

# Deep Brain Stimulation: An Evolving Technology

*Electrical brain-stimulation is used to treat Parkinson's Disease and other movement disorders in cases where drug therapies prove inadequate or ineffective.*

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**ABSTRACT** | Deep brain stimulation (DBS) is widely used as a safe and effective medical treatment for certain neurological disorders. It continues to evolve with improving techniques in functional neurosurgery and biomedical device engineering. This paper provides an overview of the enabling science and technology that have allowed DBS to successfully treat certain neurological disorders. It also points toward some of the engineering advances that will enable DBS to yield a more predictable outcome for current indications and to be systematically developed as a treatment for new indications.

**KEYWORDS** | DBS IPG; DBS leads; DBS localization; DBS programmer; deep-brain stimulation (DBS); functional neurosurgery; magnetic resonance imaging (MRI) safety; stereotactic surgery

## I. INTRODUCTION

Deep brain stimulation (DBS), following in the footsteps of cardiac pacemaker technology from the 1960s, is both in its formative stages and experiencing an exciting renaissance. The surgical concepts that were developed over the past century have potentially found new disease targets with dramatic benefits to certain patient populations. The discovery of the techniques and brain targets have been serendipitous, as the fundamental mechanism of the therapeutic effects of DBS remains unclear. Nonetheless, over the course of the past decade, more than 30 000 Parkinson's disease (PD) patients worldwide have benefited from DBS, as well as many patients with essential tremor (ET) and dystonia.

A major point of resistance has come from the concept that invasive brain surgery may be beneficial for patients on an "elective" basis and should only be used as a last resort because of the risks involved to an organ so critical to human

life. In the past, the placement of the cardiac pacemaker was met with concern due to the novelty of the procedure, but it is a commonplace and relatively low-risk procedure at this time. DBS is also a relatively low risk procedure and is expected, in time, to be similarly embraced by patients and physicians. As more patients turn to DBS for therapeutic intervention, the current state of the art needs to be continually reevaluated to spur on engineering and medical advances that will make DBS as reliable and effective as the cardiac pacemaker is now. This paper highlights some of the enabling technologies for DBS and the need for bridges to continue to be built and strengthened between neurosurgeons and biomedical engineers.

## II. THE ROLE OF FUNCTIONAL NEUROSURGERY

The aim of functional neurosurgery is to improve a patient's neurological symptoms through either the creation of selective lesions or the modulation of central nervous system (CNS) neuronal networks. Appropriate target selection and accurate localization is critical to the success of DBS [1]. The general role of the neurosurgeon in DBS is to effectively place the stimulator's leads in the appropriate region based on anatomic landmarks and physiological targeting, and the role of the neurologist at most centers is to titrate the "dose" of electric current provided through the electrode to safely minimize the patient's symptoms.

The targets are chosen based on neurophysiological studies that show the affected brain regions for a specific disease. The current indications for DBS use are the three aforementioned neurologic diseases: PD, ET, and dystonia. The associated deep-brain targets are most commonly the subthalamic nucleus (STN), the ventral intermediate nucleus of the thalamus (Vim), and the internal segment of the globus pallidus (GPi). These neuronal structures are believed to subserve the primitive motor pathways of the basal ganglia, which modulate consciously controlled movement. Alterations in the electrochemical output from these nuclei due to upstream dopaminergic cell loss

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in the substantia nigra create the constellation of symptoms seen in Parkinson's patients. However, no specific neurotransmitter changes have been identified in ET or dystonia. The mechanism of DBS is still unclear, but it is generally agreed that the mechanism is complex. For a survey of the hypotheses on DBS mechanisms, as well as models of basal ganglia pathology that implicate DBS mechanisms, readers can refer to [2]–[4].

While the complexity of the neural circuits involved in these neurologic disorders and seemingly conflicting results have hindered the deciphering of the exact mechanism by which DBS operates [5], [6], identifying appropriate DBS targets has been greatly aided by the development of functional magnetic resonance imaging (fMRI). By monitoring activity-related changes within the brain through fMRI, clinicians have the opportunity to peer into the neuronal depths and identify areas of abnormal brain activity related to psychological abnormalities in addition to motor functional impairments. Therefore, fMRI provides clinicians with the capability to discover new targets for a variety of diseases previously not considered amenable to neurosurgery (see Section V).

### III. HISTORY OF FUNCTIONAL NEUROSURGERY FOR MOTOR DISORDERS

Since its beginnings in the nineteenth century, the field of functional neurosurgery has evolved through clinical experience, a greater understanding of the neurological substrates of neurological disorders, and advances in technology.

#### A. Selective Lesioning Methods for the Treatment of Movement Disorders

J. Parkinson, in his 1817 work "An Essay on the Shaking Palsy" described six illustrative cases of the condition that later became known as Parkinson's Disease [7]. In the last of the presented cases, a patient had suffered from "shaking palsy" for many years and then subsequently suffered what appeared to be a large stroke. The stroke immediately gave the patient right-sided weakness and dysarthria but miraculously relieved his tremor. In an effort to recreate this effect in the operating room, generations of physicians have attempted to provide relief from movement disorders using a variety of controlled lesioning methods.

Early surgeries to treat movement disorders were focused on the motor cortex, corticospinal tract, and lower motor neurons. English neurosurgeon Sir V. Horsley was the first to write about lesioning the brain as a therapy for movement disorders. He presented cases from the late 1800s to the early 1900s in which he extirpated motor cortical regions to control involuntary movements and athetosis [5]–[9]. In 1912, French surgeon R. Leriche reported the first successful surgery performed to specifically treat a Parkinsonian tremor, although others were not able to duplicate his results [8], [9]. In 1936, Foerster, a

German neurosurgeon, presented data from cases of surgical extirpation of motor cortex to control unwanted movements [10]. American neurosurgeon P. Bucy also successfully treated patients with tremors by lesioning their precentral motor cortices between 1932 and 1949 [11].

Others attempted to follow Foerster and Bucy's successes, creating lesions downstream of the motor cortices, such as undercutting subcortical white-matter tracts and even severing parts of the spinal cord. However, while tremors were sometimes suppressed, the procedures often led to unwanted effects such as hemiparesis, epilepsy, aphasia, or even a Brown–Sequard syndrome [9]. With greater concern for preservation of function and a desire to have more directed therapies, lesioning of the pyramidal motor system was slowly abandoned for more targeted therapy of the basal ganglia.

Meyers performed the first reported basal ganglia surgery for a movement disorder in 1939 [12], successfully reducing a patient's Parkinsonian tremor by lesioning the head of her caudate nucleus. He went on to systematically lesion other basal ganglia structures and published a series of 38 surgeries for Parkinsonism. Meyers found that sectioning pallidofugal fibers resulted in symptomatic relief in 60% of patients, but the operative mortality of Meyers' surgeries was reported at a staggering 15.7% [13].

Eventually, neurosurgeons were able to approach the basal ganglia with lower operative morbidity and mortality via the development of better atlases of deep-brain structures, imaging techniques, and most importantly the development of stereotactic techniques in neurosurgery.

#### B. Stereotactic Surgery for Parkinson's Disease and the Development of DBS

Stereotaxis in neurosurgery refers to the method of defining any space in the brain using Cartesian or polar coordinates from an external reference point in order to locate and access it through minimally invasive and accurate methods.

Horsley and Clark in 1906 devised the first stereotactic frame for use in animal experiments [14]. E. Spiegel and H. Wycis in 1947 developed the first stereotactic system for use in humans [15]. Using pneumoencephalography, which had been introduced by W. Dandy in 1918, intracranial points could be related to coordinates using the external frame. Spiegel and Wycis furthered the field of stereotactic neurosurgery in 1952 by publishing the first stereotactic atlas of the human brain using cerebral midline structures as reference points [16] and also performed the first stereotactic surgery of the basal ganglia.

Building on the work of their predecessors, the early stereotactic neurosurgeons targeted the globus pallidus pars interna and ansa lenticularis for the treatment of Parkinsonism. Through the work of surgeons Cooper and Bravo, thalamotomy of the ventralis-oralis posterior (Vop) and Vim nuclei eventually became the standard of care for the surgical treatment of Parkinsonism. In the 1960s, more

than 40 000 stereotactic surgeries were performed worldwide, mostly for the treatment of Parkinson's disease. The advent of stereotactic techniques in neurosurgery reduced the mortality of basal ganglia surgeries for movement disorders to less than 1%. The techniques had also become more or less standardized with either thalamic or subthalamic nuclei as the targets of mechanical or thermal ablation.

Surgery was a mainstay of therapy for movement disorders, especially Parkinsonian tremor, until L-dopa was introduced in the late 1960s. Medical therapy with L-dopa aims to correct the disease state in Parkinsonism by pharmacologically modulating basal ganglia circuitry instead of surgically ablating pathways. After the introduction of L-dopa, surgery for Parkinsonism dropped off dramatically at most centers. L-dopa, however, does not affect the overall course of the disease and its benefits wane with increasing time as the depletion of endogenous dopamine progresses. With chronic L-dopa therapy, as Parkinson's disease progresses unchecked, the amount of drug necessary to control tremor increases and eventually results in side effects that can deteriorate the patient's quality of life.

Stereotactic surgery returned as a treatment for tremor in the mid-1970s with an increase in the number of thalamotomies performed. In the 1980s, the technique of DBS was introduced to treat movement disorders and has remained effective in pharmacologically resistant patients and useful in decreasing the amount of L-dopa a patient needs for satisfactory tremor control.

The first reported use of deep-brain electrical stimulation was for the treatment of depression and anorexia in a patient with Parkinson's disease [17]. Around the same time, Spiegel and Wycis had developed stereotactic methods for neurosurgery, described in the previous section, which could be used to target deep nuclei of the brain for ablation.

As stereotactic surgery evolved in the decades after its introduction, electrical stimulation became a part of the method of creating deep-brain lesions. In these early procedures, electrical stimulation through a depth electrode was often used to localize the point of ablation. It was noted that electrical stimulation of the globus pallidus at varying frequencies through these deeply implanted electrodes could produce, decrease, or possibly stop a tremor [18].

The turning point for DBS in movement disorder treatment was Benabid *et al.*'s 1987 paper on the efficacy of Vim nucleus stimulation for the treatment of Parkinson's disease [19]. Benabid's group compared tremor control in Parkinson's Disease patients who had undergone unilateral thalamotomy and contralateral placement of a DBS electrode in the Vim nucleus of the thalamus. While he found that thalamotomy was more effective in decreasing tremor than stimulation, his group made the conjecture that their stimulation parameters were not of sufficiently high frequency. Further studies by Benabid's group using optimized stimulation parameters showed a decrease in tremor in 88% of patients undergoing thalamic DBS [20].

Experimentation with a primate model of Parkinsonism elucidated further targets for stimulation. Bergman *et al.* in 1990 and Aziz *et al.* in 1992 demonstrated the efficacy of creating selective bilateral STN lesions to treat Parkinsonism in primates treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [21], [22]. MPTP selectively destroys dopaminergic neurons, including those in the substantia nigra, which recreates the symptoms of Parkinson's Disease in primates. Both studies described effects not only on tremor and rigidity but also on the primate's facial expressions, akinesia, and other nonmotor symptoms of Parkinsonism. Building on this work in animal models and taking advantage of the development of implantable battery-powered devices for other medical uses, the initial studies of long-term bilateral STN stimulations in Parkinson's disease brought DBS into the modern era [23], [24], [27].

## IV. DBS SURGICAL TECHNIQUE

### A. Stereotactic Surgical Technique

Most DBS procedures today are performed with the patient awake. The first stage of the procedure is head frame placement. Many techniques can be used to carry out functional stereotactic procedures within the standard of care. Any specific techniques described here refer to those used at our institution.

The goal of DBS surgery is to disrupt or alter the physiology of a population of cells, within the basal ganglia or thalamus, involved in the mechanism of the movement disorder. Radiologic and physiologic landmarks provide the most accurate localization of the target. We localize the anterior commissure (AC), posterior commissure (PC), and the border between the capsule and thalamus radiologically by using both CT and MRI scans through a computed tomography (CT)/MRI fusion technique. We refine the radiologic estimate of location by microelectrode physiologic localization [25] and then place the DBS electrode in the target that best fits the radiologic and physiologic data.

### B. Radiologic Localization

Radiologic targeting can be used to determine the location of the AC and PC by MRI and/or CT scans. AC and PC predict the locations of the different basal ganglia and thalamic nuclei in stereotactic space. The sagittal sections of the Schaltenbrand and Bailey atlas [26] are transformed to match the AC-PC line in the patient [27]. In this way, the nuclear locations predicted radiographically in that patient are displayed in the coordinates of the Leksell frame. The laterality of the target is determined from a fast inversion recovery MR sequence.

Ventriculography as a means of locating the AC-PC line has largely been replaced by CT and MRI scanning. CT scanning is as accurate as ventriculography [28] and does not

carry the risks of ventricular puncture and instillation of air or contrast medium into the ventricles. MRI scanning is slightly less accurate than CT scanning, with errors of approximately 2 mm on average and 4 mm at maximum [29]–[31]. These errors are due to artifacts related to inhomogeneities in the magnetic field and nonlinearities in the gradient field—the position-dependent variation in the magnetic field [32]. These artifacts can be induced by metal or magnetic susceptibility artifacts—produced at the interface between materials (e.g., air and bone), which have different tendencies to affect the magnetic field in a region.

Attempts to decrease errors in MRI scans due to these artifacts include software modifications and overlapping (fusion) of the MRI database with the CT database, which is not prone to these types of artifacts [33]. Patients undergo imaging first with a 3T MRI of the brain prior to surgery. During the day of surgery, a CT is taken with the Leksell frame in place. Then CT and MRI are fused by the computer software (Medtronic Stealthstation). Targeting can then be accomplished by computer programs that relate atlas maps of anatomy to the radiologic anatomy. These programs display atlas maps transformed either to match the AC-PC line in isolation [34] or to match the AC-PC line and other structures, such as the margins of the third ventricle or the internal capsule [35].

### C. Physiologic Localization

Radiologic targeting can be further refined by identifying the different basal ganglia nuclei (STN and GPi) and thalamic nuclei (Vim, Vop, and Vc) on the basis of their electrophysiologic properties. These properties are defined in terms of spontaneous activity, neuronal response to passive and active movements, and sensory responses to natural or electrical stimulation. Physiologic localization has been carried out by stimulation with a macroelectrode (impedance < 1000  $\Omega$ ) or by stimulation and recording with a semimicroelectrode (impedance < 100 k $\Omega$ ) or a microelectrode (impedance > 500 k $\Omega$ ).

### D. Microelectrode Localization

Microelectrodes for physiologic monitoring and recording are designed to isolate single action potentials [40]–[42]. Typically microelectrodes are constructed from a platinum-iridium alloy or from tungsten, producing a tapered tip, and insulating with glass [40], [42]–[46]. The electrode impedance is usually [36] greater than 500 k $\Omega$  [37], [38]. A microelectrode with sufficiently small surface area, and therefore typically high impedance, facilitates the isolation of single units [37].

The assembled electrode is attached to a piezoelectric microdrive and mounted on the stereotaxic frame. Some microdrive systems incorporate a coarse drive so that overlying structures can be traversed quickly. The tip is then retracted into a protective cylindrical housing while the whole assembly is advanced to a new depth [36]. The microdrive may then be used from this new depth for

detailed exploration of deeper structures. Another option is to use the microdrive throughout the trajectory by advancing it each time it reaches the end of its traverse [37].

The signal from the microelectrode is amplified and filtered. Multiple neuronal discharges of various sizes may be seen on an oscilloscope and heard by use of an audio monitor. The “all or none” principle of neuronal discharge provides that an action potential signal of constant shape and amplitude will be produced from any one neuron. Therefore, a window discriminator may be utilized to isolate individual neuronal firing activity. The continuous signal may be stored for offline analysis.

In addition to recording, microstimulation of subcortical structures through the microelectrode may be employed in physiologic localization. Current may be delivered through the same electrode that is used for recording by disconnecting it from the preamplifier and connecting it to the output of a current-isolation stimulator. To minimize cellular damage indirectly caused by charge accumulation at the electrode-tissue interface, microstimulation is delivered in biphasic, square wave pulse trains of 0.1 to 0.3 ms pulses for times up to 10 s at a frequency of 300 Hz [39]. The stimulus amplitude and pulse width determine the amount of local current spread; in general, increasing pulse width increases the extent of activation to local neurons, while increasing amplitude further increases the extent of activation to neurons even farther away [40]. Stimulation in Vc or lemniscal pathways will evoke somatic sensations [41], while stimulation in STN or Vim may alter the ongoing Parkinsonian or tremor symptoms. Furthermore, stimulation in areas too medial or lateral to the STN will elicit oculomotor side effects or capsular effects such as muscle contractions.

### E. Localization With Macrostimulation and/or Semimicroelectrode

After localization of the target and placement of the DBS macroelectrode through a cannula, macrostimulation through the DBS electrode can confirm functional effectiveness of each lead as well as elicit stimulation-related unwanted side effects. Macrostimulation through a low-impedance electrode (impedance often less than 1 k $\Omega$ ) can reliably identify the capsule by stimulation-evoked tetanic contraction of skeletal muscle at low threshold [42], [43]. Macrostimulation can also elicit oculomotor effects if the electrode is too medial in the STN. Posteriorly placed electrodes cause paresthesias by activating lemniscal systems. Therapeutic effectiveness can be confirmed by macrostimulation-related reduction in rigidity and tremor in the contralateral limb. For Vim stimulation in essential tremor, macrostimulation can confirm the effectiveness of tremor reduction as well as side effects such as paresthesias from posterior spread of current into Vc. Because of its large size, macrostimulation using the DBS electrode is typically used as a confirmatory test rather than the primary mode for localization of targets.

**Table 1** Current DBS Indications and the Main Conventional Treatments Commonly Prescribed Before DBS Is Considered

Condition	Symptoms treated	Conventional treatment*
Parkinson's Disease	Resting tremor, rigidity akinesia	Levodopa, Sinemet, dopamine agonists, enzyme (COMT) inhibitors.
Essential Tremor	Regular tremor in the 4-12Hz range associated with movement	Beta blockers, anti-seizure medication
Dystonia	Twisting, writing, abnormal postures	Botulinum toxin injection for focal and neck dystonias. No long-term effective medical treatments for the severest forms.

\* Conventional treatments for all three motor disorders often include physical therapy.

## V. CURRENT CLINICAL INDICATIONS AND INVESTIGATIONAL APPLICATIONS

As the etiology of certain diseases is being localized to particular foci in the brain, DBS is becoming more sought after as a treatment for a large number of disorders. DBS is an approved therapy for neurological motor disorders when patients are resistant to conventional treatments, as outlined in the following sections and in Table 1, or when the conventional treatments cause excessive side effects. The last section summarizes the current status of established and investigational DBS applications.

### A. Parkinson's Disease

The benefit of DBS is best evaluated by the proportion of each day the patient spends in "on" time without disabling dyskinesias. We define the "on" time as the period after ingesting anti-Parkinsonian medication during which the patient is fluid and receiving pharmacological benefit. This contrasts with the "off" time, which is the period during which the patient experiences no pharmacological benefit. Unfortunately, many advanced PD patients suffer from dyskinesias, uncontrollable writhing movements of the arms, legs, head, or torso resulting from long-term effects of levodopa ingestion. Results from the Deep Brain Stimulation for Parkinson's Disease Study Group revealed an increase in the percentage of time patients receiving DBS treatment identified as being in an "on" state without dyskinesias from 27% per day at baseline to 74% at the six-month postoperative evaluation [44]. According to the study, the percentage of "off" time also reduced from 49% to 19% of the day. This is a significant difference in that many patients with PD suffer from motor fluctuations, in which frequent fluctuations between "on" and "off" states occur during the course of the day, making it difficult to participate in daily activities.

Overall, patients undergoing subthalamic nucleus stimulation found approximately 50% improvement in both the motor and activities of daily living subsection scores of the Unified Parkinson's Disease Rating Score (UPDRS). These effects were also found to last long-term. Five-year postoperative data for bilateral STN-DBS reveal

approximately 50% improvement in scores for motor and daily-living activities off-medication and significant improvement in on-medication dyskinesias [45]. However, over the course of five years, this study showed that speech, postural instability, and freezing worsened.

Patients with PD also benefit from a reduction in medication requirements without change in functional capacity where the STN nucleus is targeted; when the GPI was targeted, patients experienced no significant change in medication dosage [46]. Early investigations comparing the benefit of DBS in the STN versus the GPI confirm more stable improvement in UPDRS scores and decrease in medication needs for the STN group [47]. In addition, for neurosurgeons, there is also the benefit of relative ease with respect to targeting the STN versus the GPI due to the size of the target nucleus and improved neurophysiological feedback.

A randomized trial of bilateral STN-DBS with best medical management confirmed the significant benefit of DBS over pharmacotherapy at six months [48]. Improvements were evidenced in assessments of mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. In addition, although serious adverse events were greater in the surgery group, the less significant adverse events were increased in the pharmacotherapy group.

### B. Essential Tremor

DBS for ET is an extremely effective treatment and is recommended when first-line pharmacotherapies fail in a disabled individual. Studies confirm approximately 50% improvement in tremor severity after DBS [49]. The electrode arrays are placed in the Vim nucleus under stereotactic guidance, although a 2004 study indicated the optimal placement of the electrodes to be just anterior to Vim, in Vop [49]. Compared with the older practice of Vim lesioning, the Vim DBS procedure can be performed bilaterally without significant side effects, the most significant of which is speech difficulty but may also include cognitive disturbance and balance difficulty.

Although ET is expressed as a bilateral disease, patients may have more difficulty with function in the dominant hand and may also complain of significant trunk and head

tremor. Unilateral Vim-DBS alone may be sufficiently effective to treat the dominant tremor. Bilateral DBS is necessary to treat axial (head or trunk) tremor [50].

The effects of Vim-DBS are durable. Sydow et al. revealed persistence of tremor control six years following implantation for both bilateral and unilateral implanted patients [51]. Scores for activities of daily living were significantly improved at six years compared with baseline (preoperative) scores and stimulation “off” scores. These investigators also identified an increase in the mean voltage requirements (from 2.0 to 2.6 V) and a corresponding increase in mean rate (156 to 172 Hz) and decrease in mean pulse width (103 to 89 s).

**C. Dystonia**

The mechanism by which DBS in the nucleus of the GPi ameliorates the symptoms of dystonia is not understood as the role of pallidal pathophysiology has not been identified. GPi-DBS for dystonia is highly effective and life-changing for those patients with primary generalized dystonia and tardive dystonias. Overall improvement in dystonia scores averaged about 50% for the primary generalized dystonia patients with greater improvement for younger patients especially with DYT-1 positive-type dystonia [52]. The latter group is defined by abnormality in the protein product dystonin. They may experience complete resolution of symptoms following DBS, a considerable change given the severe disability experienced by these young patients [53], [54]. Response following GPi-DBS for dystonia varies depending on disease type. Patients with cervical dystonias in general experience some improvement (40%) in symptoms following GPi-DBS, and patients with tardive dystonias have been shown to dramatically benefit (90%) from GPi-DBS [53].

Treatment of dystonia patients with DBS carries with it certain complexities not present in the use of DBS for PD or

ET. Target localization in the GPi is difficult due to the fact that some dystonia patients are quite young and may not be able to tolerate awake surgery, the definitive neurophysiological thumbprint at the target has not been clearly defined, and intraoperative test stimulation reveals no changes in the disease state. In fact, patients do not immediately respond to implantable pulse generator programming as do patients with other movement disorders. It may take up to six months before evidence of DBS efficacy is apparent, making it difficult to program these patients as well.

**D. Future Indications**

While Parkinson’s Disease or other movement disorders are the conditions that functional neurosurgery has most successfully treated, the field is now expanding to treat other nervous system conditions ranging from those traditionally treated with psychotropic medications to those for which there is no current medical treatment other than behavioral or physical rehabilitation. Diseases, such as depression, obsessive-compulsive disorder (OCD), and Tourette’s syndrome, are currently being investigated as future indications for DBS, and a handful of studies have already revealed positive results [52]–[56]. Minimally conscious states and epilepsy are also being considered for investigation as DBS indications farther down the road [55]–[57]. Several preliminary results have shown the benefit of DBS for psychiatric disorders, as summarized in Table 2.

**VI. SUMMARY OF CURRENT DBS DEVICE TECHNOLOGY**

There is little variety in DBS device technology, as the only device for DBS approved by the U.S. Food and Drug Administration (FDA) is manufactured and sold by Medtronic, Inc. The DBS system is marketed as the Activa

Table 2 A Summary of Current and Investigational Applications of DBS

Condition	Common Target Location	Selected Studies and Dates
Essential tremor	Vim	1996: Benabid et al, 2003: Sydow et al [51, 58]. 1997: Medtronic’s Activa therapy approved by US FDA
Parkinson’s disease	STN, GPi	2001: DBS Study Group, 2003: Krack et al [44, 45]. 2002: Medtronic Activa therapy approved in U.S., 2005: Kinetra dual-channel stim on the market
Dystonia	GPi	2000: Coubes et al, 2004: Starr et al, 2005: Vidailhet et al [52-54]. 2003: Medtronic Activa approved under HDE.
OCD	VC/VS (anterior limbs of the internal capsules)	1999: Nuttin et al, 2003: Nuttin et al, Greenberg et al, 2005: Friehs et al [59-62]. 2006: HDE approval for Medtronic Activa.
Depression	Subgenual cingulate region (BA 25), VC/VS	2003: Mayberg et al, 2004: Greenberg et al. [63-65]. 2005: ANS receives IDE
Epilepsy	Anterior nucleus, STN, caput nuclei caudati (CNC)	2002: Chabardes et al.[55, 56], SANTE trial results due in 2008 (using Medtronic’s Intercept Epilepsy Control System)
Minimally-conscious state	Central thalamus	1990: Tsubokawa et al. [66], 2007: Schiff et al.[67]

OCD = obsessive compulsive disorder. Vim = ventral intermedial thalamus. STN = subthalamic nucleus. GPi = globus pallidus internus. BA = Broadmann area. VC/VS = ventral capsule / ventral striatum. HDE = Humanitarian Device Exemption. ANS = Advanced Neuromodulation Systems. IDE = Investigational Device Exemption.

control therapy and is approved only for Parkinson's Disease and essential tremor. The FDA has also granted Humanitarian Device Exemption for Medtronic's device in patients with dystonia.

While Medtronic has the only DBS device on the market, Advanced Neuromodulation Systems, Inc. (ANS) is also building upon its leading role in the neurostimulation industry to produce its own DBS system, the ANS Libra. In the first quarter of 2005, ANS announced plans to implant 160 patients at 12 sites to investigate the safety and efficacy of the ANS Libra DBS System to treat essential tremor and 136 patients to treat Parkinson's Disease after receiving Investigational Device Exemption approval from the FDA [64].

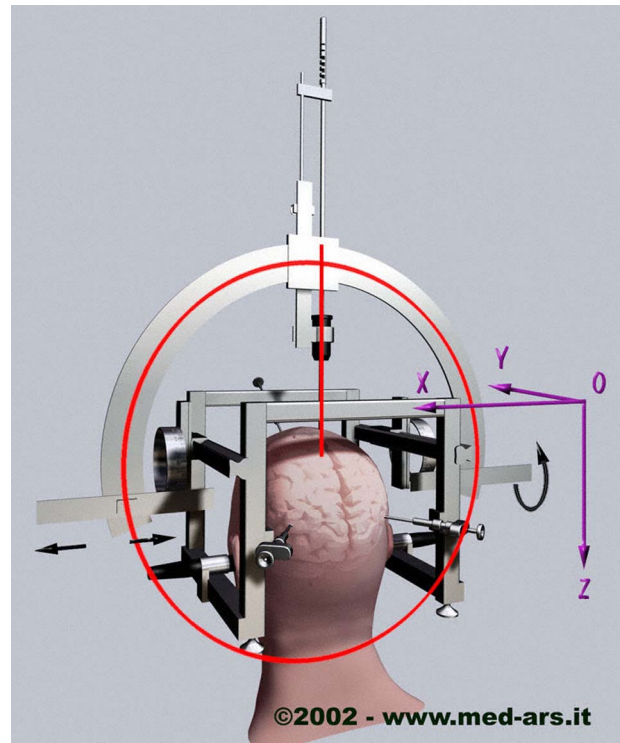
While data are not yet publicly available to make a direct comparison between the ANS and Medtronic DBS devices, ANS does have a spinal cord stimulation (SCS) system on the market that consists of components analogous to those in a DBS system. A look at the existing components in Medtronic's DBS system and some of the unique features of ANS's SCS system that could also be used in a DBS system are provided for interested engineers as a way of highlighting some of the design considerations in a DBS system.

A DBS system—and, in particular, Medtronic's Activa system—consists of three main components.

- 1) *The implantable pulse generator (IPG)*. The IPG is a device that controls the frequency, amplitude, and duration of the current pulses delivered to the targeted region in the brain. The electronic circuitry is hermetically sealed in a titanium case and implanted in the subclavicular region of the patient. Medtronic makes two IPGs for DBS available to physicians and patients.
  - a) The Soletra, with dimensions of  $55 \times 60 \times 10 \text{ mm}^3$  and weighing 42 g, is designed for unilateral implants.
  - b) The Kinetra is designed to stimulate bilaterally through two separate leads and has larger dimensions of  $61 \times 76 \times 13 \text{ mm}^3$  and weighs 83 g.

ANS offers IPGs for their SCS system that have similar capabilities necessary for DBS. Both Medtronic and ANS offer fully implantable battery-powered IPGs or externally powered IPGs by a radio-frequency transmitter; however, Soletra and Kinetra are both nonrechargeable battery-operated IPGs. ANS offers a rechargeable IPG, the Renew IPG, for spinal cord stimulation. Other companies, such as Advanced Bionics/Boston Scientific and NDI Medical, also manufacture IPGs that could be adapted for DBS.

- 2) *The electrodes*. The DBS lead is connected from the IPG, tunneled subcutaneously along the neck, and implanted through a craniotomy in the skull into the designated target (see Fig. 1). It terminates with four electrode contacts, each 1.5 mm wide and 1.33 mm in diameter. Medtronic



**Fig. 1.** A representation of the conventional frame-based stereotaxic technique. The frame is screwed into the patient's skull and an arc-center-based reference system allows the mounted microdrive to insert the electrode relative to a known coordinate system. (Image created by D. Brunelli, <http://www.med-ars.it>.)



**Fig. 2.** Medtronic's DBS Model 3387 lead with 1.5-mm spacing between contacts and the Model 3389 lead with narrower 0.5-mm spacing.

offers two models that differ in the spacing between contacts: Model 3387 contacts are 1.5 mm apart while Model 3389 contacts are 0.5 mm apart (see Fig. 2). The electrodes are composed of a



**Fig. 3. Medtronic's 8840 N'Vision Clinician Programmer for setting DBS stimulation parameters.**

platinum-iridium alloy and have impedances less than 1 K $\Omega$ . While technical information has not been disclosed on ANS's Libra system, ANS offers a number of percutaneous leads for their pain management system. Quattrode, Octrode, and Axxess are ANS's percutaneous leads, which offer doctors and patients the choice of four or eight electrodes, 4- or 6-mm intraelectrode spacing, and a 1.37- or 0.83-mm diameter.

- 3) *The programmer.* Medtronic's N'Vision Physician Programmer is a handheld device that allows the clinician to program device settings (see Fig. 3). The programmer communicates with the IPG via infrared telemetry to set the stimulus to the physician-determined amplitude, frequency, duration, and polarity. With four contacts, the stimulus can be delivered through any pair of contacts or between any of the contacts and a remote ground. ANS also demonstrated programmable capabilities in its Rapid Programmer, which has the advanced capability to program up to 16 electrodes in more complex stimulation protocols. The programmer allows the clinician to select an amplitude within the range between 0 and 10 V and a frequency within the 0–185 Hz range.

## VII. ENGINEERING ADVANCES

While fMRI imaging has aided DBS target localization, engineering needs still exist for further development of targeting and positioning devices and software to increase

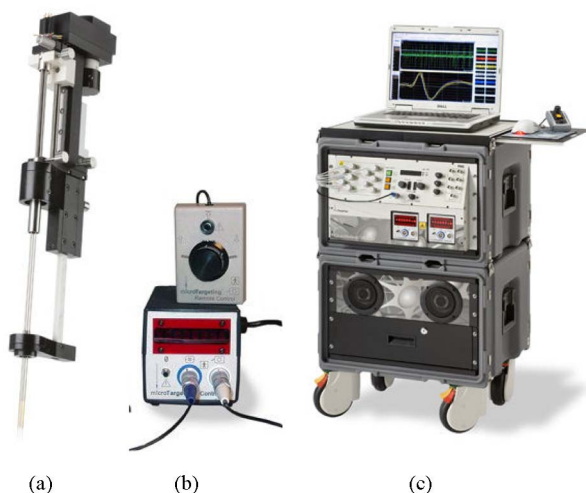
precision and ease clinicians' efforts in hybridizing fMRI and CT images and choosing appropriate targets. Such targeting systems do exist. For example, Medtronic offers the StealthMerge application, which provides a sophisticated interface for the surgeon to determine stereotaxic coordinates for the target and plan the approach of the electrode to the target (see Fig. 4). FHC, Inc. (Bowdoin, Maine; see Fig. 5) offers a reliable "microTargeting" microdrive with an easy-to-operate controller and now has an integrated system that allows simultaneous microrecording. Other systems for large-scale signal acquisition, preprocessing, and visualization are available, including Alpha Omega's Alpha-Map (Fig. 6), Plexon's Multi-channel Acquisition Processor, and Cyberkinetic's Cerebus system. A fully integrated system with the reliability and quality of all of these components, targeting software, mechanical microdrives, and microelectronic recordings would improve the quality of DBS procedures as well as simplify the procedure for physicians.

Frameless stereotaxy is gaining attention as an improvement upon conventional functional neurosurgical targeting techniques. The conventional procedure involves mounting a cumbersome, heavy frame on the patient's head using pins that penetrate the skin (Fig. 1), forces the patient to keep his or her head motionless during the procedure, and is one of the few parts of the full DBS procedure that requires injections of lidocaine or other local anesthetics; it is often noted as the only painful part of the relatively painless procedure. Frameless stereotaxic procedure reduces the strain on the patient's head, reduces the duration of the procedure, and eases preoperative fMRI scanning. Medtronic sells an innovative frameless stereotactic skull-mounted system called NexFrame Stereotactic Technology (through Image Guided Neurologics, Inc.; see Fig. 7), which uses bone markers and an electromagnetic field-based position sensor to guide navigation to the target. The frameless technique has been shown to produce a  $2.5 \pm 1.4$  mm deviation on average from the desired target, as compared to the  $1.2 \pm 0.6$  mm deviation using the conventional stereotaxic frame. These differences in deviation were reported to have no significant clinical effect [68], implicating the feasibility of frameless neuronavigation for placement of DBS electrodes. FHC also produces a neurosurgical targeting platform called STarFix, which eliminates the need for a stereotactic frame and intraoperative image guidance. Although frameless stereotaxy gained attention in the mid-1990s and studies have claimed comparable accuracy to frame-based stereotaxis [69], [70], many DBS surgeons still opt for the conventional procedure [71].

Although advances in surgical technique have made complications relatively uncommon, side effects and potential complications of DBS are still an important consideration. Adverse events include intracranial hemorrhage, wire erosion or breakage, wound infection potentially requiring device removal, postoperative confusion, and reoperation due to poor placement of the electrode



**Fig. 4.** Medtronic's StealthStation software application provides a graphical user interface for the physician to determine stereotaxic coordinates of target (intersection of red lines) and the best track for electrode penetration (yellow line). (Image courtesy of Medtronic Neuromodulation Division.)



**Fig. 5.** FHC's microTargeting system (from left to right): (a) microdrive by which electrode is lowered with precise control, (b) microdrive controller, and (c) guideline 4000 microelectrode recording system with integrated microtargeting to view up to ten channels while lowering microrecording electrode. (Image courtesy of FHC, Inc.)

array or lead migration [72]. The accuracy and security of electrode placement have been improved by Medtronic's Stimloc cranial base and cap (Fig. 8). Stimloc is affixed to the skull and clips the lead in place to prevent accidental displacement of the lead, which occasionally happens during removal of the microdrive and requires another surgery upon discovery of displacement in order to reposition the lead. Improvements in the engineering of mechanical parts, electrical stimulation, and surgical techniques to prevent other device-related or surgery-related complications are yet to be achieved.

The advent of 3T MRI scanners has improved the visualization of the subthalamic nucleus. While the STN is small and variable in location, the MR imaging at 3T has eased target localization and reduced the number of passes required to locate the desired STN location [73]. Another potential breakthrough for not only DBS patients but also any patient with implanted devices is a portfolio of patents on MRI safety recently purchased by Medtronic from the Irvine-based biomedical technology company Biophan.<sup>1</sup> Such technology can provide immunity to the electromagnetic interference that is otherwise a safety

<sup>1</sup>See <http://www.hospitalbuyer.com/medical-specialties/cardiology/biophan-sells-mri-safety-patents-to-medtronic-extends-myotech-ownership-1580/>.



**Fig. 6.** Alpha-Omega’s Alpha-Map allows monitoring intraoperative microelectrode recordings. Shown here are simultaneous microelectrode recordings from the thalamus, EMG recordings, and extracted neural spikes from selected channels.

concern for patients with implanted electronics and would allow these patients to safely go near electromagnetic equipment, including MRI scanners.

The major difficulties with programming are the great number of parameters and degrees of freedom in setting the parameters to certain values [74]. The complexity of programming these devices will increase as engineers add new features such as increasing the number of contacts, aside from the existing options of bipolar or monopolar stimulation and wide ranges of frequency and amplitudes. Auto-

mated adaptive capabilities of DBS programming through closed-loop control is being considered as a strategy for optimizing DBS control [2], [40], [75]. In present DBS systems, the current waveforms are square wave pulses with constant amplitude, duration, and frequency delivered through a fixed electrode configuration. Closed-loop control based on continuous monitoring of information contained in oscillatory local field potentials [4], [76], for example,



**Fig. 7.** Frameless stereotaxic surgery enabled by the Nexframe system. Developed to eliminate the need for heavy stereotaxic frames, as illustrated in Fig. 1, which are secured to the patients skull with sharp pins. (Image courtesy of Medtronic Neuromodulation Division.)



**Fig. 8.** Medtronic’s Stimloc technology for securing the DBS lead in place. Stimloc is used by centering and attaching the base to the skull, installing the support clip onto the base, closing the support clip around the lead, and snapping a cap on as protection for the lead. (Image courtesy of Medtronic Neuromodulation Division.)

provides a strategy for continuously maximizing suppression of disease symptoms and minimizing side effects for each patient's ongoing needs. Closed-loop systems will necessitate the development of simultaneous recording and stimulating capabilities and new technology to avoid stimulus artifacts, as described in [77].

Creating a more power efficient system that increases battery life is one tactic for reducing the frequency of surgical procedures to replace the battery in the IPG. In current DBS systems, battery replacements are needed roughly every two to three years [72], [78]. Another tactic is to develop rechargeable batteries, as has been done in other implantable devices, such as the aforementioned spinal cord stimulators. Developing an IPG that can be implanted closer to the electrode site would also allow fewer surgical procedures for the patient, since the IPG could be implanted during the same operation as the electrode implant. This will require miniaturizing the IPG to a lower profile device completely implantable under the scalp, for example. Better control over the spatial spread of current over the region surrounding the electrode also provides the possibility of optimizing power consumption [79].

Computational and simulation studies are beginning to help provide insight into new designs for "current steering" or changing electrode configuration to modify the spatial current distribution [79], [80]. The type of materials, number of contacts, dimensions and spacing of electrode contacts, and selection of electrode(s) through which to stimulate have all been shown to play a role in the nature of current spread from the stimulating electrode [79]–[81].

Understanding how current can be steered by controlling these parameters will allow control over the current density in the stimulated tissue as well as the extent of activation of neural tissue and, in turn, lead to better management of tissue damage, power consumption, and treatment efficacy.

## VIII. CONCLUSION

The concept of electrical intervention to alter the output from an abnormal brain circuit and thereby change disease outcome has attracted neurosurgeons and neurologists over a long period of history. Due to its success in alleviating severe motor dysfunction with relatively low risk, DBS is becoming more popular as a clinical treatment and as the subject of investigational study into other neurological diseases. Functional neurosurgical techniques and implantable biomedical device technology are both key components to the successful development and implementation of DBS. DBS still has much room to grow and develop and will require the collaborative work of neuroscientists, neurosurgeons, and biomedical engineers to investigate and understand its therapeutic mechanism in order to wield it in the most effective manner. ■

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