The Washington Post

The mind's biology

By Amy Ellis Nutt February 19

She relaxed in the recliner, her eyes closed, her hands resting lightly in her lap. The psychiatrist's assistant made small talk while pushing the woman's hair this way and that, dabbing her head with spots of paste before attaching the 19 electrodes to her scalp.

As the test started, her anxiety ticked up. And that's when it began: the sensation of being locked in a vise. First, she couldn't move. Then she was shrinking, collapsing in on herself like some human black hole.

It was a classic panic attack — captured in vivid color on the computer screen that psychiatrist Hasan Asif was watching.

"It's going to be okay," he said, his voice quiet and soothing. "Just stay with it."

The images playing out in front of him were entirely unexpected; this clearly wasn't a resting state for his patient. With each surge of anxiety, a splotch of red bloomed on the computer screen. Excessive activity of high-energy brain waves near the top of her head indicated hyper-arousal and stress. Decreased activity in the front of her brain, where emotions are managed, showed she couldn't summon the resources to keep calm.

"This was your brain as you were sitting there trying to relax," Asif explained afterward, rerunning the sequence for the woman, who for many of her 37 years had struggled against crushing waves of dread. "Look at what just happened. This was the area of your brain that started firing. . . . It's right there on the screen."

For the 51-year-old psychiatrist, the episode last year in his Bronxville, N.Y., practice was yet another piece of evidence that he was on the right track, burrowing past his patient's symptoms to probe the structures in her brain that produced them. Individually, all the tools he employs have been used before, but rarely, if ever, together. It's an approach that parallels some of the most cutting-edge research in the field.

Scientists have long known that the most forward part of the brain is the seat of higher cognition. But only in recent years have they been able to link certain mental disorders with specific brain circuits, the connections between neurons that are responsible for every one of our thoughts, emotions and actions. Asif's tools enable him to more precisely diagnose his patients' problems and, ultimately, to treat them.

Neuroscience's inroads have emboldened a small but growing number of clinicians and researchers to reject

diagnostic protocols on which mental health practitioners have relied for years — the cataloguing of symptoms such as sadness, fatigue, loss of appetite — and instead focus on finding biological clues associated with these symptoms in a blood test, a brain image or a saliva sample.

These are the biomarkers, the concrete measurements of mental illness, that many think will move the mental health profession into the 21st century. For Asif, some of the tools being used in the search are already yielding practical results, such as sending a patient's cheek swab for DNA analysis to help determine which psychotropic medication will be most effective and best tolerated.

This new, if controversial, approach to mental illness got a boost in 2013 when the director of the National Institute of Mental Health announced that the government, the largest funder of mental health research in the world, would drastically shift its priorities. Research based solely on the Diagnostic and Statistical Manual of Mental Disorders, the chief tool of mental health professionals, would no longer be funded. The reason, Thomas Insel said, was "its lack of validity."

First published in 1952, the manual has changed over the years. Yet its categorization of mental illnesses is based nearly entirely on symptoms either reported by the patient or observed by the clinician. New funding, Insel said, would be based on the premise that "mental disorders are biological disorders involving brain circuits." Research into diagnosis and treatments such as talk therapy would be relegated to the bottom rung of the research ladder.

Insel later softened his criticism of the DSM. But the battle had been joined, and with millions of lives and billions of dollars at stake, the fight over the future of psychiatry was on.

"There are two camps: the very biologically oriented and the patient-oriented," said Moira Rynn, director of child and adolescent psychiatry at the New York State Psychiatric Institute. Rynn, who is both a clinician and a researcher, describes herself as "in the middle" of this tug-of-war. She's worried, she says, that "we're going to lose a generation of researchers" who think that identifying the influences of a patient's environment, relationships and access to care is just as important as finding the biological markers of their illness.

Other skeptics of Insel's approach say it is impossible to understand mental illness solely by trying to understand the brain.

"The main thing is looking at what people say about their lives," said Richard Shulman, a Hartford, Conn., clinical psychologist and one of the founders of Volunteers in Psychotherapy, a nonprofit that provides affordable psychotherapy to the community in exchange for volunteer work that clients perform for charities. "What has led to a real confusion or distress in their lives, and how these things come up, that's when you get a real idea of how and why something upset them. . . . You look at things through their eyes and say, yes, this person has gone through the wringer."

From the time of the ancient Greeks, medical practitioners have searched for biomarkers for physical illnesses. Hippocrates tasted patients' urine for sweetness (he is thought to have been the first to diagnose diabetes mellitus), smelled their breath for signs of kidney and liver disease, and assessed the stickiness of their sweat. More recently, doctors relied on patients' complaints about the severity of their chest pains in order to diagnose a heart attack. Today, they measure cardiac enzymes in the bloodstream.

"Cancer treatment doesn't treat the symptoms of cancer. You don't want the swelling to go down or the pain to disappear; you want to get rid of the cancer," said Kenneth Kaitin, director of the Tufts University Center for the Study of Drug Development. "But that's what we're doing in psychiatry," treating the symptoms of mental disorders — the sadness or the restlessness or the hallucinations — not the causes.

What is known is that the brain looks different in those who struggle with mental illness. This does not necessarily mean all mental disorders originate in the brain. Post-traumatic stress disorder, for instance, occurs because of emotionally scarring experiences, but those experiences change the brain and the brain's responses to the environment.

Nearly every day, researchers report findings about genetic or cellular associations with mental illness. But despite years of searching, no one has identified a single biological cause for any mental illness, proved that a chemical imbalance in the brain is at the root of any mental disorder, or positively shown that any medication corrects such a chemical imbalance.

"There's been an intense search for biomarkers for the last 40 years, and so far we've come up empty," said psychiatrist Allen Frances, a professor emeritus at the Duke University School of Medicine. "It's been oversold. The

decade of the brain came up empty. It should teach us to be humbler."

The leading drugs for depression — the selective serotonin reuptake inhibitors, or SSRIs — are designed to ease symptoms by boosting serotonin, one of the brain's pleasure chemicals. But it's not known whether that corrects an imbalance, because there's no way to directly measure a person's neurochemical levels. Experts also can't explain why antidepressants work only 40 percent of the time or why, when they do, it takes weeks for most patients to feel the effects since the levels are boosted almost immediately.

The chief complaint about today's psychiatric medications is the same one cited by those frustrated by the lack of progress on Alzheimer's: They don't treat the disease, just the symptoms, and they don't even do that very well.

Rather than targeting brain chemistry to reduce symptoms, people such as Insel want to focus on brain circuitry. Their efforts have been bolstered by advances in technology and imaging that now allow scientists not only to see deeper into the brain, but also to study single brain cells to determine which circuits and neurons underlie specific mental and emotional states. Many of these advances come from fields as disparate as physics and electrical engineering — as well as the new field of optogenetics, which uses light to manipulate neurons.

In the past, brain imaging allowed scientists to identify which groups of neurons were active when, say, a lab mouse was aggressive, but not whether the neurons were causing the aggressive behavior. Then a few years ago, researchers at the California Institute of Technology injected into the hypothalamus of a mouse a modified gene that made certain cells sensitive to light.

They then inserted a hair-thin fiber-optic thread into the mouse's skull and delivered bursts of light into those cells to activate them. The mouse became aggressive. When the researchers turned the light off, the activity in those specific hypothalamic cells ceased, and the mouse returned to a calm, normal state.

Because the technique is too invasive for people, researchers are now looking at nanotechnology and even magnets as a way to switch cells on and off in humans. Connecting specific symptoms with specific groups of neurons, and then manipulating those cells, would represent a watershed moment.

Born and raised in Pakistan, Hasan Asif is a board-certified psychiatrist who first trained as a psychoanalyst. When he came to the United States in 1990 for post-graduate training at New York Medical College in Valhalla, he was swept up in the biological psychiatry movement. He opened a private practice in New York and eventually spent tens of thousands of dollars outfitting his office with new neurological tools. On his walls are colorful microscopic close-ups of neurons, and on his bookcase and tables are replicas of Greek and Egyptian antiquities once collected by Freud.

Asif evolved into a "neurotherapist," someone who first tries to understand a patient's brain circuitry, then combines that with both psychological and physiological information to create a treatment plan. While a traditional psychotherapist might begin sessions by asking patients about their thoughts, feelings and problems, Asif has them fill out a color-coded form that matches statements about their thoughts and feelings with the parts of the brain most likely involved. Then his patients undergo a quantitative electroencephalograph, or qEEG.

The EEG, which has been around for more than 90 years, is a map of the brain's electrical activity and reflects a patient's emotional and cognitive states. The qEEG compares that information, in real time, to a digital database of hundreds of EEGs of healthy subjects. A patient's brain map will pulse with red or blue if it is either overactive or underactive, compared with the norm.

"The brain is almost screaming out loud: 'Read me! I'm showing you everything!' " Asif said.

Patient treatment plans might include psychotherapy and medication as well as neurofeedback, a technique in which patients are trained to increase or decrease brain-wave activity in the parts of the brain related to their complaints. Another tool is transcranial magnetic stimulation, a noninvasive method of delivering pulses of energy to the head, which has been approved by the Food and Drug Administration for the treatment of depression. But almost always, Asif begins with a qEEG. It acts as a kind of map, helping him to identify a patient's troublesome brain circuits, which he then targets with his various therapeutic techniques.

Tina Raymond, 61, says her treatment produced almost immediate results. In 2006, Raymond was robbed and beaten inside her storefront office in Mount Vernon, N.Y., where she designed seasonal displays for department stores. She saw several doctors, including Asif, for memory loss and PTSD from the attack, and she eventually recovered. Then, in May 2014, just as Asif was ramping up his neurotherapy practice, Raymond returned, complaining of feelings of worthlessness.

“I was hitting a lull, an emotional lull,” she said. “I was depressed. Getting out of bed was harder than usual. I’m a pretty upbeat person in general, so for depression to hit me . . . was distressing.”

Raymond filled out the color-coded form and scored the statements on a scale of 0 to 10, with 10 being the highest.

“I feel unfocused, tired, and bored”: 7.

“I have difficulty planning and organizing”: 9.

“I worry a lot, and have difficulty stopping repetitive negative thoughts and actions”: 6.

Asif next wired Raymond for a qEEG. The most striking image was a red blotch on the right side of her brain map, indicating too much slow-wave delta activity in the temple area. It’s a part of the brain that plays a role in mood regulation and motivation, and it wasn’t firing properly or communicating well with the left side of her brain. Asif now had his target areas. He would use neurofeedback, employing a video-aided reward system, to retrain Raymond’s brain.

Neurofeedback is a descendant of biofeedback, which uses medical instruments, such as a blood pressure cuff, to monitor body functions and relay the information to patients who then try to alter their physical responses. Neurofeedback has had a popular, if controversial, commercial application as a kind of relaxation therapy, but recently psychiatry has studied it in combination with real-time brain imaging. In 2013, for example, a team at Yale University found that neurofeedback used with functional MRI, another brain imaging technology, substantially reduced depression and anxiety in patients.

For some neurofeedback sessions, Asif plays a pleasant nature movie during which the patient’s brain-wave activity is automatically compared every half-second to the goal. If the two are in sync, the patient’s brain is “rewarded” by the movie’s continuation. If they are not, the movie stops. Which means that in one 50-minute session, Raymond’s brain experienced 6,000 chances to be “rewarded” for learning how to reduce the delta-wave activity in the right hemisphere and re-establish its normal firing pattern. Her concentration kept the video — she substituted a 1992 comedy by Italian director Lina Wertmüller for the nature film — playing without interruption.

If all this seems mysterious, scientists say it is no more inexplicable than children learning on their own how to play a video game or ride a bicycle. Our brains simply figure things out because that’s what they were built to do. For patients, the sense of control over their own treatment, of helping to heal themselves, is often exhilarating.

After those five sessions, Raymond felt her depression lift. Those overactive delta waves nearly disappeared, and her improving mood matched her brain map, evident by the diagnostic form she filled in before each session. Soon

the 9's and 7's she had recorded before her first session were manageable 2's and 3's. She felt better in the same amount of time it takes for most psychiatric medications to begin working, and she experienced no side effects, except for the goop in her hair after each session.

Asif, she said,"put my pieces back together."

Internist Alexis Gopal often referred patients to Asif.

"I've sent him adolescents who have gone to successive psychiatrists and medication after medication, and he can turn them around in two or three treatments," said Gopal, who lives in Danbury, Conn., and now runs her own medical communications business.

For several years the doctor had dealt with her own, occasionally paralyzing anxiety, for which she took medication. When the problems worsened in 2014, she turned to Asif.

Gopal was skeptical about neurofeedback, having undergone biofeedback sessions for migraines with another doctor; they hadn't helped. Then Gopal went through Asif"s movie-watching exercise. She also listened to a series of pleasant tones that degenerated into noise if she didn't focus on modulating her brain-wave activity.

"You have to relax. And he tells you to focus on something," she said. "I remember specifically one session feeling like I was going to crawl out of my skin. And I remember at the end of one session I felt so relaxed and so calm, I thought, 'Wow, this really works.' "

Asif charges between $275 and $350 per session after an initial interview and evaluation, which includes a qEEG and costs about $550. Sessions are billed as either psychotherapy or medication management for insurance purposes.

Gopal said that she felt better with each visit, and there was a side benefit: Her migraines ended.

Another of Asif's patients, who asked that she not be identified, said she began treatment for major depression in January 2014 when she lost weight, became paranoid about eating and isolated herself.

"He looked at me, and I'll never forget it, he said, 'Just give me nine days, and I'll pull you out of this.' From that moment, I thought, thank God, someone's going to help me."

Five times a week, she underwent transcranial magnetic stimulation, which delivers bursts of energy designed to stimulate the underactive area of the brain thought to be involved in depression. The progress was virtually

immediate.

“As the treatments went on, I’d put a ring on or makeup. Then I noticed I started to cook. I hadn’t done my laundry in months and did it,” she said, and after two weeks she was significantly better.

“It was like being reborn,” she said.

Asif says that a person’s mental makeup is a kind of hierarchy, with personality on top, which is created by brain states that arise from circuits firing in a certain pattern below. With psychotherapy, you tweak the brain from the top down, dealing first with a patient’s personality and temperament. But with neurofeedback, combined with qEEG, he said, he tweaks his patients from the bottom up, identifying the brain areas involved and then retraining those circuits to fire differently, resulting in changed moods or mental outlooks.

“When they are shown the cause of their suffering in their brain circuits and body function,” Asif said, “it gives them immense power in having control over things.”

Because he is a full-time clinician, Asif has done little formal research, although he has been published in Neuroconnections, the journal of the International Society for Neurofeedback & Research. He also gives frequent talks to medical professionals, including the Society for the Advancement of Brain Analysis, the annual conference of the International Neuropsychoanalysis Society and the Biofeedback Federation of Europe.

Insel, who stepped down from NIMH last year, supports the direction clinicians such as Asif are taking. But he cautions that this is still “the beginning of a long road” and that “rigorous studies are required to establish evidence” for biological tests of mental illness.

“The field needs biomarkers and cognitive tools to define more specific diagnostic groups and to predict an individual’s response to treatment,” Insel said. “We call that precision medicine. It sure beats trial and error.”

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