Stereotactic Neurosurgery for Movement Disorders

Aviva Abosch, Andres Lozano

ABSTRACT: Stereotactic neurosurgery for the treatment of movement disorders focuses primarily on the treatment of Parkinson’s disease (PD), essential tremor (ET), and dystonia. The surgical targets in use are the subththalamic nucleus (STN) and the globus pallidus internus (GPI) for PD, GPI for dystonia, and ventralis intermedius (Vim) nucleus of the thalamus for ET. Following target selection, procedures include the generation of lesions or the placement of deep brain stimulating electrodes in the selected target. Additionally, transplantation has been used in the treatment of PD. The indications, outcomes, and risks of the various procedures are reviewed.

RÉSUMÉ: Neurochirurgie stéréotaxique dans les désordres du mouvement. La neurochirurgie stéréotaxique dans le traitement des désordres du mouvement cible principalement le traitement de la maladie de Parkinson (MP), du tremblement essentiel (TE) et de la dystonie. Les cibles chirurgicales sont le noyau sous-thalamique et le globus pallidus internus (GPI) dans la MP, le GPI dans la dystonie et le noyau ventral intermédiaire dans le TE. Suite au choix de la cible, on crée une lésion ou on place des électrodes profondes pour stimuler la zone ciblée. La transplantation a également été utilisée dans la MP. Les indications, les résultats et les risques de ces différentes techniques sont revus.

This review will focus on stereotactic neurosurgery for the treatment of both hypokinetic – specifically, Parkinson’s disease (PD) – and hyperkinetic movement disorders – in particular, essential tremor (ET) and dystonia. Stereotactic surgery for the movement disorders over the last 50 years fall into three different categories: the generation of lesions in various targets (thalamotomy, pallidotomy, and subthalamic nucleotomy), chronic electrical stimulation of these same targets, and neural transplantation (for PD). A general discussion of stereotactic surgery for movement disorders is outlined below, followed by more specific discussions about surgery for PD, ET, and dystonia.

Patient selection

Certain underlying medical conditions – such as bleeding disorders or refractory hypertension – pose unacceptable risks for patients being considered for either lesioning or deep brain stimulator (DBS) placement. Additionally, patients being considered for DBS placement must be able to tolerate the general anesthesia required for internalization of electrode leads and pulse generator(s).

Choice of surgery

The decision of whether to proceed with lesioning vs. DBS is arrived at jointly by the treatment team and the patient. Factors influencing this decision include the patient’s underlying medical status, as certain conditions – for instance, diabetes – increase the risk of infection and hence the likelihood of having to remove implanted hardware. Logistical factors, such as ready access to centers with expertise and the resources necessary to deal with programming and possible hardware complications, as well as the need to return to the operating room for battery replacement every three to five years, can influence the decision of whether to proceed with lesion or DBS. A description of the relative risks of lesioning vs. DBS is given below.

Surgical techniques

Surgical technique and electrophysiological targeting for movement disorders are described in detail elsewhere. The necessity of microelectrode recording in conjunction with macrostimulation vs. macrostimulation alone for targeting is a subject of some controversy, but no controlled studies have yet addressed this topic. Localization of the optimal target is followed either by the insertion of a radiofrequency probe and generation of a lesion, or by insertion of the DBS electrode (Figure). The passage of the tip of the probe or DBS leads to the

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culmination of the trial of external stimulation, the patient is lead position prior to the implantation of the IPG. At the uncertain, we obtain a postoperative MRI scan to document DBS (IPG).

For intraoperative DBS electrode screening, one end of a sterile screening cable is connected to the most distal external lead contact, and the other end is connected to an external test stimulator. Symptom relief – e.g., tremor and rigidity for PD – is evaluated for each contact in series as the current is slowly increased. Additionally, the current threshold for undesirable side effects (e.g., persistent paresthesias or dysarthria) is determined for each contact. Deep brain stimulator electrode position is considered satisfactory if no undesirable side effects result from stimulation below 4 V. We use a DBS electrode bearing contacts spaced 1.5 mm apart, although electrodes are now also available with 0.5 mm between contacts, allowing for more contacts in the target area. The DBS lead is then connected to a percutaneous extension lead, the extracranial portion of the DBS lead and its connection with the extension are inserted into a subgaleal pocket created lateral to the scalp incision, and the incisions closed. Although, at our institution, a weeklong trial of external stimulation ensues, at this point, the patient could also be discharged with the IPG turned off, returning three to four weeks later for testing, at which time programming commences. This three to four week interval allows for the resolution of micro-lesion effects and postoperative swelling after which stimulation parameters stabilize.

The goal of DBS programming is to obtain maximal relief of symptoms, with minimal side effects, at the lowest possible voltage. This goal is achieved by varying the parameters of stimulation, which include mode of stimulation, frequency, pulse width, amplitude, and contacts across which stimulation occurs. Each of the four electrode contacts can be set to positive, negative, or off. Stimulation can be set to a monopolar, bipolar, or multipolar mode. In monopolar stimulation, the IPG case serves as the ground. In bipolar mode, current flows from the negative contact to the positive contact. Given the number of parameters involved and the complexity of the various clinical syndromes treated, programming can take many hours and multiple sessions even for experienced practitioners. The patient and his or her family have the ability to turn the DBS off or on using a hand-held magnet (or, with more recent IPG models, a hand-held control device) applied to the skin overlying the IPG.

The intracranial hemorrhage rate reported for DBS varies between 0.6 - 3.5%. Deaths are very rare but have occurred as a result of hemorrhage. Infection and skin erosion rates vary between 2.5 - 23.4%. Lead fractures, short circuits, and other unspecified hardware malfunctions range between 5.8 - 17.7%. Lead migrations occurred in 14.2% of patients in one series, but
have not been reported elsewhere. Involuntary movements that result during the initial phase of subthalamic nucleus (STN) stimulation have been reported frequently, tend to be mild, and generally respond to changing stimulation parameters and/or contacts being used for stimulation. These abnormal movements can be ballistic in quality or similar to the patient’s preoperative levodopa (LD)-induced dyskinesias.

In a retrospective study of the safety and efficacy of globus pallidus internus (GPI) versus STN DBS, Volkman et al. noted a higher incidence of ongoing adverse events in the STN group (16 patients), one year postoperatively. These adverse events included depression and anhedonia (8.3%), worsening of hypophonia and dysarthria (56.3%), and apraxia of eyelid opening (12.5%). The authors also noted that LD dose was reduced by 65.3% in the STN group, whereas no significant medication change occurred in the GPI group. Levodopa dose could not be increased in nine of the 16 STN patients, owing to dose-limiting side effects. The authors concluded that STN stimulation results in a narrowing of the therapeutic window of LD therapy due to a lower threshold for dyskinesias. Thus, parkinsonian symptoms, such as hypophonia, that are less improved by stimulation than by LD therapy, may be unmasked.

Intraoperative and postoperative (lasting one to two weeks) confusion and agitation are reported as “common” in elderly patients undergoing bilateral STN surgery whereas patients under age 60 seem to tolerate the procedure better and remain lucid throughout the surgery. There are also isolated reports of acute onset of depression as a consequence of stimulation, which resolved with cessation of stimulation or changing the pattern of contacts being stimulated.

**PARKINSON’S DISEASE**

**Patient selection**

Patients being considered for surgical treatment must meet the clinical criteria for the diagnosis of PD. Patients with a diagnosis of “atypical parkinsonism” or “Parkinson-plus syndrome” are usually excluded from consideration for surgery as they are less likely to benefit. Patients should demonstrate significant motor disability despite optimization of medications. Advanced age is not necessarily a contraindication from a surgical standpoint, but patients must be able to tolerate a lengthy procedure while awake and in the off-state, during which time patient participation is necessary.

Formal neuropsychological testing is useful in assessing cognitive function and motivation and to check for the presence of underlying depression or anxiety, which are commonly associated with PD. Major mood disturbances require appropriate therapy before a patient can be considered for surgery. Evidence of dementia is a contraindication to surgery in most centers as this will compromise the likelihood of successful therapy and may even worsen during the postoperative period. The effects of DBS on cognitive outcome in elderly patients have been covered in a companion article in this issue (see also Saint-Cyr et al.).

Potential surgical candidates are evaluated in the “off” (12 hours without medication) and “on” state (one hour after morning medication dose), using an objective, standardized parkinsonian rating scale, such as the Unified Parkinson’s Disease Rating Scale (UPDRS), which predicts response to surgery. Patients demonstrating a good response to a LD challenge, and significant motor fluctuations, are considered the best candidates for surgery. Furthermore, symptoms that do not respond significantly to LD, are believed unlikely to improve significantly with surgery.

**DBS programming in PD**

Frequency is set at 120 Hz in order to achieve a lesion-like effect, but can range up to 185 Hz. Pulse width is usually set at 60–90 μsec and amplitude at 2–3.5 V, but can range from 0.1 to 10 V. Programming must be carried out in both the drug-off and drug-on states. Stimulation may generate or accentuate dyskinesias, requiring a reduction in dopaminergic drug dosages. This balancing of stimulation levels and drug doses may take several weeks to be optimized.

**Outcome for pallidal lesioning**

Laitinen reintroduced the modern posteroventral medial pallidotomy (PVP) in 1992. Since then it has become clear that PVP has major effects on LD-induced dyskinesias and, unlike ventralis intermedius (Vim) thalamotomy, improves bradykinesia and rigidity as well as tremor. Alkahni and Lozano reviewed 85 contemporary articles on pallidotomy (1,959 patients) for PD. These authors noted a consensus on the benefits of pallidotomy for off-period motor function and on-period, drug-induced dyskinesias, with variations in the extent of symptomatic benefit across studies. At one-year follow-up, the mean improvement in motor scores on the UPDRS (mUPDRS) during off periods was 45.3%, and the mean improvement in contralateral dyskinesias during on-periods was 86.4%. The overall mortality rate for these studies was 0.4%, and the rate of persistent adverse effects was estimated at 14%. Major adverse events – including intracerebral hemorrhages, contralateral weakness, and visual field defects – occurred in 5.3% of patients. The authors concluded that, based on their literature review, unilateral pallidotomy is effective and relatively safe in the treatment of PD. They cautioned, however, that limited long-term follow-up data were available. It should be noted that bilateral pallidotomy has been associated with cognitive and speech deficits, and is therefore increasingly not performed.

With respect to long-term follow-up, Fine conducted a study of 40 patients who had undergone unilateral PVP between 1993-1996. Of these, 20 patients could not be evaluated for reasons including death, dementia, and loss to follow-up. Serial postoperative assessments in the remaining 20 patients during on- and off-periods (mean follow-up of 52 months) revealed that the combined off-period score for activities of daily living (ADL) and mUPDRS was 18% better at the last evaluation than at baseline (4.9 - 31.0%). Significant improvements were found in off-period scores for contralateral tremor (65.4% improvement), rigidity (43.2%), and bradykinesia (18.2%), and in the on-period score for contralateral dyskinesia (70.6%). Thus, in the subgroup of PD patients who had undergone unilateral PVP and could still be evaluated at long-term follow-up, significant early improvements in off-period contralateral PD signs were maintained for up to 5.5 years. There was also a sustained significant improvement in on-period contralateral dyskinesia, but not in other on-period signs of PD.
Outcome for pallidal stimulation

Given the widespread success of pallidotomy in treating the symptoms of PD, attention turned to GPi stimulation as an alternative to the generation of pallidal lesions. Kumar and colleagues\textsuperscript{22} analyzed a cohort of 22 consecutive patients enrolled in a multi-center study of GPi-DBS. Seventeen patients underwent bilateral, and five patients unilateral, surgery. At six-month follow-up, the patients with bilateral GPi DBS demonstrated a marked improvement in UPDRS scores when examined in both the on- and off-states. The stimulation-induced benefit in off-period mUPDRS was 31\%, and in ADL scores was 39\%. During the on-period, the reduction in the total dyskinesia scores was 66\% and in ADL scores was 32\%. A similar pattern of improvement was seen in the group of patients with unilateral GPi stimulation, although a second cohort of 12 patients not included in the multi-center study showed greater improvements in on-period motor functioning. Although the effect of DBS is predominantly reversible, electrode insertion alone resulted in measurable clinical effects in the absence of stimulation. For instance, at six-month follow-up, the benefit observed without stimulation was up to 44\% in the on-period dyskinesias. Complications among 34 patients from all centers included perioperative infection (n=3), hardware fracture (n=2), and premature battery failure (n=3). These results demonstrate the efficacy of pallidal DBS in the treatment of PD symptoms. In contrast to bilateral pallidotomy, no specific complications were observed with bilateral GPi-DBS.\textsuperscript{22}

Outcome for STN stimulation

Appreciation of the important modulatory role played by the STN in regulating basal ganglia projections to the motor thalamus and brainstem, has led to interest in the STN as a target for the treatment of PD. In 1990, DeLong and colleagues\textsuperscript{23} first demonstrated the reversal of motor symptoms by lesioning the STN in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys. Concern about the possibility of irreversible side effects from the generation of bilateral STN lesions, and experience with the safety\textsuperscript{24} but limited efficacy of thalamic stimulation, prompted Benabid and colleagues to attempt STN stimulation instead.\textsuperscript{25} Recent reports from several centers demonstrating the safety and efficacy of chronic high-frequency STN stimulation have generated interest in the STN as a target of choice in the surgical treatment of PD.

Despite its clinical efficacy, the mechanism(s) of action of DBS for the treatment of movement disorders remains largely unknown. The prevailing theory proposes that DBS causes a blockade of neuronal firing thereby mimicking the effects of a lesion. The virtue of DBS as opposed to the generation of a lesion is that DBS is both reversible and adjustable, allowing for maximal efficacy while minimizing untoward effects. A few centers have also performed a limited number of unilateral\textsuperscript{26} or bilateral\textsuperscript{27} STN lesions, with reasonable efficacy. In a study by Alvarez et al.,\textsuperscript{28} one of 11 patients developed hemichorea-ballism following surgery, which subsequently required treatment by pallidotomy.

The effects of STN DBS on motor symptoms, LD requirements, and speech will be reviewed below. The effects of STN DBS on cognition are described in the companion article by Saint-Cyr.

Effect on motor symptoms

Since Benabid and colleagues\textsuperscript{25} first used STN DBS in the treatment of PD in the mid-1990s, a number of other groups,\textsuperscript{2,10,16,28-33} have reported on the efficacy of STN DBS in both off- and on-states (Table 1). Many series have reported STN DBS induced improvements in all motor symptoms of PD including rigidity, bradykinesia, posture, and other axial symptoms such as rising from a chair, gait, and swallowing. There is, however, a considerable range in the degree of improvement in these various categories (see Tables 1-3). These variations in outcome may be due to differences in study design, patient selection, clinical methods, or the fact that the UPDRS is a subjective rating system.

Kumar et al\textsuperscript{8} compared the effects of unilateral versus bilateral STN DBS in 10 patients, and found that bilateral stimulation was associated with much greater improvement in all axial symptoms (postural stability, gait, axial motor features) than unilateral stimulation, and that the improvement in appendicular symptoms was synergistic as opposed to additive.\textsuperscript{8} Thus, most patients with medically refractory symptoms are better served by bilateral STN DBS, although highly asymmetric, tremor-dominant PD may be treated by unilateral

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>F/U mo</th>
<th>% Improved (mUPDRS)</th>
<th>% Mean LD Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al 1998\textsuperscript{10}</td>
<td>7</td>
<td>6</td>
<td>Off meds = 65%</td>
<td>40%</td>
</tr>
<tr>
<td>Limousin et al 1998\textsuperscript{2}</td>
<td>20</td>
<td>12</td>
<td>Off meds = 60%</td>
<td>50%</td>
</tr>
<tr>
<td>Krack et al 1998\textsuperscript{16}</td>
<td>8</td>
<td>6</td>
<td>Off meds = 70%</td>
<td>56%</td>
</tr>
<tr>
<td>Moro et al 1999\textsuperscript{31}</td>
<td>7</td>
<td>12-16</td>
<td>Off meds = 42%</td>
<td>65%</td>
</tr>
<tr>
<td>Burchiel et al 1999\textsuperscript{29}</td>
<td>5</td>
<td>12</td>
<td>Off meds = 44%</td>
<td>51%</td>
</tr>
<tr>
<td>Yokoyama et al 1999\textsuperscript{13}</td>
<td>5</td>
<td>3</td>
<td>Off meds = 44%</td>
<td>0%</td>
</tr>
<tr>
<td>Houeto et al 2000\textsuperscript{10}</td>
<td>23</td>
<td>6</td>
<td>Off meds = 66%</td>
<td>61%</td>
</tr>
<tr>
<td>Bejjani et al 2000\textsuperscript{28}</td>
<td>10</td>
<td>6</td>
<td>Off meds = 62%</td>
<td>62%</td>
</tr>
<tr>
<td>Rodriguez-Oroz et al 2000\textsuperscript{32}</td>
<td>15</td>
<td>12</td>
<td>Off meds = 74%</td>
<td>55%</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>Off meds = 61%</td>
<td>N.S.</td>
<td></td>
</tr>
</tbody>
</table>

(mUPDRS = motor section of the UPDRS; F/U mo = length of postoperative follow-up in months; LD = levodopa; N.S. = not significant; STN = subthalamic nucleus; DBS = deep brain stimulator). Note that all patients in these studies received bilateral subthalamic nucleus deep brain stimulator implantation.
STN DBS in order to curtail potential morbidity and procedural costs. Kumar et al\textsuperscript{10} also examined the effects of STN DBS in a prospective, randomized, double-blinded fashion and found a 65\% reduction in off-period mUPDRS scores, a 40\% reduction in on-period mUPDRS scores, and an 85\% reduction in LD-induced dyskinesias in the seven patients evaluated (Table 1).

Reported reduction in tremor achieved by bilateral STN DBS in the off-state ranges between 74%\textsuperscript{29} - 97%\textsuperscript{34} (Table 2). Improvements reported for off-period rigidity in response to bilateral STN DBS range between 33%\textsuperscript{16} - 68\%\textsuperscript{2} (Table 2). Limousin et al\textsuperscript{2} reported a 56\% improvement in limb akinesia in response to stimulation alone over untreated baseline, but noted a 12\% worsening in akinesia scores when patients were tested on both stimulation and LD. Other reports document improvements in akinesia that range between 25%\textsuperscript{29} - 71%\textsuperscript{34} (Table 3).

Levodopa induces off-period dystonia, end-of-dose and beginning-of-dose dyskinesia, and peak-dose dyskinesia.\textsuperscript{17} Kumar and colleagues\textsuperscript{10} reported an 85\% reduction in LD-induced dyskinesias, but no direct anti-dyskinetic effect of STN stimulation (Table 2). On the other hand, one group has reported an anti-dyskinetic effect from STN DBS, which is believed to be independent of the improvements obtained by medication reduction.\textsuperscript{17} However, this stimulation-induced improvement in dyskinesias may relate to stimulation effects outside of the STN, such as effects on pallidofugal fibers in the fields of Forel.

Bejjani et al\textsuperscript{28} noted a dramatic improvement in axial symptoms, including posture, postural stability, and gait (Table 3). Dysarthria, swallowing impairment, and neck rigidity were noted to be relatively resistant to both LD therapy and STN stimulation.\textsuperscript{28} Indeed, worsening of dysarthria has been reported in some patients,\textsuperscript{35} although this could also be due to reduction of LD dosage.

Many authors interchange the terms off-period dyskinesias with off-period dystonia. In the absence of information about postoperative onset of surgically-induced abnormal movements, we assume they are referring to the phenomenon of off-period dystonia.

Note that a subsequent study by Krack et al\textsuperscript{17} reported a 90\% improvement in off-state dyskinesias, and a 30\% improvement in peak-dose dyskinesias (N = 27; 6 m F/U).

N.S. = not significant; N.R. = not recorded.

### Table 2: Range of effect of subthalamic nucleus deep brain stimulator on percent improvement in rigidity (R), tremor (T), bradykinesia/akinesia (B), on (+) or off (-) levodopa (LD), and on levodopa-induced (D + LD) and off-state dyskinesias (D – LD).

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>F/U</th>
<th>R - LD</th>
<th>R + LD</th>
<th>T - LD</th>
<th>T + LD</th>
<th>B - LD</th>
<th>B + LD</th>
<th>D - LD</th>
<th>D + LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limousin et al 1998\textsuperscript{2}</td>
<td>20</td>
<td>12 m</td>
<td>68%</td>
<td>50%</td>
<td>80%</td>
<td>43%</td>
<td>56%</td>
<td>12%</td>
<td>Decline</td>
<td>N.R.</td>
</tr>
<tr>
<td>Krack et al 1998\textsuperscript{16}</td>
<td>8</td>
<td>6 m</td>
<td>33%</td>
<td>31%</td>
<td>88%</td>
<td>57%</td>
<td>71%</td>
<td>5%</td>
<td>N.R.</td>
<td>40%</td>
</tr>
<tr>
<td>Kumar et al 1998\textsuperscript{10}</td>
<td>7</td>
<td>6 m</td>
<td>52%</td>
<td>44%</td>
<td>82%</td>
<td>77%</td>
<td>57%</td>
<td>53%</td>
<td>N.R.</td>
<td>0%</td>
</tr>
<tr>
<td>Burchiel et al 1999\textsuperscript{29}</td>
<td>5</td>
<td>12 m</td>
<td>47%</td>
<td>24%</td>
<td>74%</td>
<td>91%</td>
<td>25%</td>
<td>18%</td>
<td>N.R.</td>
<td>67%</td>
</tr>
<tr>
<td>Yokoyama et al 1999\textsuperscript{33}</td>
<td>5</td>
<td>3 m</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>33%</td>
<td>N.S.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Many authors interchange the terms off-period dyskinesias with off-period dystonia. In the absence of information about postoperative onset of surgically-induced abnormal movements, we assume they are referring to the phenomenon of off-period dystonia.

Note that a subsequent study by Krack et al\textsuperscript{17} reported a 90\% improvement in off-state dyskinesias, and a 30\% improvement in peak-dose dyskinesias (N = 27; 6 m F/U).

N.S. = not significant; N.R. = not recorded.

### Table 3: Range of effect of subthalamic nucleus deep brain stimulator on axial symptoms (posture, gait, and speech).

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>F/U</th>
<th>% IMPROVED – LD</th>
<th>% IMPROVED + LD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar et al 1998\textsuperscript{10}</td>
<td>7</td>
<td>6 m</td>
<td>49% postural stability + gait</td>
<td>33% postural stability + gait</td>
</tr>
<tr>
<td>Krack et al 1998\textsuperscript{16}</td>
<td>8</td>
<td>6 m</td>
<td>79% gait</td>
<td>N.R.</td>
</tr>
<tr>
<td>Yokoyama et al 1999\textsuperscript{33}</td>
<td>5</td>
<td>3 m</td>
<td>37% gait</td>
<td>N.S.</td>
</tr>
<tr>
<td>Bejjani et al 2000\textsuperscript{28}</td>
<td>10</td>
<td>6 m</td>
<td>39% gait + posture</td>
<td>Not further improved</td>
</tr>
<tr>
<td>Robertson et al 2001\textsuperscript{76}</td>
<td>3</td>
<td>12 - 30m</td>
<td>69% akinesia + rigidity + tremor</td>
<td>84% axial symptoms:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>72% axial symptoms*:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 77% abnormal posture</td>
<td>• 88% abnormal posture</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 76% postural stability</td>
<td>• 96% postural stability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30% gait</td>
<td>N.R.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54% up from chair</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40% speech</td>
<td></td>
</tr>
</tbody>
</table>

\*Axial categories included speech, neck rigidity, rising from a chair, posture, gait, and postural instability. All of these features, except for neck rigidity, were significantly improved by stimulation, but degree of improvement within each individual category was not provided.
Effect on levodopa requirements

The decrease in LD requirements following STN DBS has been described in numerous publications (Table 1). Reported postoperative LD reduction ranges from 40% to 100%, with some patients successfully discontinuing all dopaminergic drugs postoperatively. However, the discontinuation of all dopaminergic medications may be associated with a decline in speech as well as profound changes in mood (including anhedonia and depression). Reduction in LD dose is, however, associated with a significant improvement in on-period dyskinesias (Table 2).

Effects on speech

Although PD patients may demonstrate improvement in speech in response to LD, the improvement is usually far less than that seen in limb and axial motor performance. Dromey et al examined the effects of STN DBS on acoustic measures of voice in seven PD patients. They noted small but significant increases in vocal intensity and fundamental frequency variability in response to stimulation when patients were examined on medication at six months postoperatively. However, the overall impact of these changes was not deemed functionally significant. In contrast, Gentil et al found improvements in speech in 10 patients with STN DBS. However, this study reported results for patients only in the off-medication state. Additionally, the patients described in the study by Dromey et al, had only modest speech impairment before surgery, whereas the patients studied by Gentil et al. were selected for their speech deficits. Thus, the discrepancy in results between these two studies might, in part, reflect differences in patient selection.

GPi or STN DBS?

A prospective, double-blind, crossover study was performed by the DBS Study Group, in patients with advanced PD in whom electrodes were implanted bilaterally in either the STN (96 patients) or GPi (38 patients), with investigators choosing the site of implantation in a nonrandomized fashion. The investigators compared mUPDRS scores, when stimulation was randomly assigned to be turned on or off. Unblinded evaluations of motor function were performed preoperatively and at one, three, and six months postoperatively. Three months after surgery, double-blind, crossover evaluations demonstrated that STN stimulation (vs. no stimulation) was associated with a median improvement in mUPDRS of 49%, and GPi stimulation with a median improvement of 37%. Between the preoperative and six-month visits, the percentage of time per day that patients had good mobility without involuntary movements increased from 27 to 74% with STN DBS and from 28 to 64% with GPi DBS. Thus, although targets were chosen in a nonrandomized fashion, the authors concluded that bilateral stimulation of either STN or GPi is associated with significant improvement in motor function in PD.

Conclusions

Both GPi and STN DBS improve off-period symptoms of PD, attenuate motor fluctuations, and allow for a reduction in LD dosing which likely accounts for the decrease in LD-induced dyskinesias. The improvements in LD-sensitive symptoms are sustained at greater than two years of follow-up. As yet, the relative efficacy of STN vs. GPi stimulation with respect to long-term treatment of PD remains unclear. Finally, benefits of stimulation over pallidotomy must be weighed against the potential risks of implanted hardware.

Transplantation for PD

Although transplantation of human embryonic dopamine neurons into the brains of PD patients has proved beneficial in open clinical trials, the question of whether transplantation would be more effective than sham surgery in a controlled trial led to a landmark study by Freed and colleagues, in which the authors randomly assigned 40 patients with severe PD to receive a transplant of human embryonic dopamine neurons or sham surgery (burr holes drilled, but no dural penetration or cell implants). All patients were followed in a double-blind manner for one year. In the transplant recipients, cultured mesencephalic cells from four embryos were implanted into the putamen bilaterally. Among younger patients (≤ 60 years), significant improvements were noted in UPDRS and Schwab and England scores in the transplantation group as compared with the sham-surgery group, when patients were tested in the off-medication state, but not in the on-state. There was no significant improvement in on- or off-medication scores among the older patients in the transplantation group. After an initial improvement during the first year, dystonia and dyskinesias recurred in 15% of transplant recipients, even after reduction in or discontinuation of oral LD.

Olanow and colleagues noted that although the study by Freed et al revealed no benefit as measured on the basis of the primary outcome variable (an unvalidated subjective global assessment scale), and although severe dyskinesias developed in some patients, it is important to consider that specific details of the donor cell culture system or grafting technique used might have contributed to these outcomes. Different results may be achieved in the future with the use of different transplantation protocols.

Surgery for hyperkinetic movement disorders

Of the hyperkinetic movement disorders, the most frequently treated by surgery is ET. Surgery has also been used to treat the tremor of PD and multiple sclerosis, and the tremor following stroke and various other types of brain injury. Additionally, surgical approaches have been attempted in the treatment of Huntington’s chorea, essential myoclonus, Tourette’s syndrome, and tardive dyskinesia, but will not be reviewed here. Recently, there has been renewed interest in the surgical treatment of dystonia following the successful surgical treatment of the LD-induced dystonia of PD. Other types of hyperkinetic movement disorders have also been treated surgically, but with less frequency, and with more variable success. The surgical treatment of LD-induced dyskinesias has been covered in the previous section. The treatment of ET and dystonia will be reviewed below.

Essential tremor

Surgical treatment for ET has been in use since the early 1950s, for patients with disabling, medication-resistant tremor. Although various regions have been targeted for tremor control, the optimal target was eventually determined to be the Vim.
nucleus of the thalamus. Three modes of treatment are currently in use: radiofrequency Vim thalamotomy, high-frequency Vim stimulation (Vim-DBS), and gamma-knife (radiosurgery) thalamotomy. Of these, Vim-DBS has become the preferred technique.

**Vim Thalamotomy**

Vim thalamotomy has been reported to improve contralateral tremor in as many as 80 - 90% of ET patients. Shahzadi et al. found that thalamotomy significantly suppressed tremor in over 80% of ET patients. However, tremor recurred in 5/21 patients up to five years postoperatively. The authors contrast this finding to their experience with PD patients, in whom tremor seldom recurs after three months.

Akbostanci et al. analyzed the results of 43 Vim thalamotomies performed in 37 ET patients. All patients experienced either complete abolition of, or significant improvement in, contralateral tremor immediately following surgery. At follow-up (1-13 months postoperatively), 60.5% of patients had no tremor, and 13.9% had mild residual tremor without interference with daily life. Tremor recurrence was observed in five patients, all of whom underwent repeat Vim thalamotomy, with excellent results.

In their retrospective analysis of 60 patients with medically intractable tremor who underwent Vim thalamotomy for PD (42), ET (6), cerebellar tremor (6), and post-traumatic tremor (6), Jankovic et al. reported on follow-up as long as 13 years (mean, 53.4 months) postoperatively. At most recent follow-up, 83% of the ET patients had cessation of, or moderate-to-marked improvement in, their contralateral tremor, with a concomitant improvement in function. Immediate postoperative complications were common, occurring in 58% of patients.

**Complications of thalamotomy**

The most common complications in the study by Jancovic et al. were contralateral weakness (34%), dysarthria (29%), and confusion (23%). These complications generally resolved rapidly during the postoperative period. Persistent morbidity associated with unilateral thalamotomy, includes dysarthria, dysequilibrium, perioral numbness, weakness, and cognitive impairment. Bilateral Vim thalamotomies are associated with a substantial (30 – 50%) risk of permanent speech and cognitive deficits, and are now usually avoided.

**Vim stimulation**

The observation that acute high-frequency Vim stimulation during the mapping phase of Vim thalamotomy suppressed the tremor of PD and ET, led to the use of chronic DBS as a means of long-term tremor control. Benabid and colleagues first published their results of Vim-DBS in ET patients in 1991. In a more recent follow-up study by these same authors on 23 patients, the benefits of Vim stimulation were noted to decline over time in 35% of patients, when the tremor had an action component. Given that the side effects were often minor, well-tolerated, and immediately reversible, and the absence of permanent morbidity, the authors concluded that long-term Vim stimulation is well-tolerated by patients, even in those undergoing bilateral procedures.

Koller et al. investigated the long-term safety and efficacy of unilateral Vim-DBS in 49 ET patients. A clinical rating scale was used to assess tremor at three and 12 months, and then yearly. Three patients were not implanted, seven were explanted before 24 months, 11 were lost to follow-up, and three died from unrelated causes. For the 25 patients with follow-up of two years or more, tremor scores were significantly improved with stimulation. Three patients had asymptomatic intracerebral hemorrhages, and one patient sustained postoperative seizures. Stimulation-induced side effects were mild and easily controlled with changes in stimulation parameters. However, these authors concluded that Vim-DBS is compromised by a loss of efficacy in some patients and device complications, increasing the likelihood of additional surgical procedures.

**Side effects of Vim stimulation**

Due to the proximity of Vim to the sensory thalamus, the majority of patients report slight, temporary paraesthesias when the pulse generator is turned on, but permanent paraesthesias are also possible with stimulation. Stimulation-induced dysarthria is common (27 – 30%) in patients who have a contralateral thalamotomy, and may be subtle or marked. Stimulation-induced dysequilibrium has also been reported. In contrast to the adverse effects associated with bilateral thalamotomies, however, the adverse effects associated with Vim-DBS can usually be minimized or eliminated by adjusting the parameters of stimulation.

**Vim thalamotomy vs. Vim stimulation?**

Retrospective studies have supported or refuted the belief that Vim-DBS is safer and/or more efficacious than Vim thalamotomy. In a prospective, randomized trial, Schuurman et al. compared the effects of Vim-DBS and thalamotomy in 68 patients with drug-resistant tremor due either to PD (45), ET (13), or multiple sclerosis (10). Patients were randomly assigned to undergo non-microelectrode-guided thalamotomy or Vim-DBS. Functional status (on Frenchay Activities Index) improved more in the Vim-DBS group than in the thalamotomy group. Multivariate analysis also demonstrated a greater improvement in the Vim-DBS group vs. the thalamotomy group. Tremor was suppressed entirely or almost completely in 27/34 patients in the thalamotomy group and in 30/33 patients in the Vim-DBS group. With the exception of one patient death following intracerebral hemorrhage, Vim-DBS was associated with significantly fewer adverse effects than thalamotomy. Additionally, functional status was improved in 18 patients in the Vim-DBS group, but in only eight patients in the thalamotomy group, leading the authors to conclude that although Vim-DBS and thalamotomy are equally effective in suppressing tremor, Vim-DBS is associated with fewer adverse effects and results in greater functional improvements.

Long-term studies of both Vim thalamotomy and DBS indicate that although the benefits continue in most patients, there is a certain percentage of patients in whom the benefits decline over time. This percentage of tremor recurrence has been reported as high as 35% in one series. It should be noted, however, that tremor recurrence can sometimes be effectively treated by changing the parameters of stimulation in patients who have undergone Vim-DBS. This is obviously not an option for patients who have undergone Vim-thalamotomy.
Gamma knife thalamotomy

Young and colleagues have recently reported their long-term results of gamma knife thalamotomy (GKT) in the treatment of 52 ET patients. A team of examiners performed blinded pre- and postoperative assessments, and found that 92.1% of patients were entirely or nearly tremor-free postoperatively, and 88.2% remained tremor-free at a minimum of four years post-GKT. Statistically significant improvements were noted in the Clinical Rating Scale for tremor, and these improvements were well-maintained in the 17 patients followed for four years or more. Although these results – which have not yet been replicated – are comparable or better than those of either Vim thalamotomy or Vim-DBS in terms of efficacy, GKT is similar to thalamotomy in that its effects can neither be reversed nor modified. Furthermore, the noninvasive nature of GKT eliminates the possibility of modifying the MRI-selected target with data that could be collected from electrophysiological mapping. On the other hand, the potential for intracranial hemorrhage or infection associated with invasive procedures – although relatively small risks – are virtually eliminated by the use of the gamma knife. No long-term radiation-induced complications have been observed, to-date.

Conclusions

Various studies support the efficacy of both Vim thalamotomy and Vim-DBS in the treatment of ET. Adverse side effects resulting from stimulation can be reversed or minimized, but cannot be in the case of thalamotomy. Deep brain stimulation, however, is associated with hardware problems that are not associated with lesion generation.

Dystonia

Progress in our understanding of the pathophysiology of idiopathic dystonia, combined with successful surgical treatment of LD-induced dystonia in PD, has led to renewed interest in the surgical treatment of dystonia. The pathophysiology of dystonia has been reviewed in the companion article by Chouinard in this issue (see also Vitek et al52,53). The current state of surgery for the treatment of dystonia will be summarized here, with special emphasis on developments during the last five years. For a comprehensive review of this field prior to 1996, see Lang (1998).54

Table 4: Pallidotomy for Dystonia

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Pallidotomy</th>
<th>N</th>
<th>F/U</th>
<th>Improvement (Scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwon et al 1995</td>
<td>2º hemi-dystonia</td>
<td>Gamma Knife R-GPi</td>
<td>1</td>
<td>16 m</td>
<td>“Improved”</td>
</tr>
<tr>
<td>Iacono et al 1996</td>
<td>1º generalized</td>
<td>Bilateral Pallido-ansotomy</td>
<td>1</td>
<td>12 m</td>
<td>100%</td>
</tr>
<tr>
<td>Lozano et al 1997</td>
<td>1º generalized</td>
<td>Bilateral GPi</td>
<td>1</td>
<td>3 m</td>
<td>79% (BFMDRS)</td>
</tr>
<tr>
<td>Ondo et al 1998</td>
<td>1º &amp; 2º gen’d &amp; hemi-dystonia</td>
<td>5 Bilateral GPi</td>
<td>5</td>
<td>4 m</td>
<td></td>
</tr>
<tr>
<td>Vitek et al 1999</td>
<td>1º generalized</td>
<td>3 Unilateral GPi</td>
<td>3</td>
<td></td>
<td>61% (BFMDRS)</td>
</tr>
<tr>
<td>Lin et al 1999</td>
<td>2º generalized</td>
<td>Unilateral GPi</td>
<td>3</td>
<td>14, 11, 7 m</td>
<td>56% (BFMDRS)</td>
</tr>
<tr>
<td>Lin et al 1999</td>
<td>2º generalized</td>
<td>Bilateral GPi</td>
<td>18</td>
<td>12 m</td>
<td>13% (BFMDRS)</td>
</tr>
<tr>
<td>Lin et al 1999</td>
<td>2º generalized</td>
<td>Bilateral GPi</td>
<td>1</td>
<td>12 m</td>
<td>34% (BFMDRS)</td>
</tr>
</tbody>
</table>

BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale57

UNILATERAL AND BILATERAL PALLIDOTOMY FOR DYSTONIA

Patient selection

Pallidotomy has been used with varying degrees of success to treat primary generalized dystonia,52,55,56 off-period dystonia in PD, and dystonia associated with cerebral palsy,57 Huntington’s disease,58 Hallervordan-Spatz disease,59 and brain injury or structural lesions.56,60,61

Electrophysiology

The operative technique has been described in the previous section. Firing rates of GPI neurons in dystonia patients have been reported to be lower than those recorded in PD62,63 but recording techniques and states of consciousness may have influenced some of these data. For example, intravenous propofol has been documented to decrease neuronal firing rates in other brain regions, thereby confounding assessments of neuronal firing rate in the dystonic pallidum.64

Once the desired target within GPI has been identified, the microelectrodes are removed and either a radiofrequency lesioning probe or a DBS electrode is inserted into the target. In programming DBS stimulators for dystonia patients, a longer pulse width (> 210 µsec), than is typically used for PD (60-90 µsec), has sometimes been used to achieve clinical effects.52

Outcome of pallidotomy for dystonia

The outcome of pallidotomy for dystonia has been recorded in a number of case reports and small series, which are detailed in Table 4. The studies performed vary with respect to underlying diagnosis, surgical target, whether the surgeries were unilateral vs. bilateral, and the nature and duration of outcomes follow-up. Furthermore, to-date, no prospective, randomized, blinded trials have been reported.

The typical pattern of symptom amelioration following surgery for dystonia has been described as a moderate improvement during the immediate postoperative period with continued improvement over subsequent month(s).56,65 Although the appropriate comparison studies have not been conducted, many investigators believe that primary dystonia responds better to surgery than secondary dystonia.56,65 Based on the current literature, it is difficult to draw conclusions about the efficacy of unilateral versus bilateral pallidotomy for dystonia, and the type of procedure is often chosen based on preoperative symptom
distribution.\textsuperscript{56} In keeping with the older surgical experience, several published reports\textsuperscript{56} support the belief that axial symptoms respond better and more consistently following bilateral vs. unilateral ablative procedures.\textsuperscript{53}

There is only a very small experience with pallidal radiosurgery in the treatment of dystonia. Kwon and Whang\textsuperscript{66} published a case report concerning a woman with secondary dystonia, treated by Gamma Knife PVP (4 mm collimator; 180 Gy; Table 4). No standardized outcome rating scale was used in her evaluation but the authors reported sustained improvement in the patient’s dystonia 16 months following treatment. Her post-treatment course was marred by the appearance of a contralateral, homonymous hemianopsia at six months following radiosurgery. Subsequent investigators have recommended limiting the dose to < 160 Gy, in order to minimize complications.\textsuperscript{67} The role of radiosurgery in the treatment of dystonia is currently highly uncertain.

The discrepancies in outcome reported for the surgical treatment of dystonia (Table 4) highlight the heterogeneous nature of the dystonias and the methodologies used to treat them, and serve as a cautionary note in any attempt to apply broadly the findings of individual studies.

\textbf{Unilateral and bilateral GPI DBS for dystonia}

As with DBS for other movement disorders, pallidal DBS for dystonia, in contrast to pallidotomy, affords the advantages of reversibility and the ability to alter stimulus parameters in order to enhance efficacy or decrease adverse effects of stimulation.

Globus pallidus internus modulates primary and association areas of the motor cortex via its projections to the thalamus. Excessive activation of these motor areas has been demonstrated in both idiopathic\textsuperscript{68} and acquired dystonia.\textsuperscript{69} Although the exact mechanism of DBS is unknown, the frequency-dependent nature of the response to stimulation suggests that overriding or pacing of abnormally patterned neuronal activity may be important to the mechanism of action of DBS.\textsuperscript{70} With the more recent use of the STN as a target for the surgical treatment of PD, high frequency STN DBS has been noted to immediately suppress off-period dystonia,\textsuperscript{9,17} raising the possibility that the STN might serve as a target for primary dystonia.

\textbf{Patient selection}

The indications and patient selection criteria for pallidal DBS are the same as for pallidotomy, with the added potential benefit of creating a “lesion” that is subsequently both reversible and modifiable. These characteristics seem especially desirable in young patients, such as those with juvenile-onset or secondary dystonia in whom additional lesions may lead to potentially irreversible adverse effects.

\textbf{Outcome}

The striking benefit of bilateral pallidotomy in dystonia patients\textsuperscript{56,66} led to the placement of bilateral GPI DBS electrodes in a single patient with idiopathic generalized dystonia by Kumar and colleagues\textsuperscript{62} with significant improvement in all aspects of dystonia sustained over one year. This same patient underwent PET imaging during a motor task one year postoperatively, with and without GPI stimulation. In a double-blinded study, GPI stimulation was found, in time-locked fashion, to reduce bilateral PET activation in various motor cortical areas, including primary motor, supplementary motor, and anterior cingulate areas, as well as in the ipsilateral lentiform nucleus. Since GPI is known to modulate primary and association motor cortex activity and excessive activation of these areas is present in primary and secondary dystonia, the authors proposed that the mechanism of GPI DBS might be one of direct suppression of excessive activation in cortical motor areas.

Krauss and colleagues\textsuperscript{71} treated three patients with cervical dystonia using bilateral GPI DBS. They noted a gradual and significant improvement in symptoms over the first three months postoperatively with further improvement at later follow-up. On a modified version of the Toronto Western Spasmodic Torticollis Rating Scale,\textsuperscript{72} patients demonstrated 80%, 54% and 49% improvement in total functional disability at postoperative months 15, 12, and 6, respectively (Table 5).

Tronnier and Fogel\textsuperscript{73} reported two cases of primary and one case of secondary generalized dystonia in young adults, who improved significantly on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) at six months following bilateral pallidal DBS. Loher et al\textsuperscript{74} reported their long-term results on a single patient with post-traumatic hemidystonia who underwent GPI DBS. Their patient was a 24-year-old man who developed left-sided hemidystonia, pain, and tremor following head injury at age 15. Previous right-sided thalamotomy improved his tremor, but only transiently ameliorated the dystonia. The ventroposterolateral portion of the right GPI was chosen as the

\begin{table}[h]
\centering
\caption{Deep Brain Stimulation for Dystonia}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Study & Diagnosis & Procedure & N & F/U & Improvement (Scale) \\
\hline
Sellal et al 1993\textsuperscript{78} & 2º hemi-dystonia & L-VPL DBS & 1 & 8 m & “Improved” \\
Kumar et al 1999\textsuperscript{62} & 1º generalized & Bilat GPI DBS & 1 & 12 m & 67% (BFMDRS) \\
Islekel et al 1999\textsuperscript{79} & Cervical dystonia & R-GPI DBS & 1 & 0.75 m & “Improved” \\
Krauss et al 1999\textsuperscript{80} & Cervical dystonia & Bilat GPI DBS & 3 & 11 m & 80%,54%,49% (TWSTRS) \\
Loher et al 2000\textsuperscript{74} & 2º hemi-dystonia & R-GPI DBS +Thalamotomy & 1 & 48 m & “Improved” \\
Tronnier et al 2000\textsuperscript{73} & 1º & Bilat GPI DBS & 3 & 6 m & 59%,14%,34% (BFMDRS) \\
Coubes et al 2000\textsuperscript{65} & 1º (DYT1) generalized & Bilat GPI DBS & 7 & 12 m & 90% (BFMDRS) \\
\hline
\end{tabular}
\end{table}

BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale\textsuperscript{72}; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; DBS = deep brain stimulator; GPI = globus pallidus internus; L = left; R = right; VPL = ventroposterolateral thalamic; DYT1 = possessing the DYT1 gene mutation
target, and stimulation parameters initially set at amplitude 0.75V, pulse width 180 us, and frequency 130 Hz. Early postoperative improvements were noted in both pain and dystonia. Modifications in the parameters of stimulation (amplitude and pulse width) at several months yielded improved control of the dystonia and eliminated stimulation-induced paresthesias. There was further improvement in the patient’s dystonia at two years and sustained improvement at four years postoperatively, although no standard rating scale was used in assessing outcome (Table 5).

Finally, Coubes et al. reported the results of bilateral GPI DBS in six children and one adult carrying the DYT1 gene mutation generalized dystonia and a mean preoperative BFMDRS score of 62. Surgery was carried out under general anesthesia, using MRI-based stereotactic localization of the posteroventral GPI and no microelectrode recording. Improvement occurred gradually over three months, with a 90% improvement in BFMDRS scores at one year. The authors note that although the adult patient attained a 97% improvement in his dystonia score, secondary skeletal deformities limited his full functional recovery.

Conclusions

Accumulated reports in relatively small numbers of patients indicate that pallidotomy and pallidal DBS may both be safe and effective treatments for dystonia. However, determination of the optimal surgical treatment from review of existing literature is not possible given the variability in types of dystonia, surgical techniques, brain targets, underlying pathophysiological mechanisms, length and nature of follow-up, and the lack of adequate blinded, prospective trials.

References


64. Antikowiak B. Different actions of general anesthetics on the firing patterns of neocortical neurons mediated by the GABA(A) receptor. Anesthesiology 1999;91:500-511.


