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Deep brain stimulation: current and future perspectives

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Deep brain stimulation (DBS) has been used to treat various neurological and psychiatric disorders. Over the years, the most suitable surgical candidates and targets for some of these conditions have been characterized and the benefits of DBS well demonstrated in double-blinded randomized trials. This review will discuss some of the areas of current investigation and potential new applications of DBS. *(DOI: 10.3171/2009.4.FOCUS0982)*

Key Words • deep brain stimulation • movement disorders • epilepsy • psychiatry • brain-machine interface

Deep brain stimulation is one of the most important therapies in functional neurosurgery to date. In addition to its established role for the treatment of movement disorders, promising results have now been reported in epilepsy and psychiatric diseases. The reversibility and low profile of side effects of this therapy have made it an attractive alternative to conventional radiofrequency lesions. As a consequence, potential new applications are currently being proposed for diseases previously considered out of the realm of neurosurgical therapies.

This review will focus on areas of current and future investigation of DBS, including its potential use as a component of brain-machine interfaces. Postoperative MR images with electrodes implanted in different targets used for the treatment of movement disorders are shown in Fig. 1.

Movement Disorders

Parkinson Disease

The introduction of DBS as a therapeutic tool for advanced PD has revolutionized the clinical management of this condition. Due to its safety profile and efficacy, DBS evolved from a last-resort therapeutic option to a modality that is now routinely offered to patients. Over the years, surgical candidates and the outcome expected with this procedure became well established. In fact, there is now Class-I evidence showing that STN stimulation is more effective than the best medical therapy.[20,148] Overall, the improvement in PD that might be expected with surgery is similar to that provided by levodopa without the associated involuntary movements (dyskinesias).[1,20,41,55,59,108,148] As the disease progresses, however, nondopaminergic symptoms (gait, postural instability, depression, and sleep disorders, among others) become more prominent, leading to a significant increase in morbidity. To overcome some of these problems, the use of different surgical targets has been advocated. Perhaps the most promising application of DBS in this regard involves the use of PPN stimulation for the treatment of gait and postural instability.[85,104,123,149] In a preliminary report, Stefani and colleagues[123] have shown a significant improvement in the axial symptoms of PD after PPN DBS. Recent studies suggest that this procedure may be suited for the treatment of falls and freezing.[100] In addition to motor symptoms, our group reported an improvement in rapid eye movement sleep in patients with PD treated with PPN DBS.[74] In the future, a tailored approach to patients' specific symptoms may be possible.

Another major challenge will be to devise therapies that not only treat the symptomatology of PD but are also able to arrest the progression of the disease. Although it has been hypothesized that early surgical interventions could reduce nigral degeneration,[107] this hypothesis has not been clearly demonstrated so far. To date, outcome of the first clinical trials using DBS in patients with early-stage PD have shown that postoperative outcome was as good as that in regular surgical candidates.[114] Whether treatment will change the progression of the disease in these patients will likely be established in the future.

Dystonia and Tremor Disorders

Pallidal stimulation is currently considered the main surgical treatment for dystonia. In patients with primary

Abbreviations used in this paper: DBS = deep brain stimulation; ECoG = electrocorticography; IPG = implantable pulse generator; PD = Parkinson disease; PPN = pedunculopontine nucleus; STN = subthalamic nucleus.

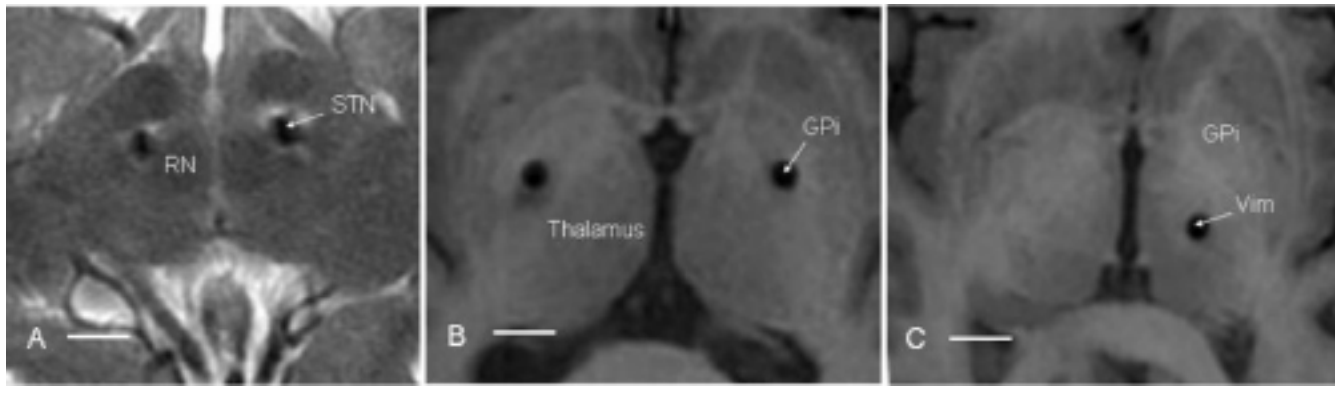

FIG. 1. Magnetic resonance images of DBS electrodes *(arrows)* implanted in the STN (A), globus pallidus internus (GPi; B), and ventralis intermedius nucleus (Vim) of the thalamus (C). RN = red nucleus. Bars = 10 mm. Reprinted from the **Encyclopedia of Neuroscience**, Laxton AW, Hamani C, Moro E, Lozano AM, Deep brain stimulation and movement disorder treatment, 369–373, 2009,[65] with permission from Elsevier.

forms of the disease, improvement rates are typically 40–70%.[4,17,24,40,50,54,60,61,64,122,141,143,144] Well-designed controlled studies have now shown that stimulation is more effective than sham treatment.[64,143] Overall, patients with secondary dystonias do not respond as well to DBS therapy. Because secondary dystonias comprise a group of different entities, an important aspect in future DBS trials will be to determine conditions associated with a good postoperative outcome. As an example, patients with tardive dystonias and pantothenate kinase–associated neurodegeneration respond well to pallidal DBS.[14,122,129,132,151] In contrast, postanoxic, postencephalitic, perinatal, and poststroke dystonias all appear to indicate a poor prognosis.[24,32,60,122] Another factor that needs to be addressed is the role of different surgical targets. For primary dystonias, the most commonly used target is the globus pallidus internus, although good postoperative results have also been reported after STN DBS.[56,64,143,144] For secondary dystonias, a good outcome has been reported with both thalamic and pallidal DBS.[14,40,122,129,132,151]

Deep brain stimulation is also used to treat various forms of tremor. In patients with essential tremor, symptom improvement has been well documented.[57,76,105,115,116,126,127] This improvement results in a better quality of life, particularly in patients who have long-term control of tremor and no associated morbidity from other diseases.[43,44,79,105,126] More variable and unpredictable results are noted with DBS for multiple sclerosis. Because the disorder is associated with a collection of debilitating symptoms, improvement in tremor does not always reflect lifestyle changes.[9,10,47]

Pain

The long-term outcome of DBS for the treatment of chronic neuropathic pain is quite variable, with most studies showing a response in 25–60% of patients (40–50% reduction in visual analog scale scores).[21,48,63,73,106,131] Part of this variability may be attributed to the surgical target and the clinical conditions treated. The main structures targeted for chronic pain are the thalamus and the periaqueductal/periventricular gray matter. Overall, thalamic DBS has been suggested to be more effective for neuropathic pain, whereas nociceptive pain responds better to stimulation in the periaqueductal/periventricular gray matter.[72,73,147] Coffey[16] has recently reported on the outcome of 2 open multicenter studies sponsored by one of the manufacturers of the stimulators (Medtronic). These trials were completed in 1993 and 1998, showing an approximate response rate of only 20%.[16]

A recent promising application of DBS in the pain field is its use for the treatment of cluster headaches and trigeminal autonomic cephalalgias. Studies with hypothalamic stimulation showed a decrease in the intensity and/or frequency of headaches.[30,68,69,83,113,121] Controlled trials with a higher number of patients and longer follow-up durations are still necessary to ascertain the therapeutic role of DBS for the treatment of these conditions.

Epilepsy

The main DBS targets investigated for the treatment of epilepsy are the centromedian nucleus of the thalamus,[137–140] the anterior thalamic nuclei,[6,46,53,67,75,95] and the hippocampus.[13,128,135,136,146] Deep brain stimulation was also explored in the subthalamic nucleus,[8,15,42,67,77,142] locus ceruleus,[25] caudate nucleus,[120] and mammillary bodies.[23] Candidates for the procedure often have frequent disabling seizures, a significant impairment in quality of life, refractoriness to treatment with multiple antiepileptic medications, and either bilateral/multifoci seizures or a nonidentifiable seizure focus. Overall, centromedian nucleus DBS has been suggested to be more effective against generalized tonic-clonic seizures, atypical absence seizures, and Lennox-Gastaut syndrome.[134,137,140] Anterior thalamic nuclei and hippocampal DBS have been primarily used for the treatment of partial epilepsies.[6,13,46,53,67,75,95,128,135,136,146]

In general, results of nonblinded studies in various targets have been very promising, but sometimes not corroborated by blinded trials comparing the frequency of seizures in "on" and "off" stimulation conditions.[26,128] A new wave of optimism has been recently brought to the field by a recent multicenter study. The "stimulation of the anterior nucleus of the thalamus in epilepsy" (SANTE)

trial collected data from 110 patients treated at 17 US centers. Double-blinded assessments after 3 months of therapy have shown a significantly higher reduction in the frequency of seizures as compared with sham treatment (38 vs 14.5%, respectively). At long term, 40% of the patients had a 50% or greater reduction in seizure rate (http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1228746390966&format=print&lang=en_US)

Also promising has been the development of trials using closed loop stimulation.[28,29,58,87,94,125] This method involves the delivery of current in response to cues, events, or commands, in contrast to the round-the-clock stimulation delivery in open loop trials. After a seizure is detected, stimulation is delivered to either the seizure focus (local stimulation) or a distant region somehow integrated to epileptogenic circuits (such as the anterior thalamic nucleus).[93,94] Preliminary reports of small case series have shown significant improvements with the use of these systems. A controlled clinical trial is currently underway and results are greatly anticipated.[125]

Psychiatric Disorders

One of the most promising recent applications of DBS is in the treatment of psychiatric diseases. Three main psychiatric conditions have thus far been considered for DBS treatment: Tourette syndrome, obsessive-compulsive disorder, and depression.

In Tourette syndrome, both thalamic and pallidal DBS have proved successful in reducing the frequency of tics.[3,19,22,49,80,117,118,133,145,150] For obsessive-compulsive disorder, the main targets are the anterior capsule and STN; stimulation of the caudate nucleus and the inferior thalamic peduncle has also been reported.[2,7,27,36,37,52,81,91,92] Overall, 40–60% of patients treated with capsular DBS had an adequate response to surgery (~ 33% reduction in Yale-Brown Obsessive Compulsive Scale scores).[2,36,37,91,92] In the initial reports using this technique, high DBS settings were needed to control the patients' symptomatology, requiring a high number of battery changes.[91,92] In recent studies, however, lower energy expenditure has been reported as the target moved ventral and posterior, closer to the ventral striatum/nucleus accumbens.[36,37] A similar outcome has been reported after STN DBS. In a recent well-designed controlled study, stimulation was significantly more effective than sham treatment.[81]

Deep brain stimulation targets used to treat refractory depression include the subgenual cingulate gyrus,[78,84] anterior capsule,[82] inferior thalamic peduncle,[51] and nucleus accumbens.[112] Results from nonblinded studies using the first 2 regions prompted the development of multicenter clinical trials, which are now underway. Of the patients receiving subgenual cingulate gyrus DBS during initial studies, 50–60% responded to the therapy (50% reduction in Hamilton Rating Scale for Depression scores).[78,84] Similarly, response rates to capsular DBS are typically 40–55%.[82] If stimulation proves to be an effective therapy for depression, the impact from an economic and epidemiological standpoint will be significant. Depression has a 6-month prevalence of approximately 5%. Although most patients respond favorably to treatment, as many as 30–40% (1.5% of the general population) will experience chronic and refractory forms of this disease. Most of these patients are unable to work. Improvements in quality of life and an eventual return to the labor market after DBS would have a major impact.

Emerging Indications of DBS

Deep brain stimulation has now been suggested as an emergent treatment for various conditions, including hypertension,[33–35] minimally conscious states,[111] obesity,[38,39] memory improvement,[39] aggressiveness,[31,45,62] and drug addiction.[124] Preliminary data are now available for some of these indications.

Green et al.[33–35] have shown that periaqueductal/periventricular gray matter DBS could modulate blood pressure in patients with chronic neuropathic pain. Depending on the stimulation site, an increase or decrease in blood pressure was recorded. In this context, the authors advocated stimulation as a potential treatment for both hypertension and orthostatic hypotension.[33–35]

Although neuromodulation therapies have been previously attempted for vegetative states,[130,152,153] Schiff et al.[111] have recently demonstrated in a double-blind study that thalamic DBS was able to modulate behavioral responsiveness in a patient who was in a minimally conscious state. We have recently reported on a morbidly obese patient treated with hypothalamic/forniceal DBS[9] in whom stimulation evoked detailed autobiographical memories and improved associative memory tasks.[39] That study led to future investigations on the potential use of DBS for conditions associated with memory impairment.

For aggressiveness, encouraging results have been reported with the use of hypothalamic DBS in a few patients with mental retardation and eventually self-mutilating behaviors.[31,45,62]

Future Perspectives for DBS Devices

Current DBS systems include multicontact intracranial electrodes, adaptors to fix the electrodes in place, an IPG, and extension cables to connect the DBS electrode(s) to the IPG. Programming of the devices is performed by telemetry via a personal digital assistant-like system. As practiced today, stimulation adjustment requires several visits to the clinic so that optimal settings can be ascertained. Each of the electrode contacts has to be tested for efficacy and side effects, and interactions between stimulation and medications need to be carefully managed. In the future, it will be necessary to develop ways of reducing the time required for programming, perhaps through electrophysiological or imaging indicators. These indicators may provide a more objective way of assessing the effects of DBS, allowing for a quicker screening of potential combinations of contacts/stimulation settings. Also important would be the ability to program pulse generators through remote access, telephone lines, or the Internet. Some of this technology is available for cardiac pacemakers and currently in use in recent trials investigating the role of stimulation for epilepsy (see below).

Another area of recent advance relates to the power source for DBS. As currently used for movement disorders, the lifespan of regular IPGs is ~ 5 years.[11] When higher charge densities are needed, however, the frequent replacement of the pulse generators is of significant concern. Rechargeable batteries have been used for spinal cord stimulation and are now commercially available for DBS. Although no long-term studies have been conducted, a lifespan of up to 9 years has been advertised for DBS rechargeable batteries (depending on usage and the number of times the patient needs to recharge the IPG). Also of interest would be the possibility of miniaturizing pulse generators and DBS systems, so they could fit the confines of a bur hole or be overlaid on the skull. This miniaturization would likely decrease the adverse effects related to therapy, because extension cables would no longer be necessary. Future technological developments will also likely lead to newer designs of electrode arrays and geometry so that efficacy may be optimized with a reduction in adverse effects.

Deep Brain Stimulation and Brain-Machine Interfaces

In recent years, the use of neuroprosthetic devices to enhance or replace nervous system function has grown considerably. In this field, brain-machine interfaces are considered promising future tools for the management of patients with neurological conditions, particularly those who are severely handicapped.[12,18,66,70,89,99] The process involves collecting, analyzing, and translating neural activity to drive machines or actuators.[66,99] The first step required is signal detection. Signals used (to date) are most commonly electrical, including those generated by single or multiunit cell recordings, local field potentials, EcoG, and electroencephalography. Changes in the pattern and rate of neuronal firing, brain rhythms, and oscillatory activity may all provide data that can be used by the interfaces. Once interpreted, information translated is fed to an actuator (robotic arm). After the action, feedback needs to be provided to compensate for potential errors and eventually improve performance in future trials.

A question that then emerges is whether DBS could be used as a component of brain-machine interfaces. Steps required for processing data and delivering closed loop stimulation are somewhat similar to those used by brain-machine interfaces. Components of the so-called external responsive neurostimulation system used in epilepsy include depth and strip electrodes, a pulse generator, and external devices (programmer, data transmitter, and telemetry wand).[29,87] Electrodes initially record local field potentials or cortical activity. Signals are then sent to a microprocessor in the generator, which stores ECoG signals. Upon detection of epileptiform events, responsive therapy (electrical stimulation) is delivered. Signals are then once again recorded and processed to assess whether epileptogenic activity is still present. If so, the patient receives new bursts of electrical stimulation. External responsive neurostimulation systems are readily assessable using telemetry. With a wand and a notebook, care providers can look at online ECoG signals and conduct test stimulation to assess the effectiveness of specific stimulation paradigms. In summary, the system is capable of detecting signals, analyzing information, delivering a therapy, and assessing efficacy.

Using DBS systems as part of brain-machine interfaces would involve a few positive aspects. Electrodes have been safely implanted in various brain targets, causing little inflammation.[88,102] These electrodes are long-lasting, with the lifespan of DBS systems currently limited by the battery life. Local field potentials have been systematically recorded from DBS electrodes[90,96,97,109] and could be theoretically used to feed brain-machine interfaces. A major disadvantage would be the inability to record single or multiunit cell activity from one or different sources. This disadvantage, in theory, could lead to a decrease in spatial and temporal resolution of the signal, potentially compromising the degrees of freedom and complexity of actions to be performed by the actuator. Nonetheless, signals from local field potentials mainly recorded from the cortex have been successfully used to predict motor patterns.[5,71,86,101,103,110,119] It has recently been shown that neuronal ensembles in subcortical motor regions (thalamus and STN) can provide informative signals to control a brain-machine interface.[98] Whether local field potentials recorded through DBS electrodes will turn into a practical means of driving brain-machine interfaces remains to be proven.

Conclusions

As the number of patients using DBS devices increases, ideal surgical candidates and targets for each application of this therapy will likely be established. In the future, we expect to see an expansion in the number of diseases treated with DBS, as functional imaging and translational research help us to identify discrete areas of the brain that may be targeted in different disorders. Future technological advances in hardware components will hopefully lead to an increase in efficacy with a reduction in adverse effects of this therapy.

Disclosure

Andres Lozano, M.D., Ph.D., is a consultant to Medtronic, St. Jude Medical, and Boston Scientific. Clement Hamani, M.D., Ph.D., is a consultant to St. Jude Medical.

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