Deep Brain Stimulation

Avoiding the Errors of Psychosurgery

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SINCE THE PUBLICATION OF WHITMAN'S PRESCIENT POEM "I Sing the Body Electric" in his collection *Leaves of Grass*, the electrical nature of brain and body has been confirmed by an abundance of scientific research. Seemingly much of what goes wrong with the brain could hypothetically benefit from finely calibrated pulses of electricity. The most promising available neuromodulatory technique is deep brain stimulation (DBS), which has shown clinical efficacy and safety in helping to improve certain brain-related problems such as movement disorders.[1] The improvement in the symptoms of many patients has captured the attention of the general public, and neuroscientists are now introducing DBS for treatment of psychiatric disorders such as depression and obsessive-compulsive disorders.

Despite this sense of great expectancy, it is important to proceed with a combination of humility and hubris. Because neurosurgery to the brain is tinkering with the very core of what makes the species human, the lessons from psychosurgery over last century must not be forgotten, and clear ethical guidelines must guide future experiments.

Efficacy and Safety of DBS

Deep brain stimulation is essentially a pacemaker for the brain, consisting of a 2-part device. A neurosurgeon uses a stereotactic frame to place 1 or 2 thin wires into carefully selected locations deep within the brain and then connects the wires to a small battery situated just beneath the skin. Continuous pulses of electricity travel from the battery to a 4-pronged electrode situated at the tip of each wire. The effects are instantaneous, sometimes 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 chronic pain, the deep pleasure of pain relief.

The technique is effective for some patients with otherwise treatment-resistant movement disorders, such as Parkinson disease,[2] dystonia,[3] and tremor.[4] Use of DBS has been approved by the US Food and Drug Administration (FDA) and has been used in more than 35 000 patients worldwide.[1] In addition to these movement-related disorders, brain stimulation has also been used for more than 50 years for treatment of chronic pain, which with careful patient selection has shown efficacy for patients with amputation, stroke, and head pain, including anesthesia dolorosa.[5] However, use of DBS for chronic pain currently has been given off-label status by the FDA and is thus performed mostly outside the United States.

The safety of DBS and the procedure involved has been demonstrated in many clinical trials and in long-term follow-up of DBS for the treatment of chronic pain. The long-term efficacy of DBS depends on the generators, most of which last 3 to 5 years depending on the demands of the pulse protocol (in some cases, dystonia for instance, they can last less than 1 year). Rechargeable pulse generators are available for spinal cord applications and are being tested for DBS.

As with any stereotactic neurosurgical procedure, DBS poses significant risks. The procedure can lead to a host of adverse effects, including intracranial bleeding and hardware-related complications such as lead dislocation, lead fracture, and infection. The procedure also can lead to stimulation-induced adverse effects (related to the location of the stimulation electrode) such as aggression, mirthful laughter, depression, penile erection, and mania.[1]

Mechanisms of DBS

Despite the long history of DBS, its underlying principles and mechanisms are still not clear. What is clear is that electrical stimulation directly changes brain activity in a controlled manner, that its effects are reversible (unlike those of brain lesioning techniques), and that DBS is one of only a few neurosurgical methods that allows blinded studies. Overall, the weight of available evidence suggests that the most likely mode of action for DBS is through

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stimulation-induced modulation of brain activity.[1] Therefore, although DBS and brain lesioning may give rise to similar therapeutic effects, they are achieved through different mechanisms.

To improve the efficacy of DBS, it is paramount to understand how brain regions communicate. This knowledge is most likely to come through translational models, as has been the case with Parkinson disease, for which the highly successful 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model has helped scientists to understand the pathophysiology of Parkinson disease[6] and to identify efficacious DBS targets such as the subthalamic nucleus[7] and the pedunculopontine nucleus in the brainstem.[8]

In a healthy brain, neurons in the basal ganglia communicate back and forth in an intricate call and response with groups of neurons in other brain areas, including the thalamus and the motor cortex. All of these areas play a role in movement and must work together for movement to be quick and fluid. These oscillations of neural activity bounce back and forth, moving at different frequencies, some serving to initiate movement, others to moderate it. The key is that the sender and recipient neurons, like two individuals rhythmically swinging a jump rope for a third to hop over, must be in sync.

In Parkinson disease, diseased neurons lose their ability to keep up, and the oscillations become unbalanced. One study found strong increases in beta (15-30 Hz) oscillatory activity in the subthalamic nucleus when patients were without dopaminergic medication, whereas therapeutic effective stimulation of the subthalamic nucleus of greater than 70 Hz suppresses activity in the globus pallidus in the beta band at around 20 Hz.[9]

Despite recent technological advances, DBS is not yet fully developed. Current devices are programmed to deliver steady, unchanging pulses of electricity. Over the next decade, much smarter, closed-loop devices are expected to be developed that can turn on and off as needed, tailoring the therapy to what is happening moment-to-moment in the patient's brain.

Lessons From Past Errors of Psychosurgery

Unlike movement disorders, most psychiatric and affective disorders do not have good translational animal models, and it is thus more difficult to develop safe and efficacious interventions. Some progress has been made by combining DBS with neuroimaging methods such as positron emission tomography and magnetoencephalography. The latter especially holds great promise for mapping the precise spatiotemporal unfolding of DBS-elicited whole-brain activity, including the normal and abnormal oscillatory synchronizations.[10]

These methods are, however, still very much in their infancy, and it is essential to proceed with care. Important lessons from the abuses of psychosurgery in the last century make it imperative to have solid hypotheses with strong scientific support and appropriate safeguards (eg, interdisciplinary review boards) before proceeding to treat patients using DBS. Psychosurgery was very popular from the late 1930s to the 1970s. From the first lesional procedures performed in the late 1930s by Moniz through the peak in the late 1940s and early 1950s, approximately 40 000 to 50 000 psychosurgical operations were performed overall, based on very little clinical evidence.[11] Some 4000 of these psychosurgical procedures were performed or supervised by Freeman, a psychiatrist; many of these used Freeman's minimal surgical technique of performing transorbital lobotomy with an icepick.[11]

Strong public debate in the 1970s led to several commissions of enquiry and regulatory legislation that restricted the use of psychosurgery considerably. Since then, all neurosurgical centers have concentrated on stereotactic surgery, with treatment of fairly focal lesions guided by brain imaging. The advances in brain imaging in 1990s have led to a second wave of ablative psychosurgery, albeit on a much reduced scale. Surgical procedures such as anterior cingulotomy, subcaudate tractotomy, limbic leukotomy, and anterior capsulotomy are being used on only very select patients with chronic and treatment-resistant major depression and obsessive-compulsive disorder, and the results are being carefully monitored and analyzed. Yet according to media reports in 2007, the significant decrease in ablative procedures has been mirrored elsewhere, with a large-scale resurgence of lesional psychosurgery on the mentally ill in China, which is alarming especially because the outcomes of past lesional procedures for schizophrenia have been exceptionally poor. Since the first appearance of these media reports, China's Health Ministry has announced that psychosurgery for schizophrenia and other mental illnesses will be tightly regulated.[12]

Deep brain stimulation is different from ablative procedures, not least since it is in principle reversible. But it is important to recognize the hard-earned ethical lessons from psychosurgery and not to provide false hope to patients for whom there sometimes is none, such as when trying to use DBS to help patients in various comatose states. Nevertheless, in recent years, neuroimaging results have inspired some important findings using DBS. One example is the treatment of cluster headache by applying electrical stimulation to the posterior hypothalamus.[13] Another example is that some success has recently been reported when stimulating the subgenual cingulate cortex in patients with treatment-resistant depression.[14] Given the large placebo component in depression, it is essential to carry out careful double-blind studies before DBS can be recommended for wider use in depressed patients.

Careful Clinical Use of DBS

At the minimum, the DBS procedure should be used only when there is a high likelihood that the lives of patients will be improved by its use and when all other possible interventions have been tried; furthermore, full informed consent must be obtained from patients.[15] The procedure must be supported by interdisciplinary teams of neurosurgeons, neuroscientists, psychiatrists, and other health professionals who can help assess patients' suitability for DBS and continuously monitor them over time. The procedure should help restore (but not augment) normal function, should provide relief from pain and distress, and should never be used for law enforcement or for political or social purposes. To properly evaluate the efficacy and safety of any surgical indication, it is important to provide follow-up for every patient enrolled in a trial if at all possible and to report the outcomes in scientific journals.

These ethical guidelines must be implemented and enforced. Only in doing so will DBS help patients reestablish the fundamental freedom and dignity of the individual that Whitman celebrated in his poem. While earlier mistakes must not be forgotten, DBS can perhaps truly fulfill its potential and elucidate some of the deep mysteries of mind and brain and perhaps even "sing the mind electric."

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