Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes

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Object. Deep brain stimulation (DBS) to treat advanced Parkinson disease (PD) has been focused on one of two anatomical targets: the subthalamic nucleus (STN) and the globus pallidus internus (GPI). Authors of more than 65 articles have reported on bilateral DBS outcomes. With one exception, these studies involved pre- and postintervention comparisons of a single target. Despite the paucity of data directly comparing STN and GPI DBS, many clinicians already consider the STN to be the preferred target site. In this study the authors conducted a metaanalysis of the existing literature on patient outcomes following DBS of the STN and the GPI.

Methods. This metaanalysis includes 31 STN and 14 GPI studies. Motor function improved significantly following stimulation (54% in patients whose STN was targeted and 40% in those whose GPI was stimulated), with effect sizes (ESs) of 2.59 and 2.04, respectively. After controlling for participant and study characteristics, patients who had undergone either STN or GPI DBS experienced comparable improved motor function following surgery (p = 0.094). The performance of activities of daily living improved significantly in patients with either target (40%). Medication requirements were significantly reduced following stimulation of the STN (ES = 1.51) but did not change when the GPI was stimulated (ES = −0.02).

Conclusions. In this analysis the authors highlight the need for uniform, detailed reporting of comprehensive motor and nonmotor DBS outcomes at multiple time points and for a randomized trial of bilateral STN and GPI DBS.

KEY WORDS • Parkinson disease • deep brain stimulation • subthalamic nucleus • globus pallidus internus

Ablative brain surgery was used as early as 1912 to treat PD. When levodopa was introduced in the 1960s, surgical interventions for PD decreased dramatically. Within a few years, however, the therapeutic limitations of levodopa became apparent. Following the administration of levodopa, PD continued to progress and treatment-related complications including motor fluctuations and dyskinesias became a major therapeutic challenge. More recently, neurosurgical interventions experienced a renaissance in the form of ablative procedures (for example, pallidotomy). Nonetheless, as the use of pallidotomy became more widespread, the shortcomings of this procedure were also realized. Adverse effects related to bilateral pallidotomy included speech impairment, balance and gait problems, visual field defects, and cognitive deficits. The search for safer and more effective surgical treatments, particularly for bilateral symptoms, fueled interest in DBS.

Deep brain stimulation, which involves the application of electrical stimuli, produces a functional lesion within a focal area of the brain. Two targets within the brain have been stimulated to treat PD: the STN and the GPI. The first reports of DBS for the management of PD were published in the mid 1990s. Studies published since then have documented significant improvement in patient motor functioning and quality of life following STN DBS. Serious adverse events have also been reported including infections, depression, mood changes, and psychosis requiring intervention as well as equipment issues such as lead fractures and dislodgements. Authors of studies on GPI stimulation have also reported improved motor function and time spent in the on state as well as an enhanced perceived quality of life. Serious complications reported for bilateral GPI DBS include hematomas, infections, and equipment issues. Oh and colleagues reported a hardware-related complication rate (including lead fractures, migrations, erosions, and infections) of 25% for DBS, whereas authors of a long-term follow-up study on STN DBS found 5% of patients with dementia and/or hallucinations and 12% with apathy not responsive to increased dopaminergic therapy. Although mortality rates have been low (< 1% in the 1st year postprocedure), the rate of serious complications reveals the need to systematically track, record, and compare adverse outcomes according to the stimulation target.

As evidenced by the increase in publications in the last
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several years, DBS for PD has gained widespread acceptance. Data from an analysis of practice patterns confirm that DBS is now the preferred surgical treatment for PD.15 Significant questions regarding DBS remain, however, including which stimulation target site leads to better outcomes. It is not yet known whether certain patients or particular symptoms respond better to stimulation of one target than another. To our knowledge, in only one small study (10 patients) have the authors randomly assigned patients to receive bilateral GPI or STN stimulation and evaluated outcomes in a blinded fashion.9 In this study improvements in motor function were documented regardless of the stimulation target. Levodopa intake decreased following DBS in the STN-targeted group but remained unchanged in the GPI-targeted group. Given the small sample size, however, a larger trial is needed to determine whether these findings are robust.

In lieu of a large randomized trial, we conducted a systematic review of the work completed to date to quantify what has been learned about the outcomes of DBS for PD. In this metaanalysis we synthesized the results of published research on patient outcomes following bilateral DBS of the STN and GPI targets in the brain.

Clinical Material and Methods

Literature Search and Article Selection

Several strategies were undertaken to identify all published reports on outcomes of bilateral DBS of either the STN or the GPI. We began with a MEDLINE search using the following MeSH terms: “Parkinson’s disease,” “deep brain stimulation,” “subthalamic nucleus,” and “globus pallidum.” This search was supplemented by examining the bibliography published with a recent Food and Drug Administration report in which the literature on bilateral DBS of the STN and GPI was reviewed.25 In addition, we reviewed the references from articles identified in the aforementioned searches to include any additional papers related to outcomes of DBS that may have been missed.

Inclusion criteria included the following factors: study patients had idiopathic PD, therapeutic intervention involved bilateral DBS of either the STN or the GPI, reported outcomes included UPDRS motor function scores off medications at baseline and off medications/on stimulation at follow up, and follow-up assessment occurred at least 3 months post-DBS. Thus, studies documenting only nonmotor outcomes (for example, cognitive function) or surgical parameters (such as microelectrode recording) were not considered in our review. We also excluded publications with motor function results that had already been published in another paper or in which DBS surgery had been performed for another indication (for instance, essential tremor), the electrode implantation site was neither the STN nor the GPI or it was not bilateral, or the study patients had previously undergone intracranial surgery for PD. Each article considered was compared with a checklist of inclusion and exclusion criteria. Only articles meeting the inclusion criteria were retained for analysis.

A data extraction table was developed to code the articles. This table included authors; journal title and year of publication; country in which the study had been performed; percentage of male patients; average age of patients; study design (single group pretest posttest, randomized trial, or quasiresearch); intervention site (STN or GPI); number of patients undergoing each intervention; duration of follow-up periods (in months); average baseline UPDRS motor score off medication, standard deviation, and standard error or range; and average follow-up UPDRS score off medication/on stimulation, standard deviation, and standard error or range. If the study also included the ADL subscore of the UPDRS we reported the baseline and follow-up scores and the conditions in which these scores had been obtained (for example, off medication or on stimulation). Finally, if the study included the average medication dosage in levodopa equivalents at baseline and follow up, we recorded this information.

Dependent Variables

The primary outcome of interest in our metaanalysis is the UPDRS17 motor score (Part III) in the off-medication/on-stimulation state. The motor subscale consists of 14 items, with score totals ranging from 0 to 104; higher scores are indicative of greater impairment. This subscale enables assessments of facial expression, speech, tremors, rigidity, gait, posture, and bradykinesia and is scored based on a trained assessor’s observation of the patient. This motor outcome score is the most commonly reported in DBS studies and reflects the effect of stimulation on patient motor function without medication. Regarding the more recently published studies—that is, those from 2001 and thereafter—in which UPDRS motor scores were not reported, we attempted to contact the authors to obtain this information, a successful strategy in only three cases.

Other frequently reported outcomes of interest include the UPDRS ADL score (Part II) and medication requirements based on levodopa equivalents before and after DBS. The UPDRS ADL are self-reported by the patient and focus on activities such as walking, writing, dressing, and speaking. The ADL scores can range from 0 (no functional impairment) to 52 (maximal functional impairment). The levodopa equivalent measure involves converting doses of antiparkinsonian medications into comparable units of levodopa. Most authors refer to the convention of Pahwa, et al.,55 who stated that 1 unit antiparkinsonian medication = 100 mg standard levodopa = 125 mg sustained-release levodopa = 100 ml liquid levodopa = 1 mg pergolide = 10 mg bromocriptine. These outcomes were examined only in the papers that also included UPDRS motor scores. In one case, we were able to obtain UPDRS ADL scores directly from the authors even though they had not been reported in the paper.66 Although we tried to reach some authors of earlier reports to obtain additional information, either we were unable to reach these individuals or they no longer had the information we needed.

Analysis of Data

Effect size expresses in terms of SD units the magnitude of a treatment difference between two groups.22 It allows for comparisons across studies and is commonly used in meta-analyses. In our study, the primary outcome variables were converted to ESs, which were measured using a standardized mean difference between pre- (baseline) and post-DBS (follow up) for each separate outcome for the STN and GPI studies. To calculate ES, the pre- and post-DBS means and
some measure of variance (that is, SD, standard error, or values for tests of significance) were needed. For studies with no variance information, SDs were estimated. The average ratio of means to SDs was obtained from studies that had both means and SDs. Then, SDs were estimated by dividing the means for studies with no variance by the average ratio. To examine the impact of estimated SDs, the overall ESs between including and excluding the studies with estimated SDs were compared. A test for the homogeneity of outcome variables was performed to address whether all studies shared the same ES. In cases in which results were not homogeneous, the overall mean ES for each outcome was obtained from a random-effects model. To figure statistical significance and to assist in determining the clinical importance of ES, 95% CIs were calculated for each individual study and all studies combined.

Possible sources of heterogeneity were explored by comparing the mean ESs for subgroups of studies categorized according to selected study level characteristics by using a formal random-effects metaregression analysis that included these characteristics as covariates. Subgroup analyses were conducted for the STN and GPI target groups separately, and metaregressions were performed for the STN and GPI combined data. In the metaregression, the dependent variable was the ES for each outcome of interest, and the independent variables were the mean age of the sample, percentage of male participants, study location (European compared with non-European), duration of follow up, study publication year, and study sample size. To evaluate the relative effectiveness of the anatomical target of stimulation (STN compared with GPI) on the UPDRS motor score, this target was included as a covariate in the model. All statisti-
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### TABLE 2

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Origin</th>
<th>No. of Patients</th>
<th>Mean Patient Age (yrs)</th>
<th>% Male</th>
<th>Follow Up (mos)</th>
<th>Mean Baseline UPDRS Motor Score</th>
<th>Follow-Up UPDRS Motor Score</th>
<th>% Change</th>
</tr>
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<tr>
<td>Limousin, et al., 1997</td>
<td>France</td>
<td>6</td>
<td>50</td>
<td>83</td>
<td>NA</td>
<td>43.8</td>
<td>26 ± 11</td>
<td>40</td>
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<tr>
<td>Pahwa, et al., 1997</td>
<td>US</td>
<td>3</td>
<td>57</td>
<td>100</td>
<td>3</td>
<td>48 ± 12.77</td>
<td>15.3 ± 11.78</td>
<td>68.1</td>
</tr>
<tr>
<td>Ghika, et al., 1998</td>
<td>Swiss</td>
<td>6</td>
<td>55</td>
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<td>6</td>
<td>66.0</td>
<td>31.0</td>
<td>35.0</td>
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<tr>
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<td>France</td>
<td>5</td>
<td>51</td>
<td>80</td>
<td>6</td>
<td>53.6 ± 10.4</td>
<td>32.5 ± 12.4</td>
<td>39.4</td>
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<td>Brown, et al., 1999</td>
<td>France &amp; Spain</td>
<td>6</td>
<td>50.7</td>
<td>67</td>
<td>8.3 (mean)</td>
<td>54.2 ± 9.2</td>
<td>27.2 ± 12.0</td>
<td>49.8</td>
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<td>US</td>
<td>4</td>
<td>46.5</td>
<td>70</td>
<td>12</td>
<td>67.0 ± 24</td>
<td>40.87§</td>
<td>39</td>
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<td>France</td>
<td>6</td>
<td>64</td>
<td>33</td>
<td>6</td>
<td>36 ± 2</td>
<td>23 ± 5</td>
<td>36.1</td>
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<td>Kumar, et al., 2000</td>
<td>Canada, France, &amp; Spain</td>
<td>22‡‡</td>
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<td>6</td>
<td>53.4 ± 3.3</td>
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<td>52.5</td>
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<td>55.4 ± 8.5</td>
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<td>38</td>
<td>55.7</td>
<td>71</td>
<td>6</td>
<td>50.8 ± 11.6</td>
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<td>Germany</td>
<td>6</td>
<td>58.5</td>
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<td>43.8 ± 8.2</td>
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<td>10.5</td>
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<td>Volkman, et al., 2001</td>
<td>Germany</td>
<td>11</td>
<td>56.6</td>
<td>NA</td>
<td>6</td>
<td>52.5 ± 14.16</td>
<td>22.9 ± 15.48</td>
<td>56.4</td>
</tr>
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<td>Loher, et al., 2002</td>
<td>Switzerland &amp; Germany</td>
<td>10</td>
<td></td>
<td></td>
<td>64.6</td>
<td>50</td>
<td>3 &amp; 12</td>
<td>63.4 ± 17.4</td>
</tr>
<tr>
<td>summary</td>
<td></td>
<td>136</td>
<td>55.0</td>
<td>69</td>
<td>6 (median)</td>
<td>40.1</td>
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</table>

* All reported probability levels were significant at a value < 0.05, except in Durif, et al., 1999; six studies did not include probability values.
† Not all authors reported an SD.
‡ Assessment data were used from the 6-month postintervention follow up or the follow up closest to 6 months postsurgery.
§† Information provided through email correspondence with author (one patient was lost to follow up).
‡‡ Demographic information is based on 22 patients; of these, 17 underwent bilateral and five underwent unilateral surgery. Outcome data were obtained in the 17 bilateral cases only.
‡‡‡ Information provided through email correspondence with author (one patient was lost to follow up).
††† This study included one patient who underwent unilateral electrode implantation.
||† Demographic information is based on 22 patients; of these, 17 underwent bilateral and five underwent unilateral surgery. Outcome data were obtained in the 17 bilateral cases only.
||| Information provided through email correspondence with author (one patient was lost to follow up).

** Motor scores ranged from 0 to 108 (scores were rescaled in the calculation); otherwise, assume a range from 0 to 104.
§§ Information provided through email correspondence with author (one patient was lost to follow up).
¶¶ Information provided through email correspondence with author (one patient was lost to follow up).

Results

Description of Studies and Study Patients

We initially identified 65 studies through September 2003, with the first paper on bilateral DBS published in 1995. (Note that some papers were counted more than once if the authors reported findings separately for STN and GPI cases [for example, Krack, et al.].[41] In one study,[56] there were separate samples of cases in two different geographic locations for both STN and GPI cases, resulting in four sets of findings). Of this total, 20 studies were excluded: five did not include UPDRS motor scores pre- and post-DBS,[10,16,24,27] six consisted of already reported data on patients in another primary DBS study,[5,20,41,27,32,50] five had either only pretreatment or only posttreatment UPDRS motor scores,[5,20,41] one had on-medication motor scores only,[55] one included uni- and bilateral cases combined,[10,16] and two involved only unilateral DBS on further inspection.[20,27] As a result, our analysis included 45 studies: 23 with STN targets only, six with GPI targets only, and eight with both STN and GPI targets, although results were reported separately for each target.

The UPDRS motor scores at baseline and post-surgery as well as the characteristics of each study included in the metaanalysis are detailed in Tables 1 (STN) and 2 (GPI). The first report of bilateral DBS was published in 1995.[46] Most of the published studies had been conducted in six European countries, with fewer studies originating in the US, Canada, or elsewhere. Thirty papers and one published abstract on bilateral STN published through September 2003 documented motor function outcomes in patients with PD. Burchiel and colleagues[8] performed the only randomized trial in which STN and GPI targets were directly compared. For purposes of our metaanalysis, however, we report the findings on the site of surgery separately. All other reports were pre- and postintervention studies. The mean sample size per study was 18 patients. The patients had a mean age of 57.8 years at the time of surgery, and 66% of those with an STN target were male. Because most studies (58%) included 6-month postsurgical outcomes, we examined 6-month outcome data or those from the time period closest to 6 months after surgery. If a 6-month follow up had not been conducted, we used data from the 3-month assessment (16%). In some cases 8-month (7%) or 12-month (9%) data only were available.

There were 13 published reports on bilateral GPI DBS (Table 2). Again, most originated in European countries, and all were pre- and postintervention designs with sample sizes ranging from three to 38 patients (mean 10 patients). The mean age of patients was 55 years and 69% were male. Only one GPI study has been published since 2001,[47] whereas one third (11 studies) of the STN reports were published between 2002 and 2003.
As shown in Table 1, all authors documented improvement in motor function following STN DBS, with 50% reporting outcomes at 6 months postintervention. The mean improvement in motor function according to the UPDRS motor score was 54.3%, a decrease from a mean baseline motor score of 51.9 to 22.8 at the follow up. Calculated ESs and 95% CIs for each study and the overall mean ES are presented in Fig. 1 upper. Note that the study by Figueiras-Méndez and colleagues had only one patient and so was not included in the ES calculation. Effect sizes of the individual studies ranged from 0.9 to 5.58. The 95% confidence limits of the ESs did not include 0 except for one study. The

**Motor Function According to the UPDRS**

**Fig. 1.** Upper: Graph demonstrating the ESs and 95% CIs for each study and overall, based on the UPDRS motor function in the stimulation on/medication off state in patients who had undergone STN DBS. Lower: Graph depicting the ESs and 95% CIs for each study and overall, according to the UPDRS motor function score in the stimulation on/medication medication off state in patients who underwent GPI DBS. Krack(98) refers to Krack, et al., 1998 in all figures.
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The overall mean ES calculated from the random-effects model was 2.59 (95% CI 2.23–2.91), which was significantly greater than 0 (p < 0.001). The UPDRS motor scores decreased significantly after STN DBS, signifying improved motor function. These studies were not homogeneous in terms of ES (Q = 92.8, df = 29, p < 0.001). The results of subgroup analyses to examine possible sources of heterogeneity showed that there was no significant difference in the ESs when comparing studies conducted in Europe and those in other countries (2.53 compared with 2.77, respectively), studies with a mean patient age of 55 years or younger and those with a mean patient age greater than 55 years (2.62 compared with 2.6, respectively), studies with sample sizes of 10 or fewer patients and those with sample sizes greater than 10 patients (2.44 compared with 2.65, respectively), and studies published between 2001 and 2003 and those published in 2000 or earlier (2.53 compared with 2.74, respectively). The calculated ESs for studies that did not include SDs and those that did were 2.9 and 2.48, respectively (the probability value was not significant).

Similarly, Fig. 1 lower provides motor function data for individuals who underwent bilateral GPI stimulation. Six-month follow-up outcomes were reported for most cases. These reports documented a mean UPDRS motor score of 52.2 at baseline and a mean score of 32.5 on follow up, as well as a 40% improvement in motor function in the on-stimulation/off-medication state following GPI DBS (Table 2). Individual ESs ranged from 0.68 to 4.58. There were three studies in which the 95% confidence limits included 0. The overall mean ES from the random-effects model was 2.04 (95% CI 1.5–2.58), which indicated that the UPDRS motor scores significantly decreased following GPI DBS. Again, there was significant heterogeneity between the ESs (Q = 32.57, df = 13, p < 0.0021). Results of subgroup analyses for GPI DBS revealed that the differences in the ESs between subgroups were more pronounced than the differences in the ESs for STN DBS subgroups. Nonetheless, there was no significant difference in the ESs when comparing the studies conducted in Europe and those in other countries (2.07 compared with 1.77, respectively), studies with a mean patient age of 55 years or younger and those with a mean patient age of 55 years (2.48 compared with 1.57, respectively), studies with sample sizes of 10 or fewer patients and those with samples greater than 10 patients (1.81 compared with 2.57, respectively), and studies published between 2001 and 2003 and those published in 2000 or earlier (1.44 compared with 2.42, respectively). The calculated ESs for reports that included no SD and those with SDs were not statistically significant (2.2 compared with 2.01, respectively; probability level not significant).

Patient (age and sex) and study characteristics (study location, duration of study follow up, publication year of study, and sample size) were not significantly associated with the ES for the UPDRS motor score in the metaregression analysis. The surgical target (STN or GPI) was not statistically significant (p = 0.361) after adjusting for the aforementioned dichotomous independent variables (excluding sex because five studies were missing this information). When the analysis was repeated including studies with sex information (37 studies) and adjusting for all patient and study characteristics, the surgical target was not significant (p = 0.743), indicating that patients in whom either target was used had comparable improvement in motor function following DBS. When STN and GPI sites were compared without adjusting for any covariates, greater improvement was associated with the STN than the GPI, but this result was not statistically significant (p = 0.09).

Because of the progressive nature of PD, we were also interested in examining the long-term effects of DBS. Unfortunately, only 11 STN and three GPI studies included 12-month or longer outcomes; therefore, we examined all studies with 12-month outcomes and those with 6-month outcomes if the 12-month results were not available. This approach resulted in 26 STN studies with a mean motor function improvement of 56.5% and 11 GPI studies with a mean functional improvement of 39.8%.

Activities of Daily Living According to the UPDRS

Authors of 50% of the STN DBS studies reported UPDRS ADL scores before and after stimulation in the off-medication state, as did 57% of the authors of the GPI DBS studies. Effect sizes and their 95% CIs for the individual studies are presented in Fig. 2. In all studies, the ESs for STN DBS were positive and none of the 95% confidence limits included 0. The overall mean ES from the random-effects model was 1.81 (95% CI 1.62–2), indicating significant improvement in ADL functioning after STN DBS. Similarly, there was only one negative ES for GPI DBS. The overall mean ES from the random-effects model of GPI studies was 1.48 (95% CI 1.14–1.81), indicating significantly improved ADL functioning after DBS. There was significant heterogeneity for both STN and GPI studies (p < 0.001 for each). Results of the subgroup analyses indicated that the ES for studies published in 2000 or earlier was greater than the ES for studies published between 2001 and 2003 (4.03 compared with 1.82, respectively, for STN and 3.89 compared with 1.1, respectively, for GPI). The ES for both STN and GPI studies with a mean patient age of 55 years or younger was greater than that for studies with a mean patient age greater than 55 years. In the metaregression analysis (excluding studies with missing sex information), the ESs for the ADL score were significantly smaller for studies with sample sizes of 10 or fewer patients, those published more recently (2001–2003), and those with a mean patient age greater than 55 years; the remaining independent variables that characterize these studies were not significantly associated with ADL. The site of surgery did not differentially affect improvement in ADL functioning in the off-medication state, with ADL scores improving by a mean of 40% over baseline for both surgical sites. The mean ADL scores in the off-medication state at baseline and follow up were 27.9 and 14.8 for STN DBS studies and 28 and 17.2, respectively, for GPI DBS studies.

Authors of several studies (11 STN and five GPI) also
reported UPDRS ADL scores obtained while the patient was on medication at baseline and follow up. Data from the STN studies revealed a decrease from a mean score of 11.3 at baseline to 8.5 at the follow up. Nonetheless, the ES was small (0.61) and the 95% confidence limits for more than half of the studies included 0, indicating that improvement in ADL functioning was not statistically significant. A change in the mean ADL scores from 19.4 to 12.4 in the on-medication/on-stimulation state was noted in the GPI studies. These studies had a mean ES equal to 1.6 and only one of the five studies had a confidence limit that included 0.

Medical Therapy and Levodopa Equivalents
Approximately half of the studies contained information on antiparkinsonian medication use. Authors of these analy-
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Fig. 3. **Upper:** Graph demonstrating ESs and 95% CIs for each study and overall, according to levodopa equivalents in patients who underwent STN DBS. **Lower:** Graph revealing ESs and 95% CIs for each study and overall, according to levodopa equivalents in patients who underwent STN DBS.

Effect sizes and their 95% CIs for the individual studies are presented in Fig. 3. Effect sizes for STN DBS ranged from 0.39 to 6.83, with an overall mean ES of 1.51 (95% CI 1.15–1.87), indicating a significant reduction in medication use following DBS. On average, authors of these studies reported a 52% reduction in daily medication dosage. Effect sizes for GPI DBS ranged from 0.06 to 0.4, and the mean ES was −0.02 (95% CI −0.29–0.26). The ES was positive in four studies (50%) and all 95% confidence limits included 0, which indicated that in none of the studies was medication use significantly reduced following GPI DBS. There was significant heterogeneity of ESs for STN DBS (p < 0.01) but not for GPI DBS (p = 0.948).

**Discussion**

Data from an analysis of several dozen studies of bilateral STN and GPI DBS for PD indicated that motor function...
based on the UPDRS motor subscale improves significantly after DBS, regardless of the stimulation target. The beneficial effect was greater, although not statistically significantly so, in STN compared with GPI cases. Medication dosages were reduced by 50% following STN DBS but did not change in patients who had undergone GPI DBS. Activities of daily living functioning improved equally in both groups in the off-medications state. GPI DBS (but not STN DBS) also led to improvement in ADL in the on-medications state.

The results presented in the metaanalysis should be interpreted cautiously. Only one study was a randomized trial and numerous factors limited our ability directly to compare outcomes according to the anatomical target of stimulation. Among these factors are differences in sample sizes, enrollment criteria, and selection criteria for DBS at one site as opposed to the other (for example, physician and patient preferences or predominant symptom). Physician experience and patient expectations may have a significant impact on outcomes and cannot be assessed in the existing literature. Other factors including targeting techniques, final location of implanted electrodes, and the extent to which stimulation is fine-tuned after DBS can also affect outcomes. This information is neither reported nor easily synthesized when available. Generalization of our findings to the general PD population may be limited, given that the mean age of patients reported in the literature (~56 years) and the age at onset of the disease (62.4 years) differ from the average age of the general PD population. Nevertheless, the findings are quite robust; when we excluded certain studies based on sample size, year of study publication, study origin, or duration of follow up, the results remained relatively stable.

A differential effect of the stimulation target was found when medication requirements were examined. Medication requirements decreased in all studies following STN DBS but not following bilateral GPI DBS. We do not know whether STN DBS and GPI DBS have differential effects on medication requirements or whether the difference is an artifact resulting from assumptions about medication needs following stimulation at these sites. In general, STN DBS allows reduced medication without adversely affecting motor function. Furthermore, STN DBS may exacerbate dyskinesias, and reduction of dyskinesias following this therapy is dependent on a reduction in PD medications. In contrast, GPI DBS may have a direct antidyskinetic effect that is not dependent on a reduction in medications, and many providers do not attempt to reduce medication in this group. Whether medications can be reduced following GPI stimulation without negative consequences has not been studied, nor have differences in medication requirements after STN and GPI DBS been compared in a prospective, blinded fashion.

Mounting evidence suggests that medication withdrawal after surgery for PD may not be desirable in all patients. The withdrawal of medication after surgery may exacerbate nonmotor symptoms, especially neuropsychological dysfunction such as affective and personality disorders. In some patients, adverse effects of STN DBS on nonmotor symptoms can negate improvement in motor symptoms. Reinstitution of medical therapy can correct these problems in some patients. In light of these observations, data indicating better ADL and disability outcomes in the on-medication state in patients undergoing GPI DBS, compared with STN DBS, are interesting. Our data revealed that patients undergoing GPI and STN DBS had improvement in ADLs while in the on-medication state as well. Burchiel and colleagues reported that medical therapy might have a synergistic effect with GPI but not with STN DBS. The Deep-Brain Stimulation for Parkinson’s Disease Study Group reported disability scores (rated separately by physicians and patients) before and after DBS for treatment of PD. The degree of improvement in disability was greater in patients who had undergone GPI DBS than in those who had undergone STN DBS (the degree of significance was not indicated). The better ADL and disability scores in patients who underwent GPI DBS support the presence of a synergistic effect between medical therapy and GPI DBS. Perhaps this result occurs through better control of nonmotor symptoms by continued medication therapy in the patients treated using GPI DBS.

In this metaanalysis we used the UPDRS motor score as its primary measure for a comparison between STN DBS and GPI DBS because this measure is most commonly reported in the published literature pertaining to the surgical treatment of PD. Objective motor function as scored using the UPDRS is relatively easy for physicians to assess but may not be the outcome of greatest functional significance to patients. Other patient and physician-related outcomes that can influence the superiority of DBS at one site compared with another include time in the on state without dyskinesias, functional disability and ADLs, complications of therapy, mood, mentation, and complexity of patient care. Whether the relative superiority of STN DBS in improving functional (UPDRS) motor scores is sufficient in and of itself to place STN DBS at the forefront of surgical therapy for PD remains unsettled. The better UPDRS motor scores achieved through STN DBS must be balanced by the postprocedural potential for increased cognitive dysfunction and greater frequency of mood changes compared with those in patients who undergo GPI DBS.

Complications and adverse events of DBS are also important to consider in a comparison of STN and GPI stimulation. We were not examined in this metaanalysis. It was not possible to synthesize these findings across studies because not all authors reported adverse events, definitions of any reported adverse events were not uniform across studies, and it was not always possible to distinguish among stimulation effects (modifiable), transient effects, and adverse events that resulted in permanent changes.

Limitations of metaanalyses pertaining to surgery for PD have been described by Bakay. Chief among these limitations is the adverse impact of including poor-quality, nonuniform data in the metaanalysis. Our review of the existing literature reveals significant variability in the quality of published reports. We have tried to minimize the inherent limitations of metaanalyses through careful selection and evaluation of published reports detailing outcomes of STN and GPI DBS. Only those reports that meet our strict inclusion criteria were incorporated into the analysis. Some reports have included patients whose data were also detailed in other publications, but this duplication was not always clear. We therefore attempted to identify and use data only from the most recent, most relevant, and/or most...
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complete publication. Additionally, in several studies the sample size changed between the baseline and follow-up assessments and it was not always clear on what sample the analysis had been conducted. Although most authors only examined outcomes at a single time point (for example, 6 months postintervention), a few reported outcomes at multiple points (for example, 1, 3, and 12 months post-DBS). We selected the time closest to 6 months postsurgery for all studies to have a more uniform assessment. In fact, 12-month data in some studies showed that the effect of DBS on motor function is greater than that found in assessments closer to the time of surgery (perhaps reflecting fine-tuning of medications and stimulation over time). Furthermore, we included three studies in which the authors did not specifically report when follow up had been conducted. When analyses were redone limiting studies to those with 6- or preferably, 12-month outcomes, the results did not change. Finally, although we excluded studies that combined unilateral and bilateral cases if the data were not presented separately, we did include one paper in which one patient had received a unilateral implant and the rest of the sample had received bilateral implants. We could not control some factors that directly affect surgical outcomes, such as physician experience, lack of blinded assessments, targeting techniques, location of implanted electrodes, and postoperative stimulation management.

Subthalamic nucleus DBS has gained significant popularity and, based on improvement in motor function and decreased medication requirements, the STN is considered the preferred site of bilateral stimulation by most PD specialty centers. Data from our analysis indicates that motor function improves equally in the GPI-targeted cases, while medication needs do not change. Additional important questions about DBS target sites remain unanswered. What are the effects of the stimulation target site on other outcomes such as cognitive and psychosocial functioning, speech, balance, gait, and quality of life? Do patients value improvement in some symptoms more than others? Are there differential costs and is cost-effectiveness dependent on the target site? Are there differential surgical risks and management complexities? These issues are critically important to the field: DBS is an expensive therapy, its use requires a long-term commitment on the part of patients as well as physicians, and there are many potential candidates for the procedure.

Conclusions

A review of the published literature and the results of our metaanalysis reveal the need for a large randomized controlled trial of STN and GPI DBS to evaluate the relative effectiveness of stimulation targets based on multiple patient outcomes at multiple time points. Within the context of a large randomized trial, patient factors such as age, sex, and race and disease factors such as the predominant symptom (for example, tremor, dyskinesia, or postural instability) that may differentially affect outcomes of DBS can be distinguished. Long-term effects (that is, those present > 1 year postsurgery) of DBS on patient functioning should also be considered. In all likelihood, certain types of patients and/or particular disease symptoms may respond better to stimulation at one target than another, but we cannot determine the difference based on the existing literature. Therapy-specific factors that could influence target selection for DBS might also be identified in a large-scale trial, for instance, incidence and severity of surgical complications, stimulation-related side effects, and management complexity. Given the promise of DBS for long-term management of advanced PD, clinicians and patients should make treatment decisions based on evidence from well-designed trials that minimize bias and provide valid findings to inform clinical practice.

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