



FEATURES

Helen Mayberg at work in her lab at Emory University. Mayberg is “really on the cutting edge of where the field of depression research needs to go,” says Steve Hollon of Vanderbilt University.

displayed lower activity levels. They didn’t in non-depressed patients.

“It made us realize that depression is not necessarily due to a chemical imbalance, as people have thought for years, but might be due to a wiring pattern in the brain that has gone wrong,” says Mayberg.

Building on this insight, Mayberg has spent her career trying to learn more about the wiring of the depressed brain. Using scanning techniques, she’s studied how brain activity changes before and after treatment. In one line of research, Mayberg found that depressed patients who improved after taking Prozac for six weeks showed increased activity in their frontal lobes, again suggesting this region plays a role in depression. But she also made another, unexpected discovery: Activity in the subgenual cingulate—a band of brain tissue known as “Area 25” that lies deep within the frontal cortex and is part of the emotion control center of the brain—went down in all the patients who recovered.

Mayberg wondered whether there might be a specific kind of interaction between these brain regions that led to depression. She speculated that a high level of activity in Area 25 might depress activity in the frontal lobes, which would prevent the frontal lobes from regulating the distressing thoughts that contribute to depression. But later she studied patients who had recovered from depression using cognitive behavioral therapy (CBT), a form of talk therapy where patients are taught how to identify negative thinking patterns and replace them with more positive ones. In that study, patients who recovered had completely different results: Activity went down in the frontal lobes instead of up, and activity in Area 25 did not change.

These two seemingly contradictory results suggested to Mayberg that depression is not caused by a single brain activity pattern, but by a brain activity pattern that is different for different patients. Area 25 and the frontal lobes, she thought, form an interactive circuit in the brain, working together to modulate mood; in depressed patients, parts of the circuit are either over-active or under-active. Medication and CBT both appear to work by correcting the balance between the frontal lobes and Area 25: Medication targets Area 25 so that it doesn’t inhibit the frontal lobes, whereas

Jack Kearse/Emory University

Closing the Circuit

Helen Mayberg’s research could revolutionize depression treatment.

BY JILL SUTTIE

AT SOME POINT IN THEIR LIVES, 5 to 12 percent of American men and 10-25 percent of women will suffer an episode of depression, making it the most commonly diagnosed mental disorder today. Unlike normal sadness, which passes with time, depression feels unstoppable and causes people to lose interest in nearly all activities. Because it affects a person’s ability to eat, sleep, work, and function normally, it exacts a huge cost on the economy, estimated at \$30 billion dollars annually. The cost in human suffering cannot be measured.

Millions of people diagnosed with depression turn to medication as a treatment, and many of the most popular depression medications—Prozac, Zoloft, and Paxil, to name a few—work by changing the chemistry of the brain, increasing or decreasing the speed of information exchanged between cells. How they alleviate depression is not well understood, but the drugs are widely prescribed—and, according to some experts, not always for good reason.

“Most people who are depressed go to their MD’s and are prescribed medication, which is easy to take and usually well-tolerated,” says Helen Mayberg, an Emory University neurologist. “But only about 30

percent of people who take meds get better. Why?”

Mayberg believes the answer may lie in her research. For years, Mayberg has studied how neural pathways are disrupted during mental illness, especially depression. Using the newest scanning technologies, she is making groundbreaking discoveries about how depression is wired in the brain—and she is developing a new technology that can literally “rewire” the brain to overcome depression. If successful, her experiments could revolutionize the field of depression treatment.

Exploring Area 25

Mayberg first became interested in brain scanning and depression when she was a research fellow at Johns Hopkins University in the mid-1980s. There, she studied stroke victims and patients with Parkinson’s and Huntington’s diseases—all of whom are at higher risk for depression—and discovered something interesting: Brain scans of depressed patients displayed a unique activity pattern. The frontal lobes of the brain—the parts associated with higher cognitive processes, like how we interpret our experiences and emotions—always

CBT targets the frontal lobes directly, making them less active. The implication to Mayberg was that different patients would require different treatments, depending on their particular brain circuitry.

These conclusions are bolstered by numerous studies of treatment effectiveness, according to Steve Hollon, a professor at Vanderbilt University and an expert in the field of depression research. The combination of CBT and medication, explains Hollon, is considered the most effective treatment for depression to date, and this mix of treatments has proven to be better at alleviating depression than either treatment alone. If each treatment affects the brain differently—as Mayberg’s work suggests—it follows that the combined treatment would have the best chance of inducing recovery for the greatest number of patients because it would help those who would benefit from one or the other treatment, as well as patients who might respond best to a mixture of the two.

“Mayberg’s research is helping identify for us what is going on in depression at the neural level, how CBT and medication affect the brain,” says Hollon. “She’s really on the cutting edge of where the field of depression research needs to go.”

Radical recoveries

Mayberg moved to Emory University in 2003, where she is now working with patients she calls the “terminally depressed”—those who’ve gone through multiple treatment approaches and still haven’t recovered. In one recent, trailblazing study, she took six terminally depressed patients and, using a new technology called “deep brain stimulation” (DBS), embedded wires in their brains at Area 25. The wires were attached to a battery, which acted like a pacemaker, delivering a steady but adjustable current to the wire. Immediately, patients reported some relief from their symptoms, and their symptoms continued to improve over the weeks that followed.

“Four patients—60 percent—recovered from their depression. It was incredible,” says Mayberg. “These are people who’d suffered for years, whose depression was considered intractable.” After a few months, Mayberg also saw activity increase in their frontal lobes, suggesting that stimulation to Area 25 helped restore balance to their brains’ circuitry. Four years later, those four patients still have their wires intact and are still in remission. Most have either stopped using medication or have greatly reduced their dosage. According to Mayberg, their

new challenge is to learn how to adjust to being healthy. “Now they need to know what it’s like to have a bad day. Before, every day was a bad day,” she says.

As impressive as these results are, DBS is clearly not for everyone. Mayberg offered it to people who, unlike most depressed patients, had not improved after years of trying other, more conventional treatments. And of course, even among people who might benefit from DBS when all other options fail, many will resist such an invasive treatment. Hussein Manji, a neuroscientist and the director of the National Institute of Mental Health’s Anxiety and Mood Disorders Program, says that while he sees Mayberg’s DBS results as promising, he questions the practicality of imbedding electrodes in patients’ brains. “She has helped narrow down where we need to intervene in the depressed brain,” says Manji. “But wouldn’t it be ideal if we could do the same thing chemically, to avoid brain surgery?”

Still, Manji commends Mayberg for making important contributions to the scientific understanding and treatment of depression. Like Mayberg, he thinks that brain scans could help identify subgroups of people who would benefit from certain forms of treatment, especially if these treatments are used in combination with one another. “It may be that one needs chemical treatments to bring oneself back to a time when the brain wiring went wrong, and then cognitive restructuring to rewire the brain so that it can follow a more positive pathway,” he says.

At the National Institute of Mental Health, Manji and a team of researchers are busy trying to develop chemical treatments that would work more efficiently than what’s currently on the market. They are searching for a “smart molecule,” a chemical that would more accurately target the parts of the brain implicated in depression. So far, they’ve had luck with ketamine, a medication that, in higher doses, can be used as an anesthetic. In a study he conducted with terminally depressed patients, published in 2006, 71 percent of those patients receiving a single intravenous dose of ketamine showed improvement within one day. This compares favorably against current popular depression medications, which tend to take weeks to work. But ketamine has severe side-effects, including hallucinations, which makes it untenable as a medication for the general public. Still, Manji believes that its fast action shows that researchers are on the right track.

“Current medications may be working at an indirect molecular target in the brain,

which is why there is such a lag time,” says Manji. “We need to move 20 steps beyond, to target the exact circuit in the brain that’s causing depression.”

Hollon agrees that medication for depression needs to be refined. “Currently, we put people with depression on medication and usually keep them there,” he says. “But what we don’t know—and we need to know—is who needs to stay on medication and who can come off of it.” Hollon hopes that Mayberg’s research will improve understanding of what is happening to patients’ brains as they progress through the healing process, so that psychologists can select not only the best course for treatment, but the best treatment over time.

Getting there

Meanwhile, Mayberg is busy recruiting more patients to do another DBS study. She is also involved in a large-scale project to see whether brain scans of depressed patients can be used to predict the best treatment for those patients. If successful, her experiments could transform depression treatment. “If we knew that a particular brain pattern indicated what type of treatment a patient would best respond to, it could save them years of unsuccessful treatment,” says Mayberg. It could also eliminate the need for drug treatment for some patients, and help those who resist medication because of personal beliefs or adverse side effects, she adds.

Despite these advances, Mayberg says the research has a long way to go.

“We can’t be so arrogant that we think we know exactly what a pattern of activity in the brain means,” says Mayberg. “When I see Area 25 light up because the person is sad, I still don’t know if that’s generating the sadness, or if that’s the signal trying to turn off the sadness.” She hopes that 10 years from now, better technology will enable scientists to uncover more specific information about the neural circuitry of depression and other mental disorders, and that future treatment approaches will involve targeting specific areas of the brain rather than flooding it with nonspecific drugs, like Prozac.

In the meantime, Mayberg is cautiously optimistic. “We need to move away from a one-size-fits-all approach to mental illness,” she says. “I think we’re getting there.”

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