Deep brain stimulation (DBS) is an effective surgical therapy for well-selected patients with medically intractable Parkinson’s disease (PD) and essential tremor (ET). The purpose of this review is to describe the success of DBS in these two disorders and its promising application in dystonia, Tourette Syndrome (TS) and epilepsy. In the last 10 years, numerous short- and intermediate-term outcome studies have demonstrated significant relief to patients with PD and ET. A few long-term follow-up studies have also reported sustained benefits. When successful, DBS greatly reduces most of parkinsonian motor symptoms and drug-induced dyskinesia, and it frequently improves patients’ ability to perform activities of daily living with less encumbrance from motor fluctuations. Quality of life is enhanced and many patients are able to significantly reduce the amount of antiparkinsonian medications required to still get good pharmacological benefit. Overall, adverse effects associated with DBS tend to be transient, although device-related and other postoperative complications do occur. DBS should be considered the surgical procedure of choice for patients who meet strict criteria with medically intractable PD, ET and selected cases of dystonia.

Keywords: Deep brain stimulation; Parkinson’s; Essential tremor; Dystonia; Tourette syndrome; Epilepsy; Obsessive-compulsive; Depression

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1. Introduction

Stereotactic thalamotomy in the nucleus ventrointermedius of the thalamus (VIM) and pallidotomy of the globus pallidus internus (GPI) were popular neurosurgical treatments for disabling tremor until they fell out of favor with the advent of levodopa therapy in the early 1970s. At its peak, thalamotomy for Parkinson’s disease (PD) had limited therapeutic efficacy. Tremor recurred in about 20% of operated cases and serious complications were common. Permanent disability often resulted [1,2]. Bilateral thalamotomy carried an additional high risk of severe impairment of speech [3]. Unilateral pallidotomy is still performed today with conflicting efficacy across studies. Rare long-term studies have shown lack of sustained benefit [4]. Similarly, subthalamotomy has been associated with improvements in contralateral bradykinesia, rigidity and tremor in the short-term [5,6], but decline in benefit has been reported at 6 months, and complete loss of benefit by 18 months [7].

Neurosurgical treatment of parkinsonism was revived in the late 1980s after two decades of experience with levodopa showed a unique set of drug-related complications in advancing PD, including choreiform and dystonic involuntary movements (dyskinesia) and response fluctuations generally referred to as “wearing-off” or “on-off” reactions. At that time, high-frequency stimulation of VIM was used intraoperatively to define the most appropriate target for ablation. Intraoperative observations revealed that stimulation applied prior to thalamotomy completely yet reversibly suppressed tremor. Subsequently, in 1987, Benabid et al. conducted a pilot study of chronic high-frequency stimulation of VIM for tremor suppression without subsequent ablation and were encouraged by the positive results [8]. This led to the first open label clinical trial of high-frequency, electrical deep brain stimulation (DBS) for medically refractory parkinsonian and essential tremor (ET) [9].

The Food and Drug Administration (FDA) approved DBS of the thalamus for parkinsonian and ET in 1997, and in 2002, of STN and GPI for PD. More recently, success in managing these disorders with DBS has opened the door to its use in other neurologic conditions, including dystonia, Tourette Syndrome (TS), and epilepsy.

2. Surgical procedure

DBS consists of stereotactically implanting electrodes through a frontal burr hole into a neural target associated with the basic pathophysiology of the disease [10–15]. During electrode insertion, electrophysiologic recordings identify anatomic boundaries of the target. After implantation of the DBS leads, clinical effects of stimulation in PD and ET are evaluated with the patient awake to assess symptom relief and the threshold of adverse effects prior to closure. Thus, intraoperative electrophysiologic recordings, stimulation and concurrent clinical observation of the patient’s signs and symptoms guide implantation for accurate target localization. DBS for primary generalized dystonia (PGD), is commonly performed under general anesthesia, since dystonic postures and involuntary movements of the head and neck can prevent placement of the stereotactic head frame. Moreover, children, who are frequently the victims of dystonia, tend to be less cooperative while awake in the operating room. The effects of stimulation are generally not acutely observable in PGD intraoperatively but emerge over the course of a few weeks postoperatively [16–19].

Once the electrode is in its fixed, correct position, the surgeon inserts the internal pulse generator (IPG) into a subcutaneous pocket adjacent to the clavicle. Although less popular, some experts favor placement of the IPG into the abdominal wall because of faster postoperative healing due to additional thickness of the skin and fatty tissue [20]. The IPG is attached to the DBS lead by a subcutaneously tunneled wire, the top end of which is anchored to the burr hole site at the top of the skull.

Clinical efficacy of DBS depends on accurate, MRI-directed targeting [21]. Pre-targeting using statistical data from atlases [22] provides neurosurgeons with coordinates chosen empirically for their effect on patients’ symptoms. Simulation software can identify the electrode’s trajectory prior to surgery, avoiding deep sulci, ventricles and superficial large veins if contrast is used.

Perioperative complication rates have been inconsistent with some small studies reporting only device-related complications, while larger series report rates of up to 26% of patients [23,24]. However, most studies note transient adverse effects, such as eyelid-opening
apraxia, dyskinesia and paresthesia, occurring often when the stimulators are adjusted during the procedure or after surgery in the follow-up period. Most complications eventually resolve although rare deaths have been reported from pulmonary emboli, myocardial infarction, stroke, intracerebral hemorrhage, and suicide. Table 1 summarizes adverse events reported in 33 studies that met our inclusion criteria for systematic review outlined in each section below [11,13,14,17, 25–53]. Some reports that met our inclusion criteria for review were excluded from Table 1 because adverse effects were not clearly documented.

### 3. DBS in Parkinson’s disease

DBS has been demonstrated to be an effective therapy in patients with PD, a neurodegenerative disorder which affects more than a million Americans today. The core clinical features of rest tremor, bradykinesia and rigidity tend to occur early in the course. Postural instability, loss of balance and freezing of gait are later features. Although pathology in PD is widespread, the principal site is the substantia nigra and its pigmented dopaminergic neurons. [55–59]. As a result of progressive neuronal degeneration in PD, the brain’s main source of dopamine is gradually depleted and clinical signs of disease eventually evolve, usually when SN neurons are depleted by at least 50–60% of normal [60]. While dopamine replacement therapy with levodopa is generally effective in treating early stages of PD, long-term therapy is associated with the emergence of motor complications in the majority of patients, including choreiform or dystonic involuntary movements (dyskinesia) and the “wearing-off” phenomenon, which is thought to be the result of levodopa’s short (90 min) half-life [61,62] and the loss of the capacity of striatal neurons to store and tonically release dopamine into the synapse. As PD progresses, intractable disability is commonly caused by medically unresponsive axial symptoms, particularly gait and postural impairment, dysphagia, dysphonia and cognitive decline [57–63].

#### 3.1. Basal ganglia circuitry in Parkinson’s disease [64]

The choice of the best anatomic targets for DBS is based on a clear understanding of the direct and indirect neural circuitry of the basal ganglia (BG) [65,66]. According to the accepted model of how the system works, there is a normal physiologic balance between indirect projections from the caudate and putamen (striatum) to the Gpi (via the external segment of the globus pallidus (GPe) and STN) and direct projections from striatum to Gpi. Final output from the BG is a modulated inhibition through Gpi to the motor nuclei of the thalamus (VA/VL complex) and beyond to motor and premotor cortex for execution of voluntary move-

ment. Normally, the STN’s output to Gpi is excitatory (onto an inhibitory assembly of neurons in the Gpi), but in PD the STN’s output is revved higher by upstream loss of dopaminergic input. The net result is greater and uncontrolled inhibitory output from Gpi to thalamus and a cascade of physiologic inhibition through connecting synapses. The discovery that high-frequency stimulation of STN and Gpi, could suppress output from these structures and relieve symptoms was a major neurosurgical breakthrough, because it offered a safer and more effective therapeutic option than the riskier ablative procedures.

Evidence accumulated to date from a large non-randomized and one small randomized clinical trial shows that DBS of either Gpi or STN produces equivalent clinical benefit in carefully selected patients with PD [25,67]. A multi-institutional, VA-NIH sponsored, randomized clinical trial has been initiated to address the possibility that one target is superior to the other. While available evidence suggests that Gpi DBS is effective treatment for motor symptoms and ADLs [68,69], only bilateral STN DBS results in sufficient improvement to permit a postoperative decrease in the dosage of anti-Parkinson medication. Moreover, Gpi DBS has been associated with more adverse effects, eventual loss of benefit, subsequent higher doses of medication and even reimplantation of electrodes into the STN [70]. Recently, STN has gained general acceptance in the United States as the preferred target for high-frequency stimulation in treating most motor symptoms of PD but without the necessary level 1 (randomized controlled trial) data to support the preference.

Bilateral STN DBS has evolved to become standard of care for surgical treatment of PD, but unilateral STN DBS is sometimes used in patients with marked asymmetry in the distribution of clinical signs. The complication rate and cost are lower than with a bilateral procedure, but it is arguably less effective in the long run. Two studies have addressed this question and have reached different conclusions. Germano et al. reported unilateral STN DBS on 12 patients who were potential candidates for bilateral STN DBS [71]. In 10 of the 12 patients, the benefit associated with the unilateral procedure—confirmed by double-blind testing—was sufficient to avoid a second operation. There were no clinically significant adverse events. In 1999, Kumar et al. compared unilateral to bilateral STN stimulation by turning off one of the stimulators in 10 bilaterally implanted patients. Unilateral stimulation provided a 25% improvement in off-period parkinsonism, whereas bilateral DBS was associated with a 55% improvement [72]. Thus, bilateral procedures appear to provide higher levels of efficacy but are associated with added risks and costs. However, some patients with highly asymmetric symptoms, particularly uncontrollable tremor, appear to be the best candidates for unilateral STN DBS [72].
Table 1
Literature review of reported complication in patients with Parkinson’s disease, essential tremor and primary generalized dystonia

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Diagnosis</th>
<th>Post-operative adverse events</th>
<th>Device-related complications</th>
<th>Treatment-related side effects</th>
<th>Neuropsychological cognitive, mood effects</th>
<th>Scotoma</th>
<th>Urinary retention</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krack et al. [25]</td>
<td>49</td>
<td>PD</td>
<td>28</td>
<td>2</td>
<td>56</td>
<td>7</td>
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<tr>
<td>DBS of PD study group [26]</td>
<td>102</td>
<td>PD</td>
<td>25</td>
<td>5</td>
<td>7</td>
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<td>57</td>
<td>PD</td>
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<td>2</td>
<td>32</td>
<td>7</td>
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<td>60</td>
<td>PD</td>
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<td>24</td>
<td>PD</td>
<td>1</td>
<td>1</td>
<td>12</td>
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<td>20</td>
<td>PD</td>
<td>3</td>
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<td>PD</td>
<td>5</td>
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<tr>
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<td>4</td>
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<tr>
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<td>49</td>
<td>PD</td>
<td>6</td>
<td>6</td>
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<td>15</td>
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<td>PD</td>
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<tr>
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<td>16</td>
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<td>PD</td>
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<tr>
<td>Kleiner-Fisman et al. [38]</td>
<td>25</td>
<td>PD</td>
<td>6</td>
<td>2</td>
<td>12</td>
<td>17</td>
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<tr>
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<td>PD</td>
<td>9</td>
<td>2</td>
<td>7</td>
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<tr>
<td>Thobois et al. [40]</td>
<td>18</td>
<td>PD</td>
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<tr>
<td>Martinez-Martin et al. [41]</td>
<td>17</td>
<td>PD</td>
<td>1</td>
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<tr>
<td>Valdecioriola et al. [42]</td>
<td>26</td>
<td>PD</td>
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<tr>
<td>Schupbach et al. [43]</td>
<td>37</td>
<td>PD</td>
<td>7</td>
<td>2</td>
<td>44</td>
<td>20</td>
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<tr>
<td>Ford et al. [44]</td>
<td>30</td>
<td>PD</td>
<td>11</td>
<td></td>
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<tr>
<td>Romito et al. [45]</td>
<td>31</td>
<td>PD</td>
<td>17</td>
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<tr>
<td>Limousin et al. [46]</td>
<td>110</td>
<td>PD, ET</td>
<td>6</td>
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<tr>
<td>Rehmorna et al. [47]</td>
<td>39</td>
<td>PD, ET</td>
<td>9</td>
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<tr>
<td>Sydow et al. [48]</td>
<td>19</td>
<td>ET</td>
<td>7</td>
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<tr>
<td>Pahwa et al. [49]</td>
<td>9</td>
<td>ET</td>
<td>2</td>
<td>3</td>
<td>16</td>
<td>2</td>
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<tr>
<td>Pahwa et al. [50]</td>
<td>17</td>
<td>ET</td>
<td>3</td>
<td>1</td>
<td>20</td>
<td>2</td>
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<td>Hariz et al. [52]</td>
<td>27</td>
<td>ET</td>
<td>10</td>
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<tr>
<td>Krause et al. [53]</td>
<td>17</td>
<td>PGD</td>
<td>5</td>
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<tr>
<td>Vidalhelt et al. [13]</td>
<td>22</td>
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<tr>
<td>Coubes et al. [14]</td>
<td>31</td>
<td>PGD</td>
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<tr>
<td>Coubes et al. [17]</td>
<td>7</td>
<td>PGD</td>
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</tbody>
</table>

*Values are total number of complications reported.

1Postoperative adverse events: infection, skin erosion, irritation, subcutaneous hematoma, contusion, intracranial hemorrhage, seizure, delirium, ballism.

2Device-related complication: diminished battery life, malfunction or malposition requiring lead or IPG adjustment or replacement.

3Treatment-related side effects (related to dopaminergic treatment, STN stimulation, or both): paresthesiae (inconsistently reported), dyskinesia, dystonia, eyelid-opening apraxia, diplopia, dysarthria (some studies reported the combination of dysarthria with hypophonia and word-finding difficulties), dysphagia, weight gain, hyperhydrosis, hypersalivation, ataxia, mild paresis, restless leg, somnolence.

4Includes headaches, pain at pocket site, connector site, pain over IPG.

5Includes adverse events reported in Jaggi et al. [15] found in Table 2.

6First three postoperative months.

7PD 67%; ET 33%.

8We combined groups since adverse events were reported collectively.

9PD 54%; ET 46%.
3.2. Mechanism of DBS

DBS produces a reversible, functional “lesion” compared with irreversibly destructive ablation. It is known that DBS results in similar therapeutic outcomes as ablative procedures. There are four strongly debated hypotheses that may in part explain the effects of DBS: (1) depolarization blockade [73], (2) synaptic inhibition [74], (3) synaptic depression [75], and (4) stimulation-induced modulation of pathological network activity [76]. Depolarization blockade and synaptic inhibition seem to explain the similar clinical effect of DBS and ablative procedures. However, in vivo studies have demonstrated increased transmitter release and sustained changes in firing of neurons in efferent nuclei consistent with activation of neurons adjacent to the DBS electrode [77,78]. While the mechanism of DBS remains unclear, stimulation-induced disruption of unopposed network activity is one hypothesis that appears to be consistent with available data [79].

STN DBS has replaced precursor ablative neurosurgical procedures, such as thalamotomy [1–3] and pallidotomy [3,4,80–83], because of superior benefit and lower risk of permanent and disabling complications [84–87]. As examples, Schuurman et al. compared VIM thalamotomy and VIM DBS and found that DBS gave more effective tremor suppression with fewer adverse effects [87]. Esselink et al. showed that bilateral STN DBS more effectively improved on and off times, dyskinesia and antiparkinson drug use than unilateral pallidotomy in a randomized, observer-blind clinical trial of 34 patients (20 STN, 14 unilateral pallidotomy) [88].

3.3. Indications

DBS for PD is indicated for otherwise healthy patients who continue to respond to medical therapy, but with disabling motor complications of levodopa therapy and/or breakthrough severe tremor [89,90]. Charles et al. demonstrated that improvement from levodopa (measured by change in the Unified Parkinson’s Disease Rating Scale (UPDRS1-III); UPDRS-III levodopa (measured by change in the Unified Parkinson’s Disease Rating Scale (UPDRS) I-III; UPDRS III (motor) score, and quality of life, as measured by the PD Quality of Life scale [r = 0.7; p < 0.001] [29]. By this measure, STN DBS improves quality of life multifactorially, including improved mood, social functioning, and involvement in hobbies. Numerous studies have reported that patients who had depended on a caregiver for activities of daily living (ADLs) prior to STN DBS, were independent postoperatively. Few studies report complete discontinuation of medication [27,96]. Speech may be more sensitive to dopaminergic therapy, although STN DBS combined with low-dose dopaminergic therapy may offer benefit despite the tendency for DBS to cause worsening speech as a complication of bilateral stimulation in some [97].

The best long-term results of DBS require the collaborative interplay of various members of the treatment team, including a skilled DBS programmer, who determines the most favorable balance between stimulation parameters, PD symptoms, and adverse effects, which will then guide appropriate alterations in dosing of medication. This process usually requires frequent outpatient visits in the first few months after surgery for “fine tuning” of DBS and drugs by the neurologist and programmer.

3.4. Clinical outcome of STN DBS

We performed a literature search for studies of bilateral STN DBS in PD with the following minimum inclusion criteria for each study: at least 10 subjects followed for 6 months after surgery; change in UPDRS as an outcome measure; other evaluations of ADLs, dyskinesia, and reported levodopa equivalent daily dosing pre- and postoperatively. Twenty-four studies met our inclusion criteria [15,25–45,92,93]. We report the longest period of follow-up in each study. Most series report highly favorable outcomes for carefully selected, levodopa responsive patients with motor fluctuations (see Table 2). Tremor, rigidity, bradykinesia and levodopa-related dyskinesia are the most responsive symptoms [94,95], while axial symptoms, including postural instability, speech and swallowing, are more resistant to DBS. One 12-month follow-up series of 60 PD patients found a significant correlation between motor improvement, according to the UPDRS III (motor) score, and quality of life, as measured by the PD Quality of Life scale [r = 0.7; p < 0.001] [29]. By this measure, STN DBS improves quality of life multifactorially, including improved mood, social functioning, and involvement in hobbies. Numerous studies have reported that patients who had depended on a caregiver for activities of daily living (ADLs) prior to STN DBS, were independent postoperatively. Few studies report complete discontinuation of medication [27,96]. Speech may be more sensitive to dopaminergic therapy, although STN DBS combined with low-dose dopaminergic therapy may offer benefit despite the tendency for DBS to cause worsening speech as a complication of bilateral stimulation in some [97].

To our knowledge, there is only one report in the literature that uses a clinically matched disease control group to evaluate cognitive change following DBS [98]. This study reported little cognitive change following surgery. When comparing the presurgical baseline to stimulation-on conditions, delayed verbal recall and decline in verbal fluency were apparent. Other reports of neuropsychological scores in category and lexical fluctuations.
<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Mean follow-up period (months)</th>
<th>Percent improvement</th>
<th>Percent improvement</th>
<th>Percent reduction</th>
<th>Percent reduction</th>
</tr>
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<tr>
<td>Jaggi et al. [15]</td>
<td>28</td>
<td>12</td>
<td>42(^n)</td>
<td>38(^n)</td>
<td>71(^n)</td>
<td>49(^n)</td>
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<td>Krack et al. [25]</td>
<td>49</td>
<td>60</td>
<td>54(^f)</td>
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<td>58(^f)</td>
<td>63(^f)</td>
</tr>
<tr>
<td>DBS of PD study group [26]</td>
<td>96</td>
<td>6</td>
<td>52(^f)</td>
<td>44(^f)</td>
<td>58(^f)</td>
<td>37(^f)</td>
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<td>50</td>
<td>47</td>
<td>71</td>
<td>53</td>
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</tbody>
</table>

NA—Not available.

*Significance not reported.

Motor evaluated using UPDRSIII.

ADL evaluated using updrsII or activities of daily living scale of Schwab-England.

Dyskinesia evaluated with UPDRS 32–33, 32–35 or the abnormal involuntary movement scale.

LEDD = all dopaminergic therapies.

\(^p<0.05\)

\(^p<0.01\)

\(^p<0.001\)

\(^p<0.002\)

\(^p<0.005\)

\(^p<0.0005\)

\(^p<0.0001\)

\(^p<0.0002\)
fluency, thought disorders, and apathy have shown significant change postoperatively. In one study, verbal fluency declined one year after surgery but remained stable at three years. This decline was inversely related to increasing postoperative apathy and the total daily dose of levodopa [99]. Impaired verbal fluency has been a consistent finding in studies of cognition after STN DBS [98]. However, another study demonstrated that long-term bilateral STN DBS does not significantly alter baseline neuropsychological function and suggested fluctuations in behavior could be modified pharmacologically and by stimulation parameters [24]. Because of the high prevalence of mild cognitive impairment in advanced PD, these patients are vulnerable and subject to decompensation in the aftermath of neurosurgical intervention. Therefore, careful evaluation of neuropsychologic function is a mandatory component of the preoperative evaluation in order to exclude those, who in the judgment of the treating physicians lack sufficient cognitive reserve to endure the procedure and the postoperative recovery.

3.6. Effects of STN DBS on mood

The reported adverse effects include inappropriate laughter [100], depression [101], mania [102], and aggression [103]. Mania and hypomania generally occur immediately postoperatively and may be explained by additive psychotropic effects of STN stimulation and dopaminergic treatment [104]. Tapering long-acting dopamine agonists prior to surgery may decrease the risk of mania following surgery [105]. In contrast, depression tends to appear many weeks after surgery and may be related to decreased dopaminergic treatment and the loss of a hypothetical antidepressant effect attributable to levodopa [104]. Such chronic adaptive changes may not be directly due to stimulation [106]. Thus, worsening of mood may occur postoperatively, and close follow-up is necessary for appropriate early therapeutic intervention [107]. Depressive episodes did not recur in patients with a diagnosis of Major Depressive Disorder preoperatively, but rather developed in patients who had no previous history. Behavioral changes may be a consequence of stimulating an untargeted neighboring neural structure [106]. Nevertheless, one case report documented aggressive outbursts in both the ‘on’ and ‘off’ drug states with complete resolution occurring days after DBS was turned off [105]. Krack et al. proposed a multifactorial biologic and psychosocial etiology to explain such disturbances, including pre-existing psychiatric illness, surgery-related stress, alterations in social life due to motor improvements, lower dose of dopaminergic therapy, and unrealistic patient expectations of outcome [24].

3.7. Complications

The overall rate of complications for DBS is generally low although a recent large series of 81 consecutive patients (160 STN DBS procedures) reported a 26% rate of hardware-related problems [108]. Most side effects of DBS are reversible by adjusting stimulation parameters [107]. Intraoperative dyskinesia is common, but it is believed to indicate proper electrode placement and disappears with stimulation adjustment, reduction of antiparkinson medication and time.

4. DBS in essential tremor

The success of DBS for PD has been paralleled in the application of DBS to ET. ET is the most common movement disorder in the Western world and is characterized by bilateral, often asymmetrical action tremor of the hands, forearms, head, and voice, without other neurological signs [109,110]. When ET is relatively mild, there is little disability and a response to medication can be satisfactory. However, a minority of patients have medically intractable, disabling tremor, which responds exceptionally well to DBS.

Benabid et al. first reported DBS in 6 ET patients, targeting the VIM of the thalamus [9]. Significant suppression of tremor was obtained in the majority of patients. Implanting electrodes into the VIM was a logical and safer extension of the strategy pioneered in the pre-levodopa 1950s of ablating VIM in patients with intractable tremor. While VIM thalamotomy significantly reduced tremor in up to 94% of patients (15 of 16 cases), immediate but transient adverse effects occurred in 40–60% of cases, and up to 40% had persisting complications, such as paresthesiae, dysarthria, and cognitive deficits [1,111]. Successful tremor control in ET has been amply demonstrated with DBS of VIM [46–52,112]. While unilateral VIM DBS has been shown to suppress limb tremor, head and voice tremor require bilateral DBS [113,114].

4.1. Clinical outcome of VIM DBS

See Table 3. We performed a literature search for VIM DBS in ET with the following inclusion criteria: 5 or more subjects, at least 6 months follow-up and reported Essential Tremor Rating Scale (ETRS) scores at baseline and after surgery. Ten studies met inclusion criteria for systematic review [42,46–51,112,115,116]. All were Class B or C investigations (no randomized clinical trials). We report the longest period of follow-up in each study. Long term follow-up studies reported sustained tremor suppression after unilateral and bilateral VIM DBS [48,117], although head and voice tremors only
improved with bilateral VIM DBS. While progressive increases in stimulation amplitude, presumably due to tolerance, were observed in studies with a small number of patients, larger studies have shown that systematic increases in stimulation parameters are unnecessary [118]. Postoperative reduction in medication dosage is substantial in most patients. The majority were medication-free in one long-term follow-up study. Complications tend to be mild, infrequent, and transient (see Table 1).

The posterior part of subthalamic white matter (clearly visible on high resolution MRI fused onto a head CT scan) has also been posited as an effective target to suppress the tremor of ET [119,120]. Insertion of electrodes into the white matter 3–4 mm posterior to the posterior border of the STN adjacent to the red nucleus temporarily arrested the tremor [121]. Murata et al. evaluated 8 ET patients who underwent unilateral DBS of the posteromedial subthalamic white matter and found immediate tremor reduction in the contralateral arm with insertion of the electrode. Average tremor reduction was 81% [120], and improvement was sustained at a median of 22 months follow-up. Adverse effects, such as paresthesia and mild-limb ataxia, occurred only when voltage was high. A previous report found that DBS of the posteromedial subthalamic white matter effectively abolished severe proximal tremor refractory to previous thalamotomy and intraoperative stimulation of the VIM nucleus [119]. These anecdotal reports are promising, but randomized clinical trials are needed to further establish whether alternative targets are superior to VIM for ET.

5. DBS in dystonia

Dystonia is a movement disorder characterized by sustained muscle contractions that cause repetitive involuntary movements and abnormal postures [122]. Anatomic distribution of dystonic postures and movements can be generalized, focal or segmental. Primary generalized dystonia (PGD) tends to start before age 25 and has an autosomal dominant pattern of inheritance [117]. The majority were medication-free in one long-term follow-up study. Complications tend to be mild, infrequent, and transient (see Table 1).

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<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>laterality</th>
<th>Mean follow-up period (months)</th>
<th>Percent improvement tremor&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Percent improvement ADL&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Percent improvement hand function&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>63&lt;sup&gt;*&lt;/sup&gt;</td>
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NR—Not reported.
<sup>a</sup>Significance not reported.
<sup>b</sup><sup>p</sup><0.025.
<sup>c</sup><sup>p</sup><0.001.
<sup>d</sup><sup>p</sup><0.005.
<sup>e</sup><sup>p</sup><0.0001.
<sup>f</sup>Tremor evaluated using ETRS (item 1–9).
<sup>g</sup>ADL-s evaluated using ETRS (item 15–21) or the tremor activities of daily living scale (TRADLS).
<sup>h</sup>Hand function evaluation using ETRS (item 10–14).
<sup>i</sup>5 of the 27 patients had undergone previous unilateral thalamotomy (2 ipsilateral).
<sup>j</sup>We include only the subgroup of ET patients from Limousin et al. and Rehncrona et al.
<sup>k</sup>This study only reports %improvement in handwriting according to ETRS item 10 only.
Certain surgical approaches have been attempted in the treatment of dystonia, including stereotactic thalamotomy and pallidotomy, which gave unpredictable benefit, often at the price of serious motor and speech complications [124–128]. The positive impact of DBS on levodopa-related dyskinesia and dystonia in PD led neurosurgeons and neurologists to direct their attention to DBS for treatment of idiopathic focal and generalized dystonia [129]. When used for this purpose, DBS is the surgical treatment of choice rather than any of the ablative procedures [130,131].

The GPi is currently considered the most appropriate target for PGD regardless of DYT1 status [17,132,133]. Bilateral DBS is preferred to unilateral given the generalized nature of this disease. Although the pathophysiology of idiopathic dystonia remains obscure, studies using positron-emission tomography have shown disturbed glucose metabolism in the GPi, suggesting secondary pathologic activation of the motor cortex by way of pallidal–thalamic–cortical neural circuitry [134]. Interruption of this abnormal pathway might be one reason that GPi DBS relieves some dystonic symptoms [135]. Since many patients undergoing surgery for dystonia are children and young adults, DBS is attractive because it can be revised and reversed according to individual needs and growth patterns.

5.1. Clinical outcome in GPi DBS for PGD

We performed a literature search for GPi DBS in PGD with the following inclusion criteria: 2 or more subjects, at least 3 months followup and reported improvement in dystonic signs and symptoms using the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Eleven studies met inclusion criteria for systematic review [12–14,17,18,53,135–139]. One trial of 31 patients with PGD reported greater clinical improvement in children compared with adults (12 adults and 19 children) at 2 years follow-up (see Table 4). Response to stimulation was the same irrespective of DYT1 status [14]. Overall, complication rates were as high as 23%. However, most were hardware-related and resolved spontaneously without permanent sequelae. See Table 1.

In 2004, Vayssiere et al. observed that patients with PGD improved following DBS GPi regardless of the location of predominant dystonic symptoms prior to surgery [12]. Placement of the electrodes in the GPi had somatotopic relevance. The contralateral leg responded best if the stimulating electrode was implanted centrally, whereas the contralateral arm was more improved if the electrode was implanted posteriorly. Future studies are needed to establish the validity of this somatotopic organization of the GPi for neurosurgical interventions.

6. DBS in Tourette Syndrome

Surgery has rarely been performed for refractory TS, a neurological disorder of childhood characterized by...
stereotyped and repetitive involuntary or semivoluntary (willfully suppressible) movements and vocalizations [140]. Patients with TS frequently have attention-deficit disorder and obsessive-compulsive personality disorder (OCD) as co-morbidities. The cause is unknown but familial aggregation of TS and the recent discovery of a candidate gene strongly point to a genetic basis [141]. A number of theories have been postulated about its obscure pathophysiology, including defective inhibitory control of the BG, and abnormal gating of output from the BG by midline and intralaminar thalamic nuclei to cortex [142–144]. Despite successful psychopharmacological therapies for some patients, many patients with TS have debilitating symptoms, including residual tics and self-injurious behavior.

When neurosurgical treatment has been tried, it has been done in patients with incapacitating symptoms, refractory to medication. Hassler and Dieckmann performed bilateral stereotactic coagulations of the rostral intralaminar and medial-thalamic nuclei in 9 such TS patients, resulting in partial improvement in tics [145]. Babel et al. treated 17 TS patients with stereotactic zona incerta and ventrolateral/lamella medialis thalamotomy, resulting in immediate reduction of vocal and motor tics that was sustained through seven years of followup in some [146]. Patients remained on multidrug therapy postoperatively. Despite significant improvements, frequent side effects included cerebellar signs, hemiplegia, dystonia, dysarthria, cognitive impairment and worsened tics.

Vandewalle et al. performed bilateral DBS of the thalamic nuclei targeted by Hassler and Dieckmann on a patient with refractory TS [147]. All tics had been abolished at the 1 year follow-up evaluation. The authors surmised that the resolution of symptoms may have been due to suppression of thalamic-cortical overactivity. Vandewalle later reported long-term effects of bilateral DBS of the centromedian nucleus, substantia periventricularis, and the nucleus ventro-oralis internus, respectively, in 3 patients [16]. Fifty four to 82.5 percent improvement had been achieved in all motor and vocal tics by the first week after surgery. At long-term follow-up (8 months patient 1; 1 year patient 2; 5 years patient 3), tics were reduced by 82.6%, 72.2% and 90.1%, respectively. Compulsions completely disappeared in all patients. DBS appeared to only partially relieve facial grimaces.

Several recent individual case reports of DBS in TS have been intriguing. A prospective double-blind “n of 1” study was recently reported on a patient with refractory TS who was treated with high-frequency bilateral stimulation of the centromedian–parafascicular complex of the thalamus, GPi or both in a randomized order [148]. Stimulation of either target reduced the severity of tics by 70% and ameliorated vocalizations and self-injurious behavior, persisting for 24 months postoperatively. In another study, long-term follow-up of GPi stimulation in a patient with TS demonstrated a 73% decrease in tic frequency at 14 months [149]. Finally, a report of a case of TS and OCD indicated that stimulation of the anterior limb of the internal capsule, a target which has been successfully stimulated in the surgical treatment of OCD without TS, resulted in significant reduction in the severity of medication refractory vocalizations and severe head and arm jerks.

There have been no serious complications of DBS in TS, but a subjective feeling of reduced energy at voltage levels necessary for maximal tic control, mild-impairment on timed tasks, and altered sexual drives have been reported. Hypomania and depression occurred in the case of anterior capsule DBS but immediately disappeared with adjustment of stimulatory parameters [150]. One patient developed a mild, persistent hemiparesis after implantation of electrodes [149]. Thus, preliminary open label trials on small numbers of patients have yielded enough positive information to suggest that DBS can play a role in the treatment of intractable TS. Larger randomized trials are now necessary to confirm or refute these results.

7. DBS in epilepsy

Many patients with epilepsy have persistent seizures despite maximal antiepileptic drug therapy and are not candidates for resective brain surgery. Since DBS has been shown to be more efficacious and safer than ablative procedures in the treatment of movement disorders, its application to the treatment of recurrent seizures is a logical extension of the successful therapeutic paradigm [151]. Seizure suppression with DBS is effective in animal models using various targets [152–154]. Early clinical trials of DBS for refractory seizures have reported only marginal efficacy [155,156]. A recent pilot study of intermittent DBS of the anterior nucleus of the thalamus reported significant reduction in frequency and propagation of generalized tonic-clonic seizures and complex partial seizures in 4 of 5 patients [157]. Discontinuation of stimulation resulted in immediate increase in seizure frequency and intensity. There were no complications.

A recent encouraging study demonstrated that “intelligent” brain devices can produce bursts of stimulation that react to and terminate epileptiform activity [158]. These stimulators may provide more effective seizure suppression than their “blind” counterparts that stimulate intermittently without reacting to any physiological changes. “Intelligent” detection may be less toxic than chronic cyclic stimulation and the use of anti-epileptic drugs [158]. A research group at the University of Pennsylvania, using EEG recordings in mesial temporal lobe epilepsy, has identified a spontaneous
progression of premonitory changes in brain activity that can lead to a full blown and potentially harmful convulsive seizure. These premonitory changes before the seizure can last up to seven hours and if detected can be successfully suppressed by an implanted stimulator [159]. Mapping cortical networks involved in seizure generation and determining the most effective time of stimulation relative to seizure onset still require further investigation.

8. DBS in obsessive-compulsive disorder

Functional neuroimaging has implicated certain brain regions in the pathogenesis of a variety of psychiatric disorders, providing neurosurgeons with another set of disorders potentially ripe for treatment with DBS. Recent case reports and pilot studies have reported remission in patients suffering from refractory OCD and depression following DBS of the anterior limb of the internal capsule and the ventral caudate nucleus [160–162]. A double-blind, controlled trial of DBS for treatment-refractory OCD had promising results [163]. One of 4 patients showed more than 35% improvement in OCD symptoms. Two of 4 showed this level of improvement during the open phase of this trial. Larger clinical trials are being planned.

9. DBS in treatment-resistant depression

Depression is unlikely to be a disease of a single brain region, however, functional neuroimaging has demonstrated consistent involvement of the subgenual cingulate in both acute sadness and antidepressant medication effects [164]. A recent pilot study of 6 patients with treatment-resistant depression demonstrated sustained clinical remission following DBS of white matter tracts adjacent to the subgenual cingulate gyrus [165]. These findings are evidence that DBS has potential for success in yet another common disease of the brain that is often refractory to medical therapy.

10. Conclusion

DBS is the surgical therapy of choice for carefully screened and selected patients with medically intractable PD, ET, and possibly PGD. Clinical efficacy of DBS in the treatment of medically refractory PD, ET, and PGD has been supported by an increasing number of published reports, which demonstrate the relative safety of the procedure as well as its often remarkable benefit. Optimal neural targets vary among these disorders and continue to be debated. They include STN, Vim or posterior subthalamic white matter, and GPi for PD, ET, and PGD, respectively. Short-term follow-up studies have demonstrated overall improvement in motor function, ADLs and quality of life, with post-operative reduction in medication requirement for all conditions for as long as 5 years. Longer follow-up has not been reported, but it has become apparent after 15 years of experience with DBS in PD that progression of the underlying neurodegeneration continues to be reflected in worsening disability, especially of axial symptoms such as postural instability, and non-motor symptoms such as cognitive impairment [24]. Adverse neuropsychological changes have been minor, and most adverse sensorimotor complications can be reversed by adjusting stimulation frequency and modifying drug dosage. Other complications related to the surgical procedure and the hardware of DBS are infrequent and remediable. The success of DBS in these three movement disorders has led to pilot studies of DBS in refractory TS and epilepsy. With these models as a solid foundation, other applications of DBS in neurologic and psychiatric disorders are likely to emerge in the near future.

References


