Can deep brain stimulation find success beyond Parkinson's disease?

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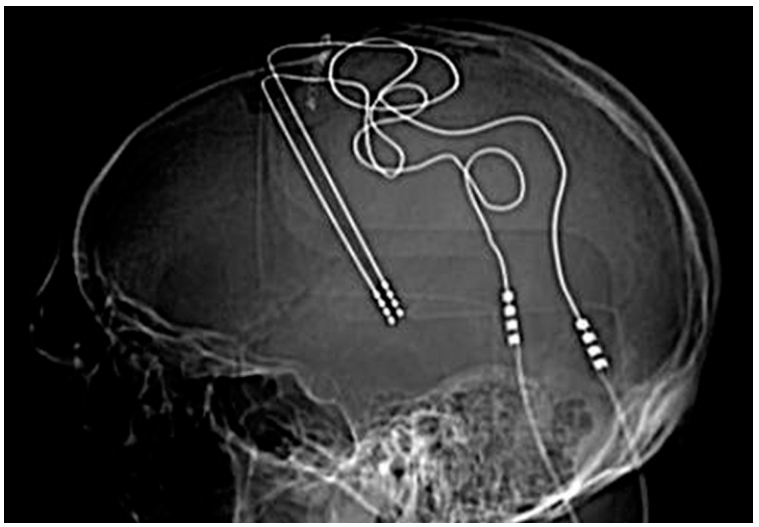
In 2003, neurologist Helen Mayberg decided to try a bold new surgical treatment for severely depressed patients. Imaging work by Mayberg and others implicated a brain region called area 25, or the subcallosal cingulate, as a signaling hub in depression. Successful treatment with antidepressants and other therapies had been linked to quieting activity in this area. Mayberg hoped to achieve similar results using thin wire electrodes to deliver tiny current pulses to area 25.

This technique, known as deep brain stimulation (DBS), had been used since the 1990s to treat Parkinson's disease. Might it help depressed patients as well? Starting in 2005, Mayberg published a series of pilot studies that showed promising outcomes, with around 40 to 60% of patients responding to treatment (1). Other small studies, including some targeting other brain areas, followed.

But in December 2013, the fledgling field of DBS depression treatments suffered a major setback when preliminary clinical trial results leaked at a scientific meeting—findings that fell short of Mayberg's earlier results (2). For a time, Mayberg struggled to publish articles and obtain grant funding. Some reviewers, she says, took a fatalistic view on the entire prospect of DBS for depression.

Slowly, however, the tide has begun turning back. As shown in the clinical trial's full results, finally published in 2017, many of the trial's patients who didn't initially show improvement eventually recovered after prolonged treatment (3). Now at the Icahn School of Medicine at Mount Sinai in New York City, Mayberg is seeing renewed interest in her research. "There was a big spike, where everyone was really enthusiastic, and then there was a bump in the road," she says. "Now there's a re-emergence, a reality check of what we do and do not know." In 2017, as part of the US Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, the NIH awarded Mayberg a grant to monitor how brain activity changes during DBS and to study how these changes might correlate with different stages of recovery.

As engineers and researchers continue to improve on DBS technologies and treatments for Parkinson's disease, Mayberg is one of a number of researchers pushing to establish the technique for a range of psychiatric disorders, including severe obsessive-compulsive disorder (OCD), Tourette syndrome, Alzheimer's disease, and other maladies that don't respond well to existing medications and therapies. "I see it as a huge unmet need," says neuroscientist Helen Bronte-Stewart, who studies DBS for Parkinson's disease at the Stanford University School of Medicine in Palo Alto, CA.



In some patients with treatment-resistant depression, researchers are trying to use deep brain stimulation. This postoperative lateral X-ray shows DBS leads implanted in the left and right subcallosal cingulate region. Image credit: Helen Mayberg.

Stimulating Roots

DBS traces its roots to medical practices of the 1930s when neurosurgery became a popular last-resort treatment for a range of psychiatric, movement, and other neurological disorders. Before removing or destroying culprit brain regions, surgeons probed the brain with mild electrical stimulation to confirm their target. By the 1960s, several groups had discovered that targeting certain locations could quiet tremors and other symptoms in people with movement disorders—suggesting that electrical stimulation itself could be therapeutic. Today's therapy entails an implanted DBS system, which consists of electrodes threaded into the brain through holes in the skull. It's

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all powered by a small battery pack, typically placed under the skin near the collarbone.

Early experiments with DBS systems explored treatments for chronic pain, epilepsy, cerebral palsy, and various movement disorders. But by the 1980s, the technique had gained the most traction in Parkinson's disease and other movement disorders. The US Food and Drug Administration (FDA) gave its first approval of DBS for Parkinson's disease in 1997; the European Union later granted similar approvals (4).

After decades of DBS studies, fundamental questions remain. "If someone tells you they know the mechanism of action, they're being a bit ambitious," says Michael Okun, a neuroscientist at the University of Florida in Gainesville, FL. Some studies suggest that DBS can either excite or inhibit individual neurons, depending on whether electricity hits a particular cell's body or its branches (5). Across a population of neurons, these effects can activate or suppress a brain area and influence activity in connected regions. There are also signs that DBS induces supporting brain cells to release neurochemicals (6) or alters the brain's vasculature (7). How these various effects lead to improved health remains unclear—and likely differs across disorders.

Seeking Approval

Gaps in understanding haven't stopped researchers from exploring new DBS applications and making improvements on existing ones. In April 2018, the FDA approved the treatment of intractable epilepsy with the use of a DBS device in the brain's anterior thalamus—a region connected to highly seizure-prone brain areas. The approval followed a clinical trial funded by medical device maker Medtronic, Inc. in Minneapolis. Patients saw a median 40% reduction in seizure frequency after 3 months of DBS (8) and about 70% after 5 years (9). Control group participants who received sham stimulation—implants that were not turned on for the first 3 months—saw only a median 15% decrease during those months (8). "The most likely theory is that it's disrupting synchrony in epileptic networks," says Robert Fisher at the Stanford University School of Medicine, the epileptologist who led the trial. (Fisher now consults for Medtronic.)

Epilepsy researchers have also scored a regulatory victory in a hot new area of the DBS field: closed-loop stimulation. Conventional or "open-loop" DBS implants deliver a preprogrammed sequence of pulses (usually at a set voltage and frequency), but closed-loop devices monitor and respond to a patient's brain activity. In 2013, the FDA approved an implanted closed-loop device with electrodes and a built-in microprocessor to sense epileptic activity as it starts (in those patients whose seizures can be localized to one or a few sites) and interrupt it with current pulses. In most other disorders, however, researchers are still working out what signatures of "abnormal" brain activity should trigger or tweak stimulation.

In the case of Parkinson's disease, signatures could include abnormal subthalamic nucleus activity in two frequency ranges, known as the beta and gamma bands (10, 11). Preliminary studies suggest that DBS devices that respond to these aberrant signals could be more energy-efficient and potentially more effective than conventional DBS systems (12, 13). "The outstanding question for me is whether all this works in the long run," says neurologist Peter Brown, who has conducted some early closed-loop studies at the University of Oxford in the United Kingdom.

After implanting electrodes in the subcallosal cingulate region of a patient's brain, Helen Mayberg and her team test the device. By monitoring changes in the patient's mood, they confirm proper placement and identify the settings that provide the most effective treatment. Image credit: Michael Konomos (Emory University, Atlanta), ©2017 Emory University.

Diverse Applications

As DBS treatments for Parkinson's disease and epilepsy continue to mature, researchers are hoping to make inroads into a variety of other conditions. A raft of recent DBS studies for intractable OCD, addiction, Tourette syndrome, depression, and Alzheimer's disease have yielded encouraging although preliminary results (1), generally via the open-loop approach. Much of the data come from relatively small open-label trials, in which patients and researchers know when treatment is administered and may be influenced by placebo effects and other biases.

But a handful of recent larger, double-blind, controlled clinical trials, in which some participants received a placebo treatment, have so far failed to yield dramatic breakthroughs. A 2016 study of 42 people with mild Alzheimer's disease showed no clear cognitive benefits of DBS in an area called the fornix, a bundle of nerve fibers that carries information for a key memory circuit (14). Patients older than 65 years seemed to exhibit slower deterioration with stimulation. But younger patients appeared to worsen with treatment compared with patients receiving sham stimulation. "Our interpretation is that the younger people have a much more severe and malignant disorder which progresses more rapidly, and we're not able to compensate with electrical stimulation," says Andres Lozano, a neurosurgeon at the University of Toronto in Canada who led the study. He's now

focusing his studies on older patients with Alzheimer's disease.

Depression researchers are also regrouping after the results of two clinical trials, each stimulating a different brain area. In 2015, a Medtronic-funded study of 30 patients reported that DBS in the ventral capsule/ventral striatum performed no better than sham stimulation (15).

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–Helen Mayberg

In parallel, the device maker now known as Abbott in Abbott Park, IL, sponsored and ran a DBS trial in the subcallosal cingulate, licensing the procedure from co–patent-holders Mayberg and Lozano, who advised the company on the trial's design and procedures. The study, called BROADEN (BROdmann Area 25 DEep brain Neurostimulation), did not go smoothly.

BROADEN was set to include more than 200 participants, but a preliminary analysis of the first 90 patients with implants fell far short of expectations. During 6 months of double-blind observation, only 20% of patients responded to DBS—half of the predicted figure and roughly equal to the response rate among sham-stimulated patients. The company chose to curtail the trial and stopped enrolling new patients.

But most of the 90 patients continued the treatment, and researchers continued to observe them for at least 2 years, by which time response rates rose to nearly half (3). Nevertheless, the improvements were slower than many had expected. "I was disappointed," says Mayberg.

The new results may have fallen short in part because double-blind, controlled trials factor out placebo effects. But Mayberg notes other differences, too. The patients in BROADEN had treatment-resistant depression for an average of 7 years longer than those in Mayberg's own earlier studies. Subtle differences in electrode placement may also have played a role because BROADEN investigators at 13 different institutions used MRI to find the target area. After the trial began, Mayberg's team turned to a different technique, called diffusion tensor imaging, which has helped the researchers detail the crisscrossing network of nerve fiber bundles that surround and invade the subcallosal cingulate. The findings suggest that hitting specific fiber tracts within this network may be essential to effective DBS treatment (16)—tracts that could have been missed in some of the patients in BROADEN.

Mayberg is pressing ahead with her own work, eager to understand how brain activity changes during DBS and how recovery can best be monitored and measured. At the same time, she hopes to identify the types of patients with depression who are most likely to respond to DBS and to further optimize electrode-placement techniques. These efforts could eventually lead to studies with more widely reproducible outcomes. "I know I have something that works," says Mayberg. "It just shows you have to be very exact in order to get good results."

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