# Deep Brain Stimulation for Neurological Disorders

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*Clinical Application Review*

***Abstract*—Deep brain stimulation (DBS) involves the delivery of precise electrical signals to specific deep anatomical structures of the central nervous system, with the objective of altering or modulating neural functioning and achieving a reversible, adjustable and therapeutic or clinically beneficial effect.**

**The exact mechanism of action of DBS is still the subject of ongoing investigations. However, based on extensive clinical investigations, it has become an established modality for the surgical treatment of advanced and medication intractable movement disorders such as Parkinson's disease, essential tremor and dystonia. DBS is also being investigated for conditions such as intractable epilepsy, neurobehavioral and psychiatric disorders such as treatment resistant depression, obsessive compulsive disorders, addiction, obesity, Alzheimer's disease and traumatic brain injury. The advantage of DBS over older deep brain lesioning procedures is its reversibility and adjustability. The design of the DBS systems allows for dynamic adjustment of the effects of electrical stimulation by altering the contacts at which electrical pulses are delivered to the brain and changing the stimulation parameters of those pulses.**

**The clinical results from studies on DBS show that it has great potential making it one of most promising fields which could be used to address challenging neurological problems.**

***Index Terms*—Deep brain stimulation (DBS), neurological disorders.**

## I. Introduction

DEEP brain stimulation (DBS) is now considered the neurosurgical therapy of choice for intractable movement disorders and is being explored in a growing number of neurological and behavioral disorders. DBS has a safety track record. There is as of 2011, over 23 years of clinical research regarding DBS safety with over 80 000 implants performed worldwide and over 3000 published articles.

Several key factors have led to the rapid growth and development of DBS. Advances in the understanding of the physiology of normal brain function and the pathophysiological basis of neurological and psychiatric networks and systems underlying disease, the localization of specific nodes and hubs in these circuits/networks, significant improvements in the safety, precision and widespread use of imaging and physiological guided stereotactic neurosurgery, and the development of reversible and adjustable neurostimulation devices have accelerated the development of DBS.

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In this paper, we will explore the history and current framework of DBS.

## II. Historical Background

The ability to manipulate neural activity by the external application of electricity has always been an attractive idea. In fact, the efforts to translate this idea into action had begun almost 200 years ago since the work of Luigi Galvani (1737–1798) who recognized the relationship between electricity and animation in his treatise published in 1791, and the work of Emil du Bois-Reymond (1818–1896) who later defined electrical activity as the basis of neural activity [1], [2].

The recognition of the functional organization of the cortical and subcortical regions of the brain prompted further interest in the manipulation of neural activity by the external application of electricity, as it became possible to predict which areas of the brain should be stimulated in order to achieve a specific functional objective. This principle was tested as early as 1874, when Robert Bartholow stimulated the cerebral cortex of a patient whose brain cortex had been exposed by a scalp skin cancer and reported that the patient experienced tingling sensations and had contralateral limb movements [3]. However, precise electrical stimulation of subcortical structures had to wait until the development of the human stereotactic surgery apparatus by Horsely and Clark [4]. In 1947, Spiegel and Wycis performed subcortical electrical stimulation using this apparatus and from that point the principles of subcortical stimulation have evolved to become established in current DBS practice [5].

The underlying principles and neural mechanisms of DBS are not yet fully understood but research suggests that DBS directly changes brain activity in a controlled manner [6]. Generally speaking, two hypotheses have been proposed to explain the effect of DBS: the inhibition-based theory and the activation-based theory.

The first theory comes from the observation that DBS produces similar effects to an ablative lesion. The second theory proposes that DBS implantation leads to the introduction of a high-frequency stimulation (HFS) driven activity in a point of the neuronal network that propagates and consequently modifies the pathological spontaneous activity in many nuclei. In fact, current biochemical, metabolic, and electrophysiological data in experimental models and patients together with modeling studies provided consistent evidence in favor of activation [8]. Nevertheless, based on current available data, the mechanism of DBS could be considered a combination of inhibition of neurons, modulation of abnormal patterns of activity, and activation of axons [8].

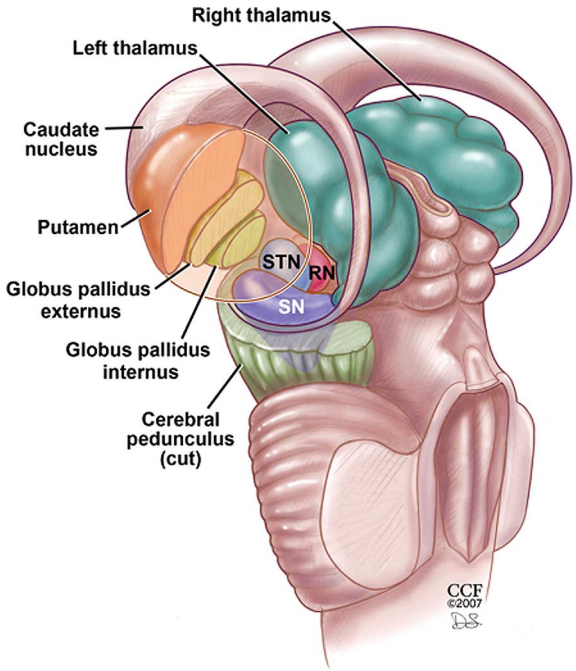


Fig. 1. Targets for DBS. (Reprinted with permission from Rezai *et al.* [16].)

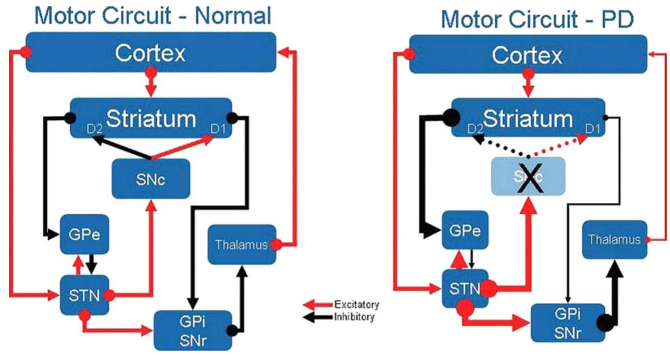


Fig. 2. Cortico-striato-pallido-thalamo-cortical (CSPTC) neural circuits in normal state (A) and in Parkinson's disease (B). (Reprinted with permission from Rezai *et al.* [16].)

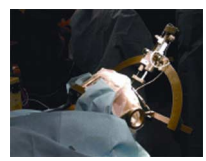

Fig. 3. Leksell stereotactic frame. With this system, target can be approached from any angle as it uses a center-of-arc principle. (Reprinted with permission from Rezai *et al.* [16].)

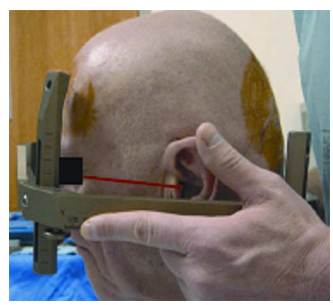

Fig. 4. Stereotactic head frame placement. Frame placement is performed under local anesthesia with sedation with patient sitting up. Frame should be placed parallel to a line extending from lateral canthus to tragus (line illustrated in red) to approximate plane of the anterior commissure-posterior commissure (AC-PC) line. (Reprinted with permission from Rezai *et al.* [16].)

## III. Overview of Neurocircuitry: Fundamentals of DBS

DBS is an invasive neural circuitry-based neurosurgical intervention [9]. Understanding of brain circuitry in terms of neural networks for various neurophysiological interactions and neurologic disorders is essential to define specific relay "nodes" which may be targeted within this neural network for electrical perturbation by DBS.

The current common targets or "nodes" for DBS are the subthalamic nucleus (STN) for Parkinson's disease, the globus pallidus pars internus (GPi) for dystonia and Parkinson's disease, and the ventralis intermedius nucleus (VIM) of the thalamus for essential tremor (see Fig. 1).

The fundamental underpinning of the neurocircuitry of various neurological and neurobehavioral disorders is the existence of cortico- striato-pallido-thalamocortical (CSPTC) loops [10], [11].

Different cortico-striato-pallido-thalamo-cortical (CSPTC) circuits exist for limbic, associative, and motor function and each circuit is linked to a specific area of the striatum [11]. The above-mentioned circuits maintain some degree of anatomical separation. However, these circuits are not strictly isolated from each other, as some interface between these circuits were demonstrated in primates [12]. This interface allows the more medial limbic circuits to influence more dorsolateral motor circuits and ultimately allows for a link between emotion and motivation (limbic circuits) with cognition and planning (associative circuits) which finally manifests with a motor output and behavior (motor circuits).

The motor circuit is the most commonly described loop. It is linked to the dorsal striatum and has been implicated in the pathogenesis of Parkinson's disease (Fig. 2). Limbic and associative circuits are linked to the ventral and dorsomedial striatum, respectively, and are implicated in the pathogenesis of neuropsychiatric conditions including obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). Therapeutic effects can be achieved by applying electrical stimulation to specific critical points or "nodes" along the anatomical pathway of these circuits.

Quantitative analysis of complex networks allows evaluation of the functional organization of the overall network and hence the "nodes" or critical junction points in the networks [13]. A leading method in this regard is graph theoretical analysis. According to graph theoretical analysis, we can look at network as a matrix of functio-anatomical stations. Information (the neurological signal) is transferred between these stations. Most nodes are not neighbors of each other, but most nodes can be reached from other nodes by a few connections. However, some of these stations have higher traffic than other. These stations with a higher traffic have a more critical role in the overall function of a given neuronal network, and targeting it by treatment has more impact on modulating the overall function of the neuronal network. Graph theoretical analysis techniques have been used

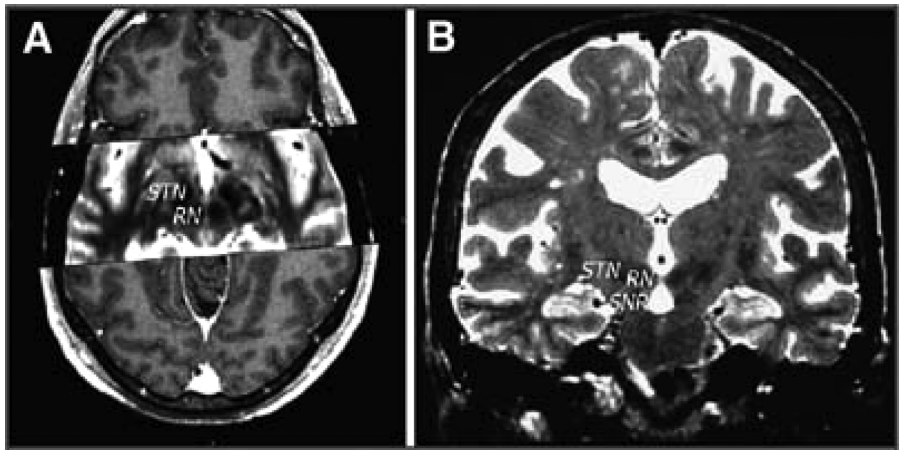


Fig. 5. STN on MRI high resolution axial (A) and coronal (B) T2-weighted MRI scans. Anatomical location of STN is anterosuperolateral to substantia nigra pars reticulate (SNR) and red nucleus (RN). (Reprinted with permission from Rezai *et al.* [16].)

to analyze both the fMRI signals as well as the EEG recordings in these experimental models [13].

These nodes or critical junction points in the networks can be targeted for lesioning or DBS implants with submillimeter accuracy using modern imaging and neurophysiologically guided stereotactic surgery.

### *A. Implantation of DBS Device: Surgical Procedure*

As stated earlier, the common targets for DBS are the subthalamic nucleus (STN) or globus pallidus internus (Gpi) for Parkinson's disease, ventral intermedius nucleus (VIM) of the thalamus for essential tremor, Gpi for dystonia and the subgenual cingulate or nucleus accumbens/VCVS (ventral capsule ventral striatum) for neurobehavioral disorders including OCD, depression, and alcoholism. Stereotactic principles are fundamental to the operative procedure of DBS (Figs. 3 and 4). It involves the definition of and targeting of any point within the brain based on a Cartesian coordinate system (which defines this point in a 3-D space).

The main components of the DBS system are an intracranial electrode and an implantable pulse generator which are connected by an extension wire. The surgical technique of implantation of a DBS device consists of two stages; the first stage is the DBS-electrode placement, the second is DBS-battery placement. Both stages can be done in the same occasion or in two different occasions.

With regard to DBS-electrode placement, this stage can be divided into the following steps.

1) Planning (preoperative) step: In this step, an anatomical point of the brain in a 3-D space is defined by employing direct and indirect techniques. Direct targeting involves the direct visualization of these deep nuclei using high definition magnetic resonance imaging (Fig. 5). Indirect targeting utilizes stereotactic atlases which are based on previous cadaveric dissections. The main challenge in planning this step is that patients' anatomy does not always match atlases and the brain can move and shift in the skull during the surgery. To overcome the first problem, new methods of registration are being developed which utilize nonrigid registration by employing probabilistic atlases.
2) Intraoperative stage: In this step, the placement of the deep brain stimulator lead in the defined deep nuclei is accomplished by using a stereotactic apparatus which may have a frame-based or frameless design. In addition to the help of imaging guidance technology, the correct location is further confirmed before final placement of the leads, by using a microelectrode to record the characteristic electrophysiological signature of the targeted nuclei, in order to ensure that the earlier anatomically defined target corresponds to the actual physiological target.

The detailed sequence of the steps of the intraoperative stage are as follows. After placing the stereotactic frame and acquisition of a stereotactic CT scan, the patient is positioned supine with the stereotactic head frame fixed to the operating room table. The stereotactic CT is then merged with the previously acquired MRI scan that used in planning step and the stereotactic coordinates are obtained. The stereotactic coordinates are set on the frame and used to determine the site for skin incision and burr hole location. After the burr hole is performed, the dura is opened and pia coagulated for corticotomy. The microelectrodes are then inserted with tip of the electrode placed at a defined offset above the target. At this time microelectrode recording (MER) is executed as the electrodes are advanced in submillimeter steps. All sedation should be stopped before the beginning of microelectrode recording as the sedation may affect the electrophysiological mapping. MER allows for definition and verification of the physiological signature of a given target. The frequency and pattern of activity of the various nuclei and white matter tracts encountered in the path to the physiological target are observed to determine the relationship of the trajectory to the target. Later, macrostimulation is carried out to determine benefits and side effects of the stimulation and for further confirmation. After the target is confirmed, the electrode is implanted at the target. The two currently available electrodes are the Medtronic 3389 which spans 7.5 mm and the 3387 which spans 10.5 mm (each model has four contacts which are 1.5 mm in height with 0.5 mm spacing between the contacts in the 3389 and 1.5 mm in the 3387 model). The implantation is carried out under fluoroscopy guidance. After the implantation, another round of intraoperative stimulation using the actual DBS lead is

performed to assess for final confirmation of clinical improvements and side effects of stimulation.

Next, the DBS electrode is affixed to the skull using anchoring devices such as the Navigus Stim-Loc device or the Medtronic bur hole ring and cap. Other options are cement or plates to secure the electrode. The distal tip of the electrode is covered by a connector or plug to protect the contacts and the electrode wire is buried in the subgaleal to be used later at the time of the implantation of the pulse generator.

In the postoperative stage, further confirmation of lead location is performed by obtaining a volumetric CT scan and uploading it into a planning station. Also, this postoperative CT scan helps in ruling out any intracranial bleeding which may occur after the implantation procedure. Furthermore, a close observation to the patient is undertaken to monitor any postoperative complications.

With regard to DBS-battery placement stage, the implantation of the pulse generator (the battery) can be executed on the same day of the implantation of the DBS electrode or on a different day (Fig. 6). During the surgery at this stage, the patient is placed supine and the head is turned to the side opposite the intended side of the battery implantation. An infraclavicular incision (one figure beneath the clavicle and two figures later to the midline) is made and a subcutaneous or subpectoralis major fascia pocket is fashioned. Next, IPG is buried in this pocket. The advantage of this subpectoralis major fascia pocket is that there is less chance of downward migration and drift of the IPG with time compared to location within a subcutaneous pocket. Available IPGs include single-channel, dual-channel, rechargeable, and nonrechargeable devices. These devices can be programmed to adjust the typical stimulation parameters of voltage, pulsewidth, frequency, and electrode polarity transcutaneously.

The surgical technique of DBS described is the technique that is being used in our institution. In fact, a variation of techniques and steps of DBS from one institution to another is the norm. For example, some institutions use frameless techniques instead of frame-based techniques. In the same way, some institutions do not utilize microelectrode recording and physiological mapping.

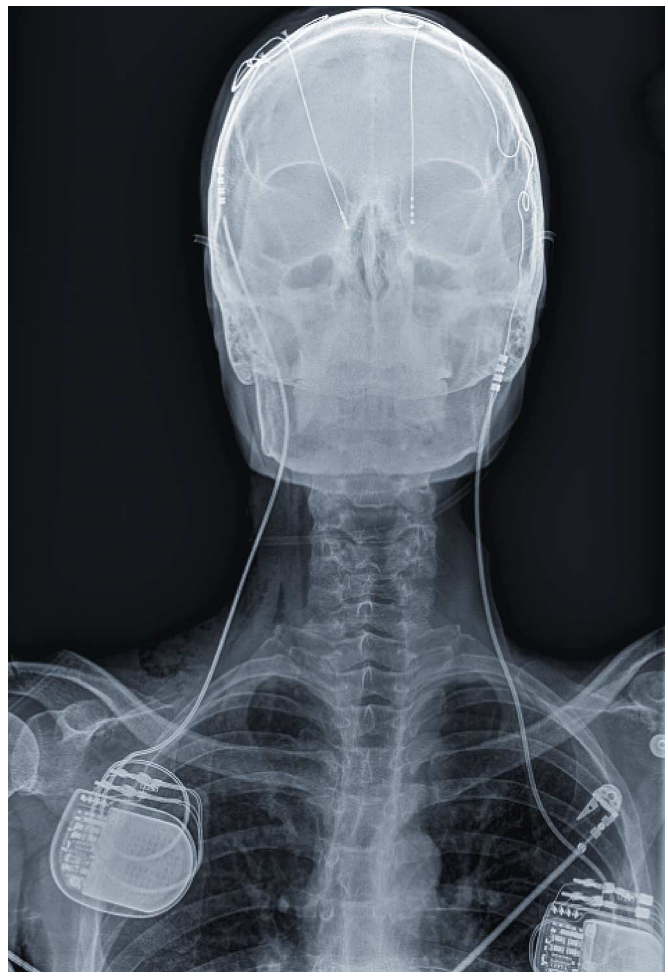

Fig. 6. Skull X-ray shows bilateral DBS leads, connectors and implantable pulse generators.

## IV. Current Clinical Applications for DBS

DBS has been applied to movement disorders, neurobehavioral disorders, epilepsy and pain management.

### *A. DBS for Movement Disorders*

Prospective, randomized controlled studies have confirmed that DBS results in improvements in quality of life, medication intake and the associated chronic care costs in certain movement disorders such as Parkinson's disease, essential tremor and dystonia [8]–[19]. DBS of the subthalamic nucleus (STN) has been shown to improve motor symptoms in patients with Parkinson's disease [14]. Motor disabilities of patients with primary generalized and segmental dystonias are significantly improved by DBS of the globus pallidus internus [17], [18]. Based on the results from these studies, the U.S. Food and Drug Administration (FDA) approved the use of DBS for essential tremor in 1997, Parkinson's disease in 2002, and dystonia in 2003.

Generally speaking, DBS is a surgical treatment typically used as a last resort when drug therapies are no longer effective. According to current referral practices for DBS only approximately 50% of the referral is a good candidate for this kind of surgery [20].

The details of the manifestations, indications, and outcomes of these three groups of diseases are as follows.

*1) Parkinson's Disease (PD):* PD is a progressive neurodegenerative disorder characterized by resting tremor, bradykinesia and rigidity. It is due to the progressive loss of dopaminergic neurons in the substantia nigra. The mainstay of treatment for PD is the use of dopamine agonists and L-dopa. However, with time, increasing amounts of medication are required to maintain therapeutic benefit. These increasing doses are associated with motor fluctuations as well as dyskinesias which are involuntary movements [14], [15], [19], [23]–[27]. The direct and indirect dopaminergic pathways have been implicated in the pathogenesis of PD. These two loops exist for the associative and limbic circuits, as well as for the motor circuits [8]. The direct loops connect from the striatum to the globus pallidus pars interna (GPi), substantia nigra pars reticulata (SNr), and ventral tegmental area (VTA). From there, the projections depart to the thalamus. Indirect loops join the striatum to the globus pallidus pars externa (GPe), and then project to the subthalamic nucleus (STN) before reaching to the GPi, SNr, and VTA.

The pathogenisis of Parkinson's disease begins with decreasing dopamine release in the substantia nigra with downstream effects on the globus pallidum, striatum, thalamocortical projections and the subthalamic nucleus (Fig. 2). The resultant effect is a decrease in glutamatergic excitation in the thalamocortical projections leading to hypokinesia.

DBS of the subthalamic nucleus (STN) has been shown to be effective in improving symptoms particularly those affecting the extremities. It is also known to decrease oral dopamine replacement requirement and to improve dyskinesias [23]–[27]. In a recent randomized study in patients younger than 75 years with advanced PD and severe motor complications, DBS of the STN was shown to be more effective than medical treatment alone [28]. In the same way, stimulation of the GPi is known to improve PD motor symptoms and although some evidence suggests it may be superior to the stimulation of STN, other recent evidence reveals there is no difference in results achieved [29]. A multicenter study of 299 patients done in 2010 revealed an equivalent primary motor outcome following either stimulation of GPi or STN. There was, however, a documented increase in depression rates as well as worsening visuomotor processing in patients that had STN stimulation compared to those that had GPi stimulation. In addition, an increase in intracerebral hematomas was seen in patients that underwent GPi stimulation and this has also been noted in other studies [15], [16]. In summary, based on current available data, GPi and STN are equally effective at least at motor symptom control of Parkinson's disease.

There are numerous considerations to be made in the selection of a patient with PD for DBS. These considerations are related to the patient's ability to tolerate surgery and hence improve the chance of achieving maximal therapeutic benefit from the procedure. The tolerance for surgery in these patients is affected by both medical and psychosocial factors.

With regards to patient selection for DBS, patients with classical PD are ideal candidates. Patients with atypical Parkinsonism are not candidates for DBS. In these patients with atypical Parkinsonism such as patients with progressive supranuclear palsy and Lewy body disease, no significant improvement has been shown and symptoms may even worsen after surgery. A positive response to L-dopa has been shown by several authors to be a predictor for a beneficial outcome from DBS [23], [30]–[32]. This was originally demonstrated in patients who underwent stereotactic pallidotomy [33]. A good indication of levo-dopa responsiveness for DBS candidacy is in general at least a 30% improvement of the Unified Parkinson's Disease Scale (part III) score. There is, however, an important exception to this in patients with tremor predominant PD who despite levo-dopa unresponsiveness have shown good tremor control with STN DBS. Generally, surgery has been shown to improve symptoms involving the extremities compared to axial symptoms affecting posture, balance, speech and gait [19].

*2) Tremor:* Essential tremor is a common movement disorder with an estimated prevalence of 0.4% to 5% [34]. It is a 4–12 Hz tremor which is often familial, postural or intentional in occurrence and tends to disappear with rest. It is commonly worsened by anxiety but improves with alcohol intake. It is usually treated with propanolol or primidone [35]. DBS of the VIM thalamus is a treatment option for disabling tremors in which optimal medical management have not been helpful. Surgery has been shown to be most beneficial in patients with distal, resting or postural tremors of the upper extremities [36]. Distal tremors tend to respond better than proximal tremors. Bilateral DBS is often required in patients with axial, head, neck, voice tremors which are more difficult to treat [19]. With regards to DBS for upper extremity tremors, the success rate is excellent and in 70% to 90% of patients, there is significant resolution of the tremors [35]. In a prospective single blinded randomized trial, DBS of VIM thalamus was shown to be more effective than thalamotomy in the suppression of drug-resistant tremors with relatively fewer adverse effects [37]. Recently, Morishita *et al.* reported three cases of dystonic tremor, a subtype of dystonia, which were treated successfully by stimulation the VIM thalamus [38].

*3) Dystonia:* Dystonia is a heterogenous group of movement disorders which is characterized by sustained muscular contractions with repetitive movements, abnormal postures and twisting. It is divided broadly into four groups which includes primary dystonia, secondary dystonia, dystonia plus syndromes and heredegenerative dystonia.

The etiology of primary dystonias is unknown. Patients with primary dystonia have no other clinical signs or symptoms other than dystonia. Brain imaging, CSF analysis and other laboratory results are normal in these patients. A subset of these patients have been found to have a mutation denoted DYT-1, which encodes the Torsin A gene that is localized to the 9q34 locus and expressed predominately in the substantia nigra pars compacta [39]. This is the most common mutation found in primary dystonia seen in childhood [40].

Secondary dystonia is usually secondary to insults to the brain which include drugs, stroke, tumors, trauma, infections, and perinatal anoxic injury. Dystonia plus syndromes are often associated with other movement disorders. These include dopa-responsive dystonia (Segawa syndrome), rapid onset dystonia-Parkinsonism, and myclonus dystonia syndrome. Heredodegenerative dystonia includes hereditary neurodegenerative disorders such Huntington's disease, Wilson's disease, pantothenate kinase associated neurodegeneration (PKAN), mitochondrial diseases and Lesch-Nyhan disorder [41].

Dystonia may also be classified according to body parts affected and includes generalized dystonia, focal dystonia and segmental dystonia. Generalized dystonia involves several body parts. Focal dystonia affects a single body part as seen in blepharospasm, writer's cramp, laryngeal dystonia, cranial dystonia (Meige syndrome) and torticollis (cervical dystonia). Segmental dystonia involves two or more adjacent body parts such as in cranial-cervical dystonia, crural dystonia and brachial dystonia.

The therapeutic pharmacological options for dystonia are limited and as a result alternative surgical options have been developed. These surgical options include peripheral procedures such as intrathecal baclofen pumps, botulinum toxin injections, denervation as well as central procedures which includes DBS and thalamotomy. Previously, thalamotomy was

the treatment of choice although the results have been variable. DBS however is a controlled, reversible therapy comparable to ablative procedures [40].

At this time, brain stimulation is recommended only for patients with severe dystonia despite optimal medical therapy. The surgical treatment of choice for generalized dystonia is DBS of the GPi [19], [40]. In 40% to 80% of cases an improvement in motor and disability scores based on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS) has been reported [41]–[47].

Vidailhet *et al.* performed this procedure in 22 patients with primary torsion dystonia, with double-blind evaluation up to 12 months after surgery [17]. Dystonia rating scales and disability scores improved by approximately 50% at 12 months. The BFMRS movement subscore improved from a mean 46.3 before surgery to 21.0 at 12 months.

Vidailhet *et al.* findings support the efficacy and safety of the use of bilateral stimulation of the internal globus pallidus in selected patients with primary generalized dystonia [17]. Similar results have been described in segmental dystonia as well [40], [42], [47]–[50].

Kupsch *et al.* compared this surgical treatment with sham stimulation in a randomized, controlled clinical trial [18]. They found that bilateral pallidal neurostimulation for 3 months was more effective than sham stimulation in patients with primary generalized or segmental dystonia [17]. During the open-label extension period, this improvement was sustained among patients originally assigned to the neurostimulation group, and patients in the sham-stimulation group had a similar benefit when they switched to active treatment. The combined analysis of the entire cohort after 6 months of neurostimulation revealed substantial improvement in all movement symptoms (except speech and swallowing), the level of disability, and quality of life, as compared with baseline scores [17].

Although GPi stimulation has been the primary target for DBS surgery of severe medication-refractory dystonia, Ostrem *et al.* showed in a prospective study that bilateral STN DBS resulted in improvement in dystonia and they suggested that STN DBS may be an alternative to GPi DBS for treating primary cervical dystonia with the advantage of overcoming the bradykinetic side effect that is usually associated with GPi stimulation [51].

The predictors for a good outcome in generalized dystonia includes age of onset and lack of multiple orthopedic deformities [52]. In addition, appendicular symptoms appear more responsive than axial symptoms [53]. With regards to focal dystonia, bilateral and unilateral GPi DBS have also been found to be effective in the management of cervical dystonia with improvements on the Toronto Western Spasmodic rating scale (TWSTRS) noted in 40% to 60% [45], [54], [55]

Disappointing and mixed clinical results have, however, been noted with secondary dystonia. The only exception seems to be those with tardive dyskinesia, in which some benefit has been documented [55]–[58]. DBS has also been shown to be beneficial in post-anoxic dystonia [40]. Although data is sparse, DBS may also play a role in dystonia related to neurodegenerative disorders which includes Lesch-Nyhan, Hallervorden-Spatz and Huntington's Disease [59]–[64].

### *B. DBS for Neurobehavioral Disorders*

Although most patients with neurobehavioral disorders respond well to medications, at least 20% of patients can become medication refractory and disabled over time [65]. Remarkable advances in functional neuroimaging have resulted in improved insights into the underlying dysfunctional neural networks of these disorders. For example, in patients with depression, brain imaging has shown abnormalities in the orbitofrontal and ventromedial frontal cortices, dorsolateral and ventrolateral prefrontal cortices and the anterior and subgenual cortices [66].

The two main areas of stereotactic targeting for neuromodulation by DBS in neuropsychiatric and psychiatric disorders are the basal forebrain (ventral striatum/ventral internal capsule region, VC/VS) and the subgenual cingulate gyrus. The results that have been achieved so far are promising. Malone reported a 50% response rate in 15 patients who underwent DBS of the VC/VS region for depression [67]. Likewise, Mayberg reported remission of depression in four out of six patients who had DBS electrodes implanted into the subgenual cingulate cortex bilaterally [65].

Obsessive compulsive disorder (OCD) is a disabling condition which is characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions) such as repetitive cleaning or washing. This disorder is due to dysfunction of cortico-striato-thalamo-cortical loops involving the basal gaglia, cortex (OFC) and anterior cingulate cortex (ACC) [68]. DBS of internal capsule and adjacent ventral striatum was proposed as a treatment option for severe and extremely treatment-resistant obsessive-compulsive disorder.

Bilateral stimulation of the VC/VS region causes several types of affect changes depending on stimulation programming parameters and the contact combinations. For example, some patients who underwent this treatment reported sudden happiness, joy and a good feeling. Some smiled and laughed, sometimes extensively after stimulation was switched on with particular contact combinations. In the same way, worsening mood, depressive feelings and greater anxiety also were reported. Turning the stimulation off abolished these feelings [69].

Greenberg *et al.* studied DBS of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) in four centers across the U.S. and Europe over an 8-year period. They found significant symptom reductions and functional improvement in about two-thirds of patients [70]. Nuttin *et al.* showed that capsular stimulation using implanted quadripolar electrodes in both anterior limbs of the internal capsules in six patients reduces core symptoms 21 months after surgery in patients with severe, long-standing, treatment-refractory obsessive-compulsive disorder. There were also changes in regional brain activity demonstrated by using functional magnetic resonance imaging and positron emission tomography [71].

In an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase study of 16 patients, Denys *et al.* found that bilateral DBS of the nucleus accumbens led to a decrease of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) by 46%, from 33.7 at baseline to 18.0 after 8 months ($P < .001$). In the

double-blind, sham-controlled phase ($n = 14$), the mean (SD) Y-BOCS score difference between active and sham stimulation was 8.3, or 25% ($P = .004$). Denys *et al.* findings suggested that bilateral DBS of the nucleus accumbens may be an effective and safe treatment for treatment-refractory OCD [72].

In six adult patients with treatment-refractory OCD, Goodman *et al.* placed DBS electrode bilaterally in an area spanning the ventral anterior limb of the internal capsule and adjacent ventral striatum. After 12 months of stimulation, four (66.7%) of six patients met a strict criterion as "responders" ($>$ or $= 35\%$ improvement in the Y-BOCS and end point Y-BOCS severity $<$ or $= 16$). Patients did not improve during sham stimulation. Depressive symptoms improved significantly in the group as a whole while global functioning improved in the four responders. Adverse events associated with chronic DBS were found to be generally mild and amendable with programming [73].

Based on such trials, DBS has been approved since 2009 by the FDA [as a humanitarian device exemption (HDE)] for the treatment of OCD [70], [74].

### C. DBS for Epilepsy

In spite of advances in the development of antiepileptic medications, up to 30% of patients with epilepsy still have poorly controlled epilepsy. Neurosurgical interventions for epilepsy have traditionally adopted an ablative approach with initial determination and then excision of the epileptogenic brain tissue. Sometimes, such an extirpative approach is impractical. This may be either because there are multiple epileptogenic areas in the brain or because the epileptogenic region is situated in a region of the brain that has a vital neurological function that cannot be compromised.

Electrical neuromodulation has evident advantage in this situation because of its intrinsic reversibility and adjustability. DBS has been applied to the anterior nucleus (AN) of the thalamus, centromedian (CM) thalamus, hippocampus and subthalamic nucleus (STN) for the treatment of drug resistant epilepsy [74]–[78]. These thalamic structures are targeted with DBS because thalamocortical connections involving them and cortical structures have been demonstrated to be involved in the development and propagation of different types of seizures [74].

The anterior thalamic nucleus (ANT) was chosen as the target for a large multicenter DBS epilepsy trial [Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE)], in part because of its targetable size, evidence in animal models of epilepsy, and promising data in human studies [75]. The results of the SANTE trial were published in 2010. The SANTE trial is the first randomized, controlled trial to provide evidence that bilateral stimulation of the ANT reduces seizure frequency in patients with medically refractory partial and secondarily generalized seizures up to 2 years after placement. DBS of the ANT is being reviewed by the FDA for approval in the U.S., whereas it is CE Mark approved in Europe.

Responsive neurostimulation, as exemplified by the RNS System[1] is a novel stimulation paradigm which employs "closed loop neurostimulation". In this situation, stimulation to abort epileptic episodes is coupled to real time physiological recordings which detect epileptic seizures thus closing the loop on the stimulation. The objective of the design is to abort seizure propagation prior to its clinical manifestation. The design of RNS consists of a neurostimulator that is connected to sensing electrodes which may be in the form of a subdural strip and/or depth electrodes. The neurostimulator contains a battery, connection ports for the electrodes, data storage, the wireless communication system, and seizure detection electronics. RNS System is a "closed-loop stimulation" process, which refers to its use of signal processing algorithms to initiate bursts of stimulation in real time during the evolution of abnormal activity. This is in contrast to the conventional DBS stimulation or vagus nerve stimulation which are both "open-loop stimulation" paradigms which are programmed to provide continuous stimulation regardless of the brain's electrical activity and does not provide any mean of recoding brain's electrical activity [79].

[1]Trademarked, Neuro-Pace, Mountain View, CA.

### D. DBS for Pain

A significant proportion of patients with chronic neuropathic pain continue to suffer pain in spite of using advanced pharmacotherapy. For this group of patients, electrical neuromodulation by DBS may be an option. Currently, the indication for DBS in pain management is the intractable pain syndromes that do not respond to less invasive options [80].

The DBS targets for the modulation of pharmacoresistant neuropathic pain include the ventral posterior (sensory) nucleus of the thalamus, the periventricular gray (PVG) and the periaqueductal gray (PAG) areas.

## V. Rising and Promising Indications

DBS is currently being utilized to address several medical conditions such as the Tourette's syndrome [81], minimally conscious state (MCS) following severe traumatic brain injury (TBI) [82], obesity [83], dementias (including Alzheimers) [84], addictions [85], tinnitus [86] and anorexia [87].

### A. Tourette's Syndrome

Tourette's syndrome (TS) is characterized by chronic vocal and motor tics which typically start in early school age and is often associated with other disorders such as OCD and ADHD. It has a prevalence of 0.7% to 4.2% [88].

Disruptions in the CSPTC circuits are thought to mediate the behavioral disturbances in TS [89]–[91]. Abnormalities in the metabolism of the ventral striatum have been suggested by neuroimaging studies in patients with TS [92].

The diagnostic criteria for Tourette syndrome requires the presence of multiple motor tics and at least one vocal tic that develop before the age of 18 years and last for at least more than 1 year from their onset [93]. Tourette syndrome is associated with multiple psychiatric comorbidities such as attention-deficit hyperactivity disorder, obsessive-compulsive disorder anxiety, depression, personality disorders, learning disability, poor anger management, and rage.

Currently, DBS is an investigational therapy for managing drug-resistant forms of Tourette syndrome [93]. Numerous reports have suggested that stimulation of the GPi and thalamus

are effective in the reduction of tics [79]–[109]. However, other areas of areas of the brain have been targeted by DBS, including the subthalamic nucleus, centromedian–parafascicular complex of the thalamus, nucleus accumbens and anterior limb of the internal capsule. Until now the optimal location and the optimal stimulator settings that provide the most advantageous outcome remain unclear. In addition, beneficial effects do not occur in all patients and the criteria for selection of patients need to be optimized [93].

### *B. Disorders of Consciousness and Cognition*

Bilateral thalamic DBS in a patient in a minimally conscious state leading to improvement in arousal was reported was reported by Schiff *et al.* [82]. The bilateral DBS targets were the anterior interlaminar thalamic nuclei and the paralaminar regions. These targets have projections into the supragranular cortical regions and are thought to play a role in arousal. There have other larger trials of DBS in patients in vegetative states but the results have been mixed [110]–[113]. The mixed results may have been as a result of the heterogenous nature of the head injury in these patients. [114]

*1) Alzheimer Disease:* Alzheimer disease (AD) is a progressive degenerative disorder. It results in a functional disorder that affects the neural circuits underlying cognitive and memory functions [115]. Hamani *et al.* reported memory improvement in a patient after placing fornix/hypothalamus DBS for obesity [116]. Following this finding, Laxton *et al.* conducted a phase 1 trial of fornix/hypothalamus DBS in six patients with mild AD. Positron emission tomography was used to estimate the pre- and postoperative cerebral glucose uptake to quantify the impact of DBS [117]. They found an increase in glucose metabolism in the temporal and parietal cortical areas at 1 month in all patients, and this effect was sustained in most of the affected areas at the 1-year followup. Additionally, they found evidence of improvement in cognitive function or at least slowing of anticipated rate of decline at 6 and 12 months after DBS. Although the study by Laxton *et al.* did not provide a conclusive answer regarding the efficacy of DBS in AD, their findings are promising and deserve further investigation given the need for advances in treatment options for this disabling disease [115], [117].

### *C. Addiction and Eating Disorders*

The reward connections underlying eating disorders and addiction have become a target for DBS. Stereotactic electrocoagulation of portions the lateral hypothalamus was shown to achieve weight reduction in three patients by Quaade *et al.* [118]. In addition, some studies in animals have identified the lateral hypothalamus (LH), ventromedial hypothalamus (VMH) and nucleus accumbens (NAc) as potential targets for managing obesity [119]. The lateral hypothalamus and nucleus accumbens connections overlap and may be involved in the food reward circuitry. The NAc plays a central role in the reward circuitry making it an appealing target for treating addiction. Studies in rats have suggested that DBS of the NAc may reduce cocaine dependence and addiction [120]. DBS of the NAc for other disorders such as Tourette's and OCD have been shown in preliminary studies to also have an impact on smoking cessation [121]. There has been a recent report of both smoking cessation and weight loss in a single patient following NAc stimulation [122]. Also, a reduction in alcohol dependence was reported in a single patient following DBS of the bilateral NAc for anxiety disorder [123]. In addition, DBS of the NAc, ventral striatum and subgenual cingulated cortex may be promising in the management of anorexia nervosa [73], [124].

## VI. Future Technical Horizons

Advances in biomedical engineering will continue to drive the development and refinement of implantable DBS devices. Designs of DBS leads with the capability of directional stimulation or DBS systems with feedback sensors that can detect changes in the electrical activity of the brain networks and concentration of relevant neurotransmitters and adjust the degree of stimulation as needed are promising future potentials.

This concept of closed-loop stimulation could lead to the development of personalized therapy as the current stimulation technology is mainly based on predetermined and fixed stimulation parameters. Furthermore, closed-loop DBS paradigms modulate pathological oscillatory activity rather than the discharge rate of the basal ganglia-cortical networks. Thus, closed loop stimulation technology may offer a better effective management of advanced Parkinson's disease and a better adaptation to personal patient needs which may result in a higher patient quality of life [125].

Pulse shape modification is a new technology that increases the options of programming and is being currently investigated. This parameter (pulse shape) could be added to the classical programming parameters (the intensity, the frequency and the pulsewidth) to improve the efficacy of DBS [126].

Compatibility of DBS leads with MRI is another area of great interest as MRI scans are often required for the assessment of other neurological conditions in patients with DBS systems. The development of rechargeable powering mechanisms capable of harnessing the body's mechanical energy are also of immense interest as current pulse generators (batteries) used for DBS have a limited lifespan. Other areas of active biomedical engineering interests are the miniaturization of the pulse generators and improvements in programming capabilities.

## VII. Conclusion

DBS is now an established treatment modality for different chronic neurological disorders, such as movement disorders, and is finding increasing applications in the treatment of epilepsy, neurobehavioral disorders and chronic pain.

Advances in the neurosciences, functional brain imaging and the understanding of neural circuits underlying different neurological conditions will continue to drive the applications of DBS. Further research still needs to done to understand the basic mechanisms of DBS action. Finally, innovations in biomedical engineering and technology will continue to be applied to DBS and the ideal platform for the development of these innovations is the active collaboration between basic scientists, engineers and clinicians.

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