Sparking Recovery with Brain "Pacemakers"

Applying electricity to the brain with deep-brain stimulation could ease Parkinson's disease, pain, depression, and more

By Morten L. Kringelbach and Tipu Z. Aziz

The video is brief, just a couple of minutes, but it's reality TV as riveting as anything you'll ever see. A man in his mid-50s, affable, articulate, faces the camera and talks a bit about a medical procedure he's had. He holds in his hand what looks like a remote control. "I'll turn myself off now," he says mildly. The man presses a button on the controller, a beep sounds, and his right arm starts to shake, then to flap violently. It's as if a biological hurricane has engulfed him, or perhaps it's that his arm is made of straw and some evil sprite is waving it about. With effort, the man grasps the malfunctioning right arm with his left hand and slowly, firmly, subdues the commotion, as if he were calming a child in the throes of a temper tantrum. He's breathing hard, and it's clear he can't keep it up much longer. With an almost desperate gesture, he reaches out for the controller and manages to press the button again. There's a soft beep, and suddenly it's over. He's fine.

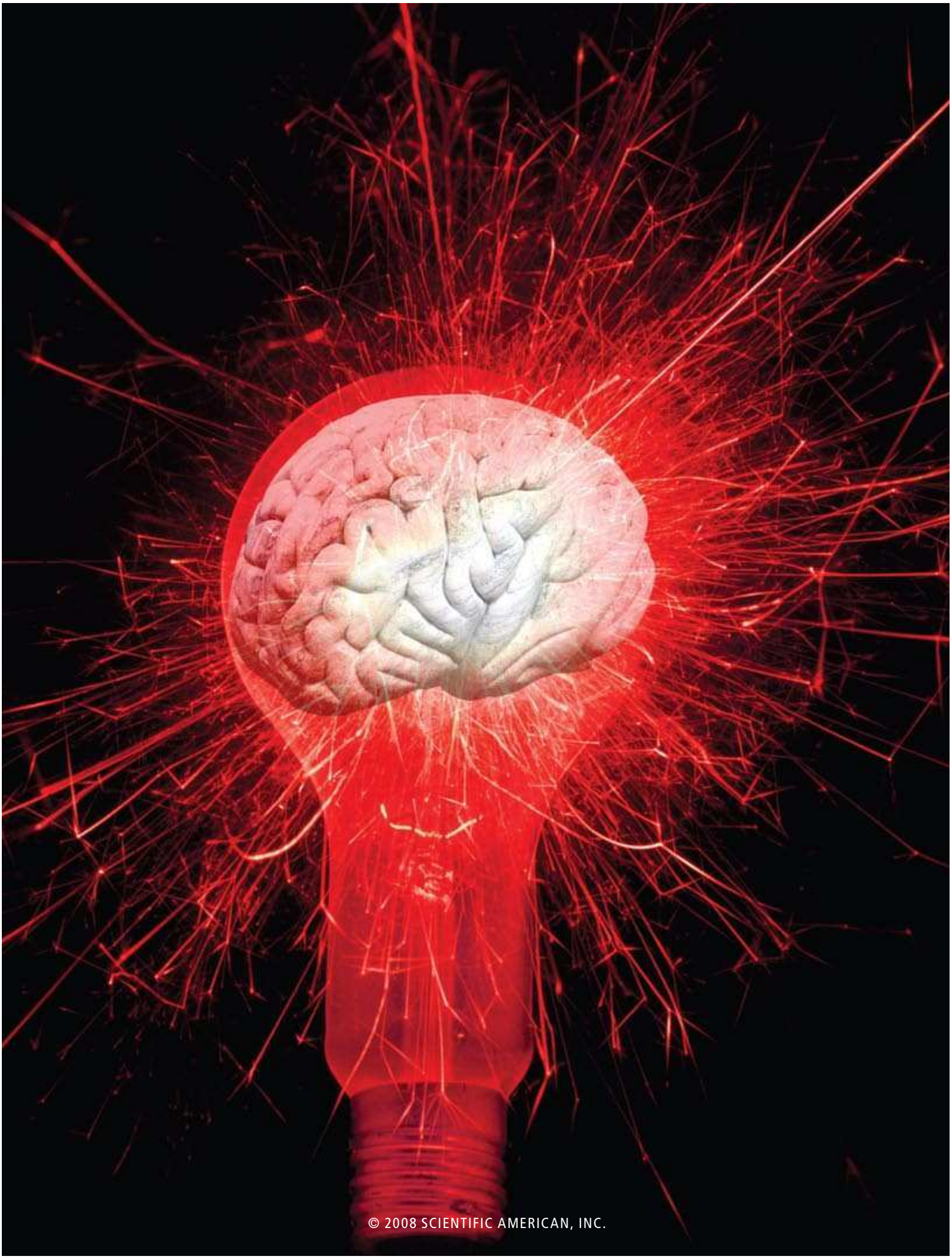
Composed, violently afflicted, then composed again. All with the flick of a switch. As before-and-after moments go, this one is potent, verging on the miraculous. It's the kind of thing you'd expect to witness under a revival tent, not in the neurology ward of a British hospital. Once you've seen it, you'll have an indelible image of Parkinson's disease. The word "tremor" doesn't convey what can happen to people—the way they are thrashed and harassed by their own bodies. But this scene, involving a patient of ours, informs viewers about more than a disease; it's a vivid window onto a powerful medical technology known as deep-brain stimulation (you can watch the video at www.kringelbach.dk/nrn).

Sudden, radical transformation is the hallmark of deep-brain stimulation. The treatment, essentially a pacemaker for the brain, consists of a deceptively simple two-part device. A surgeon threads one or two thin wires into carefully selected locations deep within the brain, then inserts a small battery just underneath the skin near the collarbone. Pulses of electricity travel from the battery to four electrodes situated at the tip of each wire. The effects are instantaneous, usually appearing while the patient is still on the operating table—the quieting of a tremor, the ability to walk again or, in some patients with otherwise treatment-resistant depression, a renewed energy for life.

Deep-brain stimulation came into its own in the 1990s, and since then surgeons have performed it on more than 35,000 people, mostly to quell Parkinson's disease and other movement-related disorders. It is not a cure, but it can keep symptoms at bay for years. Recently, as the electrodes have become safer and the batteries smaller and longer-lasting and as advances in brain-imaging techniques such as magnetic resonance imaging have made it possible to place electrodes with greater precision, neurosurgeons have begun investigating the technology as a way to ease a host of other health problems.

The technique has made it possible for children with a disabling movement disorder called dystonia to leave their wheelchairs and lead nearly normal lives. It has brought immediate relief to people suffering from cluster headaches and other kinds of unremitting pain. It has shown tantalizing promise for some psychiatric disorders, including severe cas-

VICTOR DE SCHWANBERG SPL/Photo Researchers, Inc.



In the 1780s Luigi Galvani observed that by applying electricity

es of depression, obsessive-compulsive disorder and Tourette's syndrome. It has been attempted as a cure for anorexia and obesity. Some neuroscientists speculate that it could help stem the memory loss brought on by Alzheimer's disease. The brain is an electrical organ, so there is little that goes wrong with it that could not, hypothetically, benefit from finely calibrated pulses of electricity. Clinical trials of deep-brain stimulation—preliminary testing on small groups of patients—are multiplying at hospitals around the world, from Cleveland and Toronto to Bristol, Grenoble and Milan.

Despite the recent advances, technologically speaking, deep-brain stimulation is not yet fully mature. Today's devices are programmed to deliver steady, unchanging pulses of electricity. Over the next decade we expect to see a much "smarter" device, one that would turn itself on and off as needed, tailoring its therapy to what is happening moment to moment in the patient's brain.

GETTY IMAGES (*head with switch*); PASIEKA SPL/Photo Researchers, Inc. (*electric brain in banners*)

FAST FACTS

The Electric Cure

1» **Brain cells, called neurons, communicate with one another through electrical impulses.**

2» **In deep-brain stimulation, a battery implanted in a person's chest delivers steady pulses of electricity to a targeted area of the brain. The artificial current interrupts or corrects dysfunctional electrical activity that is causing medical problems. Doctors can tailor the speed, strength and length of the pulses to get the desired result.**

3» **Well established as a way of quelling the tremors that can afflict people with Parkinson's disease, deep-brain stimulation is showing promise for a host of other ailments, including chronic pain and depression.**

The Body Electric

Often when people want to make a difficult task seem easier, they say, "After all, it's not brain surgery." And for good reason. Although we know a lot about the brain, there is still a lot of mystery packed into the three pounds of wrinkled tissue that house a human consciousness, and we neuroscientists must proceed with a combination of humility and hubris.

But deep-brain stimulation has an advantage over most other kinds of neurosurgery—namely, it is reversible. If the electrodes malfunction or if they are simply ineffective, they can be turned off or removed. The procedure is not without risk—1 to 3 percent of patients experience bleeding that leads to a stroke, and a slightly larger number develop treatable infections. Unlike most surgeries, however, deep-brain stimulation does not change the physical structure of the brain; electricity does all the work.

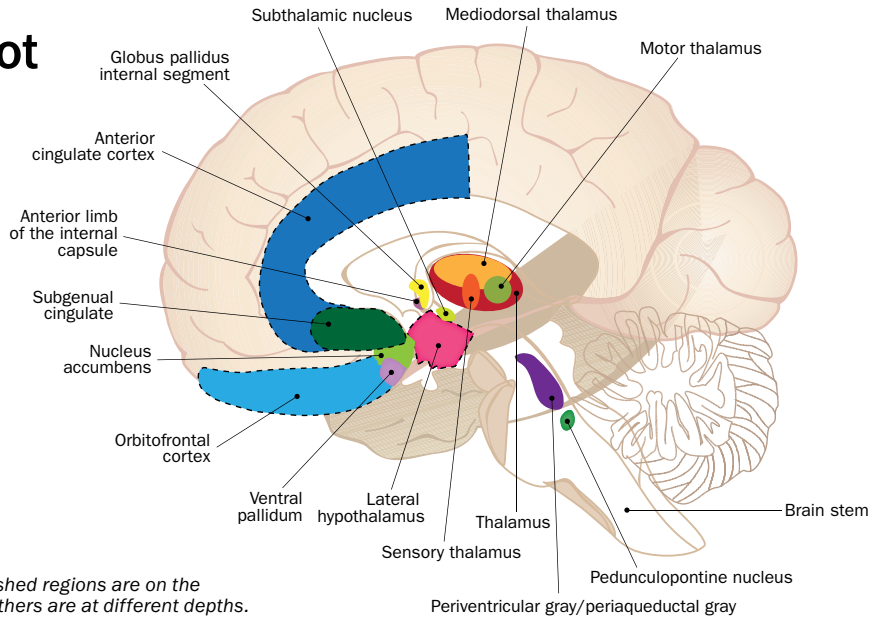
Awareness of the role of electricity in the body dates to A.D. 43, when Scribonius Largus, court physician to the ancient Roman emperor Claudius, wrote that headaches and gout could be soothed by the touch of the torpedo fish, which emits an electrical charge when startled. In 1774 Benjamin Franklin noted that static electricity can lead to muscle contraction, and a decade later Italian physician Luigi Galvani observed that by applying electricity to the sciatic nerve he could make the leg of a dead frog twitch in a lifelike manner. His breakthrough inspired Mary Shelley's *Frankenstein,* in which a monster cadged together from parts of dead people was animated by a massive electrical charge.

Galvani's discovery did more than ignite sci-fi fantasies; it ushered in a host of medical advances. In 1870 German neuropsychiatrist Eduard Hitzig and anatomist Gustav Fritsch selectively manipulated the limbs of a live dog by stimulating specific areas of the brain region now known as the motor cortex—in other words, they showed that each muscle of the body, every finger and toe, is controlled by electrical impulses from a dedicated patch of brain tissue. In the 20th century researchers had the tools to investigate the cellular level. They deciphered

to the sciatic nerve he could make the leg of a dead frog twitch.

Finding the Right Spot

The first puzzle for neurosurgeons attempting to treat patients with deep-brain stimulation is figuring out where in the brain to place the electrode. Much of this work is done through animal experimentation. Noninvasive brain scans of people suffering from various disorders also offer clues to which brain areas are involved in controlling the problematic behaviors and sensations.



NOTE: Dashed regions are on the midline; others are at different depths.

DISORDER	ESTABLISHED SITES	PROMISING SITES	POTENTIAL SITES
Parkinson's disease	Motor thalamus, globus pallidus internal segment, subthalamic nucleus, pedunculopontine nucleus		
Dystonia	Globus pallidus internal segment		
Essential tremor	Motor thalamus		
Depression		Subgenual cingulate, nucleus accumbens	Orbitofrontal cortex, anterior cingulate cortex, ventral pallidum, mediodorsal thalamus
Pain	Periventricular gray/periaqueductal gray, sensory thalamus		Orbitofrontal cortex, anterior cingulate cortex
Obsessive-compulsive disorder	Anterior limb of the internal capsule		
Cluster headache	Lateral hypothalamus		
Minimally conscious			Thalamus

how electricity travels through a single brain cell, or neuron, and from there to its neighbor, creating the complex networks that dictate our thoughts, actions, memories and desires.

Before long, investigators asked: But what happens when those neural networks short-circuit? In the 1950s and 1960s neurosurgical pioneers, including Natalia Bechtereva in the U.S.S.R., Robert Heath of Tulane University and J. Lawrence Pool of the Neurological Institute of New York, began experimentally applying electricity to the brains of people suffering from chronic pain, depression and movement disorders. The batteries then available were much too large to be implanted, so the devices were kludgy and the relief, sporadic. Still, these investigations established a medical precedent for targeted electrical pulses.

Parkinson's disease turned out to be an ideal proving ground. In this disorder, neurons die off in a brain area that coordinates movement, the basal ganglia. In a healthy brain, neurons in the basal ganglia communicate in an intricate call-and-response with groups of neurons in other areas, including the thalamus and the motor cortex. For movements to be quick and fluid, these parts of the brain must work together. Messages traveling between them are called oscillations. They bounce back and forth, moving at different frequencies, some serving to initiate movement, others, to moderate it. But what is key is that the sender and recipient neurons, like

MELISSA THOMAS

There are no nerve endings in the brain, which meant that our

two girls rhythmically swinging a jump rope for a third to hop over, must be in sync. In Parkinson's, diseased neurons lose their ability to keep up, and the oscillations become unbalanced. Neurons fire wildly, and a person moves in a chaotic way or is unable to initiate movement at all.

In the late 1980s surgeons found that if they stimulated either the thalamus or the globus pallidus (a part of the basal ganglia) with fast pulses—up to 180 times per second—they could override the faulty connections. Scientists do not completely understand how deep-brain stimulation works, but we do know that the pulses sent to the electrode sometimes drive and sometimes inhibit the natural activity of neurons. Faster pulses, such as those used in Parkinson's patients, tend to overwhelm and thus inhibit activity, whereas slower pulses tend to drive it by creating a tempo that the neurons strive to meet.

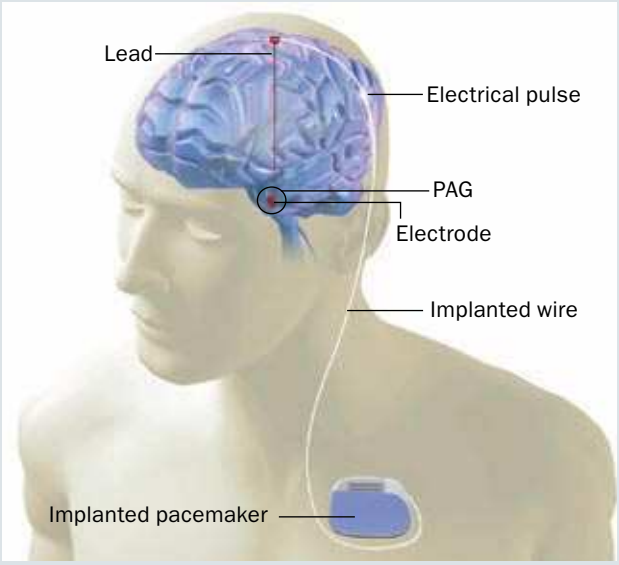
Working with monkeys that had been given parkinsonian symptoms, one of us (Aziz), as well as other teams led by neuroscientists Mahlon R. DeLong of Emory University and Abdelhamid Benazzouz of the Bordeaux Neuroscience Institute in

Deciphering Brain Signals

Today's deep-brain-stimulation devices are relatively simple: the battery sends constant, unchanging pulses through the wire lead to the electrode. The surgical team tailors those pulses to be of the precise strength, frequency and duration that will best ease the patient's symptoms, but after that the battery is set to run indefinitely and does not change its signals in response to the patient's symptoms.

In the future, however, neuroscientists envision a device that will analyze the patient's neural activity, searching for problematic patterns. Most of the time, this next-generation pacemaker will simply monitor the brain, delivering no electricity. But when it detects a problem—say, a tremor or a seizure about to occur—it will deliver a specially calibrated series of pulses designed to derail that event.

To program such next-generation deep-brain-stimulation devices, neurologists first need to decode the brain patterns that signify trouble and those that represent normal activity.



Our team made an exciting discovery last year that is a step in this direction for patients with chronic pain. We may have discovered a brain "signature" for pain: a specific pattern in which neurons fire when people are in intense distress.

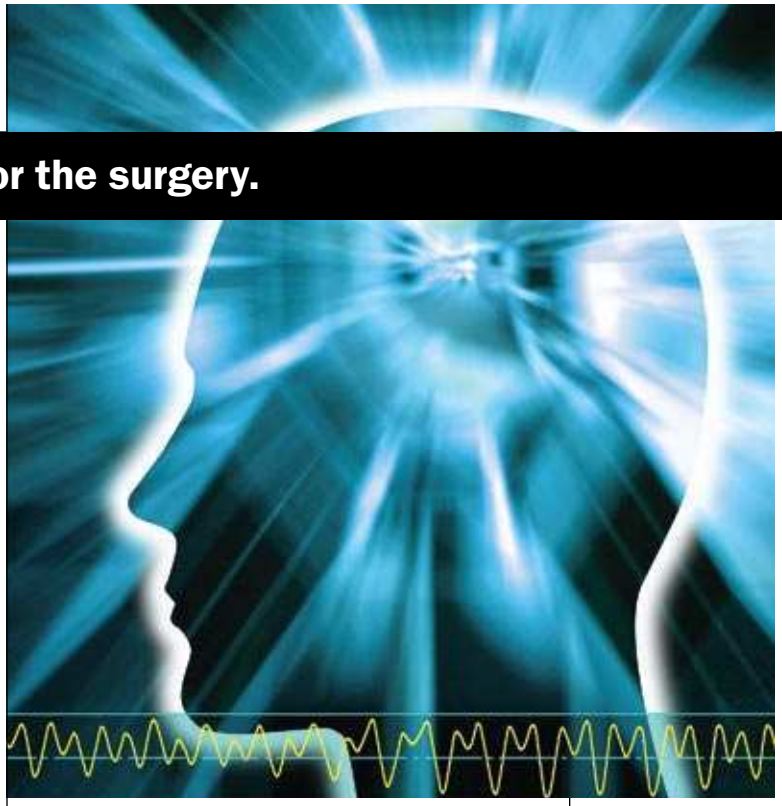
Neurosurgeon Alex Green, our colleague at John Radcliffe Hospital in England, designed a study using 12 patients who had had electrodes implanted in their thalamus or in a part of the brain stem known as the periventricular gray/periaqueductal gray (PAG) to treat chronic pain. We recorded activity from the electrodes while team members touched either a painful or a pain-free area of the patients' bodies. We also asked patients to rate their pain at one-minute intervals. We found that the brain activity measured by the electrodes correlated perfectly to the amount of subjective pain the patients felt. The recordings showed spindles—a specific neural code that peaked at a frequency of 10 to 12 hertz—at precisely the moments when the patients reported the greatest discomfort.

Neuroscientists could theoretically program an advanced electrode to listen for these pain spindles and send jolts of corrective electricity whenever they appear. —*M.L.K. and T.Z.A.*

Still experimental, but highly successful, is the use of deep-brain stimulation (*left*) to relieve debilitating pain. Recently, investigators recorded neural signals from patients who had undergone the procedure and discovered a spiking electrical pattern that correlated to patients' subjective feelings of pain (*below*). This work—deciphering brain signals that correspond to various disease states—could usher in future "smart" deep-brain-stimulation devices.

BRYAN CHRISTIE DESIGN (*pacemaker illustration*); ALEX GREEN *Oxford Functional Neurosurgery* (*electrical pattern*)

patient could be fully awake for the surgery.



France, helped to establish that another part of the basal ganglia, the subthalamic nucleus, can be an even more effective implantation spot (it has since become the most popular stimulation target). More recently, Aziz discovered a fourth target for the 20 percent of Parkinson's patients who do not respond to medication or to stimulation in the three established brain regions. After observing that a part of the brain stem called the pedunculopontine nucleus was underactive in a parkinsonian monkey, Aziz showed that stimulating this area brought stunning results to human patients for whom until recently nothing could be done. Many people who would otherwise be freezing in mid-step or falling over find themselves suddenly able to walk again.

Thanks to this kind of research and to the fact that the requisite batteries are now as small as the ones in cell phones, more than 250 hospitals in the U.S. alone perform deep-brain stimulation for movement disorders. Although other applications are considered experimental, in part because they are not yet approved by the Food and Drug Administration, strong evidence is mounting in their favor. Take, for example, the treatment of pain. Over the past 30 years more than 700 people have had deep-brain stimulation for otherwise treatment-resistant pain; the average long-term success rate is 60 to 70 percent, and when doctors are skilled in patient selection, the success rate approaches 100 percent.

A Sudden Calm Descends

In May 2001 a man named Robert Matthews fell and broke his left leg. The fracture did not heal properly, and the leg developed a stubborn antibiotic-resistant infection. Fearing that it would spread, doctors amputated his leg above the knee, but Matthews's problems did not end there. Although his leg was gone, he felt as if it were still there and in excruciating pain. He tried medications, hypnosis and stimulation of the spinal cord nerve, but nothing helped.

When Matthews was referred to us, he was 58 years old and had been suffering from phantom-limb pain for four years. He was taking large daily doses of opiates and, understandably, felt anxious and depressed. We had previously shown that stimulation of the brain stem, the most ancient part of the brain, can ease otherwise treatment-resistant pain; Matthews seemed an ideal candidate.

On the day of the surgery, our team clamped Matthews into a stereotactic frame—a metal rectangle that surrounds the head and provides three-dimensional coordinates for any point within the brain. We scanned his brain twice—with MRI before the frame was attached (metal objects are unsafe in an MRI machine) and with computed tomography afterward—and used software to merge the images. Like a nose or a foot or any other body part, the brain varies slightly from person to person, so structures deep within it will not always be found in exactly the same location. Now Aziz had a personalized map he could use to plot his trajectory with millimeter precision.

Matthews received an injection of local anesthesia so that he would not feel Aziz drill a small hole in his skull. There are no nerve endings in the brain itself, though, which meant Matthews could be fully awake—and we would need his participation to make the hour-long operation come off. Aziz gently guided a wire tipped with four platinum-iridium electrodes through the jellylike brain tissue and into the area known as the periventricular gray/periaqueductal gray (PAG). While methodically

(The Authors)

MORTEN L. KRINGELBACH holds a dual appointment at the University of Oxford and the University of Aarhus in Denmark, where he is senior research fellow and professor of neuroscience, respectively. He is director of the TrygFonden Research Group, whose main focus is the connections among pleasure, movement and reward. TIPU Z. AZIZ helped to pioneer the field of deep-brain stimulation with the discovery of two efficacious brain targets for the treatment of Parkinson's disease. He is professor and consultant neurosurgeon at John Radcliffe Hospital in England and directs Oxford Functional Neurosurgery, a clinic that performs many deep-brain-stimulation procedures.

PASIEKA SPL/Photo Researchers, Inc.

One depressed woman found her world

electrifying first one, then another, of the four electrode prongs, Aziz asked Matthews to describe out loud what he felt.

This is one of the trickiest moments in deep-brain stimulation—banishing the symptom without causing side effects by accidentally activating the wrong spot. The electrode is only about a millimeter and a half wide, but it straddles up to a million neurons. Packed tightly within the PAG are cells that communicate with each part of the body; we wanted to affect only those related to Matthews's left leg. If he reported feeling tingling or warmth in his hands, arms, face or other leg, Aziz would move the electrode, stimulate a different prong or change the pulses. Moreover, we were prepared for reactions even further afield. The PAG is the seat of the so-called fight-or-flight response, and in the past we have had a patient suffer an anxiety attack on the table. Side effects that can result from imperfect electrode placement in other parts of the brain include eye bobbing, inappropriate laughter and depression.

We gave Matthews a relatively mild amount of current: 1.5 volts—the strength of an AA battery. As for the speed, or frequency, of the pulses, we knew that fast pulses make pain worse, so we started him at about 10 per second and ultimately settled on seven. When we stimulated two of the prongs at these specifications, Matthews felt a sudden calm descend—a comfortable feeling of warmth in his phantom leg. After four years, finally, relief.

Aziz affixed the electrode-tipped wire to Matthews's skull and implanted a battery over his right pectoral muscle. The battery connects to the electrode by a lead that runs under the skin of Matthews's chest and neck and behind his ear to his scalp. Matthews has a magnetic remote control to turn the deep-brain stimulator on or off—but he rarely uses it, because as soon as he does, the agony returns. He reports that his pain is 75 percent reduced, and he has been able to resume his life.

Good as that outcome is, in the future we should be able to do better, using technology similar to that of today's cardiac pacemakers. Computer software in these devices monitors the patient's heart, sending a jolt of electricity only when it recognizes that the heart is not beating properly. When brain pacemakers become this precise, they will not have to be on all the time, which means, among other things, that the batteries will not have to be changed as often (they currently typically require surgical replacement every six months to five years, although rechargeable batteries are also starting to become available). Before deep-brain stimulation can advance, however, scientists must decode the language of neurons. We need to learn the details of how brain regions communicate, such as which electrical patterns might signify an oncoming tremor, headache or epileptic seizure. Then we can program the device to recognize when a problem is coming on and to deliver the specific pattern of pulses that will short-circuit it. Our team has made an intriguing advance toward discovering just such a "brain signature" [*see box on page 40*], and other studies are under way.

The Hype and the Potential

The transformative power of deep-brain stimulation is especially striking in the psychiatric realm. Investigators in Toronto, Leuven, Bonn and elsewhere have been enthusiastically reporting results from small trials. There is the report of a 31-year-old man who had such violent tics from Tourette's syndrome that he could not get a decent job or go out in public without being snickered at, whose body suddenly relaxed. There is the story of a woman whose world literally became brighter—looked newly washed—as soon as the electrode was activated. Other depressed patients said their sensations of "painful emptiness" disappeared. These changes abruptly vanished when patients' electrodes were switched off.

This is heady stuff, given that we do not understand exactly how deep-brain stimulation works nor do we know for sure what goes wrong in depression, Tourette's or many of the other syndromes for which stimulation is being attempted, such as obsessive-compulsive disorder, anorexia, overeating and drug addiction. There is potential here—the work on de-

KIYOSHI TAKAHASE SEGUNDO /*Stockphoto*

literally became brighter as soon as the electrode was activated.

pression in particular seems promising. But some scientists are getting ahead of themselves, and the media have been delighted to assist. In August 2007 neuroscientists at New York–Presbyterian Hospital/Weill Cornell Medical College and the Cleveland Clinic Foundation received lots of attention when they reported using deep-brain stimulation to wake a 38-year-old man from a minimally conscious state. Six years after a brutal beating, the man can eat without a feeding tube and speak a few words, an undeniable improvement. But the fact is that Japanese neurosurgeons have experimented for decades with deep-brain stimulation for just this kind of patient and found that such revivals are rare.

In another recent incident, a man undergoing experimental deep-brain stimulation to treat obesity incidentally retrieved a long-forgotten memory, whose clarity intensified when doctors turned up the voltage. Consequently, some have expressed optimism about brain implants for Alzheimer's. The problem is that deep-brain stimulation is a relatively blunt tool—it either inhibits or excites a brain region (and in turn, the other brain structures that region talks to). That is fine for Parkinson's, in which an overactive brain area may need quieting. But in Alzheimer's what we see are neurons that lose their connections to one another and can no longer store memories. It is unlikely that deep-brain stimulation could repair such intricate connections.

Perhaps contributing to all the excitement about deep-brain stimulation is the fact that it is more than a promising therapy. It is a powerful tool neuroscientists can use to gain insights into the fundamental structure and function of the brain.

Until now our best view of the living human brain has been through imaging studies such as MRI and positron-emission scans, but what we get from them is vague, along the lines of "When a person does such-and-such or thinks such-and-such, there are changes in blood flow or oxygenation in certain parts of the brain that are likely related to changes in neural activity." With deep-brain stimulation, on the other hand, what you essentially have is an on-off switch located in a specific part of the brain. By observing what happens to the brain as a whole when that switch is activated, you can glean detailed information about how various brain structures interconnect. One particularly exciting avenue that we have pioneered is to combine deep-brain stimulation with an imaging technique called magnetoencephalography (MEG). MEG tracks neural activity on the scale of milliseconds (MRI, in contrast, gives average brain activity over a six-second period and PET over a scale of minutes), providing an exceedingly accurate, moment-to-moment report.

When we used this technique on Matthews, the phantom-limb patient, we saw that the electrode in his brain stem appeared to drive activity in many other brain regions. Among the most active when he felt pain relief was the midanterior orbitofrontal cortex. This structure, located just above the eyes, has been shown in other studies to play a pivotal role in pleasurable (or rewarding) activities such as eating, using drugs and sex. Thus, cessation of pain is an intense form of pleasure, along the lines of snorting a line of cocaine or devouring a delicious pastry. This finding confirms that the orbitofrontal cortex might be an effective new stimulation target for people suffering from anhedonia, a lack of pleasure, which is common to depression and other mental illness.

We expect more revelations. By studying people with brain implants, we might answer questions such as how the brain coordinates learning a new language or solving an algorithm. We might even get new big-picture perspectives, such as how something as elusive as subjective experience can arise from electrical activity. Perhaps most important, we will be able to identify the brain areas where electrical stimulation will be most effective, further helping patients in dire need. M

(Further Reading)

- **Reversal of Experimental Parkinsonism by Lesions of the Subthalamic Nucleus.** Hagai Bergman, Thomas Wichmann and Mahlon R. DeLong in *Science,* Vol. 249, pages 1436–1438; September 21, 1990.
- **Lesion of the Subthalamic Nucleus for the Alleviation of 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-Induced Parkinsonism in the Primate.** T. Z. Aziz, D. Peggs, M. A. Sambrook and A. R. Crossman in *Movement Disorders,* Vol. 6, No. 4, pages 288–292; 1991.
- **Reversal of Rigidity and Improvement in Motor Performance by Subthalamic High-Frequency Stimulation in MPTP-Treated Monkeys.** Abdelhamid Benazzouz et al. in *European Journal of Neuroscience,* Vol. 5, No. 4, pages 382–389; April 1, 1993.
- **Reversal of Akinesia in Experimental Parkinsonism by GABA Antagonist Microinjections in the Pedunculopontine Nucleus.** Dipankar Nandi et al. in *Brain,* Vol. 125, No. 11, pages 2418–2430; November 2002.
- **The Human Orbitofrontal Cortex: Linking Reward to Hedonic Experience.** Morten L. Kringelbach in *Nature Reviews Neuroscience,* Vol. 6, No. 9, pages 691–702; September 2005.
- **A Depression Switch?** David Dobbs in *New York Times Magazine;* April 2, 2006.
- **The Pleasure Center: Trust Your Animal Instincts.** Morten L. Kringelbach. Oxford University Press, 2008.
- **Translational Principles of Deep Brain Stimulation.** Morten L. Kringelbach, Ned Jenkinson, Sarah L.F. Owen and Tipu Z. Aziz in *Nature Reviews Neuroscience,* Vol. 8, No. 8, pages 623–635; August 2007.