NEUROSCIENCE

TREATING DEPRESSION AT THE SOURCE

Electrical stimulation deep within the brain may alleviate devastating mood disorders

By Andres M. Lozano and Helen S. Mayberg

IN BRIEF

Some 17 percent of the U.S. population suffers from what psychiatrists call a "major depressive episode" at any given time.

Available treatments—ranging from medication to electroconvulsive therapy—provide little relief in up to 20 percent of sufferers.

Implanting electrodes deep in the brain, now commonly used to treat Parkinson's disease, is being studied in people for treating severe depression.

Specific brain circuits linked to depression have been identified, and knowledge of them provides guidance for where to place the electrodes.

Illustration by Goni Montes

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"I SUDDENLY FEEL CALM."

Our patient, a middle-aged woman who suffered from severe depression, uttered these beautiful words in the operating room just a few seconds after one of us (Lozano) applied electrical stimulation to a selected area deep in her brain. The operation, which took place in 2003 at Toronto Western Hospital, relied on only local anesthesia so that the woman could remain conscious and talk to us.

Then, as the current's strength was increased, we asked her if she noticed anything different. To our surprise, she described the room as going from "black-and-white to color"—as if a light switch had been flicked that instantly elevated her mood.

This test was the first of many studies that have led to the development of a potentially new way to treat depression: deep-brain stimulation, a technique that is already in use for some other disorders, such as Parkinson's disease. Novel treatment options for depression would meet an acute need. Over a lifetime, some 17 percent of the U.S population suffers one or more bouts of what psychiatrists call a "major depressive episode"; at any given time, an estimated 8 percent of women and 5 percent of men are afflicted. These are not mere episodes of sadness. Major depressive disorder, which occurs intermittently, is marked by a period of sustained sorrowful mood, feelings of guilt, a sense of worthlessness and a loss of interest in everyday activities. It can impair thinking, sleep, appetite and libido and can be experienced as physical aching. Winston Churchill, who battled the condition, called it his "black dog."

Depression can be lethal. An estimated 15 percent of patients with major depression die by committing suicide. It can also exacerbate such medical problems as heart disease and diabetes, reducing the life expectancy of people with those conditions.

Available treatments—graduating from psychotherapy to medication to electroconvulsive therapy—are generally effective in most patients. But in an estimated 10 to 20 percent of depressed patients, these treatments provide little or no relief. This subset of patients may become candidates for deep-brain stimulation as the technique becomes established.

The technology has not yet been approved for routine use in hospitals but has been tested in about 200 people worldwide. It requires doctors to drill holes in the skull and to implant electrodes permanently within the brain, and so it will never be anyone's first choice for therapy. If further testing pans out, however, it should offer a lifeline to people who might otherwise be doomed to endless despair.

IT'S ALL IN THE CIRCUITS

THE 2003 TEST grew out of research conducted by one of us (Mayberg) to pinpoint the brain regions involved in depression. Neuroscientists recognized by then that the symptoms of depression and various other brain disorders arise from disturbances in the functioning of specific neuronal circuits. The tremor or rigidity of Parkinson's occurs because of misfiring in circuits that control movement. Circuitry involved in forming new memories or retrieving old ones goes awry in Alzheimer's disease. Similarly, considerable evidence in the early 2000s pointed to disturbances in circuits mediating mood as being at the core of depression.

The circuits themselves are formed by connections among subsets of the brain's 86 billion neurons. Each cell links up with thousands of others, some to the next neuron, some reaching out great distances through the central nervous system. Whether a link extends to one cell or another depends on genetics, early life experiences and stress. The malfunctioning of the circuits involved in depression probably involves many brain regions. But pinpointing the location of this web of connections remains an ongoing challenge for neuroscientists.

Starting in the mid-1990s, Mayberg designed a series of experiments to identify brain areas involved in the regulation of mood in both healthy subjects and patients with depression. In an early experiment, healthy volunteers had to go through a mental exercise of reliving a sad experience in their life.

A type of brain scan known as positron-emission tomography (PET) mapped out areas that had a marked change in activity when the patient was feeling despondent. One type of PET imaging found that depressed patients had increased blood flow, a measure of brain cell activity, in a particular area in the middle of the brain when compared with healthy individuals. In contrast, areas of the brain involved in motivation, drive and executive functions showed diminished activity.

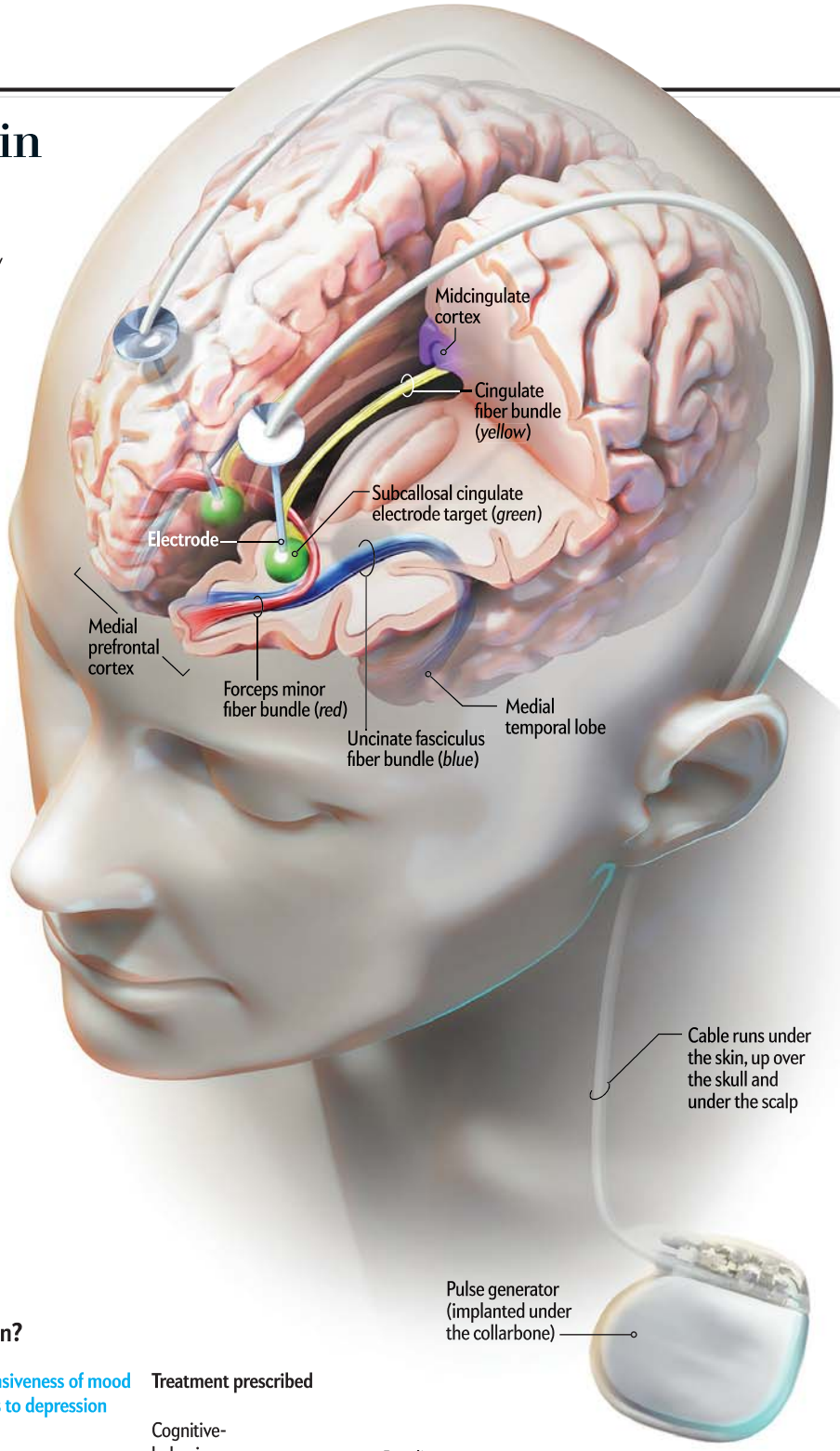
The spot on the scan that exhibited the most activity was a small region in the middle of the brain called the subcallosal cingulate area—also known as Brodmann area 25, a surname bor-

Giving the Brain a Reboot

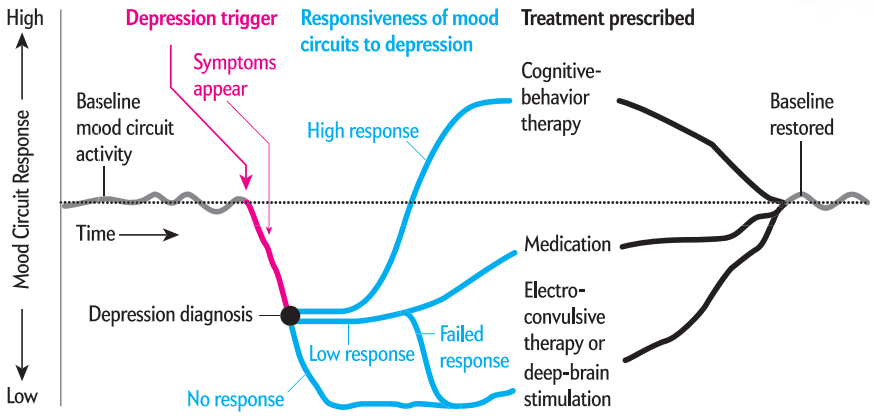
Deep-brain stimulation uses surgically placed electrodes to send an electric current through neural circuits (nerve fiber bundles that connect brain regions). These circuits do not function properly in people suffering from major depression. The therapy, which has yet to be approved for routine clinical use, can sometimes correct signaling impairments and thereby rapidly dissipate feelings of hopelessness and lack of pleasure.

The Target

The electrodes are positioned to affect several interconnected brain areas. They are put close to the subcallosal cingulate (*green*), a hub region from where circuits involved with decision making, emotional responses and memory branch out to other parts of the brain. Some of the branches (*red* and *blue*) connect to the medial prefrontal cortex and the medial temporal lobe (*blue*). And another (*yellow*) links to the midcingulate cortex. All become dysfunctional in a depressive episode.



Who Benefits from Brain Stimulation?



Depression upsets the ordinary functioning of neural circuits. But brain scans may point to therapies that enhance circuits' own natural tendency to respond to and correct this imbalance. A scan might show whether cognitive-behavior therapy or medication could assist in restoring equilibrium. Other therapies, such as deep-brain stimulation, would be used if the circuits had lost this self-corrective responsiveness.

SOURCES: "DEFINING CRITICAL WHITE MATTER PATHWAYS MEDIATING SUCCESSFUL SUBCALLOSAL CINGULATE DEEP BRAIN STIMULATION FOR TREATMENT-RESISTANT DEPRESSION," BY PATRICIO RIVA-POSSE ET AL., IN *BIOLOGICAL PSYCHIATRY*, VOL. 76, NO. 12; DECEMBER 15, 2014 (*brain*); "TARGETED ELECTRODE-BASED MODULATION OF NEURAL CIRCUITS FOR DEPRESSION," BY HELEN S. MAYBERG, IN *JOURNAL OF CLINICAL INVESTIGATION*, VOL. 119, NO. 4; APRIL 1, 2009 (*chart*)

Illustration by David Killpack, Graphic by Jen Christiansen

rowed from the German neuroanatomist who created a map of the brain in 1909 using numerical designations based on the way cells were arranged at a particular location. Mayberg also found that the frontal cortex ratcheted down activity in proportion to the degree of sadness experienced.

In a second set of experiments by Mayberg, depressed patients received antidepressant medication for several weeks. Afterward, PET imaging showed that when patients' symptoms resolved, improvement was accompanied by a decrease in activity in Brodmann area 25, along with an increase in activity in the frontal cortex. Although brain changes also occurred in other areas, the striking differences in the subcallosal cingulate area pointed to that region as playing a critical role in modulating negative moods.

Brodmann area 25 sends out and receives connections to many other major brain sites, including the orbital and medial sections of the frontal lobes, the hypothalamus, the nucleus accumbens, the amygdala and the hippocampus, the periaqueductal area and the dorsal raphe. These areas govern the way the brain regulates basic attributes of human behavior, including the sleep-wake cycle, motivation, responses to perceived threats and novel stimuli, feelings of reward and reinforcement, short-term memory, and the ability to use past experience to guide thinking about future events. Such critical brain processes all go awry in depression. Hence, Mayberg reasoned, perhaps stimulating this hub of neural activity with an electric current could help depressed individuals.

BRAIN SURGERY FOR DEPRESSION

BY 2002 DEEP-BRAIN STIMULATION of other brain regions had been approved for Parkinson's and a condition called essential tremor, so we knew it could feasibly be used in humans. Today more than 100,000 patients worldwide have received it to ease the symptoms of Parkinson's. The basic surgical procedure for depression is identical. Patients are selected for study who meet criteria similar to those required of our first patient at Toronto Western. They must have been ill for a minimum of a year without any improvement on at least four different types of medications. In addition, they must have failed to improve after electroconvulsive therapy or refused its administration.

Deep-brain stimulation is not just another form of electroconvulsive therapy—which induces a controlled but generalized seizure while the patient is anesthetized and is delivered in short sessions that are repeated over several weeks. The new technology applies small electric pulses in a specific brain region that has connections to many other brain areas implicated in depression. Patients must undergo major surgery to implant the electrodes that will deliver ongoing stimulation, but they do not suffer memory loss, as can happen in electroconvulsive therapy.

On the day of surgery for our first depression patient at Toronto Western, the surgical team affixed a frame to the patient's head to keep it stable. Magnetic resonance imaging identified the particular place in the subcallosal cingulate area where the electrode was to be placed. In the operating room, under local anesthesia and without sedation, the surgical team drilled two holes in the skull through which the electrodes could be inserted.

With the aid of William D. Hutchison and Jonathan O. Dostrovsky, both expert neurophysiologists at Toronto Western, we recorded from the neurons in the subcallosal cingulate region, for the first time, to chart the activity of the neurons there to learn about their function. Based on imaging experiments conducted previously, we suspected that these areas would be involved in processing emotions related to sadness. Using a microelectrode with a tip finer than a human hair, we obtained direct measures of cellular activity of neurons that populated this brain region.

While recording from the neurons, we presented the patient with various photographs depicting a range of emotional scenes, both positive and negative. We discovered from the recordings that these neurons became most active when the patient looked at sad and disturbing photographs and that they did not react at all to happy, exhilarating or neutral scenes.

We then inserted stimulation electrodes into Brodmann area 25 on both the right and left sides of the brain. Within seconds of turning on the current, our patient reported a marked reduction in mental pain and emotional heaviness. A burdensome weight somehow lifted, a sensation that we have found occurs in most but not all patients. The effects became most pronounced when the stimulation was first applied. When repeated subsequent times, the effects occurred again but were less robust. We now know that if the treatment is continued over days or weeks in this same spot, a patient generally receives long-lasting benefits.

A few moments after the electrodes activated, our patient experienced a lightening of mental pain and emotional heaviness.

We learned from this surgery and others we have performed about the need for precise placement of the electric contacts that deliver a constant level of stimulation. In that first surgery, relief came when one or two of the four electric contacts delivered a constant current to the patient.

From continuing observations, Patricio Riva-Posse and Ki Sueng Choi, both in Mayberg's laboratory at Emory University, have developed a new imaging approach to more precisely pinpoint the bundles of nerve wiring, or white matter, that intersect at Brodmann area 25 and that seem to produce both immediate relief and long-term antidepressant effects when stimulated.

Once the electrodes are in place and fixed to the skull, a surgeon implants a pulse generator, which is similar to a cardiac pacemaker, under the skin below the collarbone—a battery-powered pacemaker that stimulates the target area continuously with 130 pulses per second. We chose the stimulation parameters, in part, based on our experience in treating Parkinson's patients, and so far it appears that this high-frequency pulsing provides the best benefit for the patient.

Once the settings are made, the operation is complete. Afterward, physicians use a handheld, wireless remote to fine-tune the stimulation each patient receives. In our experience, once an effec-

tive setting is established, no additional adjustments are necessary. Further work will determine if different settings might be required for those who do not respond to the standard adjustments or if different ones might speed up antidepressant effects. Batteries need replacement every three years or so when they become depleted, and rechargeable units are now available.

WHY DOES A BRAIN PACEMAKER HELP?

SOME PATIENTS have seen their symptoms completely disappear, but responses have varied, and not everyone has been helped. The proportion of patients who show a clinical response—a 50 percent or more reduction on scales that measure depression—can differ among hospitals and has ranged from 40 to 70 percent within a six-month period. The variability of the findings may relate to the continuing challenge of using symptoms and brain scans to identify the best patients for deep-brain stimulation.

One study that has received some attention has shown poor results. This industry-sponsored investigation, conducted by St. Jude Medical, headquartered in St. Paul, Minn., decided in 2013 to suspend taking on new patients, although patients who have already begun the trial are continuing with the therapy. No major safety concerns arose, but an analysis required by the U.S. Food and Drug Administration at the experiment's halfway point showed that patients with stimulator implants did not receive sufficiently greater symptom relief compared with a group in which the electrodes had remained off for six months. Researchers are reviewing the study's methodology to determine whether the therapy might improve with a different design.

We do not fully understand the reason for the disparities among different studies that have examined deep-brain stimulation. Explanations may relate to differences in criteria for patient selection. Some patients may have had depression combined with other psychiatric symptoms. Varying surgical techniques—where the electrodes are placed or the way stimulation is delivered—may also be critical. A potential confounding factor is that some patients who improve may do so simply because they believe in the power of surgery (the placebo effect, in other words) or because they benefit psychologically from the sometimes intense interactions they have with the treatment team. Some of these concerns may diminish over time because a few more recent studies suggest that the therapy has a genuine effect: patients deteriorate when the battery is low or stimulation is turned off. They recover again when stimulation resumes, making the placebo effect a less likely explanation.

Several experimental clinical research studies are under way in Atlanta, Hanover, N.H., and Toronto that will provide important new information as to what the technique can really achieve. All the while, researchers continue to refine surgical techniques to implant the electrodes. They also want to develop an understanding of how to optimize the precise amount of stimulation for a given patient while also learning about short- and long-term effects of deep-brain stimulation on depression.

Some new avenues of investigation are exploring different sites for stimulating brain circuits because the subcallosal cingulate area may not prove ideal for every patient. Volker Coenen and Thomas Schläpfer, both then at the University of Bonn in Germany, have achieved rapid improvement in a small number of patients in a region called the medial forebrain bundle. Other regions deep within the brain are also potential targets—the ventral striatum, the anterior limb of the internal capsule, the inferior thalamic peduncle and the habenula.

Testing different brain locations that may be involved with depression may allow for the selection of targets based on specific symptoms, as is done in Parkinson's. Patients with depression have varying combinations of symptoms that are reflected in a different pattern of brain scans. Looking at these patterns of aberrant brain activity already shows promise for making decisions about whether drug or cognitive-behavior therapy is the best option—and it may eventually do so as well for deep-brain stimulation.

Attempts to refine these techniques must be supplemented by more basic research to understand how the technology changes brain functioning. After a prolonged period of stimulation, antidepressant effects can persist for days or weeks even when the stimulation is turned off. The brain may undergo long-lasting alterations—a process known as neuroplasticity—as brain circuits change as a consequence of stimulation. Indeed, rodent studies point to evidence that deep-brain stimulation alters the activity of large networks of brain circuits and that it may also induce the birth of new neurons in the hippocampus, a process that other work has shown is important both for forming new memories and for easing depression. If the therapy is discontinued for an extended period, however, symptoms return, suggesting that the brain does not permanently heal itself through this therapy.

The ability to control electric circuits with deep-brain stimulation has generated interest in using the technique for other psychiatric maladies, including bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, and alcohol and drug addiction. Deep-brain stimulation has potential for treating patients who have failed other options and whose disorder has been linked to abnormally functioning circuits.

Lozano's group has recently applied deep-brain stimulation to the same subcallosal target used in depression to treat severe chronic anorexia nervosa. In some patients who have lived with the eating disorder for 10 years or more, deep-brain stimulation eased symptoms of depression, anxiety and obsessiveness. Subjects became less anxious about eating and gaining weight and were able to participate in therapeutic programs. In about half of the 18 cases, the change in patients' moods enabled them to return to normal weight a year later.

The results so far point in new directions. Growing understanding of the functioning of brain circuits is helping to explain abnormal brain activity. With this knowledge, neurosurgeons should be able to place electrodes in strategic locations deep in the brain to give needed relief to depressed patients who fail to respond to drugs and talk therapy, as well as to people grappling with a range of other disorders, from anorexia to Alzheimer's. SA

MORE TO EXPLORE

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