

Deep brain stimulation for movement disorders

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Introduction

Movement disorders encompass a number of neurological diseases affecting the ability to control movement. Movement is in command of several interacting brain structures, including the motor cortex, the cerebellum, and the basal ganglia (BG). The BG comprises a group of interconnected deep brain nuclei [caudate and putamen (C-P), Globus pallidus (GP), substantia nigra (SN), subthalamic nucleus (STN)] that, through their connections with the thalamus and the cortex, primarily influence the involuntary components of the movement and muscle tone. Disruption of this complex circuitry within the BG causes the most frequent movement disorders, such as Parkinson's disease (PD), essential tremor (ET), and dystonia ([Alexander et al., 1990](#)). The treatment of these disorders with the deep brain stimulation (DBS) technique is the topic of the present review, which describes the current clinical use and approval of DBS indications.

Already in the 1950s, some early studies evaluated the possible therapeutic benefits of chronic stimulation of the subcortical structure in psychotic patients ([Hariz et al., 2010](#)). Nevertheless, modern DBS was first clinically used in the treatment of movement disorders. Several reviews provide a comprehensive account of the symptoms/syndromes that might be the target of this treatment, its clinical efficacy, as well as its possible complications and side effects ([Skidmore et al., 2006](#) ; [Wichmann and DeLong, 2006](#) ; [Collins et al., 2010](#)). The DBS surgical treatment of movement disorders has its foundations in two seminal papers by the “Grenoble Group” of [Benabid et al. \(1987\)](#) describing the combined (thalamotomy and stimulation) stereotactic surgery of the ventral

intermediate (VIM) nucleus of the thalamus and, in 1993, DBS of the STN for PD patients ([Pollak et al., 1993](#)). Modern DBS followed ablative stereotaxy that was performed for most of the twentieth century for medically refractory severe movement disorders, mostly PD and ET, with selective destruction of parts of the GP or of the thalamus ([Schwalb and Hamani, 2008](#)). Although the procedure was largely effective in relieving the symptoms, it was irreversible, and in some cases side effects were actually encountered. As a result, in the 1970s, following the advent of the highly effective levodopa treatment for PD, ablative surgery was largely abandoned. However, after the initial enthusiasm for the medical treatment of PD, it was apparent that long-term levodopa therapy had significant drug-induced complications (the so-called “ long-term levodopa syndrome”) mainly consisting in involuntary movements (dyskinesias) and motor fluctuations, which could have a severe disabling effect in a significant percentage of levodopa-treated PD patients. In addition, among the classic symptomatologic triad of PD – bradykinesia, rigidity, and resting tremor – this latter symptom is always less responsive to levodopa treatment ([Fishman, 2008](#)). Therefore, many clinical centers took advantage of the fact that DBS technology is less invasive than stereotactic surgery, and is also reversible and adjustable, more suitable for an increasing number of medically treated PD patients with disabling dyskinesias/motor fluctuations and/or medically refractory tremor ([Collins et al., 2010](#)).

The DBS technique uses continuous high-frequency stimulation of specific brain regions through chronically implanted electrodes, connected to a pulse generator, similar to a cardiac pacemaker, that is telemetrically

programmable. Electrodes are implanted into the target brain area by using a stereotactic surgical procedure with electrophysiological recordings. Clinically, the effects of DBS mimic those produced by lesioning the target structure ([Schwalb and Hamani, 2008](#)). However – at the cellular or pathway level – the actions of high-frequency DBS that mediate its clinical efficacy are not fully understood. Indeed, recent evidence suggests that DBS has more complex mechanisms of action than the pure functional inactivation of the target region. For instance, high-frequency stimulation of the most used target structures for DBS in PD and ET, i. e., the STN and the internal part of the GP (GPi), not only produces both inhibitory and excitatory effects on local neurons, but has also a modulatory influence on the afferent inputs to the target nucleus and on the efferent outputs ([McIntyre et al., 2004](#)). In any case, the ultimate effect of modulating the network activity within the BG can be viewed as the takeover on hyperactive elements or structures of the cortico-BG-thalamo-cortical complex circuit ([Gradinaru et al., 2009](#) ; [Kopell et al., 2009](#) ; [McIntyre and Hahn, 2010](#)).

Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease. Its complex multifactorial etiology might comprise, from recent genetic and epidemiological studies, genetic susceptibility factors, and environmental risk factors. PD is a progressive disease with age-dependent increasing prevalence (from 1 to 3% in the population aged over 65 years; [Wirdefeldt et al., 2011](#)). Loss of SN pars compacta (SNc) dopaminergic neurons projecting to the C-P is considered the neuropathologic hallmark of PD. The consequent reduced dopaminergic input is considered the cause of the motor

manifestations of the disease (bradykinesia, rigidity, resting tremor, and postural instability) and the reason for the remarkable clinical success of dopamine replacement therapy. However, it has become increasingly apparent that the neuropathological changes of PD (mostly alpha-synuclein pathology) extend far beyond the nigro-striatal system, affecting also the olfactory bulbs, and the autonomic nervous system, many structures of the lower brainstem, the limbic system, as well as the mesocortical and neocortical regions. Most of the extra-nigral pathological alterations are considered responsible of the non-motor symptoms of the disease, such as hyposmia, autonomic dysfunctions, sleep disorders, depression, and cognitive impairments ([Braak et al., 2003](#)).

Nevertheless, with regard to DBS treatment in PD, the main focus is on the progressive degeneration of the nigro-striatal dopaminergic projections and the appearance of disabling side effects, i. e., motor fluctuations and dyskinesias, in a large percentage of PD patients on long-term dopaminergic therapy ([Schrag and Quinn, 2000](#)). Because such complications are often poorly managed by oral therapy, it is estimated that more than 10% of PD patients could benefit from DBS treatment. The selection of candidate patients for DBS has strict inclusion/exclusion criteria. The best candidates are PD patients with severe motor symptoms in the off-medication condition that continues to indicate a substantial benefit from levodopa therapy, despite the disabling drug-induced motor complications. Main exclusion criteria are the presence of symptoms suggesting an atypical parkinsonian syndrome that usually does not respond to levodopa therapy, or the

presence of neuropsychiatric (depression) or cognitive alterations ([Bronstein et al., 2011](#)).

There are four possible target sites for the placement of the stimulating electrodes: although stimulation of the VIM thalamic nucleus has a clear effect on tremor, DBS of the STN, or GPi has a broader influence on all parkinsonian symptoms and represents, nowadays, the treatment of choice in most PD patients. A more recent, still experimental, target is the pedunculo-pontine nucleus (PPN) that may be appropriate for patients with gait freezing ([Stefani et al., 2007](#) ; [Wilcox et al., 2011](#)). Because most patients undergoing the DBS procedure have bilateral symptoms, both right and left STN or GPi are usually implanted for maximal benefit. Any parkinsonian symptom that can improve with levodopa can also improve with DBS. Three recent randomized controlled studies in patients with PD reported that STN DBS plus best medical therapy was more effective than best medical therapy alone in improving motor function and quality of life, but was also associated with an increased risk of serious adverse events ([Deuschl et al., 2006](#) ; [Weaver et al., 2009](#) ; [Williams et al., 2010](#)). After neurostimulation, the clinical response is more stable during the day, with significant lessening of the “ off” periods that are so frequent and disabling in PD patients. Furthermore, DBS reduces levodopa-induced dyskinesias. In the case of STN DBS, this effect could be mostly ascribed to the reduction in medication dose, possible when the stimulation is active. GPi stimulation patients experience a reduction in dyskinesias without any levodopa dose reduction ([Weaver et al., 2009](#) ; [Follett et al., 2010](#)). In addition, reduction of dopaminergic therapy after STN DBS may help in reducing some

psychiatric symptoms, like visual hallucinations and impulse control abnormalities, which are frequent behavioral complications in the treatment with dopamine agonists ([Lulé et al., 2012](#)).

Complications related to surgery are primarily intracerebral hemorrhage (less than 2% in most centers) and infection (in about 4% of the cases; [Kleiner-Fisman et al., 2006](#)). STN DBS can worsen speech and gait in some patients, requiring an adjustment of stimulation parameters. A recent study reported that depression worsened with STN DBS but was improved with GPi DBS ([Follett et al., 2010](#)). There are several reports that describe neuropsychiatric symptoms following STN DBS in PD patients. However, such symptoms were generally transient and mild if managed appropriately ([Volkman et al., 2010](#)). With these possible complications in mind, we can say that DBS offers important symptomatic benefits in cognitively intact PD patients with moderate disability who still maintain a therapeutic response to levodopa. Medium- and long-term studies have provided evidence that stimulation-induced motor improvement was still evident at 5–8 years' follow-up ([Fasano et al., 2010](#) ; [Moro et al., 2010](#)). However, DBS does not modify the progression of the underlying PD pathology, so, after years, patients can still develop disabling levodopa-resistant symptoms, like gait disturbances and cognitive impairment.

Essential Tremor

Essential tremor is one of the most common movement disorders with prevalence that varies depending on age, raising up to 5% in the population over 60. The typical postural and action tremor is most often located in the upper limbs; less frequently it affects the head, the tongue, and the lower

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limbs. Even though the quality of life is impaired by tremor in more than 70% of patients, only 10% are medically treated. In addition, only 50% of treated patients show a good response to therapy ([Lyons et al., 2003](#)). In the middle of the twentieth century the ventrolateral thalamus became the main surgical target for parkinsonian and various other types of tremor, including ET. After the introduction, in the early 60s, of micro recording during stereotactic surgery, it became apparent that small lesions of the VIM could suppress tremor. Afterward, unilateral stereotactic VIM lesioning was a frequent procedure in many clinical centers worldwide and resulted in a permanent significant contralateral improvement of the most common types of tremor. However, the very satisfactory results in controlling ET and other types of tremors (significant reduction of limb tremor in 80-90% of patients with ET) obtained thanks to the thalamotomy, were accompanied by a relatively high complication rate, especially if the procedure was performed bilaterally. In fact, almost 30% of patients who underwent the ablative procedure bilaterally experienced permanent speech and cognitive deficits. Introduction of DBS of the thalamic VIM nucleus in ET treatment helped to reduce complication rate with remaining high efficacy. Therefore, VIM DBS is viewed as the target therapy for these patients with a debilitating ET. Although the exact etiology and pathophysiology of ET is still unknown, it is believed that high-frequency stimulation of the VIM nucleus may block the abnormal oscillatory activity within the interconnected regions, including the cerebellum and the motor cortex ([Dostrovsky and Lozano, 2002](#)).

The main exclusion criteria of DBS treatment for ET include altered cognition and the presence of an untreated or disabling psychiatric illness. Patients

with ET are considered good DBS candidate if they were also refractory to an adequate trial of accepted oral medications ([Katz et al., 2011](#)). The most frequent stimulation-induced side effects are paresthesias, followed by dysarthria and pain, symptoms that are reversible when the stimulation is turned off. Furthermore, gait/balance may worsen following DBS for medication refractory ET ([Hwynn et al., 2011](#)). The high initial efficacy of VIM DBS declines over time ([Schuurman et al., 2008](#)). However, most patients experience a good response for several years.

Dystonia

Dystonia is a movement disorder that presents with sustained, uncontrolled, often painful muscle contractions causing repetitive movements and abnormal postures. Depending on the localization, dystonia is divided into focal (affecting a single body region), segmental (two or more adjacent areas), or generalized (involving the legs, or one leg and the trunk, plus at least one other area of the body). Depending on etiology, dystonia might be primary (idiopathic) or secondary to a known structural lesion of the brain, like perinatal hypoxia, infections, stroke, and trauma. Idiopathic dystonia in adults is most commonly a focal/segmental disease, like cervical dystonia (the most common form), blepharospasm, or writer's cramp, whereas in children and young adults the generalized inherited forms are more common. There are multiple forms of inheritable dystonia, with the DYT-1 gene mutation, responsible for early-onset generalized dystonia, as the most frequent form ([Albanese et al., 2011](#)). Medical therapy is very effective in a very limited subset of dystonia patients (20–40%). In addition, doses of drug(s) required for therapy often produce intolerable side effects. Dystonia

is still one of the most important indications for botulinum toxin (BT) therapy that selectively blocks the cholinergic innervation of the muscles. BT can be used to treat focal dystonias and also the most relevant target muscles in segmental and generalized dystonias. Combinations of BT therapy with all other treatment options, including DBS, are possible.

Patients with dystonia who might be evaluated for DBS treatment should have symptoms that cause significant disability, despite maximally tolerated medical treatment. The factors that influence the selection of patients with various types of dystonia for treatment with DBS have been recently reviewed by [Bronte-Stewart et al. \(2011\)](#). Patients candidate to surgery should undergo DBS treatment before the onset of orthopedic deformities that may impede functional benefit even if dystonia is ameliorated by DBS. The exact pathophysiological mechanisms of dystonia are not completely understood and the best brain target for DBS in dystonic patients has not been quite identified yet. However, a lot of evidence indicates that the interplay between the BG and cerebellar circuits has a major role. In particular, the GPi has been proven to show an abnormal firing activity in dystonia, and GPi is the usual target of DBS for such patients. On the other hand, previous studies on STN stimulation in dystonia gave contrasting results ([Detante et al., 2004](#) ; [Sun et al., 2007](#)). In a 3-year follow-up study, the beneficial effects of bilateral GPi stimulation in young patients with identified DYT-1 mutation reached 90% ([Coubes et al., 2000](#)). Positive effects of DBS on dystonia scales, quality of life, and pain reduction have been confirmed in different studies also in adults with primary generalized dystonia and in heterogeneous groups comprising patients with secondary or

focal disease ([Vidailhet et al., 2005](#) ; [Kupsch et al., 2006](#) ; [Andrews et al., 2010](#)). Dynamic movements are the first that respond to DBS, whereas improvement of persistent dystonic posture could be observed after months or years ([Welter et al., 2010](#)). Because improvement may take months to occur, the evaluation of the efficacy of DBS treatment is more challenging than in patients with PD or ET. Another difference with the DBS system in PD is that the optimal frequency and amplitude stimulation settings needed for DBS in many dystonia patients are higher than for GPi DBS in PD, and much higher than for STN DBS in PD patients.

Perspectives on Evolution of Deep Brain Stimulation

Currently, the DBS technique uses electrodes of 1.3 mm in diameter integrating four contacts of 1.5 mm length each, connected to an internal pulse generator. Minimizing the hardware dimensions remains one of the goals of DBS development, to allow the implantation of the internal pulse generator in the scalp or within the skull. Minimizing the size of the hardware would also allow implanting multiple electrodes to multiple anatomical targets of the brain more precisely and effectively. Further development of DBS will probably depend on the use of multiple electrodes with “closed-loop” systems that include macro recordings and stimulation. The influence of local monitoring of neurotransmitter activity might impact on the patterns of stimulation, particularly with regard to the interactions between stimulation and medications. Moreover, since the introduction of the DBS technique the lifespan of the battery has increased twice, but programming the stimulation today is performed via telemetry that requires several time-consuming visits before the best therapeutic effect can be reached. In the

future, development of “ closed-loop” DBS systems and neuroimaging modalities might allow the performance of effective and safe programming through remote access, such as the telephone or the Net ([Andrews, 2010](#) ; [Shah et al., 2010](#)).

The role of DBS for PD, ET, and dystonia is a well-established treatment option, currently approved for use in the United States (DBS for drug refractory primary dystonia received in 2003 the FDA approval as humanitarian use device - HUD), Canada, Europe, and Australia. As the indications for DBS broaden to include other neurological and psychiatric conditions, the number of DBS implants worldwide is expected to grow in the next years. In 2009, treatment with DBS of obsessive compulsive disorder (OCD) was approved by FDA as HUD and received the CE mark approval. In 2010, the CE mark for DBS treatment of Epilepsy refractory to medical treatment was also granted. On-going clinical trials with DBS in the treatment of mood disorders, tremor in multiple sclerosis, pain and cluster headache, hypertension, minimally conscious state, obesity, memory impairment, aggressiveness, drug addiction, and other CNS disorders will increase the number of indications for DBS in the future ([Lyons, 2011](#)). However, the fact that FDA allowed DBS to be used in dystonia or OCD under an humanitarian device exemption (HDE) application, thereby without the need for a randomized clinical trial of sufficient size to demonstrate statistically significant benefit without undue harm, has spurred impassioned debate on the regulatory and ethical issues linked to the clinical use of DBS ([Fins et al., 2011](#)). These issues likely will become even more urgent as the number of indications for DBS treatment will increase.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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