A meta-regression of the long-term effects of deep brain stimulation on balance and gait in PD

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ABSTRACT

Objective: Deep brain stimulation (DBS) alleviates the cardinal Parkinson disease (PD) symptoms of tremor, rigidity, and bradykinesia. However, its effects on postural instability and gait disability (PIGD) are uncertain. Contradictory findings may be due to differences in stimulation site and the length of time since DBS surgery. This prompted us to conduct the first meta-regression of long-term studies of bilateral DBS in the subthalamic nucleus (STN) and globus pallidus interna (GPi).

Results: Eleven articles reported a breakdown of the Unified Parkinson's Disease Rating Scale score before and beyond 3 years postsurgery (mean 4.5 years). Random effects meta-regression revealed that DBS initially improved PIGD compared to the OFF medicated state before surgery, but performance declined over time and extrapolation showed subjects would reach presurgery levels 9 years postsurgery. ON medication, DBS improved PIGD over and above the effect of medication before surgery. Nevertheless, for the STN group, PIGD progressively declined and was worse than presurgery function within 2 years. In contrast, GPi patients showed no significant long-term decline in PIGD in the medicated state. Improvements in cardinal signs with DBS at both sites were maintained across 5 years in the OFF and ON medication states.

Conclusions: DBS alone does not offer the same improvement to PIGD as it does to the cardinal symptoms, suggesting axial and distal control are differentially affected by DBS. GPi DBS in combination with levodopa seemed to preserve PIGD better than did STN DBS, although more studies of GPi DBS and randomized controls are needed. *Neurology*® 2010;75:1292-1299

GLOSSARY

DBS = deep brain stimulation; **GPi** = globus pallidus interna; **PD** = Parkinson disease; **PIGD** = postural instability and gait disability; **STN** = subthalamic nucleus; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Balance and gait are gradually, and inevitably, impaired as Parkinson disease (PD) progresses, resulting in significant impairment of mobility. Mobility disability is one of the most important causes of diminished quality of life, morbidity, and mortality in patients with PD.^{1,2} Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus interna (GPi) is an increasingly common therapy for mid- to late-stage PD. With optimized stimulation settings, DBS typically lessens the motor symptoms of tremor, limb rigidity, bradykinesia, and akinesia. However, the long-term effects on balance, locomotion, and speech, often referred to as axial motor signs, are debated.

Despite improvements in clinical ratings of PIGD immediately after DBS surgery, patients tend to fall more.³ These seemingly contradictory findings are not altogether surprising given that balance and gait are complex behaviors consisting of many sensorimotor subsystems that may not be fully characterized by the PIGD items in the Unified Parkinson's Disease Rating Scale (UPDRS). So although posture and gait are affected by bradykinesia, rigidity, and to a lesser extent tremor, other sensorimotor systems underlying posture and gait, such as set-dependent flexibility,⁴ sensory integration,⁵ and postural synergies,⁶ do not show the same responsiveness to levodopa. Therefore, each subsystem underlying control of posture and gait may be related to different neural circuits with varying sensitivities to levodopa or DBS.⁷⁻¹⁰ As

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STN and GPi project to different motor pathways within the CNS, stimulation at these sites may contribute differently to axial control.

The choice of target for DBS is dependent on the experience and judgment of the neurologist and neurosurgeon. STN DBS has more of a proven record than GPi stimulation, although the choice of STN is questioned in patients with cognitive or speech impairment.¹¹⁻¹³ However, in cases where a reduction in dopaminergic medication has been the postsurgical goal, due to medication intolerance or compulsive behaviors, STN has remained the target of choice. The relative effects of DBS in the STN and GPi on postural stability and gait are unclear because experimental studies almost always report only one or the other DBS target.

A meta-analysis by Bakker and colleagues¹⁴ of the effects of DBS on the international gold standard clinical assessment for PD, the UPDRS, suggests that PIGD is improved by DBS in both the STN and GPi when tested within a year after surgery. The meta-regression of the current study follows the progression of both PD cardinal and PIGD symptoms over several years to better understand the relative long-term effects of DBS on bradykinesia, tremor, and rigidity vs posture and gait. If improvement in PIGD changes differently over time than the cardinal signs, this is consistent with differential effects of DBS on the distal and axial neural control circuits. Additionally, if the long-term progression of DBS in STN and GPi on PIGD differ, this could influence the target for patients with PD who have significant balance and gait problems. The study complied with the Meta-analysis of Observational Studies in Epidemiology guidelines.¹⁵

METHODS Search strategy and selection criteria. References were identified by search of PubMed, Medline, and Scopus electronic databases published before July 2009 with the terms “PD” and “deep brain stimulation,” or “subthalamic nucleus stimulation,” or “globus pallidus stimulation.” Articles were also identified through examination of the reference lists of relevant publications and a search of the authors’ own reference database. Articles were selected for inclusion only if they provided UPDRS ratings before surgery and follow-up ratings with a final assessment a minimum of 3 years after surgery. Statistical variance, the number of subjects at each assessment period,

levodopa-equivalent daily dosage, and stimulation settings were also required.

Thirteen observational studies fulfilled the selection criteria. Two of these studies were excluded^{16,17} because the population samples were subsets of the populations in 2 other articles that were included because they had larger sample sizes.^{18,19} Of the remaining 11 studies, 3 examined bilateral GPi, 9 examined bilateral STN stimulation, and 1 study included both STN and GPi target sites.¹⁹ In the Lyons et al.²⁰ study, 3 of the 9 subjects had unilateral GPi stimulation but the results lumped the unilateral and bilateral cases. As there were so few studies of the GPi, this study was included but the reported effects may be underestimated for this reason.

In all studies, the UPDRS was assessed by a neurologist specializing in movement disorders and patients with cognitive impairment were excluded. Subjects were evaluated in the mornings in the “practically off” state a minimum of 8 hours after withdrawal of antiparkinsonian medication, with most studies waiting at least 12 hours. The “best on” state was assessed within 90 minutes of administration of a dose of levodopa. In 4 studies, this was a supratherapeutic dose (as a % of normal dose), and the remaining studies administered the subjects’ usual morning dose.

The clinical characteristics of the patient groups included in the analysis are presented in table 1. At baseline assessment the patients who would go on to receive STN and GPi DBS were equivalent in terms of motor UPDRS (part III), disease duration, and length of maximum follow-up time, but the GPi subjects included more females and were slightly younger at onset, although distributions overlapped.

Composite score calculation. UPDRS scores were collated for the cardinal signs of tremor (items 20 and 21, with a maximum score of 28), rigidity (item 22, with a maximum score of 20), and bradykinesia (items 23, 24, 25, and 26, with a maximum score of 32) as well as for the PIGD signs of gait (item 29, with a maximum score of 4) and postural stability (item 30, with a maximum score of 4). Arising from a chair (item 27) and posture (item 28) were not consistently reported so these items could not be included in the PIGD composite measure. Initial meta-analyses showed that scores of tremor, rigidity, and bradykinesia had similar outcomes and thus were normalized so each had equal weight in a composite “cardinal” measure with a maximum possible score of 4. Gait and postural stability scores were also combined and normalized to have a maximum score of 4 in a single measure “PIGD.” Not all studies presented the values of individual UPDRS items. For the 2 studies that reported only a composite “axial score”^{25,26} that included rise from a chair and postural alignment as well as items 29 and 30, the axial score was normalized to a maximum of 4 and was included as a measure of PIGD. As can be seen in table 1, there was no systematic difference before surgery in PIGD or total UPDRS between STN and GPi groups.

Medication and stimulation changes over time. The modifications to levodopa medication dose and stimulation frequency across time are presented in table 2. On average, by the final follow-up the levodopa equivalent medication dosage was approximately half its level before surgery in the STN group (48.1%), whereas the mean dose for the GPi group had not changed significantly, although it was quite variable among studies. All studies reported a levodopa-induced dyskinesia score either from the UPDRS IV questionnaire or from patient diaries. The percentage changes in dyskinesias were measured by comparing the postoperative condition with medication ON and stimulation ON to the preoperative state with medication. For all studies there was a significant decrease in the amount of time

Table 1 Clinical baseline characteristics of populations^a

Study	Site	No.	% Male	PD onset, y	PD duration, y	OFF UPDRS III total/108	OFF PIGD mean/4
1 Gan et al., 2007 ¹⁸	STN	36	61	42.8	12.5	42.2 (14.6)	1.65 (1.05)
2 Ostergaard and Aa Sunde, 2006 ²¹	STN	22	77	44.0	19.0	51.3 (12.1)	2.3 (1.0)
3 Rodriguez-Oroz et al., 2005 ¹⁹	STN	49	51	44.4	15.4	56.7 (15.7)	2.75 (1.0)
4 Visser-Vandewalle et al., 2005 ²²	STN	20	75	45.9	15.0	42.3 (9.3)	2.8 (0.8)
5 Krack et al., 2003 ¹³	STN	39	49	40.4	14.6	55.7 (11.9)	2.8 (0.9)
6 Piboolnurak et al., 2007 ²³	STN	17	73	39.8	13.5	47.7 (11.2)	1.85 (1.2)
7 Romito et al., 2009 ²⁴	STN	20	55	42.1	14.3	60.5 (9.5)	2.1 (1.1)
8 Schupbach et al., 2005 ²⁵	STN	37	65	39.7	15.2	51.9 (17.2)	2.9 (1.0)
9 Wider et al., 2008 ²⁶	STN	21	60	50.5	14.4	47.2 (14.4)	1.6 (0.8)
10 Rodriguez-Oroz et al., 2005 ¹⁹	GPI	20	65	40.4	15.4	51.7 (13.6)	2.4 (1.1)
11 Lyons et al., 2002 ²⁰	GPI	9	56	39.0	10.0	47.8 (15.6)	2.1 (1.2)
12 Volkmann et al., 2004 ²⁷	GPI	11	37	34.6	11.2	52.7 (14.9)	2.2 (0.7)

Abbreviations: PD = Parkinson disease; PIGD = postural instability and gait disability; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

^a Values are means (SD).

spent ON with dyskinesia after surgery, and this was maintained across time. The studies with the most marked reduction in dyskinesias were for STN DBS. As can be seen in table 2, stimulation frequencies were in the range of 138 to 181 Hz with no systematic difference between STN and GPI sites. It was generally reported that stimulation settings of the DBS did not change significantly over time.

Statistical analysis. To investigate changes in motor function with DBS, a weighted meta-regression was performed for PIGD and cardinal measures. For each study, a standardized change

score was calculated for each follow-up assessment, which was the difference between the composite score at the assessment time and the presurgery score, divided by the average SD of each score. Two sets of scores were compared: 1) postoperative OFF medication and ON DBS function compared to preoperative OFF medication function and 2) postoperative ON medication and ON DBS function compared to preoperative ON medication function.

Despite low heterogeneity (with I^2 values ranging from 0 to 0.4), a random effects model was used to provide greater rigor to

Table 2 Medication and stimulation changes across time^a

Study	Site	Testing, y	LEDD	LEDD % reduction at retest	ON dyskinesia reduction at each retest (%)	Stimulation at each retest (Hz)
1 Gan et al., 2007 ¹⁸	STN	0, 1, 3 ^b	1,228 (647)	62, 49	79, 65	147 (20) across retests
2 Ostergaard and Aa Sunde, 2006 ²¹	STN	0, 1, 4	1,197 (532)	19, 29	86, 90	179 (22), 181 (15)
3 Rodriguez-Oroz et al., 2005 ¹⁹	STN	0, 1, 3, 8	1,309 (649)	41, 34	51, 59	148 (22), 151 (23)
4 Visser-Vandewalle et al., 2005 ²²	STN	0, 0.25, 4	1,133 (383)	61, 47	79, 79	138 (23), 135 (19)
5 Krack et al., 2003 ¹³	STN	0, 1, 3, 5	1,409 (605)	59, 63, 63	71, 71, 71	143 (19), UA, 145 (19)
6 Piboolnurak et al., 2007 ²³	STN	0, 3, 5	1,263 (525)	48, 40	76, 76	170 (23), 154 (25)
7 Romito et al., 2009 ²⁴	STN	0, 0.5, 1, 3, 5	1,458 (786)	59, 66, 62, 62	90, 85, 83, 81	UA
8 Schupbach et al., 2005 ²⁵	STN	0, 0.5, 2, 5	1,468 (811)	64, 63, 58	86, 86, 79	153 (29), 152 (27), 149 (27)
9 Wider et al., 2008 ²⁶	STN	0, 0.5, 2, 5	1,128 (493)	83, 65, 57	85, 83, 85	148 (24), 152 (24), 151 (26)
10 Rodriguez-Oroz et al., 2005 ¹⁹	GPI	0, 1, 3, 9	1,074 (462)	-16, -32	72, 76	169 (22), 163 (25)
11 Lyons et al., 2002 ²⁰	GPI	0, 0.25, 1, 4	1,130 (UA)	UA, 12	50, 68, 64 ^c	158 (34), 155 (20)
12 Volkmann et al., 2004 ²⁷	GPI	0, 1, 3, 5	961 (467)	24, -3, 21	58, 63, 64 ^c	175.2 (19.8) across retests

Abbreviations: GPI = globus pallidus interna; LEDD = L-dopa-equivalent daily dose at baseline in mg/day; STN = subthalamic nucleus; UA = data unavailable.

^a Values are means (SD).

^b 0 = Presurgery baseline assessment, generally performed 1 to 2 weeks before surgery.

^c Diary reports of % of time with levodopa-induced dyskinesias; the other studies reported Unified Parkinson's Disease Rating Scale IVa values.

the analysis, particularly given the lack of randomization.²⁸ Uncontrollable sources of heterogeneity between studies include differences in surgical techniques, skill of the surgeons, the length of time between initial assessment and surgery (ranging from a couple of days to 6 weeks), as well as environmental and lifestyle differences in the populations. Time since surgery (years) was a continuous covariate in the regression analysis. Levodopa reduction was not used as a covariate because the values provided by the articles were mean values, so as the variability across studies was less than variability within studies the utility of this measure is limited.²⁹

A random effects meta-analysis was also performed to determine the effect of medication on the PIGD and cardinal scores by comparing standardized changes in the presurgery OFF and ON states within studies. Confidence intervals and the effect size were calculated for each study. Custom written syntax in Predictive Analytics SoftWare (PASW) version 18 was used to perform all statistical analyses.³⁰

RESULTS Summary. DBS surgery initially improved PIGD scores. However, as time progressed, PIGD significantly worsened. In contrast, the initial improvement in cardinal scores with DBS was maintained over 5 years. The standardized change scores of at each assessment time for each of the studies are presented in the figure.

Posture and gait changes. The regressions for PIGD in the OFF medication state were similar for STN and GPi groups ($\chi^2 = 0.19, p = 0.66$). DBS initially improved PIGD when compared to the OFF medication state before surgery (figure, A). This initial improvement is revealed by a constant in the regression which is less than zero (95% CI -1.869 to $-1.015, p < 0.001$). However, DBS was associated

Figure Random-effects meta-regression of the change in postural instability and gait disability (PIGD) and cardinal scores after deep brain stimulation (DBS) surgery across time

The plots show the standardized difference between scores recorded at various time points postsurgery and the equivalent medication state presurgery. A change score <0 indicates an improvement, and >0 indicates a worsening. The blue data points are studies of globus pallidus interna (GPi) DBS and the red points are those of subthalamic nucleus (STN) DBS. The area of each point is proportional to the number of subjects. The number on the data point corresponds to the study number in table 1. Regression lines are split into STN (red) and GPi (blue). An asterisk (*) identifies when the coefficient of time was significant in the regression and corresponding coefficients of determination (R^2) values are shown. (A) shows the change in PIGD scores post-pre DBS surgery OFF medication and (B) shows the difference in PIGD scores post-pre DBS surgery ON medication. (C) Shows the change in cardinal scores post-pre DBS surgery OFF medication and (D) shows the change in cardinal scores post-pre DBS surgery ON medication.

with worsening of PIGD symptoms as the years progressed, as indicated by a positive slope of the regression with follow-up time (95% CI 0.017 to 0.296, $p = 0.029$). Extrapolating from the regression slope, patients would be predicted to have worse PIGD with DBS than their presurgery medicated OFF state by 9 years postsurgery.

Presurgery, PIGD ratings were improved ON medication compared to OFF medication, with a pooled effect of -1.67 (95% CI -2.02 to -1.32). Postsurgery, there was an initial improvement in PIGD with DBS over and above the effects of medication (figure, B), with the intercepts of the regression different from zero for both STN (95% CI -0.747 to -0.090 , $p = 0.016$) and GPi (95% CI -1.40 to -0.267 , $p = 0.029$). This was a larger effect in GPi compared to STN ($\chi^2 = 12.1$, $p = 0.001$). As time progressed, the STN group had worsening of PIGD (95% CI 0.105 to 0.318, $p = 0.001$) and by 2 years PIGD was on average worse than the presurgery medicated ON state. In contrast, the GPi group did not have deterioration in PIGD function over time (95% CI -0.098 to 0.304, $p = 0.338$), with the gradient of the PIGD change over time (time coefficient in the regression) less than half the STN group (0.103 vs 0.212).

Cardinal changes. The cardinal symptoms of tremor, rigidity, and bradykinesia were improved by both STN (95% CI -2.025 to -1.322 , $p < 0.001$) and GPi (95% CI -1.841 to -0.488 , $p = 0.016$) stimulation in the medication OFF state (figure, C). The cardinal features did not deteriorate over time ($p = 0.623$ for STN and $p = 0.937$ for GPi).

ON medication, cardinal symptoms with DBS initially improved over and above medication alone presurgery for both STN and GPi sites (95% CI -1.302 to -0.519 , $p < 0.001$) (figure, D). The gradient of the regression slope over time was not different from zero for both the STN ($p = 0.085$) and GPi groups ($p = 0.553$).

DISCUSSION This meta-analysis of the long-term effects of DBS on PD motor symptoms shows that despite initial improvement in posture and gait, PIGD scores declined after surgery. In contrast, the improvement in cardinal signs after DBS were maintained. GPi stimulation combined with medications preserved balance and gait function better than STN stimulation combined with medications.

Effect of DBS OFF medication. The effect of DBS on the progression of the symptoms of PD is revealed by motor function in the OFF medication state before and after surgery. After an initial improvement in both cardinal and PIGD symptoms, the improve-

ment in cardinal symptoms is maintained while PIGD symptoms worsen. One explanation might be that the stimulation settings are programmed to alleviate the cardinal symptoms, but not the PIGD symptoms. However, a review of the long-term settings showed that the voltage, pulse width, and frequency of stimulation were not modified significantly beyond the first 6 months in the studies included in the meta-analysis. So, with the stimulation settings stable over time, the decline in PIGD function without a decline in cardinal symptoms implies a different mode of action of DBS on axial motor control.

The initial benefit of DBS surgery observed in the PIGD symptoms may be a direct result of improvements in rigidity and bradykinesia that were constraining posture and gait. Meanwhile, other sensorimotor circuits involved in balance and gait control that are not responsive to DBS continue to decline as the disease progresses. Laboratory studies quantifying the effects of DBS on particular systems underlying balance control supports this theory as they suggest that DBS can improve some balance subsystems but impair, or not improve, others. For example, DBS improves rigidity affecting postural control. Reducing excessive postural muscle tone improves static postural alignment.³¹ Improvement of bradykinetic postural movements with DBS produces faster and larger voluntary movements of the body center of mass.¹⁰ However, other systems underlying the control of balance are worse after surgery, such as anticipatory postural adjustments prior to rising onto toes,³² and recent work shows no improvement in automatic, feet in place, postural responses.³³ Thus, balance is comprised of many physiologic functions, some of which are improved and some potentially worsened by DBS.

Similarly, DBS improves some gait subsystems but not others. Stride length and gait speed, both related to bradykinesia, increase during STN DBS.³⁴⁻³⁹ Improved postural alignment during gait, related to reduced rigidity, also is seen.³⁵ In contrast, the timing characteristics of gait, such as cadence^{36,37} and variability in stride and swing time,³⁸ may not improve with DBS. More challenging locomotor tasks such as changing direction and dual tasking, which are often associated with falls,³⁹ have not been evaluated. Quantitative laboratory studies comparing the effects of DBS in the STN and GPi on spatial and temporal characteristics of gait are also lacking.

The notion that axial and distal PD motor symptoms are controlled by different physiologic mechanisms is supported by the observation of different latencies to changes in particular PD signs after turning DBS on.⁴⁰ Tremor is affected almost instantly,

followed by rigidity and bradykinesia, whereas maximal locomotion and balance changes are delayed for a few hours.⁴¹

Effect of DBS ON medication. Investigating the effects of DBS while patients are taking levodopa provides insight into the interaction between levodopa and DBS in patients' clinically functional state. The improvement in PIGD scores with GPi stimulation combined with levodopa is maintained for up to 5 years. In contrast, the improvement of PIGD scores with STN stimulation combined with levodopa declines over time. What are the possible reasons for this difference between the effects of DBS in GPi and STN over time? One possibility is that the difference in doses of antiparkinsonian medications associated with STN and GPi stimulation is responsible. Medication doses did not change significantly between presurgery and postsurgery for subjects receiving GPi DBS, whereas the presurgery levodopa dose was reduced by half in the subjects receiving STN DBS. The higher relative levels of dopaminergic medication taken by patients after GPi may prevent progression of PIGD by improving aspects of balance or gait not adequately treated with DBS. Indeed, across the studies the percentage reduction in the levodopa equivalent dose was correlated with worsening of the ON medication PIGD change score ($R = -0.54$, $p = 0.003$). However, within the STN group this correlation did not reach statistical significance. This could be because levodopa-induced dyskinesias are confounding the effects in this group because implantation at STN tends to be favored for patients who have the most severe problems with levodopa-induced dyskinesias. This tendency is reflected in the analyzed studies with the STN populations showing a greater reduction in medication and associated dyskinesias postsurgery (table 2). Therefore, reducing the medications in the STN group may be pulling the PIGD score in 2 opposing directions: 1) reducing dyskinesias, which serves to improve PIGD; and 2) reducing the function of dopaminergic circuitry, which serves to worsen PIGD.

Another possibility to explain the differences in GPi and STN stimulation over time is that the GPi site may have greater influence on PIGD in the medicated state by its more direct connections to the motor and premotor cortex via the thalamus or because of activation of axons of passage in dorsolateral GPi to the midbrain.⁴² Increased understanding of the mechanism of DBS and the pathophysiology of the basal ganglia are needed to resolve this issue. Recent studies examining stimulation optimization have shown improved gait and balance by stimulating at lower frequencies (~ 60 Hz) in STN,⁴³ or stimulating lower contacts (inside SNr).⁴⁴ The stimulation fre-

quencies were similar among the articles in the current analysis (table 1); however, subtle differences in site-specific responses to the stimulation settings may have some bearing on the response.

Cardinal signs, compared to the treated state before surgery, are improved with DBS alone and combined with medication therapy out to 5 years after surgery. DBS is generally considered to be a symptomatic treatment that does not modify the disease progression. However, these results are consistent with a disease-modifying effect.

Possible disease-modifying effects. Motor function examined with the stimulator turned off may better reveal the natural state of the disease and whether DBS has modified progression of motor symptoms. A handful of the long-term studies report these effects. Cardinal signs of tremor and rigidity were not significantly different between the OFF DBS/OFF medication state 4 to 5 years postsurgery and the OFF medication presurgery²¹⁻²⁴ but bradykinesia had worsened somewhat.²¹⁻²³ In contrast, PIGD scores OFF DBS and OFF medication had deteriorated significantly 4 to 5 years after DBS, compared to the pre-DBS OFF medication scores.²¹⁻²³ Two of these studies tested patients with the stimulator turned off for 10–12 hours.^{21,22} Given this long duration, it is unlikely that the cardinal symptoms were affected by lingering benefit from the stimulation.⁴¹ Unfortunately, there are currently no longitudinal studies of patients with PD who are candidates for DBS but who did not get DBS surgery to compare the natural history of symptom progression at this stage of the disease.

DBS may slow functional progression because patients are more active and exercising more after surgery. In rodent models of PD, exercise has been shown to have neuroprotective benefits, preventing dopaminergic neuronal loss in regions of the basal ganglia.⁴⁵⁻⁴⁷ There also is evidence that exercise may improve function without preserving dopaminergic neurons^{48,49} presumably through compensatory mechanisms. In human subjects with PD, treadmill training has produced improvements in gait, quality of life, and levodopa efficacy.⁵⁰⁻⁵² So although the precise mechanisms remain to be determined, there is growing evidence that physical activity can curb the rate of motor function decline.

Limitations. Assertions about the relative benefits of GPi over STN surgery for PIGD must be tempered by the fact that fewer long-term studies of GPi stimulation exist and there are no randomized control subjects without surgery. This meta-regression suggests the possibility that GPi may be a superior site for DBS to maintain posture and balance associated

with PD and stresses the need for more studies of DBS in the GPi to determine whether this is unequivocally the case.

A problem with studies stretching over many years is that the data belong to subjects who survived for the duration of the study, and neglect those who died along the way. All studies had dropouts; overall 11% of the original recruits died before the final assessment for various reasons.

CONCLUSIONS This meta-analysis of the long-term efficacy of DBS has shown that the benefits to posture and gait function are not maintained to the same extent as are the benefits to the cardinal symptoms of PD. Further, the results suggest that GPi may be a superior site to STN for sustaining gait and posture function in combination with levodopa. Long-term follow-up of the randomized controlled trial comparing DBS in GPi and STN will be important.³ It is hoped that this analysis will foster renewed interest in the underlying neural mechanisms for gait and balance in PD and the effects of levodopa and DBS on these mechanisms.

AUTHOR CONTRIBUTIONS

All authors participated in the drafting of the paper and have seen and approved the final version. R.S.G. performed the literature search, analysis, and wrote the first draft. J.G.N. contributed ideas to the statistical analysis and critically reviewed the article. K.J.B. provided contributions to the text. F.B.H. had overall supervision of writing this meta-analysis.

DISCLOSURE

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