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Electronic  
implants  
and  
electromagnetic  
pulses  
are picking up  
where  
psychoactive  
drugs have  
failed

*Psychiatry's Shocking New Tools*

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Illustrations by Matt Mahurin  
and Bryan Christie

## Imagine a crushing sadness so severe

it keeps you from eating, sleeping, or socializing. Though you can't sleep, you lack the energy and the will to get out of bed. Everyday decisions, like which clothes to wear, leave you paralyzed. You've no desire to do the things you once thought were fun; in fact, you can't bring yourself to do much of anything. Now, add to all that the realization that you've tried everything known to medicine, it hasn't worked, and there's a good chance you won't feel any different. Ever.

"I had nothing to lose," says Karmen McGuffee, who suffered from severe depression for a decade and was hospitalized five times for it. So she had surgeons cut open her neck, gently wrap an electrode around one of the nerves there, and plug the electrode into a pulse generator, which they slipped under the skin of her chest. About every 5 minutes, the pocket-watch-size device sends a buzz of current through the nerve and into her brain.

Six months after doctors switched on the pulse generator, called a vagus nerve stimulator, McGuffee's world looked totally different. "I had no idea that life didn't have to have a dark veil over it all the time," she says. Once unable to concentrate enough to read a newspaper, McGuffee is now an executive secretary.

Depression is distressingly common, affecting more than 120 million people around the world and sucking tens of billions of dollars out of the global economy through the cost of care and lost productivity. It's also deadly. Every year 850 000 people worldwide take their own lives, and 9 out of 10 of them are suffering from depression, another mental illness, or substance abuse. Statistics show that of those who had had treatment for depression just through visits to a doctor's office, 2 percent ultimately committed suicide, as did 4 percent of those who had to be hospitalized for depression.

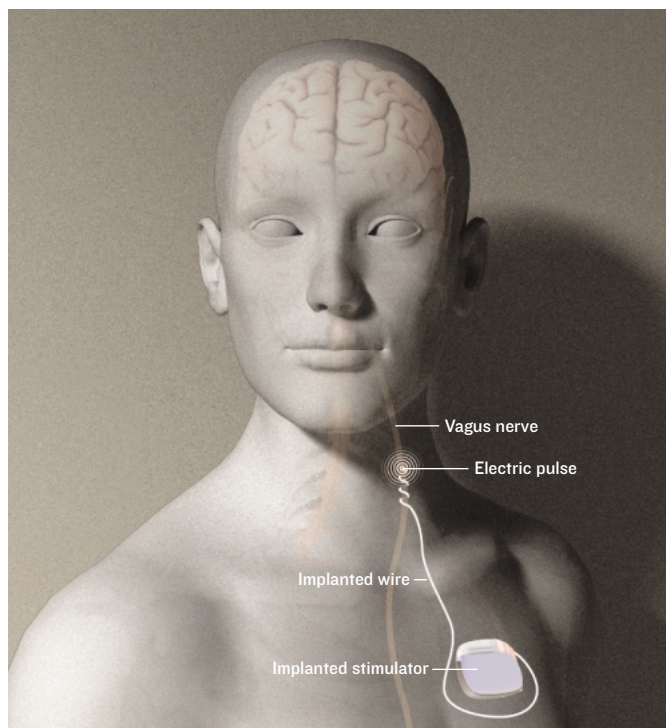
Twenty-five percent of people with depression have no access to any form of mental health care; of those who do have access to care, only a quarter seek treatment. Of those who consult doctors, some 80 percent find relief in the form of drugs or some kind of talk therapy, such as cognitive therapy. But for the rest—people like McGuffee, prone to the most severe and chronic forms of depression, about 11 million of them in the developed world alone—drugs don't work.

For decades, the only other option for these people was electroconvulsive therapy, which because of the frightening side effect of amnesia is often rejected by patients. But this grim outlook is at last beginning to change. McGuffee was one of the first to benefit from a new crop of electromagnetic brain stimulation technologies that psychiatrists are testing, with the hope of curing—or at least

helping—patients for whom little else works. By electrically manipulating specific portions of the brain with implanted electrodes, electric current, or magnetic fields, doctors aim to succeed where drugs fail, by producing long-lasting changes in the brain—and to do it without electroshock's significant side effects.

For a variety of reasons, including the large number of potential patients and the accumulated knowledge of how the disease works, depression is the primary target of most of these technologies. But some of these methods are already showing great promise for treating such other mental maladies as bipolar disorder, obsessive-compulsive disorder, and bulimia.

The technology McGuffee uses, vagus nerve stimulation, was the first to enter routine clinical use. A pacemakerlike device about



the size of a pocket watch, implanted under the skin of the chest, pulses a nerve in the neck [see illustration, "Vagus Nerve Stimulation"]. In about 16 percent of patients like McGuffee, according to clinical studies, that electric pulsing completely quashes the symptoms of depression. It was approved as a depression therapy, for use in conjunction with drugs, by government regulators in the European Union and Canada in 2001. Last June, it became the first psychiatric device to be reviewed and approved in the United States, which has more stringent requirements for medical devices. Nevertheless, a number of psychiatrists remain unconvinced that the therapy works in enough people to outweigh the risk and cost of surgery.

Vagus nerve stimulation isn't the only technology being touted for treatment of the severely depressed. Another technique, repetitive transcranial magnetic stimulation, uses powerful magnets to generate current in well-defined portions of the brain [see illustration, "Repetitive Transcranial Magnetic Stimulation"]. Many research groups

around the world have experimented with the technology. At last count the results of more than 60 depression trials performed in Australia, Israel, Taiwan, the United States, Europe, and elsewhere had been published. But clinical use is just beginning. The technology is winding its way toward a review by U.S. regulators, and the company behind it, Neuronetics Inc., in Malvern, Pa., says it could be approved within the year.

And these two are just the ones closest to the clinic. Researchers are exploring three other, more experimental technologies. One uses direct current to produce a change in the brain similar to that of magnetic stimulation. Another uses transcranial magnetic stimulators to spark seizures just as electroconvulsive therapy does but, it is hoped, without the amnesia that can accompany it. The third experimental technology borrows a device used

## Vagus Nerve Stimulation

A pulse generator implanted in a patient's chest sends electric pulses to the vagus nerve, one of 12 nerves that emanate from your brain rather than your spinal cord. The pulses send signals into the brain that reduce or eliminate severe chronic depression in some people.

**+** Approved for sale in the United States, Canada, and the European Union as a depression treatment. Unlike other treatments, including drugs, it appears to keep working for years.

**-** Completely eliminates depression in only one out of six patients. Requires surgery.

to control the tremors of Parkinson's disease. Surgeons have begun implanting electrodes in patients' brains to switch off malfunctioning brain circuits involved in depression and obsessive-compulsive disorder.

The coming clutch of medical devices, if proven to work, could represent not just hope for the hopeless but a profound change in psychiatry. "I think it's not too big a jump to say we haven't had a new [nondrug] treatment for 40 years," says Paul Fitzgerald, an associate professor of psychiatry at Monash University, and deputy director of the Alfred Psychiatry Research Center, both in Melbourne, Australia. Fitzgerald, who does transcranial magnetic stimulation research, notes that even the drug therapies are largely derivative of each other. "Now we're really faced with the potential for a significant expansion of treatments, as long as they are introduced carefully," he adds. Noting psychiatry's often disastrous history of nondrug treatments, such as the embrace of prefrontal lobotomy in the mid-20th century, he thinks the field is approaching a watershed, for the better. "We're getting it right this time."

**THAT PSYCHIATRISTS CAN USE** both drugs and electricity to battle illness testifies to the fact that the brain is both a chemical and an electrical organ. Every brain cell has a halo of short projections attached to its body and a long trunk, called an axon. To communicate with another cell, it sends a pulse of voltage down the axon. The axon usually terminates at one of the short projections of another brain cell. Rather than make a direct electrical connection, two brain cells communicate via a puff of chemical transmitters released from the end of the axon when the voltage pulse reaches it. These transmitters cross the nanometers between the end of the axon and the next cell's projections and bind with receptor molecules there. Depending on the type of chemical signal, this binding can lead to a variety of things, but the simplest is an influx or outflow of current that briefly raises or drops the target cell's voltage. The cell integrates the voltage changes from its many projections, and, if the combination of them is big enough, it will trigger a voltage pulse down the target cell's axon. The process of integration and signaling continues as signals propagate through the brain's millions of specialized circuits and is the basis of everything that occurs inside our heads: thoughts, emotions, moods, memories, and dreams.

Psychoactive drugs, such as Prozac, work on the chemical side to ultimately affect electrical signals. Depression, at least in part, involves a problem with the electrical signaling between certain parts of the brain whose cells signal with a chemical transmitter called

serotonin. By inhibiting the reabsorption of serotonin, Prozac lets more of the chemical accumulate in the space between the end of the axon and the next brain cell, thus restoring the signaling.

One problem with this approach is that drugs work everywhere in the brain that their chemical target exists, regardless of whether those parts have anything to do with depression or any other disease, and that leads to side effects. Prozac, for example, has been known to reduce sex drive and can cause insomnia. Another problem is that brain chemistry varies from person to person, so no single drug will work in everyone.

The shared goal behind the new electromagnetic therapies, on the other hand, is to use electricity itself to restore the signaling, ideally, only in those parts of the brain affected by disease. Decades

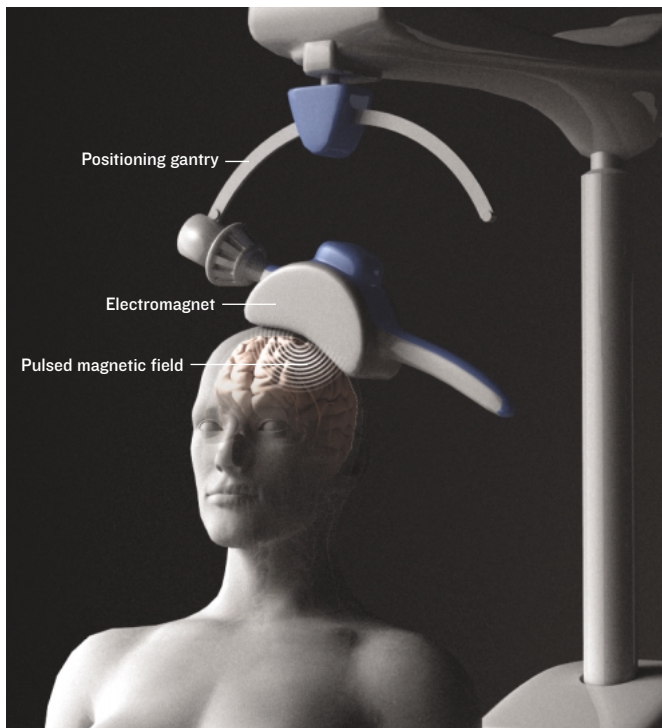
ago, neuroscientists demonstrated that electrically stimulating a neuron alters, in the long term, the strength of its connections to other neurons—making an electrical signal from one neuron more likely or less likely to jump to the next neuron. Though little is known in detail about how the new therapies work, it's likely that, to varying degrees, they depend on that phenomenon.

**BECAUSE THEY ARE NEW** and in some cases relatively unproven, the device-based technologies are being tested exclusively in people for whom all the available drugs have failed to work. For a minority of these patients, electroconvulsive therapy, a 70-year-old technique, is the treatment of last resort. So it is with electroconvulsive therapy that the new technologies are generally compared.

Unfortunately, your view of electroconvulsive therapy, like that of many potential patients, was probably formed by the 1975 movie *One Flew Over the Cuckoo's Nest*, in which it was used as a means of punishment and control. Even if Jack Nicholson's performance has no influence on

your view of psychiatry, the idea of the therapy's main side effect, amnesia, is far more fearsome than Prozac's decreased libido or even the maladies associated with more powerful drugs, because memory is so tied up with our sense of self. But the reality is that the severity of electroconvulsive therapy's side effects has been minimized over the years, its use is carefully controlled, and, quite simply, nothing is as effective at breaking through the worst forms of depression. Still, in the United States, only about 100 000 people a year agree to it, despite the millions whom no drug helps.

"Electroconvulsive therapy can be dramatically effective at restoring a person's health and getting their life back on track," says Sarah H. Lisanby, director of the Brain Stimulation and Neuromodulation Division of the Columbia University Medical Center, in New York City. "The potential for the new brain stimu-



## Repetitive Transcranial Magnetic Stimulation

A powerful electromagnet positioned over a part of the brain implicated in depression induces the flow of current in neurons there. Though the stimulation is done only for minutes a day over a period of weeks, it alters the activity of the neurons in the long term.

**+** Few side effects. Could gain approval by U.S. government regulators this year.

**-** Long-term risks and long-term effectiveness are unknown.

lation techniques is to get those kinds of dramatic effects in medication-resistant populations without the downside.”

**VAGUS NERVE STIMULATION** began in the 1980s with Jacob Zabara, a neurophysiologist at Temple University, in Philadelphia, demonstrating that he could quell epileptic seizures in a dog by electrically jolting its vagus nerve, one of twelve pairs of nerves that emerge from the brain instead of the spinal cord. He showed the technique to pacemaker designer Reese Terry, and a few years later they formed a company called Cyberonics Inc., in Houston, to develop a treatment for epilepsy.

Using off-the-shelf integrated circuits, design help from friends in the field, and a new kind of helical electrode, Terry put together an implantable device that periodically shocks the vagus nerve. Cyberonics has made more than 30 000 of them, using the same basic design. The implantable device looks and acts like a heart pacemaker. Though a doctor can program in a wide range of stimuli, the device typically delivers 1- to 2-milliampere, 250-microsecond pulses at 20 to 30 hertz for 30 seconds every 5 minutes.

Terry and his co-workers always envisioned uses beyond epilepsy. Depression was a good place to start, because the malady has been linked to epilepsy for so long that even Hippocrates wrote about it. About a quarter of people with severe epilepsy also have chronic depression—a far greater ratio than in either the general population or other groups with chronic illnesses. Also, intriguingly, early in Cyberonics’ tests, some epilepsy patients reported that the device had improved their mood.

Researchers don’t really know why the device works against depression. But they do have some theories. Phillip C. Jobe at the University of Illinois College of Medicine, in Peoria, proposes that the brain’s natural defenses against both epileptic seizures and depression are weakened by chemical and structural flaws in the same two systems of neurons buried deep within the most primitive part of the brain. Vagus nerve stimulation alters activity in both those areas, although the nerve does not connect directly to either of them.

Terry, naturally, takes an engineer’s view of things. “The way I look at it,” he says, “the brain is a very finely controlled feedback system.” For some diseases, he suggests that the “control system is a little bit out of balance.” The periodic pulses from his device in effect “pace” the vagus nerve, he believes, restabilizing the control system.

But a bigger question than how it works, and one the company is still trying to answer for doctors, is whether or not it actually

does work. In the late 1990s, a pilot study of patients with chronic or recurrent depression that resisted treatment with drugs gave promising results. McGuffee was among the first patients to receive an implant, in February 1999. One month after she got the implant, her family began to see an improvement; a few months later, McGuffee noticed it, too.

The pilot study was enough to convince European and Canadian regulators to allow the stimulator’s use in their jurisdictions. To get more conclusive data that might satisfy the tougher U.S. regulations, Cyberonics embarked on a 235-patient, eight-week study. To tease out any placebo effect, all the patients received implants, but only half of the implants were turned on. Here again, too few patients improved to tell if the device was the

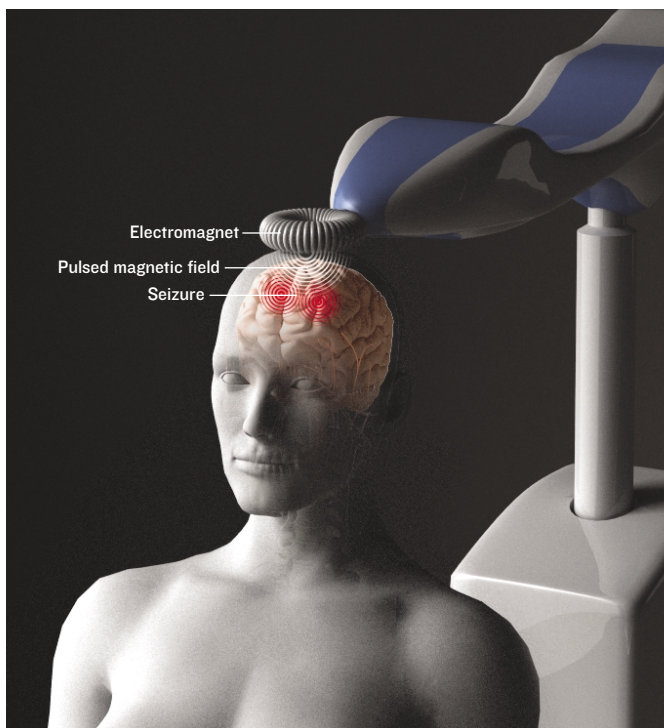
cause of the improvement. So at the end of the study the company asked doctors to turn on the implant for anyone who wanted it and instructed them to continue treating the patients with anything that might benefit them. “It would have been inappropriate to withhold treatment,” says chief medical officer Richard Rudolph. “But now we had nothing to compare the outcomes with.”

Strapped for cash but not ready to give up on a group of patients with no options, to say nothing of a potential US \$1 billion market, the company continued to try to prove the stimulator would work for depression. Plan B, according to Rudolph, was to follow the patients from the original study, find a group of very similar patients without stimulators, and compare how they fared over two years, a much longer period than is generally used in a trial of a new antidepressant drug.

After one year, one in six patients treated with the nerve stimulator was free of depression, and 56 percent got some meaningful benefit—as measured by a standardized questionnaire used to rate the severity of a patient’s depression.

Of those who did respond, about 70 percent continued to benefit after two years. But waiting a year to see if the treatment worked in a disease that comes at irregular intervals was highly unusual. The lack of a control group that had the device implanted but not turned on to counteract the placebo effect was stranger still. In August 2004, the U.S. Food and Drug Administration, which regulates the marketing of medical devices, decided not to allow Cyberonics to sell the vagus nerve stimulator as a depression treatment, overruling its own advisors in the process.

Cyberonics’ CEO, Robert P. (“Skip”) Cummins, who lost both his mother and grandfather to depression-related suicide, refused to give up. His company gathered more data, and went straight to



## Magnetic Seizure Therapy

This therapy uses a more powerful electromagnet than repetitive transcranial magnetic stimulation does; it is basically a magnetic version of electroconvulsive therapy. Magnetic seizure therapy induces a high-frequency current in a small portion of the brain until it sparks a seizure. The hope is that a magnetically induced seizure will be as effective at treating depression as an electrically induced seizure while causing less memory loss.

**+** Could be more effective than other brain stimulation techniques.

**-** Requires daily anesthesia and careful medical monitoring for a period of weeks. Few patients have undergone this treatment; little is known about how well it works or its side effects.

the FDA's top brass. By February 2005 the company had won conditional approval. But it still had hoops to jump through on the way to full approval: there was controversy when Public Citizen, a prominent Washington, D.C., advocacy group, questioned whether the device worked at all. At the same time, an investor lawsuit began regarding the timing of some executive stock sales. And then there was a halfhearted investigation by a U.S. Senate committee into why the FDA had decided against the device. Full approval finally came last July.

Cyberonics says it has trained 2000 psychiatrists in vagus nerve therapy so far, but many physicians are still skeptical. Perminder Sachdev, a professor of psychiatry at the University of New South Wales, Sydney, Australia, thinks the technology has shown some promise but has a way to go before the results are convincing. "It's a hard area to investigate," he says. The placebo effect is difficult to eliminate, the nature of depression is that it waxes and wanes, and the treatment takes a long time to show an effect. The combination of all that means you need a great many patients to prove a device is working, he believes. Sachdev and others expect the picture to clear somewhat after the results of a study going on now in Europe are reported. In the meantime Cyberonics is running pilot trials to see if the device will work to control other mental illnesses, such as bulimia and obsessive-compulsive disorder.

**CYBERONICS' DUEL** with U.S. regulators was watched closely by psychiatrists, patients, and competing companies. Executives at Neuronetics were particularly interested, because their device, a repetitive transcranial magnetic stimulator specially designed for treating depression, will be the next such technology weighed by the FDA. The company plans to send its data to the agency next month and could get a decision before the year is out.

How the vagus nerve stimulator fared offers some important lessons for Neuronetics, says Mark Riehl, the company's vice president of product development and operations and the leader of the team that designed the device. "The FDA and the market expect a trial modeled after pharmaceutical trial design," he says. Drug tests are designed so that patients are selected at random to get the treatment or get a placebo—and neither the patients nor their doctors know which patients are getting the treatment. So that's what Neuronetics is doing (and, of course, that's what Cyberonics originally set out to do).

The basic idea behind repetitive transcranial magnetic stimulation (rTMS) is to use a strong, varying, and concentrated magnetic field to induce the flow of current in a few cubic

centimeters of the part of your brain above your eyeballs. This block of neurons, the prefrontal cortex, has to do with making decisions, but neuroscientists have also implicated it in depression, and it connects directly to mood-regulating structures deeper in the brain. The neural activity in the prefrontal cortex is abnormal in people with depression, but electroconvulsive therapy and drugs like Prozac alter it to restore normal mood. The theory is that you can get the same restoration by repeatedly generating a magnetically induced current there. To treat depression, the current must be strong enough to trigger spikes of voltage in brain cells but not so strong or high in frequency that it sparks a seizure.

A transcranial magnetic stimulation device is simple. Basically, it's just a very big capacitor that discharges into the coil of an electromagnet, which generates the magnetic field. But the magnetic field it generates is impressive. At 2 tesla, the field is 50 percent stronger than that of a typical full-size magnetic resonance imager. To make a field like that, 8000 amperes, driven by more than a kilovolt, typically course through the coil's windings.

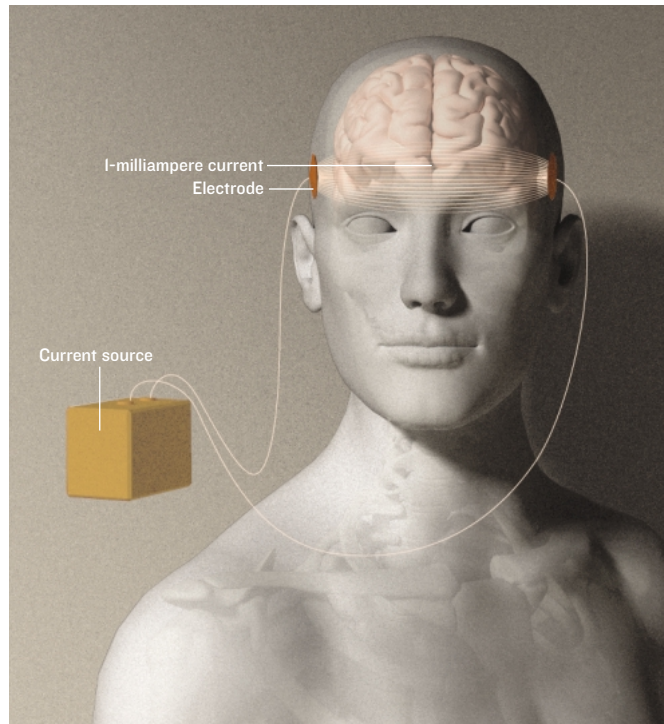
Early research on the use of rTMS to fight treatment-resistant depression showed inconsistent results and relatively small rates of response, providing a benefit on average to only about 30 percent of patients. The problem with the early work, according to Monash University's Fitzgerald, was that there was little consistency as to exactly where in the brain the stimulator was producing its current.

But incorporating magnetic resonance maps of patients' brains and other techniques have improved the therapy's accuracy. And now a few carefully done direct comparisons between rTMS and electroconvulsive therapy, hitherto the most effective treatment, suggest that with

certain exceptions, the same proportion of patients would benefit from either. There are many, however, who think the seizures provoked by the long-used electroconvulsive therapy will prove more effective than rTMS.

Columbia's Lisanby is one. Electroconvulsive therapy "had great value in helping patients who were extremely depressed, but it also had some drawbacks," she says, referring to the possible amnesia. So she has been developing magnetic seizure therapy, a version of rTMS that triggers seizures [see illustration, "Magnetic Seizure Therapy"].

Electroconvulsive therapy triggers seizures with pulses of current that are spread over a large area of the brain. Because rTMS limits current to well-defined, centimeter-scale portions of the brain, Lisanby reasons, magnetic seizure therapy could allow doc-



## Transcranial Direct Current Stimulation

A device drives a small direct current through the front part of a patient's brain. Though the stimulation is done only for minutes a day over a period of weeks, it appears to alter the activity of neurons in the long term.

**+** Simple and cheap.

**-** Few studies have been performed; very little is known about how well it works.

tors to better control where in the brain a seizure originates and where it spreads to, with the aim of minimizing side effects.

So far, rTMS practitioners have been studiously avoiding inducing seizures in their patients by limiting both the device's power and its frequency, so the available technology was not easily suited to actually inducing seizures by magnetic means. The first system, used in neurology experiments in London in 1985, could generate a single on-off pulse only every four seconds, says Reza Jalinous, its coinventor and vice president of operations at The Magstim Co., in Carmarthenshire, Wales. The device could generate pulses only at a low frequency, because all the energy from the charge was lost as heat in the coil winding, so the capacitor had to be completely recharged after each pulse. But scientists, and later psychiatrists, wanted higher frequencies, to more closely match the electrical characteristics of brain cells. So Jalinous reshaped the technology.

"To go faster you have to dissipate as little energy as possible in the winding in the coil," he says. It turned out to be a simple matter to go from one pulse every four seconds to five pulses per second. Jalinous replaced the on-off pulse with an alternating-current sinusoid, so current flowed first in one direction and then in the other. The system loses little energy in the coil and returns about 70 percent of it to the capacitor. So the power supply can top off the capacitor quickly, and the stimulator can produce its next pulse in a fraction of a second. By upgrading the power supply and making a few other improvements, Jalinous has produced a system for Lisanby with a top frequency of 100 Hz, as opposed to the more typical 20 Hz or less, that can be sustained for up to 10 seconds. Lisanby expects to begin using the new device on patients this year.

Of course, too many pulses too close together will generate too much heat for the coil windings to handle. "The bottleneck right now is actually heating in the stimulating coil," says Angel Peterchev, a power electronics engineer doing postdoctoral research in Lisanby's laboratory.

In the devices now in use, there are two types of electromagnetic coils: air-core and iron-core. The air-core types, favored by Magstim and Medtronic Inc., of Minneapolis, are meant to be handheld and easier to move, so neurologists can experiment with their effects on different parts of the brain. But the air-core coils are less efficient and generate more heat. The iron-core kind, used by Neuronetics, is meant for clinical use. Although it consumes less power and generates less heat, it would have to be redesigned using a different core material and fewer coil windings to deliver magnetic field strengths of more than 2 T, which might be useful in magnetic seizure therapy.

**PSYCHIATRISTS ARE BEGINNING** to look at an even simpler technology than transcranial magnetic stimulation to fight depression. "It's like hooking the patient up to a car battery," jokes Sachdev. "But with safety features," his colleague Colleen Loo, a senior research fellow, hastily adds. Crude or not, it's a pretty accurate description of an experimental technique called, or tDCS. Basically, it subjects the front half of the brain to a minutes-long 1-mA direct current once a day for several weeks [see illustration, "Transcranial Direct Current Stimulation"].

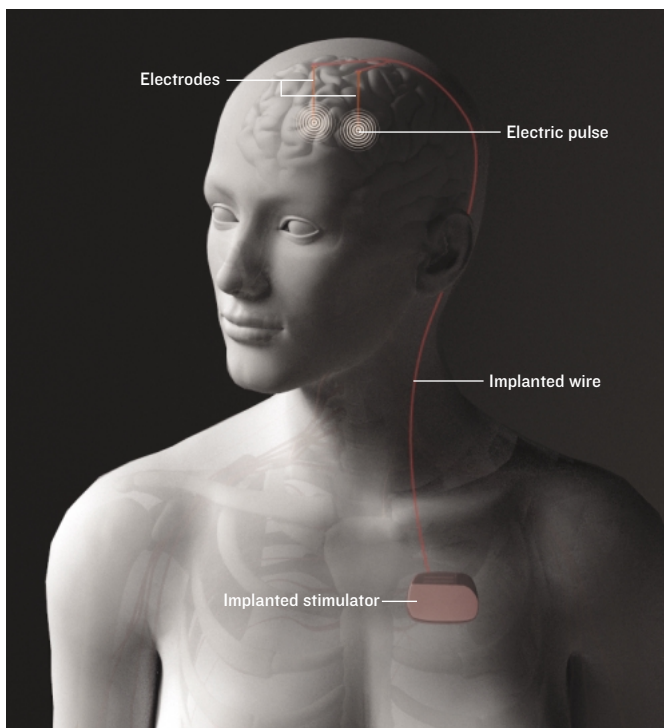
The simplicity of tDCS makes it sound almost suspicious, and indeed its origins stretch back into the murk of 19th-century quackery. But the principle of how tDCS seems to work in the brain is roughly the same as that of rTMS. They both seek to make

neurons in the prefrontal cortex, the decision-making part of the brain, more excitable, that is, more likely to propagate a signal from neuron to neuron. In tDCS's case a small current, delivered via electrodes on the temples, biases brain cells, making them more likely to emit a spike of voltage, says Alvaro Pascual-Leone, associate professor of neurology studying tDCS at Harvard University, in Cambridge, Mass. The effect, studies have shown, lasts long after the current is turned off.

The concept and technology are so simple, in fact, that Pascual-Leone and his colleagues suggested in *The British Journal of Psychiatry* that tDCS be used in the developing world as a first-line treatment for depression instead of rather expensive antidepressant drugs. But Sachdev thinks this is a terrible idea. "We need to know a lot more about tDCS before it is accepted as an effective treatment and must await the results of many ongoing trials," he wrote in a rebuttal. "In the meantime, depressed patients in the developing world should be dissuaded from unplugging

their car batteries and clamping them on their foreheads." Pascual-Leone says he has results showing tDCS fought treatment-resistant depression as well as rTMS did in experiments done at the University of São Paulo School of Medicine, in Brazil, but at press time the study had not yet been published in a peer-reviewed journal.

**IF "HOOKING THE PATIENT UP TO A CAR BATTERY"** is the least invasive new psychiatric technology, then deep-brain stimulation is its opposite. It is meant only for the most desperate patients, those not helped even by electroconvulsive therapy. It requires having a surgeon bore two holes in the skull, insert a pair of electrodes deep into the brain, run wires beneath the skin of the neck, and connect them with a pacemakerlike device implanted in the chest



## Deep Brain Stimulation

A stimulator implanted in a patient's chest sends pulses of electricity to electrodes embedded deep within the brain. The stimulation switches off neurons within a few millimeters of the electrodes. It can cure severe depression by interrupting malfunctioning brain circuits implicated in the disease.

**+** Some effects are almost immediate and seem to last. Allows doctors to target brain circuits with great accuracy.

**-** Requires brain surgery. Few patients have received implants; little is known about how well it works.

under the skin. The device sends pulses of electricity to the electrode tips, shutting down activity in the few cubic millimeters of brain tissue there [see illustration, “Deep Brain Stimulation”].

The results can be instantaneous. Thomas Schlaepfer, vice chair and professor of psychiatry and psychotherapy at the University of Bonn, in Germany, described the case of one of his patients to *IEEE Spectrum*. A host of drugs and even electroconvulsive therapy had failed to lift her depression and halt her desperate urge to kill herself. But last August she had one of Medtronic’s deep-brain stimulators implanted. When Schlaepfer turned the device on and asked her how she was feeling, she replied that she was still as depressed as ever but that she would like to start bowling again.

Bowling had once been her favorite pastime, but she had not enjoyed it for years. The inability to enjoy things that once gave you pleasure—psychiatrists call it anhedonia—is a key characteristic of major depression. The parts of the brain responsible for it, the reward centers, are among the prime targets of the new therapy.

Deep-brain stimulation has been in use for years to treat the tremors of Parkinson’s disease. In that case, 3- to 5-volt pulses at about 100 Hz are applied to a part of a brain circuit that malfunctions and causes the tremors. The stimulation suppresses the activity of neurons near the electrode, mimicking their surgical destruction, but with a key twist. “Basically, it’s reversible and tunable brain surgery,” says Schlaepfer. Turn the device on, and that section of the brain goes off-line. Turn it off, and the neurons spring back into action. It’s a simplistic view, of course, and scientists still don’t know if the electrode’s current blocks brain traffic by holding the cells at too high a voltage to propagate a signal, exhausts their supply of chemical transmitters, overlays a meaningless jamming signal on them, or does something different entirely.

The device has also been used to treat severe obsessive-compulsive disorder; indeed, this was its first use in psychiatry. In that treatment, neurosurgeons had been destroying a few cubic millimeters of a particular structure in the brain. Now surgeons have begun inserting electrodes instead of destroying those tiny parts of the brain.

A group based at the University of Toronto and led by neurosurgeon Andres Lozano and neurologist Helen S. Mayberg reported the first trial of deep-brain stimulation for depression only a year ago. (Mayberg has since become a professor at Emory University, in Atlanta.) Imaging studies led them to Brodmann area 25, a pair of structures deep in the brain just above and behind the eyes that become active when people are sad. It has abnormally high blood flow in people with treatment-resistant depression; antidepressant drugs tend to reduce the amount of blood flow there. So the Toronto researchers implanted electrodes powered by a Medtronic stimulator in that spot in six patients. Five of the six responded well initially, and four continued to do so six months out. According to Lozano, those four are still doing well two years later. Lozano, who has been implanting deep-brain stimulators for more than a decade, says that not enough is known about why patients respond or don’t respond to the procedure to say if there is a need to tweak the technology. “We don’t know if it’s the electrodes or the patients,” he says.

Although the seminal work was done using stimulators made by Medtronic, another maker of implantable stimulators, Advanced Neuromodulation Systems Inc. (ANS), in Plano, Texas, holds the relevant intellectual property rights, according to Rohan Hoare, the company’s vice president of corporate strategy and

development. ANS is now replicating Mayberg and Lozano’s results in a pilot study using its Libra deep brain stimulation system. The main difference between the Medtronic systems used in Toronto and Bonn and ANS’s devices is that Medtronic’s delivers a constant-voltage pulse, which allows the current to vary depending on the impedance of the brain, while its competitor delivers constant current, allowing the voltage to vary. ANS’s vice president for scientific affairs, Tracy Cameron, notes that most animal research has been done using constant-current stimulators and hypothesizes that this approach may be more in tune with the brain’s physiology.

The debates don’t end with the technology. Researchers also disagree about which brain structures to stimulate, although all the contenders are in the same neighborhood, behind and above the eyes. Research at Brown University Medical School and Butler Hospital, both in Providence, R.I., stimulate a much larger structure than Brodmann 25, called the anterior limb of the internal capsule. And Schlaepfer and his colleagues in Europe are working on the area related to anhedonia, called the nucleus accumbens.

**ASSUMING THAT ALL THE NEW** brain stimulation techniques prove effective in the many upcoming trials, the psychiatrist’s toolbox will look very different a decade from now. Patients will probably first be offered the less invasive techniques, such as transcranial direct current and magnetic stimulation; then the more invasive ones, such as the seizure therapies; and finally such surgical technologies as deep-brain stimulation and vagus nerve stimulation. “A significant portion of patients will want to try the less invasive treatment first,” says Monash University’s Fitzgerald. “For some it will be sufficient.”

But don’t cash out of your drug company stock just yet. Even if the more easily applied therapies are proven effective, drug firms have little to worry about. “Drugs are always the first preference, because you don’t have to show up every day,” says the University of New South Wales’s Sachdev.

Of course, a better way than simply trying one therapy after another is to figure out how each works and why they work well for some people rather than others. That won’t happen soon, because it will require experience with many patients and a much better understanding of the brain. And though such brain-imaging technologies as positron-emission tomography have been useful for finding target areas for deep brain stimulation and for understanding the effects of stimulation technologies, they can’t yet predict who will respond to a treatment and who won’t. “We’ve got the diagnostic tools; we just need to refine them,” says Harvard’s Pascual-Leone. And when that’s done, psychiatrists will have both a road map of the mind and the tools to fix the potholes. ■

## TO PROBE FURTHER

For a more complete roundup of the clinical research into the new device-based therapies, see *Brain Stimulation in Psychiatric Treatment*, edited by Sarah H. Lisanby, Washington, D.C., American Psychiatric Publishing (2004).

A Neuronetics executive teaches you how to design a transcranial magnetic stimulator in “Designing Transcranial Magnetic Stimulation Systems,” by K. Davey and M. Riehl, *IEEE Transactions on Magnetics*, March 2005, pp. 1142–48.

More details of vagus nerve stimulators are laid out in “Vagus Nerve Stimulation for the Treatment of Depression,” by Dorin Panescu, *IEEE Engineering in Medicine and Biology Magazine*, November–December 2005, pp. 68–72.