PHOTOGRAPH BY CATHERINE LEDNER

SURE SIGNS THAT ELECTROCONVULSIVE THERAPY HAS FLOWN THE CUCKOO'S NEST:
Low-energy devices tread lightly on the limbic system // Magnetic pulses feel as harmless as a haircut //
Electrodes embedded deep within the brain help lift patients from profound depression.

Out of Despair

BY CATHRYN DELUDE

She wasn't strapped to a table and didn't thrash in agony, as in the popular conception of this once-notorious treatment, and no massive bolt of electricity surged through the electrodes attached to her head. And although it ultimately failed to lift her spirits, at least the electroconvulsive therapy (ECT) that Mustafa Husain's patient received for her severe depression wasn't brutal. Patients today usually get general anesthesia and a muscle relaxant. Then a three-second pulse of current causes a 30-second seizure in the brain. Throughout the treatment, the patient remains almost motionless.

The usual course of treatment calls for six to eight outpatient sessions spread out over two to three weeks. After each session, the patient will likely feel disoriented and will stay in recovery for half an hour to become fully alert. She may not remember events just before and after the procedure. Some patients describe longer-term cognitive deficits, including memory loss, although studies have not been able to demonstrate these objectively.

Often, however, ECT works where other therapies have failed, and an estimated 100,000 people receive the treatment yearly. Husain, professor of psychiatry and internal medicine at the University of Texas Southwestern Medical Center, has often seen treatment-resistant patients respond well, and hoped it would help this patient, whom he had already treated with long courses of psychotropic drugs and psychotherapy. But ECT, too, failed to brighten his patient's guilt-ridden gloom. "I did everything I could think of," he says. "I changed the placement of the leads and the stimulus dosage, and used caffeine to lower her threshold. But she just didn't improve much. Some patients don't improve no matter what you do."

Now, though, ECT-inspired treatment options are expanding. Several alternative brain stimulation devices have already entered clinical practice, and more are in clinical trials or research studies. The new tools come with their own acronyms—VNS for vagus nerve stimulation, rTMS for repetitive transcranial magnetic stimulation and DBS for deep brain stimulation—and their own distinctive approaches to correcting malfunctioning brain circuitry.

These brain stimulation devices, while expanding therapeutic options, are also changing the understanding of depression as a medical disorder, as researchers learn more about underlying abnormalities in the brain. "Before, we couldn't establish direct links between brain location, brain function and behavior noninvasively. Now, we can use these tools to probe circuits to understand how the normal brain works, and what impact illnesses have on functional connections in the brain,"

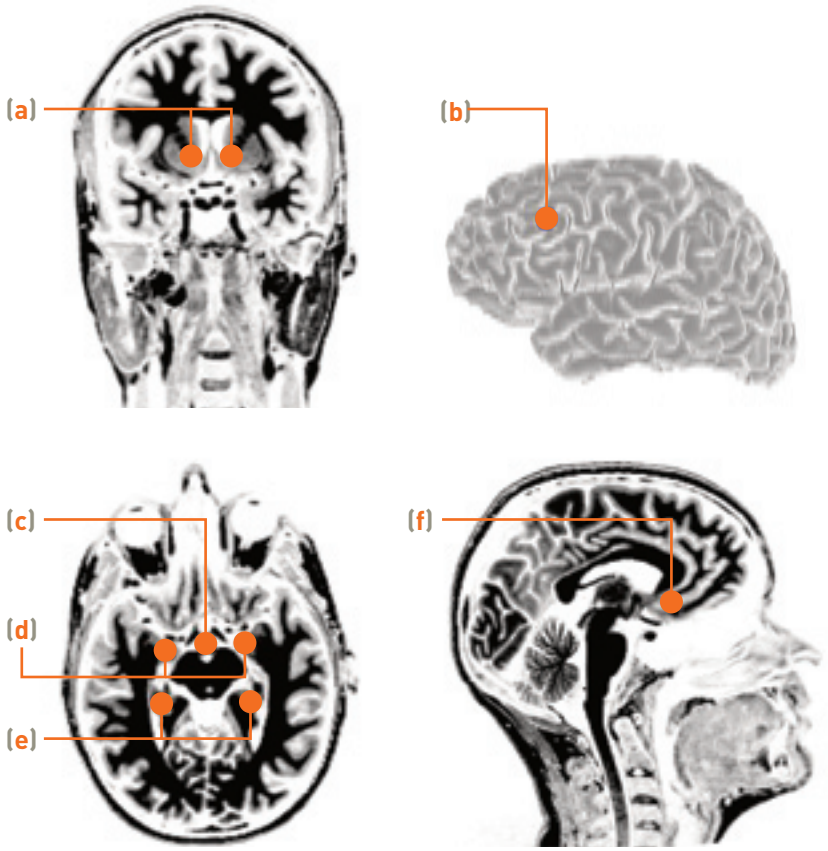
Home free after years of severe depression, Karmen McGuffee credits vagus nerve stimulation, a controversial therapy.

says Sarah Lisanby, director of the Brain Stimulation and Neuromodulation Division at Columbia University.

Major depressive disorder is often a lifelong, recurring condition that can sap vitality, hobble motivation, ruin relationships, derail careers, squelch libido, exaggerate anxiety, banish sleep and lead to suicide. It has such an eclectic appearance that two people may share the diagnosis but have few or no symptoms in common. Those varied manifestations of the disease may result from different malfunctions in the brain, and could explain why multiple patients may respond very differently to the same treatment.

Some patients benefit from talk therapy, but others require medications that restore a balance in the brain's neurotransmitters, the chemicals that relay messages among neurons. Prozac and the other selective serotonin reuptake inhibitors (including Paxil, Zoloft and Celexa) effectively increase levels of the neurotransmitter serotonin by prolonging the process by which neurons take up the chemical after it has transmitted an impulse across a synapse.

Electrical brain stimulation, in contrast, targets the neural circuitry. Brain disorders, including depression, are thought to result when the electrical signals that travel through neural circuits are disrupted in a particular region. ECT induces a seizure that, in a way still not fully understood, resets the circuitry of large regions of the brain, possibly restoring the proper release and uptake of neurotransmitters. But in causing a seizure, ECT acts like a blunt instrument, sending a large current through the skull, basically to see what happens. Nonconvulsive devices hold promise because they attempt to achieve the same results by targeting a pivotal place, without inducing a seizure.



Danger Zones //

STUDIES OF BRAIN IMAGING AND INJURY HAVE LINKED SPECIFIC REGIONS TO DEPRESSION.

ANTERIOR LIMB OF THE INTERNAL CAPSULE (a) // This deep structure, made of connective white matter, relays information between the thalamus, which is involved in mood regulation and sensory-motor functions, and the cerebral cortex, where higher-order thinking processes occur. Studies of brain injury and stroke have trained attention on this region's role in depression, while ablative surgery has shown that severing the connection could treat very severe cases.

DORSOLATERAL PREFRONTAL CORTEX (b) // People with damage to the left side become depressed more frequently than patients with damage to other parts of the brain. The region (the left side in particular) appears hypoactive in brain scans of depressed people.

LIMBIC SYSTEM // This network, thought to be important in regulating emotion, includes such structures as the hypothalamus (c), amygdala (d) and hippocampus (e). Another key structure, Brodmann area 25 (f), is found in the subgenual cingulate, which in turn lies in the anterior cingulate, where the cortex folds inward toward the brain's center. Imaging studies have shown that the feeling of deep sadness in depression is linked with abnormal activity in area 25, and that people recovering from depression have subdued activity there, while autopsies have shown structural abnormalities in the same region, with fewer glial cells.

ANDREA GOLD AND ERIC FECZKO

Whether depending on implanted devices (for vagus nerve stimulation, top, and deep brain stimulation, middle) or a current-inducing wand (for repetitive transcranial magnetic stimulation, bottom), today's alternative therapies seek a direct path to depression's trouble spots in the brain.

The new options are all variations on the ECT theme of using electricity to change the pattern of brain activity. Several of them work on specific regions of the brain that research has linked to abnormalities, and all stimulate the brain with lower doses of energy than ECT, and without causing seizures. Their efficacy depends on the brain's plasticity, its ability to be remodeled by learning, experience, drugs—and electricity.

Vagus nerve stimulation, which the FDA approved as a complementary treatment for long-term management of treatment-resistant depression just last year, uses a back door to the brain. The vagus nerve, one of the body's 12 cranial nerves, threads its way through far-flung regions of the body, sending signals to and from the digestive tract, stomach, heart and other places, through the neck and into the brain, where messages are relayed to the widely distributed limbic system, beneath the outer cerebral cortex. While the cortex governs higher-order cognitive processes, the limbic system helps rule emotions. It includes the hypothalamus, hippocampus, amygdala and other regions, to which we owe our feelings of fear, anxiety and sadness, as well as drive and motivation. The brain stem produces the bulk of the mood-regulating neurotransmitters serotonin, dopamine and norepinephrine, which are central to communication in the limbic system. Stimulating the vagus nerve helps gain access to those brain regions and systemically influences the neurotransmitters.

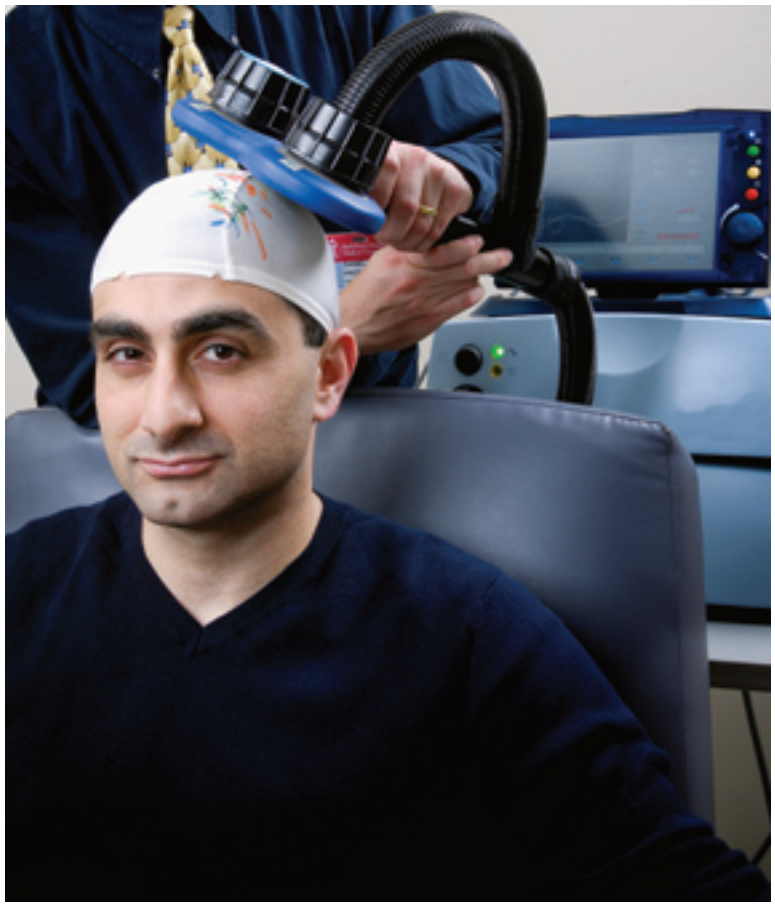
In 1999, in a pilot study, Karmen McGuffee of Garland, Texas, another of Husain's patients, was fitted with a two-part VNS device. Electrodes were attached, via a quarter-inch incision, to the vagus nerve in her neck. Then wires were threaded down to her chest, where a small hockey-puck-shaped disk was implanted beneath the skin. The disk sends pulses to the electrodes at the vagus nerve, much the way a cardiac pacemaker regulates the heart. Husain can adjust the settings using a handheld device that functions like an electronic prescription pad, delivering the correct dosage of milliamps. If something goes wrong, the device can be turned off in an instant. But for McGuffee, it has remained on—even through her pregnancy and the delivery of a child in 2003—and to heartening effect. She is among the 15% of patients in the Phase III trial of VNS who ceased to be clinically depressed. (Another 27% saw their symptoms reduced by at least half.)

Those aren't stellar scientific results for a device as invasive, risky and expensive ($20,000) as VNS, and many researchers criticize the FDA approval based on what they consider paltry evidence. But Husain sees even these relatively modest numbers of positive outcomes as significant and meaningful to patients who have failed to benefit from other treatments and tend to be in desperate straits. Moreover, Husain says, patients seem to benefit the longer the VNS device is in place, and even those whose symptoms don't improve significantly may be able to go longer between ECT sessions.

Repetitive transcranial magnetic stimulation has been approved in Canada for treatment-resistant depression and, although not yet cleared for that purpose in the United States, it is offered "off label," much as some drugs are prescribed for conditions other than those for which the medications are FDA-approved. Like ECT, rTMS works from outside the skull, but rather than shocking the brain with a surge of externally generated electricity, it creates a focused magnetic field that induces a current inside the dorsolateral prefrontal cortex, at the front of the skull, where brain-imaging studies of some depressed patients have shown abnormal activity patterns. But the neuroscience isn't yet clear about which depressive symptoms these abnormal activities may produce—or whether stimulating

the brain region with rTMS increases beneficial activity, promoting optimism and motivation, or inhibits negative brain activity, reducing anxiety and agitation.

Yet, while there is much to be learned about how rTMS works, some patients seem to be benefiting. J.T. of Arlington, Mass., sidelined by depression throughout his twenties, has been receiving rTMS for three years at a clinic run by Alvaro Pascual-Leone, director of the Center for Non-Invasive Brain Stimulation at Boston's Beth Israel Deaconess Medical Center. J.T. describes his treatment sessions as "routine as getting a haircut." He reads a magazine while a technician circles a wand containing a stimulation coil over the left side of his forehead. For half an hour, with brief pauses, the device fires magnetic pulses at a rate of 20 times per second into J.T.'s left dorsolateral prefrontal cortex. Researchers think this bombardment gradually affects the brain activity there, perhaps restoring the proper balance of neurotransmitters.



For patients such as J.T., the wand that delivers repetitive transcranial magnetic stimulation is magical, keeping depression at bay while barely touching his head.

PHOTOGRAPH BY JASON GROW

J.T. says he knew the treatments were beginning to help when the musical score of his life changed from the dark strains of Metallica to a Mozart symphony. At first, J.T. received treatment several times a week, which tapered off to once a month. But then symptoms returned, and he is now on a biweekly schedule.

Some critics contend that because rTMS penetrates only a few centimeters into the cortex, it's unlikely to have much effect on the brain circuitry or chemistry implicated in depression. (Pascual-Leone counters that although the effect is directly exerted in part of the cortex, it spreads through this "window" to deeper parts of the brain along specific connections.) They note that in a double-blind trial of the treatment, only one in three patients appeared to benefit—not a clinically significant improvement, in some views. But the success rate approaches that for VNS and is not much worse than the roughly 40% achieved by ECT administered at community hospitals. (At academic medical centers, four out of five ECT treatments succeed, presumably because physicians there are better trained and more experienced.)

Deep brain stimulation (DBS), approved for severe cases of Parkinson's disease but used on only a relative handful of patients in research studies of depression, uses electrodes implanted directly into the brain in a region that has been implicated in depression. The electrodes are connected to a pacemaker-like device in the chest or neck that can be controlled externally, as in VNS.

DBS is being explored as a reversible alternative to brain surgery, the last, desperate recourse for severely depressed patients who have exhausted all conventional alternatives. When used to treat depression and Parkinson's disease, DBS can have an effect described as astonishing and immediate, as if there were switches in the brain waiting to be thrown.

There may be no single switch for depression, but several groups of researchers using DBS for obsessive-compulsive patients have noted that stimulating the anterior limb of the

Shock Values //

15–20 Percentage of depressed American adults who do not respond to more advanced pharmaco- and psychotherapy

1938 Year the first patient with a mental disorder was treated with electroshock

25 Percentage of medical students in a 2002 study who, after watching the portrayal of electroconvulsive therapy in five movies, said they would dissuade a relative or friend from undergoing the treatment

2 Centimeters rTMS penetrates through the skull to the prefrontal cortex

4 Minimum number of traditional treatments (antidepressants or ECT) that must fail to work for a patient before a physician can consider vagus nerve stimulation, as stipulated by the FDA

8 Number of years that VNS has been in use for treatment-resistant depression

30 Estimated number of patients who have been treated with deep brain stimulation in ongoing international pilot studies

internal capsule improved patients' moods, lessened their anxiety and boosted their motivation. That made sense because neurosurgeons frequently target that portion of the brain, part of a fan-shaped structure in front of the ears that mediates communication between the thalamus, the main relay nucleus in the brain, and parts of the frontal lobes involved in emotion.

Benjamin Greenberg, at Butler Hospital and Brown Medical School in Providence, R.I., is now studying DBS at this brain site for depression. In a pilot study, two patients had clinically significant responses and two others had "more inconsistent benefits," Greenberg reports. Another team, led by Helen Mayberg, a neuroscientist formerly at the University of Toronto and now at Emory University, is targeting a section of the subgenual cingulate known as Brodmann area 25, which she found highlighted in brain-imaging studies among patients reporting profound sadness as well as in studies of various antidepressants. In the March 3, 2005, issue of *Neuron*, Mayberg published encouraging "proof of principle" results from six patients, with four patients showing a sustained remission of their depression well past one year with continued DBS treatment. An additional nine patients have undergone the procedure, and they appear to show a comparable rate of response.

"DBS has powerful effects on behavior," Greenberg says, though he cautions that further testing will require carefully selected patients at specialty centers that maintain close, long-term contact between the patients and the psychiatric team.

These devices and their current uses are just the tip of the iceberg, says Columbia's Lisanby. Yet despite the excitement generated by new approaches to brain stimulation, many experts caution that the rush to put them into practice should not outstrip the science. Clearly, at least for now, these devices have limited effectiveness. Yet the same is true for ECT and psychotropic drugs, and even modest results can make a major difference in the real world, helping some people function at work or at home, or making them more responsive to talk therapy.

The research involving brain stimulation is also helping change the understanding of depression as a medical disease that arises from abnormalities in the brain. The new devices seem to be taking us closer to determining what those abnormalities are—and that, in turn, could lead to still other tools and strategies for brightening depression's darkness. ■

→ DOSSIER

1. **"Magnetism on the Brain: Researchers Probe Transcranial Magnetic Stimulation," by Tracy Hampton. Medical News & Perspectives; *JAMA*, April 13, 2005.** An overview of the history of transcranial magnetic stimulation and its therapeutic potential for depression and other conditions.
2. **"Deep Brain Stimulation for Treatment-Resistant Depression," by Helen S. Mayberg et al., *Neuron*, March 3, 2005.** Report of findings that the subgenual cingulate region is metabolically overactive in treatment-resistant depression and that DBS applied to this region effected sustained remission in four of six patients.
3. **"VNS and depression: current status and future directions," by Sally P. Walsh and Mitchel A. Kling, *Expert Review of Medical Devices*, September 2004.** A summary of research findings and the questions that still need to be addressed.