and Zoloft than to SNRIs like Cymbalta or Effexor.

It was this trial that initially brought Williams to Palo Alto. She came to Stanford, which was one of the study's 12 sites, in 2011 as a visiting professor. In early 2013 she joined the faculty as a professor of psychiatry and behavioral sciences with a joint appointment at the Palo Alto Veterans Affairs Health Care System. Shortly thereafter, she was awarded the RDoC grant and began recruiting for the RAD trial.

The RAD study envisions a future in which a physician with an anxious or depressed patient would order various neurobiological tests, such as an fMRI brain scan, to help make a more precise diagnosis and to guide treatment choice. Currently, the diagnostic categories are extremely broad, Williams says. Patients with anxiety or depression could have widely varying symptoms, and the cause could be very different, yet the first-line treatment is often the same. The model she is developing breaks down these broad diagnostic categories into "types" based on brain circuit dysfunctions. Matching each type of depression or anxiety with the best evidence-based treatment is the ultimate goal.

In the study, researchers scan six of the large-scale neural circuits that most neuroscientists agree are associated with anxiety and depression. These circuits are evoked during different tasks like the one Ford underwent in the fMRI machine. The intrinsic architecture of these circuits is also scanned when the patient is at rest inside the machine.

The six brain circuits are mapped out for each of the participants, then compared with how the circuits should look in a healthy brain. Any deviations — faulty connections that are generating too little or too much communication between brain regions — are used to diagnose a specific brain-based type of anxiety or depression.

For example, the "threat" circuit, which follows a circular path of neuronal activity from the amygdala to several other parts of the brain and back to the amygdala, is involved with how we react to threat or loss. Terrifying facial expressions, like those in Ford's fMRI brain test, trigger this circuit. A breakdown in the "threat" circuit can result in a type of depression Williams refers to as the "negativity bias."

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"In depression, you will see some people get stuck in one of those circuits for negative emotion," she says. "They'll say they feel bad, that everything feels bad. Trying to concentrate and switch to a different mode — a different circuit — can be really hard, almost impossible." In this case, a clinician should pick a treatment that will help get the patient unstuck. There is evidence certain antidepressants work well for this because the action of the medication matches the function of the circuit, she says.

"We are trying to link all this science to the real world," Williams says. "We talk to participants about their symptoms, their work experiences, their quality of life, how they cope, how they regulate their emotions. All the things that could be pertinent to how your brain functioning relates to your experiencing the world."

As a neuroscientist conducting clinical research, Williams says it has been important to build strong partnerships with clinicians. Since she is no longer a therapist, she needs this pipeline for study recruitment, but she also believes communication with patients and therapists is essential if she wants to know how best to translate her research into clinical care.

"I always think, how can we translate this back to the patient?" she says.

"I talked to one software engineer who was finding it hard to concentrate at work," she says. "He was needing to take a nap in the afternoon."

Using mappings of the engineer's brain circuits, Williams explained how his "default mode" circuit was in overdrive even when he was at rest, which put him into a state of rumination about his negative thoughts. This disruption meant the man, who was depressed, had problems engaging his "cognitive control" circuit and dampening down the ruminative thoughts in order to focus. Instead, his brain was stuck in overdrive, making it difficult to concentrate at work.

When she talks to participants stuck in this state of rumination and dysregulated circuits, she asks:

"When you wake up in the morning is your brain immediately overwhelmed? Are you like 'Oh my God, I've got this to do, that to do, and I can't see a way through'?

"When I give the feedback, I tell them to try things that will help shift them out of that state of overdrive. I think of analogies from heart health where the best current

evidence suggests combining new interventions, drugs and lifestyle changes. As a lifestyle change, try really fast walking, or listening to music, something that will get your brain into a different kind of rhythm because you can't ruminate while walking really fast or while dancing, for example."

The software engineer told her that he enjoyed Latin dancing, so she recommended he try that as a way to break out of rumination and over-firing of his default mode circuit. A complementary option was transcranial magnetic simulation, which can help regulate the default mode circuit and the way it interacts with the cognitive control circuit.

"So that's the concept of the personalized approach," she says. "Thinking of mental illness in these types of brain terms seemed more reasonable than the concept of mental illness being someone's fault or a lack of trying hard enough."

While it's not yet clear how to deploy these individualized treatments on a broad scale, Williams says, she believes it's time to try.

"I don't understand why we can't do it now. It's not unsafe. We are still giving the same treatments. It's hard to see a bad outcome. Why not try it?" **SM**

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FEATURE

Ahead of time

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preventing preterm labor have not improved in decades. Similarly, when women come to the hospital in premature labor, doctors' tools are rudimentary: drugs that only sometimes, temporarily, stop contractions — maybe buying enough time for a few doses of other medications that temper the effects of prematurity on the baby's brain and lungs.

Gaddam thought a lot about the possibility of a second tragedy. "It was really hard, knowing it was likely that my body wouldn't be able to sustain a pregnancy to term, to be aware that it was my responsibility to gauge what was happening internally and communicate it to the medical team," she says. "I felt like I had no idea what was happening in the first pregnancy, and it was hard for me to believe that I would be able to tell if something happened again."

Asked about her wish list for preventing prematurity, Chueh is succinct: She wants tools that reduce the guesswork for expectant moms and their doctors. "It would be really nice to have a test we could use in the first part of pregnancy to identify people at risk for prematurity," she says. "And we would love to have an etiology, something we could treat."

Several scientists are trying to understand the exact molecular path connecting risk factors such as maternal obesity or PTSD to early contractions of the uterus. Their working hypothesis: While myriad genetic and environmental factors play into prematurity risk, one major biologic mechanism must translate these into a delivery trigger. Mounting evidence suggests inflammation is key.

"Think of pregnancy as a state of immune tolerance that suppresses inflammation," says Martin Angst, MD, professor of anesthesiology, perioperative and pain medicine. As long as the mother's immune system accepts the immunologically foreign fetus, the pregnancy continues. "But at some point, her body is no longer immune-tolerant; instead it's now more in a pro-inflammatory state."

Inflammation is the immune system's and body's way of getting rid of potentially harmful material. It's also associated with obesity, stress, infections and diabetes — a litany of prematurity risk factors.

Angst and his collaborators published a study comparing immune cells from the blood of mothers who had preterm deliveries against similar cells from mothers who had full-term pregnancies. The researchers used a relatively new technique, called cytometry by time-of-flight mass spectrometry, to test the inflammatory response of specific immune cell subsets. The technique lets scientists take a simultaneous look at all immune cell subsets represented in blood. They wanted to see if, under lab conditions, immune cells taken from women who had had a preterm birth were more sensitive to an inflammation trigger.

Indeed, immune cells called monocytes from women who had given birth prematurely responded differently when the researchers induced inflammation in the lab. In particular, certain components of the toll-like receptor 4 pathway, which acts like the stone that starts the avalanche of the inflammatory response, were more readily activated in these mothers' monocytes.

"There is a change in the immune disposition of these people and we can see it," Stevenson says. A future in which at-risk women receive targeted immunotherapy to block the pathways involved in preterm birth now seems possible, he adds. "We can probably understand not just the biomarkers of preterm birth but also the associated changes in gene expression — it's a really interesting story."

Stevenson is alluding to work by another Stanford researcher, Stephen Quake, PhD, professor of bioengineering and of applied physics, whose team has developed a technique to track RNA in the maternal blood that may function as a "molecular stethoscope" to detect the signature of impending prematurity. RNA, the message genes send as they act, is released in tiny amounts by dying cells. Quake's team now has the ability to read these signals not just from the mom's cells but also from the fetal cells that make their way into the mother's blood. They can detect physiological changes in the tissues and organs of both the mother and the baby, and hope to use this information to measure genetic