



◀ **Operation better mood.** Doctors in Germany prepare to implant DBS electrodes in a man with severe depression.

cord—a far less invasive procedure—may have comparable benefits.

Even less is known about how DBS might help people with psychiatric conditions, yet its use in this area is mushrooming: Last month, the U.S. Food and Drug Administration (FDA) approved DBS for treating severe, intractable cases of obsessive-compulsive disorder (OCD), and in the past year, two clinical trials for major depression were launched. All told, DBS is being used or investigated as a treatment for at least a dozen disorders. “The bionic age is here,” says Michael Okun, a neurologist and DBS researcher at the University of Florida in Gainesville. “Over the next 10 years, there’s going to be several hundred thousand people worldwide with these devices for all sorts of different disorders.”

All this progress makes even some proponents of DBS slightly uneasy. Haunted by the frontal lobotomies and other horrors of early 20th century psychosurgery, they insist that rules be developed to ensure that the errors of the past are not repeated. Fortunately, knowledge of the brain, not to mention ethical standards, have improved considerably since then. Even so, many researchers and clinicians agree that DBS should be an option only when it’s backed by a strong scientific rationale and the fully informed consent of patients—not necessarily a trivial matter in those with severe mental disorders.

Moving forward

Parkinson’s disease affects the basal ganglia, a neural circuit deep in the brain that plays a crucial role in regulating movement. When dopamine-releasing neurons in one part of the basal ganglia die off, the circuit malfunctions, resulting in the disease’s hallmark tremor, rigidity, sluggish movement, and impaired balance. Drugs that restore dopamine help many patients but often stop working with time.

The rationale for DBS grew out of studies with animal models of Parkinson’s disease that found that destroying certain nodes in the basal ganglia circuit reduced symptoms. Pulsing electrical current through thin wire electrodes placed in these brain regions had a similar effect, presumably by disrupting abnormal patterns of neural activity caused by the loss of dopamine. In people, DBS can reduce Parkinson’s symptoms for years. But the exact mechanism is unclear, and researchers don’t even agree on whether

Rewiring Faulty Circuits in the Brain

A wide range of neuropsychiatric disorders seems to respond to deep brain stimulation—but how does it work, and where will it lead?

For some patients with severe movement disorders like Parkinson’s disease, years of struggle and frustration end with a flip of a switch that sends pulses of electric current through electrodes implanted deep inside the brain. Although it’s considered only as a last resort for patients who’ve failed to respond to less invasive treatments, deep brain stimulation (DBS) has helped more than 55,000 people suffering from Parkinson’s disease, essential tremor, or dystonia

regain control of their bodies and their lives.

But despite the many success stories, remarkably little is known about how DBS works. Two studies in rodent models of Parkinson’s disease published this week by *Science* provide some intriguing clues—and underscore how much remains to be figured out. One uses a sophisticated combination of genetic engineering and optics to investigate the mechanisms of DBS. The other suggests that stimulating the spinal

the benefits result from exciting or inhibiting neurons near the electrode's tip.

The answer may be neither, according to work reported online this week in *Science* (www.sciencemag.org/cgi/content/abstract/1167093) by researchers at Stanford University. Led by Viviana Gradinaru and Murtaza Mogri in the lab of Karl Deisseroth, the team used exciting new "optogenetics" methods (*Science*, 15 December 2006, p. 1674) to dissect the neural circuitry in a component of the basal ganglia that's a common target for DBS therapy, the subthalamic nucleus (STN). The researchers injected viruses into the STN of rats and mice to introduce genes encoding light-sensitive ion pumps and channels originally found in archaeobacteria and algae. When neurons produce these proteins and stick them on their outer surface, their activity can be stimulated or inhibited—depending on the type used—by pulses of laser light delivered by an optical fiber inserted into the brain. By linking the pump or channel genes to stretches of regulatory DNA expressed only in certain cell types, the researchers could target them to just those cells. This approach is, in effect, a smarter form of DBS: Whereas the metal electrodes used in DBS create an electrical field that indiscriminately affects all nearby cells, the laser affects only the targeted cells.

In one experiment, the researchers inserted light-activated chloride pumps into the primary type of excitatory neuron in the STN. Pulses of laser light activated the pumps and squelched neural firing, enabling the researchers to test the popular hypothesis that turning off these neurons—and thereby dampening the overall level of neural activity in the STN—is the key to the therapeutic effect of DBS for Parkinson's disease. That doesn't appear to be the case. Turning off the excitatory STN neurons had no effect on movement abnormalities in Parkinsonian rats. Additional experiments failed to turn up evidence for a competing hypothesis: that DBS works by evoking rapid firing in the STN neurons, or for yet another proposal, that it works by activating nearby glial cells.

Instead, Deisseroth and colleagues suspect that the key may be manipulating axons that carry signals into the STN from other areas, including the primary motor cortex, a movement-control region on the surface of the brain. When they optically stimulated cortical neurons whose axons extend down into the STN in Parkinsonian mice, symptoms diminished as much as they did with standard DBS.

The study demonstrates the power of optogenetics for dissecting the circuits involved in brain disorders, says Helen Mayberg, a neurologist and DBS researcher at Emory University in Atlanta, Georgia. When Deisseroth presented the work at psychiatry grand rounds at Emory a few weeks ago, Mayberg says, "people sat there with their mouths open in total awe of the possibilities." Mayberg and others think it might eventually be possible to develop optogenetics therapies for people. In

principle, such treatments could maximize efficacy and minimize side effects, such as some of the mood and cognitive disturbances in some Parkinson's patients with DBS—but only if the method, particularly the genetic manipulation, proves safe to use in people.

In the meantime, a paper on page 1578 hints at the possibility of a simpler alternative to DBS. Romulo Fuentes, Per Petersson, and Miguel Nicolelis of Duke University and their colleagues report that stimulating electrodes placed on the surface of the spinal cord dramatically improved locomotion in mouse and rat models of Parkinson's disease. Nicolelis's team also monitored neural activity in the basal ganglia and motor cortex during spinal stimulation. These recordings suggested that spinal stimulation helps restore normal communication between these two brain regions by disrupting abnormal oscillations in neural firing caused by dopamine depletion. Nicolelis notes that the spinal electrodes stimulate fibers that convey tactile information to the brain, including the motor cortex, and he speculates that this indirect stimulation of cortex somehow breaks up the aberrant oscillations.

"If this were to be scalable to humans with Parkinson's disease, it would be a major achievement," says Andres Lozano, a neurosurgeon at Toronto Western Hospital in Canada. It's a much simpler and potentially safer procedure than implanting DBS electrodes in the basal ganglia, he says.

Both *Science* papers point to the cortex as an important player in the therapeutic effect of DBS for Parkinson's disease, says Cameron McIntyre, a biomedical engineer at the Cleveland Clinic in Ohio. That idea has gotten relatively little attention because researchers interested in the mechanisms have focused on neurophysiological effects within the basal ganglia, McIntyre says. "We need to start understanding more about what's happening at the cortical level," he says.

Mental stimulation

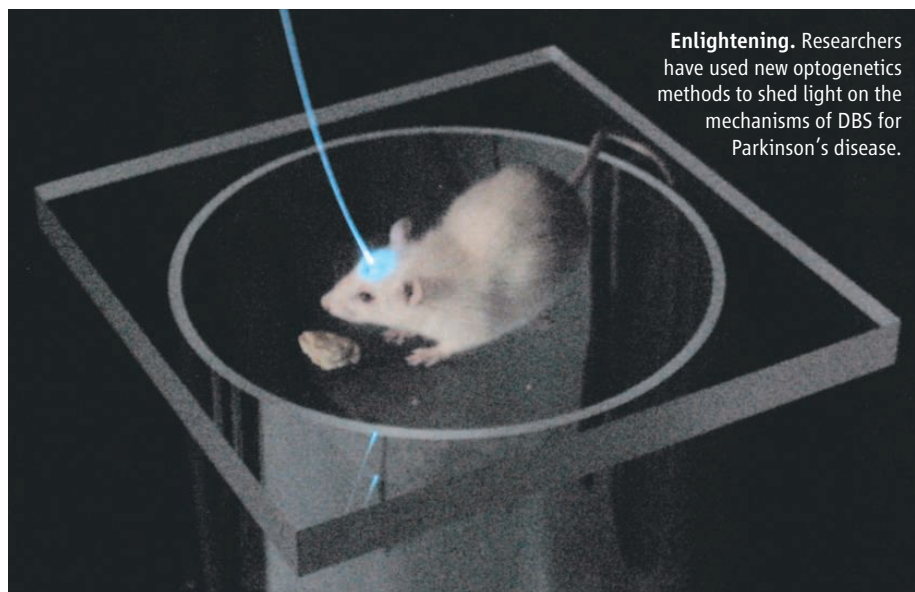
For all the questions remaining about DBS and movement disorders, even less is known about why electrodes implanted in the brain help many patients with severe psychiatric illness. The first such condition to be treated experimentally by DBS was OCD. In a 1999 pilot study in *The Lancet*, Belgian and Swedish researchers reported encouraging results in three of four OCD patients achieved by implanting electrodes in the anterior limbs of the internal capsule, an axon bundle deep in the brain. Destroying this part of the brain had been shown to help people debilitated by severe cases of OCD, and the Belgian team reasoned that electrodes that disrupt neural activity might provide similar benefits without the finality of destroying brain tissue.

Brain surgery may seem like an extreme intervention for OCD, but the worst cases are incredibly debilitating, says Wayne Goodman,

Online

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Podcast interview
with author
Greg Miller.



Enlightening. Researchers have used new optogenetics methods to shed light on the mechanisms of DBS for Parkinson's disease.

director of adult translational research at the National Institute of Mental Health (NIMH) in Bethesda, Maryland, who helped develop the clinical scale that's used to assess the severity of OCD symptoms. Among other things, it considers the amount of time spent on obsessive thoughts. "For the patients who are candidates for DBS, we're talking more than 8 hours a day, and sometimes every waking minute being bombarded by thoughts and being driven to perform rituals over and over," Goodman says. "Their life is consumed by their illness."

Approximately 50 such patients have now received experimental DBS implants. Last year, researchers reviewed 26 cases in *Molecular Psychiatry* (Goodman and Okun were among the 20 co-authors). All had tried multiple courses of medication and behavioral therapy without success. With DBS, more than one-third of the patients went into remission, and about two-thirds were living more independently and functioning better at school or work. Based largely on these findings, in February 2009, the FDA granted DBS device manufacturer Medtronic Inc. of Minneapolis, Minnesota, a humanitarian device exemption for chronic, severe OCD. This type of limited approval applies to treatments for relatively rare conditions, and it marks the first approval of DBS for a psychiatric condition in the United States.

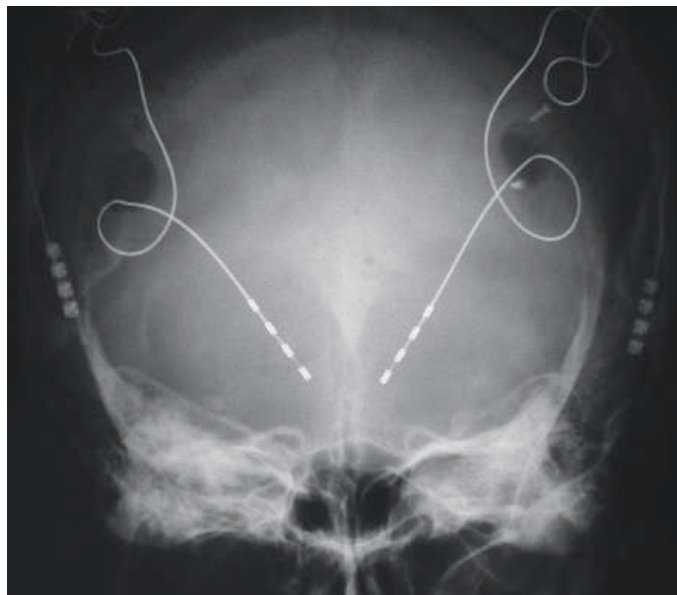
A far larger patient population that might benefit from DBS is people suffering from major depression. In a landmark 2005 *Neuron* paper, Mayberg, Lozano, and colleagues reported that electrodes implanted in the subcallosal cingulate gyrus and adjacent white matter caused remission in four of six patients who hadn't responded to drugs, psychotherapy, or electroconvulsive therapy. Neuroimaging studies indicate that this region is hyperactive in people with depression, and its anatomical connections suggest it is a hub in a network of brain regions involved in regulating emotion, Mayberg says. In 2008, she and her colleagues reported in *Biological Psychiatry* positive effects in 12 of 20 patients, and the device manufacturer St. Jude Medical began a multicenter trial to test the treatment.

In February, Medtronic announced it is starting its own trial to test DBS for depression, targeting the same region that proved useful for treating OCD. In the initial OCD

studies, some patients reported elevated mood, and a pilot study funded by Medtronic and published in February in *Biological Psychiatry* found that eight of 15 patients with treatment-resistant depression improved with DBS and four met the criteria for remission. The clinical trial will ultimately enroll 200 patients and, like the St. Jude trial, will have a double-blind, placebo-controlled design in which some patients will not have the electrodes turned on immediately after implantation.

More research is needed to see which DBS target is most effective for depression, or whether different targets might work better for different patients, says Thomas Schlaepfer, a psychiatrist at the University of Bonn in Germany. He and colleagues have been investigating a third target, the nucleus accumbens, an integral part of the brain's reward circuitry. Until the advent of DBS, Schlaepfer says, psychiatrists had little to offer patients with the most resistant forms of depression and OCD beyond ever-changing combinations of drugs and ever-higher doses. "DBS is a new hope."

And not just for depression. Studies are under way to investigate its use for Tourette



Shocking behavior. An x-ray image shows DBS electrodes implanted in a patient with severe OCD.

syndrome, epilepsy, and cluster headache, among other disorders. A smattering of case studies published in recent years hint at additional possibilities. In 2006, for example, researchers reported that electrodes implanted in the thalamus partially restored some cognitive function in a minimally conscious man with traumatic brain injury (sciencenow.sciencemag.org/cgi/content/full/2006/1016/1).

And in 2007, Lozano and colleagues described the curious case of a 50-year-old man who'd received experimental electrode implants in his hypothalamus to try to treat morbid obesity. He didn't lose weight, but in the process of calibrating the electrodes, the researchers discovered that certain stimulation parameters evoked vivid memories from the man's youth and improved his performance on memory tests. Lozano suspects that the memory-enhancing effect resulted from the electrodes' proximity to the fornix, a bundle of axons conveying signals to and from the hippocampus, a crucial memory center. The serendipitous finding prompted the team to try a similar procedure in people with early stages of Alzheimer's disease. They have implanted electrodes in six people in hopes of staving off additional memory declines. "So far, we can tell you that it's safe and it's looking promising," says Lozano, who plans to submit the findings for publication later this year, after all six patients have had the implants for a full year.

In response to the growing interest in DBS, some researchers have called for guidelines to ensure that studies adhere to stringent ethical standards and employ placebo controls, long-term follow up, and other experimental designs that maximize their scientific value. In the checkered history of early 20th century surgical interventions for psychiatric illness, informed consent and scientific rigor were often lacking, Goodman and NIMH Director Thomas Insel note in a February editorial in *Biological Psychiatry*. "The clinical and scientific community must assure the public that the kind of mistakes made before are not repeated," they wrote.

Even if DBS is developed safely and ethically into a mainstream treatment, its very success might raise new quandaries. Would people with implants for obesity or addiction have the right to turn the stimulator off—and if so, would there be any point to the treatment? Could violent criminals be given implants to inhibit aggression in exchange for reduced sentences? Should healthy people be allowed to receive implants to boost their memory or other cognitive faculties? If the bionic age is indeed upon us, such questions may beg for answers sooner than we think.

—GREG MILLER