The 4-hour-long surgery involves drilling two nickel-sized holes in the skull and snaking long metal electrodes into tiny nodules of tissue in a deep brain region called area 25. Once the electrodes are in place, the operating team flips a switch on an external generator and high-frequency bursts of electricity begin to stimulate the tissue. The device remains in the brain indefinitely, with a battery implanted below the clavicle supplying continuous electrical stimulation like a pacemaker.

Patients remain semiconscious through part of the surgery so that Mayberg and her team can probe their mental and emotional states when the current starts to flow. Patterson recalls feeling as though she was being lifted out of a deep ocean vortex and returned to dry land. After the surgery, “I felt the best I’ve felt in my entire life—joy, exhilaration, contentedness,” she says. “My cognitive abilities were sharper. I was living in a different world.”

More than 6 months later, Patterson has shown no signs of relapse. Carol, her partner of 11 years, also sees a profound difference in Patterson’s well-being. “She has the ability to feel joy again, to set goals and say things she wants to do.”

Mayberg first tried DBS of area 25 on a depressed person a decade ago. She and other groups, some targeting different brain regions, have subsequently used DBS to treat depression in more than 200 others. Between 40% and 60% of these patients demonstrated significant improvements, she says. The prospect that this experimental procedure can bring recovery for people who had given up hope has “reinvigorated
Last resort. Neurologist Helen Mayberg (in scrubs) oversees while a neurosurgeon performs deep brain stimulation surgery on a person with severe depression, a procedure she has been refining for more than a decade.

In the field” of depression treatment, says Husseini Manji, former director of the National Institute of Mental Health’s Mood and Anxiety Disorders Program and head of therapeutic neuroscience at Janssen Pharmaceuticals. And it has given researchers a powerful way to pursue an old but largely untested hypothesis: that much depression results not from an imbalance in the soup of neurochemicals that bathes the brain, but from disrupted neural “circuits.”

The tools to properly test hypotheses about the neural circuitry underlying mood weren’t available until quite recently, notes Scott Russo, a neuroscientist at Mount Sinai Hospital in New York City. That changed as DBS was shown to be effective in brain disorders such as Parkinson’s disease and obsessive-compulsive disorder, demonstrating that it is possible to precisely alter the activity of key neural circuits in the brain, while leaving others intact. And in “just the past 5 years or so,” Russo says, new techniques such as optogenetics, in which brain cells are made light-sensitive, have allowed scientists to begin tracing and manipulating neural networks in animal models of depression. “It’s a great time to be doing this research,” says psychiatrist Ronald Duman of the Yale University School of Medicine.

And research it remains, Mayberg cautions. Patterson’s recovery has been an “extraordinary success,” she says, but not all depressed people who receive DBS experience such immediate or lasting benefits. Hoping to move beyond anecdotal success stories, Mayberg and several other groups are now running DBS clinical trials, targeting area 25 and other brain regions. To rule out a placebo effect, which can be powerful in surgical procedures, the researchers compare subjects who receive DBS with those who undergo the same surgery but receive no electrical stimulation during the trial, or parts of it. All eyes in the field are on these “sham” studies, says Wayne Drevets, a neuroscientist at Janssen: “There’s a sense of people holding their breath to see that this is really going to work.”

Tuning the circuit

The concept of manipulating neural circuits with electricity to influence mood is not new. Indeed has a reset button, Mayberg thinks area 25 may have it. Labeled in 1909 by the neuroanatomist Korbinian Brodmann, area 25 abuts the corpus callosum, a band of nerve fibers that connects the brain’s right and left hemispheres. At a July meeting at Cold Spring Harbor Laboratory in New York, Mayberg zoomed through a tour of this region and its web of connections, emphasizing every preposition. “It speaks to the nucleus accumbens—goes to the shell, not the core—connects up the cingulum bundle to the dorsal anterior and mid-cingulate, out to the medial frontal cortex, and deep into the amygdala via both branches of the uncinate fasciculus, then down to the dorsal raphe and periaqueductal gray matter as well as to the nucleus reuniens of the thalamus. Basically, area 25 dysfunction or problems with its connections can wreak potential havoc on every functional circuit ever implicated in patients with major depression.”

Mayberg and other groups first identified area 25 as a subject of interest by examining brain scans of people with depression who were being treated with Prozac. In those who responded well to the drug, she noticed that the region’s metabolic activity was dampened. In patients who did not respond to the drug, area 25 did not change. Later studies showed that the region lights up when someone recalls a sad event—seeing their grandmother on a hospital respirator, or tak-
ing care of a friend who was dying of AIDS, for example. But in healthy people, it calms down when the memory passes.

Imaging studies of area 25 indicate that its activity is yoked to many other regions affected by depression, Mayberg says. Some are involved in cognitive skills such as attention, while others have to do with emotional regulation, self-awareness, and rumination. Still more are involved in more visceral sensations of unease. When area 25 is hyperactive, these linked regions also alter their activity, as though they’re different instruments in the same orchestra, Mayberg notes.

“All roads seemed to lead to area 25, so I said, ‘Why don’t we tune it there?’”

Since 2003, Mayberg and others have used DBS in area 25 to treat depression in more than 100 patients. Between 30% and 40% of patients do “extremely well”—getting married, going back to work, and reclaiming their lives, says Sidney Kennedy, a psychiatrist at Toronto General Hospital in Canada who is now running a DBS study sponsored by the medical device company Medtronic, there was no difference in the level of depression after 16 weeks when people were having “sham” stimulation versus real electrical pulses.

One possible reason the trial failed, Rezai suggests, is that 16 weeks may simply not be enough time to detect a benefit. Although some patients, like Patterson, experience immediate effects after DBS, most people do not recover immediately, he says. Instead, they may see the first benefits after a few weeks, then progress gradually over the long term, he says.

Or the researchers may have chosen the wrong brain area to target. They implanted the DBS electrodes not in area 25 but in a brain region called the ventral striatum, which they chose because the Food and Drug Administration has approved it as a DBS target for obsessive-compulsive disorder and because Rezai and others had noticed mood alterations when the area was stimulated.

The ventral striatum is just one of many brain regions that depression researchers are targeting (see diagram, p. 551). They include the nucleus accumbens, a brain region involved with pleasure and reward; the inferior thalamic peduncle, implicated in depression and obsessive-compulsive disorder; and the lateral habenula, a brain region that shows higher-than-average activity in people with depression.

The range of brain circuitry at which researchers are aiming their electrodes reflects fundamental differences in how they view depression. For Mayberg, its core is an unrelenting mental pain. “Patients say, over and over, ‘There’s something in my way,’ and ‘Take away this pain,’” she says. “If you’re so turned inward that nothing else matters, then by definition you are disconnected from the outside world.” With stimulation of area 25, she says that burden appears to lift and patients are free to enjoy their lives again.

Researchers who focus on stimulating brain areas associated with reward, in contrast, tend to think of depression’s most important symptom as anhedonia—the inability to anticipate or experience pleasure. “The reward system is there all day; it guides us,” says Volker Coenen, a neurologist at the University of Bonn in Germany. “You think, ‘I will have a shower. I will have a coffee. I will shave and put on a nicely washed shirt.’” This ability to look forward to coming pleasures has been extinguished in his most depressed patients, Coenen says.

Consequently, he focuses on the medial forebrain bundle, which connects reward-
related brain areas to the prefrontal cortex. In a recently published study, he reported that in six of seven people with depression, stimulating the medial forebrain bundle through DBS surgery caused that joie de vivre to return.

In the most severely depressed patients, Mayberg suspects that more than just one neural circuit involved in depression is dysfunctional. For those patients, a recommendation to “think of all the good things” or go for a run will not help, because it “assumes the machinery still has that adaptive capacity,” she says. In those cases, the electrodes implanted in DBS surgery have to take over before recovery begins, Mayberg suggests.

Scalpels versus sledgehammers
It’s an appealing picture, but some researchers think that before DBS should be used on a large scale, Mayberg and other researchers need a much better map of the brain’s pathways. “The problem is that the highways all converge,” says Kay Tye at the Massachusetts Institute of Technology in Cambridge. “We have no idea which projection that is in this white matter bundle is actually the critical one.”

It’s also unclear what the electrical stimulation in DBS actually does to networks of brain cells, says Eric Nestler, a neuroscientist at Mount Sinai Hospital who studies animal models of depression. Neural circuits are made of many different types of neurons linked together. Depending on their structure and chemical makeup, some cells make their neighbors more excitable and ready to fire, while others put a brake on neural signaling. This complexity raises an important question, Nestler says: “When you lower an electrode into the brain and crank it up really high, what are you doing that might make a person feel better?”

One tool helping scientists dissect how DBS affects depression circuits at the cellular level desired by Tye and others is optogenetics, which allows researchers to manipulate specific cells and nerve circuits with light. Nestler and his colleagues, for example, have used the technique to study the antidepressant effects of DBS in mice. No mouse is truly “depressed” in a human sense, Nestler emphasizes. Features of depression such as suicidal tendencies, guilt, and sadness are, so far as we know, uniquely human. However, mice do show symptoms that resemble depression under certain kinds of stress—when threatened by bigger, meaner mice, for example, the rodents lose interest in food, withdraw from other mice, and don’t struggle as hard to escape from threats.

In 2010, Nestler, Herbert Covington and Ming-Hu Han, also at Mount Sinai, joined forces with Karl Deisseroth at Stanford University to try a DBS-like treatment on mice that had become depressed after prolonged bullying. Rather than inserting electrodes into the animals’ brains, the team used light to stimulate the rodents’ medial prefrontal cortex (mPFC)—an area that some neuroanatomists consider homologous to a human brain region called the anterior cingulate cortex, which contains area 25. When the researchers shone high-frequency bursts of light on this region, the gloomy rodents instantly rebounded, taking newfound interest in companions and sweets, Nestler says.

Along with Russo’s lab at Mount Sinai, Nestler and his team have since further used optogenetics to pinpoint which neurons in the mPFC are key to the antidepressant effect, and what brain regions they influence. According to Russo, neurons within the mouse mPFC that use the chemical glutamate to transmit signals may be central. Some of these nerve cells extend out of the mPFC to the nucleus accumbens, a brain region that assigns positive or negative meanings to our experiences. When the researchers stimulated activity of the mPFC neurons at the place where they attach to the nucleus accumbens, the mice perked up. Inhibiting the same neurons with toxins caused the mice to become depressed again, Russo says.

It’s too early to know whether the same mechanism helps explain how DBS works in humans, Russo emphasizes. For one thing, “there’s a real question” about whether the region that the team stimulated in mice is indeed a homolog of a DBS target in humans, he says. However, neurons of the same subtype atrophy and die in people with depression, suggesting that the researchers are on the right track, he says. The group is preparing their results for publication and plans to present them at the Society for Neuroscience conference this month.

The fact that changing the firing rates of a few neurons can transform a mouse’s mood shows just how sensitive and complex neural circuitry is, Tye says. To her, it suggests that DBS researchers should proceed cautiously. “If you actually get a bigger behavioral change using a scalpel than a sledgehammer, that really tells you something about how the brain works,” she says. Eventually, she hopes that treatments for depression will be able to target not just brain regions, but specific neurons.

Mayberg shares Tye’s dreams of greater precision, and hopes that combining results from animals and humans will lead to treatments that don’t involve surgery. Eventually, she says, it might be possible to target cells in area 25 with a drug, or tweak the circuit noninvasively with current applied precisely to the skull. Yet she, and people like Patterson, aren’t willing to wait until then. “Even with our noisy ways and cattle prods in the brain, we have to take care of sick people, now,” Mayberg says. —EMILY UNDERWOOD