



STN vs. GPi deep brain stimulation for tremor suppression in Parkinson disease: A systematic review and meta-analysis



Joshua K. Wong^a, James H. Cauraugh^b, Kwo Wei David Ho^a, Matthew Broderick^a, Adolfo Ramirez-Zamora^a, Leonardo Almeida^a, Aparna Wagle Shukla^a, Christina A. Wilson^a, Rob MA. de Bie^c, Frances M. Weaver^d, Nyeonju Kang^e, Michael S. Okun^{a,*}

^a Department of Neurology, Center for Movement Disorders and Neurorestoration, University of Florida College of Medicine, Gainesville, FL, USA

^b Motor Behavior Laboratory, University of Florida, Gainesville, FL, USA

^c Department of Neurology, Academic Medical Center, Amsterdam, the Netherlands

^d Hines Veterans Affairs Hospital, Center of Innovation for Complex Chronic Healthcare, Hines, IL, USA

^e Division of Sport Science, Incheon National University, Incheon, South Korea

ARTICLE INFO

Keywords:

Subthalamic nucleus
Globus pallidus interna
Tremor
meta-analysis
Parkinson disease

ABSTRACT

Objective: To compare subthalamic nucleus (STN) deep brain stimulation (DBS) with globus pallidus interna (GPi) DBS for tremor suppression in Parkinson disease (PD).

Background: DBS is an effective surgical therapy that has been shown to provide significant benefit for motor symptoms in PD. Currently, two main structures targeted to treat motor complications in PD are the STN and GPi. Although some groups traditionally favor STN over GPi for tremor suppression, evidence demonstrating superiority in long-term tremor control is limited.

Methods: We performed a systematic review for all randomized trials comparing STN vs GPi DBS in PD that were published before March 2017. Five studies were examined in a random effects model meta-analysis. We conducted moderator variable analysis to determine if there was a treatment effect difference for STN versus GPi.

Results: We compared DBS ON versus OFF and found a significant overall standardized difference mean effect: Effect Size = 0.36; 95% CI = 0.316–0.395; $P < 0.0001$. These findings indicate that DBS reduced tremor symptoms in PD patients with a medium effect size. Moderator variable analysis of STN vs GPi revealed two significant standardized effect sizes: STN effect size = 0.38 and GPi effect size = 0.35. A Z-test showed that effect sizes between the STN and GPi were not significantly different ($P = 0.56$).

Conclusions: DBS is effective in reducing tremor in PD patients regardless of stimulation target. However, the degree of tremor suppression in STN DBS versus GPi DBS was equivalent.

1. Introduction

Parkinson disease (PD) is a progressive neuro-degenerative syndrome characterized by cardinal motor features of tremor, bradykinesia, rigidity, and gait disturbance. Tremor has been a focus for many therapeutic interventions such as deep brain stimulation (DBS). DBS has been shown to provide significant benefit particularly for the motor symptoms in PD and is more effective than best medical therapy in improving motor function, quality of life, and on-time (periods of adequate control of PD symptoms) without troublesome dyskinesia [1]. The most common DBS targets pursued in PD are the subthalamic nucleus (STN) and globus pallidus interna (GPi).

Historically, the ventralis intermedius nucleus (VIM) of the

thalamus was the target of choice for PD and essential tremor based on encouraging results observed with ventrolateral thalamotomies [2,3]. VIM DBS offered effective tremor control while minimizing the speech and cognitive side effects observed in bilateral thalamotomies [4,5]. Although VIM DBS effectively suppressed PD tremor, patients experienced mixed results in terms of achieving an acceptable quality of life as the other symptoms of PD continued to worsen with time [4,6,7]. The failure of VIM DBS to address symptoms beyond tremor led to the search for alternative targets and the field converged on STN and GPi. Early, non-randomized comparative studies suggested that bilateral GPi DBS was less effective and suffered from waning motor benefits over time. Studies also proposed that STN DBS provided superior improvement in off-period bradykinesia [8–10].

* Corresponding author. 3450 Hull Road 4th Floor, Gainesville, FL, 32607, USA.

E-mail address: okun@neurology.ufl.edu (M.S. Okun).

Many groups began implanting STN DBS preferentially over GPI despite a lack of randomized studies [11,12]. Randomized controlled clinical trials comparing both targets revealed a similar motor efficacy and improvement in quality of life [13–17]. Despite the equivalence of findings in motor outcomes, many groups have maintained a preference for STN over GPI and specifically cite medication reduction and superior tremor suppression as the main concepts underpinning their choice [11,12]. Although the available literature clearly supports that STN DBS is associated with a greater medication reduction, data regarding tremor reduction is lacking. The current systematic review and meta-analysis provides clarity to the question as to whether STN or GPI is a superior target for tremor suppression in PD.

2. Methods

Between May–September 2017, we conducted a systematic literature search following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines: (a) PubMed, (b) ISI's Web of Knowledge, (c) Cochrane Database of Systematic Reviews, and (d) Clinicaltrials.gov. Keyword input for searching included: (a) Deep brain stimulation, (b) Subthalamic nucleus, and (c) Globus pallidus interna. All citations were exported and first screened for duplicates and parsed for title keywords by a single author (JW). A second round of screening was then performed by two additional independent investigators (KWDH, MB) based on the abstract implementing the eligibility criteria as described below. Disagreements between the two authors were resolved via a discussion.

We excluded review papers and studies that failed to report values for calculating individual effect sizes. Selected studies reported multiple comparisons on tremor sub-scores before and after patients received DBS electrodes, as well as on-medications and off-medications.

Included studies met the following criteria: (1) randomized control trial that examined placement of DBS electrodes in the STN or GPI in PD patients, (2) no other interventions investigated in the study, (3) at least 10 or greater patients in each study arm, (4) standardized tremor assessment, and (5) a within-group comparison involving a pre-DBS tremor assessment (i.e., pretest) and at least one post DBS tremor assessment (i.e., posttest). Our systematic literature search and comprehensive meta-analysis identified five studies that investigated the effects of DBS on tremor. Fig. 1 outlines our study approach according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Two of the five studies initially had insufficient published data to be included in our analysis. Specifically, they did not report the complete tremor outcome measurement as described below. These two principal investigators (PI) were approached for additional information and we were able to identify supplementary unpublished data that qualified for inclusion in our original analysis [14,16]. Importantly, the five data sets provided 46 total comparisons for our meta-analysis. Table 1 lists details for each of the five studies.

2.1. Tremor outcome measurement

The primary outcome measure for determining tremor control was the Unified Parkinson's Disease Rating Scale (UPDRS) Part III tremor sub-score. Tremor sub-score was defined as the sum of UPDRS Part III items 20 and 21.

2.2. Data synthesis and analysis

The Comprehensive Meta-Analysis software (ver. 3.0, Englewood, NJ, USA) was used for all analyses. Individual effect size for each of the 46 comparisons was quantified using changes in UPDRS tremor sub-scores for the DBS implantation site, on-off medications, baseline session (pretest), and posttest sessions. Baseline pretest and posttest session refer to evaluations prior to and following DBS implantation, respectively. To calculate the effect sizes from each comparison, we used

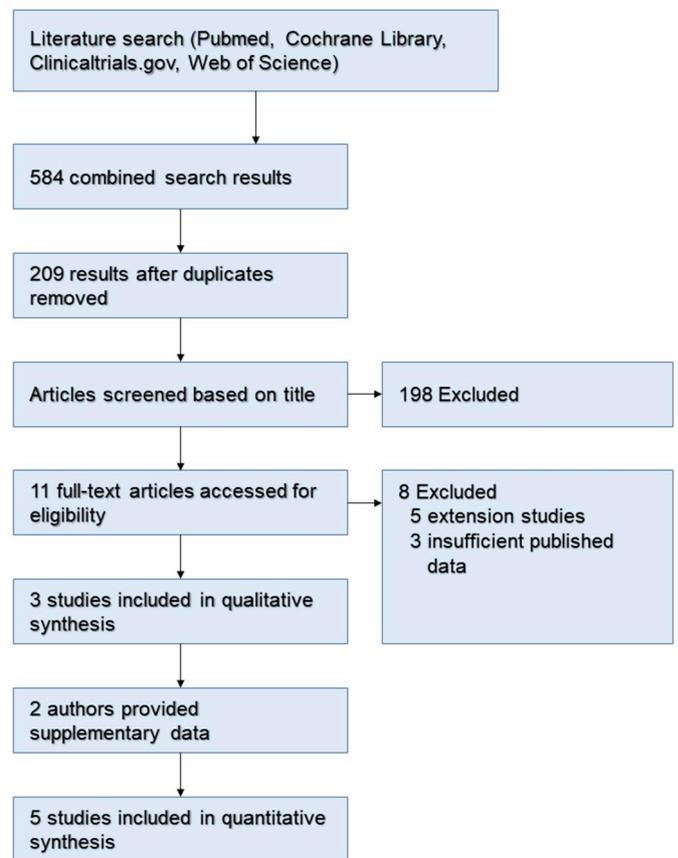


Fig. 1. PRISMA flow diagram outlining search strategy and results based on screening of titles and full-text articles.

mean tremor sub-score for baseline and posttest(s), sample sizes, and *P*-values. Based on our data set from published and unpublished studies as well as being consistent with traditional meta-analysis approaches, we conducted a random effects model [19–21].

Further, consistent with the traditional approaches for analyzing the mean effect for different subgroups we conducted a *Z* test and used the mean and variance of the estimated effects [19]. (The three formulas used for the *Z* tests are shown in Appendix A.)

3. Results

Accepted conventional meta-analyses involve calculating standardized mean effects for individual study comparisons and determining an overall effect size [19]. Data from five longitudinal randomized control trials (RCT) consisting of stimulation targets, UPDRS scores obtained on- and off-medication states, and pre-and post DBS implantation tremor sub-scores were synthesized for this meta-analysis. Tremor sub-scores for pre-op DBS implantation (pretest) and post DBS implantation (months post electrode placement) represented the number of data collection test sessions. The combination of stimulation targets, medication conditions, and test sessions totaled 46 comparisons and a total $N = 3267$.

3.1. Standardized mean difference effect

We conducted a random effects model meta-analysis on the 46 comparisons and found a significant overall standardized mean difference effect: (effect size: $ES = 0.36$; $SE = 0.02$; 95% $CI = 0.316$ – 0.395 ; $P < 0.0001$; $Z = 17.80$). This significant positive *ES* indicates lesser severity of tremor during the post-DBS implantation sessions in comparison to the baseline (i.e., no DBS implantation; pretest session). The

Table 1
Characteristics of participants included in the present meta-analysis.

Study	Total N	Gender	Mean Age (years)	Mean PD Duration (years)	UPDRS Motor Score (pre-op)	DBS	Site
Anderson et al. (2005)	12	N/A	61.0 ± 9.0	15.6 ± 5.0	49.0 ± 13.0	BI	STN
	11	N/A	54.0 ± 12.0	10.3 ± 2.0	51.0 ± 22.0	BI	GPI
DBS for PD Study Group (2001)	96	36 F, 60 M	59.0 ± 9.6	14.4	54.0 ± 15.1	BI	STN
	38	11 F, 27 M	55.7 ± 9.8	14.5	50.8 ± 11.6	BI	GPI
Odekerken et al. (2016)	63	19 F, 44 M	60.9 ± 7.6	12.0 ± 5.3	41 (33.8–55)	BI	STN
	65	21 F, 44 M	59.1 ± 7.8	10.8 ± 4.2	43 (32.5–53)	BI	GPI
Okun et al. (2009)	22	7 F, 15 M	59.8 ± 10.0	13.3 ± 4.0	45.2 ± 12.6	UNI	STN
	23	8 F, 15 M	60.2 ± 6.2	12.5 ± 3.6	40.6 ± 9.5	UNI	GPI
Weaver et al. (2012)	70	14 F, 56 M	60.7 ± 8.9	11.3 ± 4.7	42.5 ± 12.4	BI	STN
	89	12 F, 77 M	60.4 ± 8.3	11.4 ± 4.9	41.1 ± 12.2	BI	GPI
Total =	489	F = 128 M = 338	GM = 59.1 Median = 60.0 SD = 2.4	GM = 12.2 Median = 11.7 SD = 1.7	GM = 45.8 Median = 44.1 SD = 4.9		

Data are mean ± SD. Abbreviation. F: female; M: male; BI: bilateral stimulation; UNI: unilateral; STN: subthalamic nucleus; GPI: globus pallidus interna; UPDRS motor score (tremor subscale) pre-op DBS implantation without medication; GM = grand mean; SD = standard deviation.

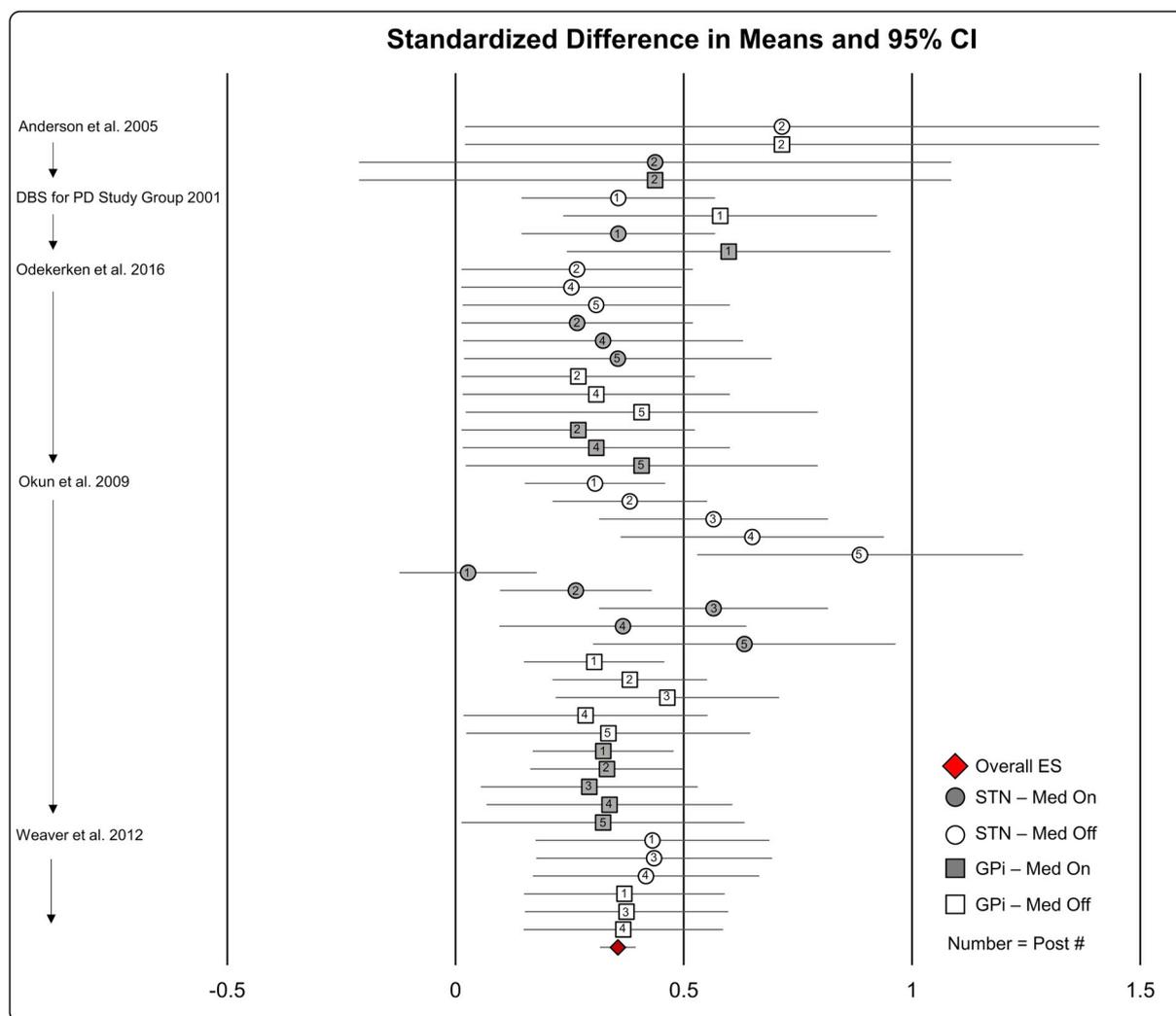


Fig. 2. Forest plot showing summary data as individual weighted effect sizes (standardized mean difference), 95% confidence intervals, Z values, and P values.

forest plot shown in Fig. 2 reveals individual effect sizes ranging from 0.027 to 0.886. Importantly, these findings indicate that DBS reduced tremor symptoms in individuals with PD. Moreover, Table 2 shows that 44 of the 46 comparisons revealed less tremors post-op DBS implantation.

3.2. Heterogeneity and publication bias

We conducted three traditional meta-analysis tests to determine heterogeneity in our five-longitudinal studies and 46 comparisons. Each variability test revealed a relatively low heterogeneity value between comparisons: (1) Cochran's $Q = 43.47$, $P = 0.18$; (2) Tau squared = 0.002; and (3) Higgins and Green's $I^2 = 1.78\%$. These values

Table 2
Summary statistics for the 46 comparisons in the random model meta-analysis.

Study	Primary Outcome Measure	Percent Change in Tremor	SMD	95% CI	Weight		
Anderson et al. (2005)	Tremor sub-score in UPDRS III (STN/Med off/12 m)	-88.8	0.72	0.02	1.41	0.31	
	Tremor sub-score in UPDRS III (GPi/Med off/12 m)	-78.5	0.72	0.02	1.41	0.31	
	Tremor sub-score in UPDRS III (STN/Med on/12 m)	0	0.44	-0.21	1.09	0.36	
	Tremor sub-score in UPDRS III (GPi/Med on/12 m)	-100	0.44	-0.21	1.09	0.36	
DBS for PD Study Group (2001)	Tremor sub-score in UPDRS III (STN/Med off/6 m)	-79.5	0.36	0.14	0.57	2.83	
	Tremor sub-score in UPDRS III (GPi/Med off/6 m)	-59.4	0.58	0.24	0.92	1.20	
	Tremor sub-score in UPDRS III (STN/Med on/6 m)	-56.3	0.36	0.14	0.57	2.83	
	Tremor sub-score in UPDRS III (GPi/Med on/6 m)	-85.0	0.60	0.24	0.95	1.13	
Odekerken et al. (2013)	Tremor sub-score in UPDRS III (STN/Med off/12 m)	-36.5	0.27	0.01	0.52	2.09	
	Tremor sub-score in UPDRS III (STN/Med off/36 m)	-63.3	0.25	0.01	0.50	2.27	
	Tremor sub-score in UPDRS III (STN/Med off/60 m)	-80.9	0.31	0.02	0.60	1.61	
	Tremor sub-score in UPDRS III (STN/Med on/12 m)	-80.7	0.27	0.01	0.52	2.09	
	Tremor sub-score in UPDRS III (STN/Med on/36 m)	-68.2	0.32	0.02	0.63	1.48	
	Tremor sub-score in UPDRS III (STN/Med on/60 m)	-93.9	0.36	0.02	0.69	1.25	
	Tremor sub-score in UPDRS III (GPi/Med off/12 m)	-24.6	0.27	0.01	0.52	2.06	
	Tremor sub-score in UPDRS III (GPi/Med off/36 m)	-59.5	0.31	0.02	0.60	1.61	
	Tremor sub-score in UPDRS III (GPi/Med off/60 m)	-67.1	0.41	0.02	0.79	0.97	
	Tremor sub-score in UPDRS III (GPi/Med on/12 m)	-53.6	0.27	0.01	0.52	2.06	
	Tremor sub-score in UPDRS III (GPi/Med on/36 m)	-37.8	0.31	0.02	0.60	1.61	
	Tremor sub-score in UPDRS III (GPi/Med on/60 m)	-36.6	0.41	0.02	0.79	0.97	
	Okun et al. (2009)	Tremor sub-score in UPDRS III (STN/Med off/6 m)	-23.8	0.31	0.15	0.46	4.65
		Tremor sub-score in UPDRS III (STN/Med off/12 m)	-41.6	0.38	0.21	0.55	4.04
Tremor sub-score in UPDRS III (STN/Med off/24 m)		-60.2	0.57	0.31	0.82	2.13	
Tremor sub-score in UPDRS III (STN/Med off/36 m)		-43.4	0.65	0.36	0.94	1.66	
Tremor sub-score in UPDRS III (STN/Med off/60 m)		-54.4	0.89	0.53	1.24	1.12	
Tremor sub-score in UPDRS III (STN/Med on/6 m)		+6.47	0.03	-0.12	0.18	4.80	
Tremor sub-score in UPDRS III (STN/Med on/12 m)		-23.7	0.26	0.10	0.43	4.15	
Tremor sub-score in UPDRS III (STN/Med on/24 m)		-55.8	0.57	0.31	0.82	2.13	
Tremor sub-score in UPDRS III (STN/Med on/36 m)		-33.1	0.37	0.10	0.64	1.86	
Tremor sub-score in UPDRS III (STN/Med on/60 m)		-59.7	0.63	0.30	0.96	1.29	
Tremor sub-score in UPDRS III (GPi/Med off/6 m)		-33.6	0.30	0.15	0.46	4.65	
Tremor sub-score in UPDRS III (GPi/Med off/12 m)		-49.5	0.38	0.21	0.55	4.04	
Tremor sub-score in UPDRS III (GPi/Med off/24 m)		-49.4	0.46	0.22	0.71	2.21	
Tremor sub-score in UPDRS III (GPi/Med off/36 m)		-41.7	0.28	0.02	0.55	1.90	
Tremor sub-score in UPDRS III (GPi/Med off/60 m)		-48.3	0.33	0.02	0.65	1.45	
Tremor sub-score in UPDRS III (GPi/Med on/6 m)		-38.2	0.32	0.17	0.48	4.63	
Tremor sub-score in UPDRS III (GPi/Med on/12 m)		-36.4	0.33	0.16	0.50	4.09	
Tremor sub-score in UPDRS III (GPi/Med on/24 m)		-34.6	0.29	0.06	0.53	2.33	
Tremor sub-score in UPDRS III (GPi/Med on/36 m)		-43.8	0.34	0.07	0.61	1.87	
Tremor sub-score in UPDRS III (GPi/Med on/60 m)		-47.8	0.32	0.01	0.63	1.45	
Weaver et al. (2012)		Tremor sub-score in UPDRS III (STN/Med off/6 m)	-52.3	0.43	0.18	0.69	2.05
		Tremor sub-score in UPDRS III (STN/Med off/24 m)	-69.2	0.44	0.18	0.69	2.01
	Tremor sub-score in UPDRS III (STN/Med off/36 m)	-75.4	0.42	0.17	0.67	2.17	
	Tremor sub-score in UPDRS III (GPi/Med off/6 m)	-40.0	0.37	0.15	0.59	2.66	
	Tremor sub-score in UPDRS III (GPi/Med off/24 m)	-58.5	0.37	0.15	0.60	2.60	
	Tremor sub-score in UPDRS III (GPi/Med off/36 m)	-56.9	0.37	0.15	0.59	2.69	
Model	Overall Weighted Effect Size (SMD)	SE	Confidence Level (95%)	Q Statistics	I ²	T ²	Egger's Regression
Random	0.36	0.02	0.32–0.40	43.47	.018	0.002	P < 0.001

Abbreviation. DBS: deep brain stimulation; Percent Change in Tremor: negative values represent a decrease tremors; SMD: standardized mean difference; STN: subthalamic nucleus; GPi: globus pallidus interna; Med: medication; m: months; SE: standard error; Q statistics: Cochran's heterogeneity statistic; I²: Higgins and Green's heterogeneity statistic. T²: tau squared heterogeneity statistic.

point to homogenous DBS and tremor comparisons.

Three classic meta-analysis techniques evaluated publication bias: (a) created an original funnel plot (e.g., SMD on the horizontal axis and standard error on the vertical axis), (b) plotted an adjusted funnel plot according to Duval and Tweedie's trim and fill technique (i.e., imputed funnel plot values) [22], and (c) conducted Egger's regression test. Symmetry of the comparisons is displayed in a funnel plot with standardized mean differences on the x-axis and standard error for each comparison on the y-axis (see Fig. 3). Visual inspection of the funnel plot (i.e., open circles) shows two clear distinctions: (a) a slightly skewed right side and (b) relatively small standard error for 95% of the comparisons. To accommodate a relatively unbiased distribution, we conducted Duval and Tweedie's technique to balance the funnel plot with 11 imputed values displayed as black circles (see Fig. 3).

The third publication bias test we conducted evaluated the 46 comparisons by determining the relation between actual effect sizes

standard error values as a metric of precision. Egger's regression findings indicated a significant intercept (P ≤ 0.001). Egger's regression test indicates that bias could be a concern. However, our original funnel plot as well as Duval and Tweedie's imputed funnel plot are less indicative of bias. Thus, we cautiously conclude that publication bias overall is within acceptable guidelines. Further confirmation that our data set is acceptable are the unpublished data included from Okun et al.'s [16] and Odekerken et al. [14,23].

3.3. Moderator variable analyses

To answer the primary questions of DBS and tremors, we conducted three moderator variable analyses: (a) stimulation sites, (b) medication states (on and off), and (c) posttest sessions.

Stimulation Sites: STN and GPi. The moderator variable analysis on the two stimulation sites determined the treatment effects of DBS

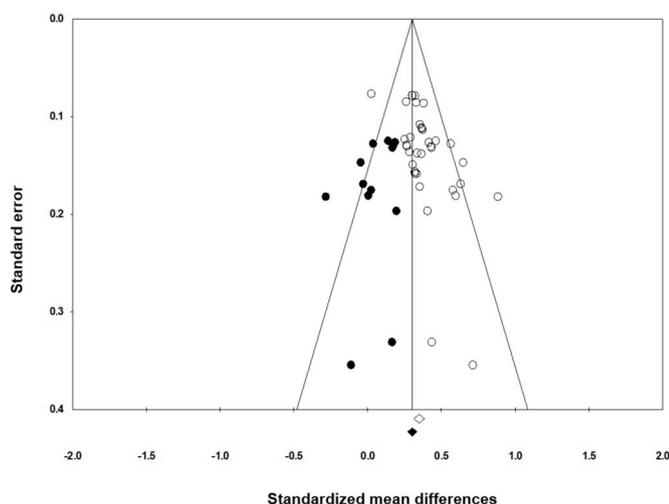


Fig. 3. Open circles and open diamond represent the original funnel plot. Black circles and black diamond are imputed funnel values according to Duval and Tweedie's technique.

between the STN and GPi brain areas. This analysis revealed two significant standardized effect sizes: (a) 23 STN comparisons: $ES = 0.38$; $SE = 0.038$; $95\% \text{ CI} = 0.314\text{--}0.385$; $P < 0.0001$; $Z = 10.06$; $T^2 = 0.02$; $I^2 = 0.001\%$; and (b) 23 GPi comparisons: $ES = 0.35$; $SE = 0.26$; $95\% \text{ CI} = 0.30\text{--}0.40$; $P < 0.0001$; $Z = 13.53$; $T^2 = 0.001$; $I^2 = 0.0\%$.

Conducting a Z test, as outlined above, showed that the effect sizes between the STN and GPi comparisons were not significantly different ($P = 0.56$). Thus, these moderator variable findings indicate that both DBS protocols reduced tremor symptoms in individuals with PD.

Medication States: On and Off. The second moderator variable analysis involved dopaminergic medicines. Analysis of tremor sub-scores during the two medication conditions indicated: (a) on-medication $ES = 0.32$; $SE = 0.02$; and (b) off-medication $ES = 0.38$; $SE = 0.24$.

Z testing revealed that the effect sizes between the on- and off-medication comparisons were not significantly different ($P = 0.28$). DBS reduced the severity of tremor regardless of the medication condition.

Posttest Sessions: DBS during Posttest 1–5. Our third moderator variable analysis compared tremor sub-scores and DBS as time since electrodes were inserted in the STN or GPi. Months since electrode placement defined the posttest sessions: (a) 6 months: post 1, (b) 12 months: post 2, (c) 24 months: post 3, (d) 36 months: post 4, and (e) 60 months: post 5. We included data for all valid posttests (1–5) reported in the five studies, and programmed the meta-analysis to evaluate each baseline (pretest) with the posttest sessions.

Importantly, each of the five-posttest sessions reached significance with effect sizes ranging from 0.33 to 0.45. However, individual Z testing failed to differentiate the posttests. Consequently, these findings indicate an efficacy of DBS across time; a reduction in tremor sub-scores starting at 6 months and maintained through 60 months.

Additional Analyses: Does DBS Site Differentially Decrease Tremors Across Posttest Sessions? We performed additional moderator variable analyses to determine whether effect sizes across five posttest sessions were different according to the two stimulation sites (i.e., STN vs. GPi). Our initial moderator variable analysis on brain stimulation sites showed comparable effect sizes between STN ($ES = 0.38$) and GPi ($ES = 0.35$) collapsed across five posttest sessions. However, the level of sustained improvements in motor symptoms based on different retention time points could be influenced by DBS stimulation sites because prior findings indicated that DBS on STN significantly reduced motor impairments in 90 PD patients after three years as compared to DBS on GPi [13,23]. To answer this question, we

conducted separate posttest sessions moderator variable analyses for each stimulation site.

The analysis revealed significant effect sizes for all posttest sessions ($P < 0.05$), and these patterns were observed for both STN and GPi. Specifically, Z testing revealed that for only STN, the effect size at post 3 (24 months; $ES = 0.52$) was significantly higher than at post 1 (6 months; $ES = 0.28$), whereas we failed to find this pattern for GPi DBS. These findings indicate that the STN DBS population experienced more benefit (i.e., reduced tremor symptoms) at 24 months as compared to 6 months.

4. Discussion

The current study is the first large prospective dataset to evaluate the effect of DBS on tremor suppression in PD patients. The meta-analysis involving 46 comparisons and 3267 data points examined longitudinal data from five RCT with up to 60 months follow-up. This meta-analysis revealed that both STN and GPi DBS reduced tremor symptoms with a medium effect size without significant differences between the two stimulation targets. These findings are congruent with the previous head-to-head randomized controlled studies that found no difference in overall motor outcomes in STN and GPi DBS [13–17].

Although there was no overall difference in effect size between the two targets, we found that the effectiveness of STN vs GPi DBS on tremor symptoms varied with time. Specifically, at 24 and 60 months post implantation, STN DBS reduced tremor symptoms with a larger effect size when compared to 6 months post implantation. GPi DBS tended to have a more stable post-operative course and maintained a steady degree of effectiveness on tremor throughout the entire study period. Although both targets were effective, practitioners should be aware that it is possible one target could appear superior in studies depending on the duration of follow-up. Further, although many expert clinicians have observed that tremor suppression may be delayed for days to weeks in the GPi, the available studies did not address this time-frame, thus, this question remains unanswered.

Tremor is a debilitating symptom and plays a significant role in the quality of life of PD patients [24]. Moreover, tremors are highly prevalent as studies estimate between 47 and 90% of PD patients have an action tremor and 76–100% have a resting tremor [25–29]. As such, treatment optimization can significantly impact the PD community. Unfortunately, tremor can be difficult to treat and is often refractory to medications. The circuitry and architecture driving tremor in PD is still not fully understood and effective targeted therapy has been difficult to solidify [30]. Eight previous meta-analyses examined PD studies comparing STN and GPi DBS for the treatment of PD motor symptoms, however, these analyses did not focus on tremor [1,31–37]. The multiple treatment protocols and differing motor outcome measures have presented challenges for clinicians trying to decide between STN and GPi DBS. Determining potential differences among targets therefore remains a relevant concern within the DBS community.

The current meta-analysis findings add important information for clinicians tasked with choosing a PD surgical target. Target selection for DBS should be assessed primarily based on the patient's specific concerns and goals. Our analysis indicates that there are no advantages or disadvantages for either target when considering long-term tremor suppression. Tremor that is unresponsive to levodopa may be adequately treated with neuromodulation based on the differences noted between on or off medications assessments in our study. Our results support that long-term tremor benefit is achieved with both targets. When PD patients present with tremor as the primary complaint or as an issue adversely affecting quality of life, practitioners should be aware that current data indicated both the STN and GPi are equally viable options. In this setting, target selection should focus on accommodating any existing comorbidities such as cognitive impairment, speech difficulties, presence of mood disorders, and presence of impulse control disorders [38].

4.1. Limitations

Our meta-analysis has potential limitations. Firstly, the reporting of outcome data was non-uniform among the studies included in this analysis. One study reported statistical data in the form of median and interquartile range whereas all other studies reported mean and standard deviation [15]. Additionally, another study only reported UPDRS tremor sub-scores in the medication off state whereas all other studies reported tremor sub-scores for both medication on and off states [13]. Also, follow-up time intervals and study protocols within the included studies varied greatly and could potentially introduce variability into the statistical analysis. Further, two of the studies observed a significant decrease in sample size over time as they had much longer duration of follow-up than the other studies [14,16]. Lastly, we explored the overall effect size for the four bilateral DBS studies. Importantly, without including the unilateral DBS study in the analysis, a slight reduction in the overall effect size was found (i.e., ES = 0.34, SE = 0.05).

Appendix A

Consistent with the traditional approaches for analyzing the mean effect for different subgroups we conducted a Z test and used the mean and variance of the estimated effects [19]. Further, we calculated P values on differences in the estimated effects between two subgroups with the three formulas below. In hypothesis testing, the true effect size is the same for both subgroups (H₀: Effect Sizes = 0). Given the three equations below, if we reject H₀, then P ≤ 0.05 will reveal that the treatment effect is significantly different between the two subgroups.

$$Difference = M_B - M_A \text{ and } SE_{Diff} = \text{Sqrt}(V_A + V_B) \tag{A.1}$$

$$Z_{Diff} = Diff / SE_{Diff} \tag{2}$$

$$P = 2[1 - ((\Phi|Z_{Diff}|))] \tag{3}$$

M_A is the estimated effect for subgroup A, M_B is the estimated effect for subgroup B, V_A is the variance of the estimated effect for A, V_B is the variance of the estimated effect for B, and Φ(Z) is the standard normal cumulative distribution.

Appendix B

Study	Total N	Dropouts	DBS Site
Anderson et al. (2005)	12	2	STN
	11	1	GPI
DBS for PD Study Group (2001)	96	5	STN
	38	2	GPI
Odekerken et al. (2016)	63	20	STN
	65	18	GPI
Okun et al. (2009)	22	0	STN
	23	0	GPI
Weaver et al. (2012)	70	22	STN
	89	17	GPI

References

[1] F. Weaver, K. Follett, K. Hur, D. Ippolito, M. Stern, Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes, *J. Neurosurg.* 103 (6) (2005) 956–967.

[2] L.V. Laitinen, A.T. Bergenheim, M.I. Hariz, Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease, *J. Neurosurg.* 76 (1) (1992) 53–61.

[3] F. Alesch, M.M. Pinter, R.J. Hellscher, L. Fertl, A.L. Benabid, W.T. Koos, Stimulation of the ventral intermediate thalamic nucleus in tremor dominated Parkinson's disease and essential tremor, *Acta Neurochir.* 136 (1–2) (1995) 75–81.

[4] K.E. Lyons, W.C. Koller, S.B. Wilkinson, R. Pahwa, Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for parkinsonian tremor, *J. Neurol. Neurosurg. Psychiatry* 71 (5) (2001) 682–684.

[5] P.R. Schuurman, D.A. Bosch, P.M. Bossuyt, G.J. Bonsel, E.J. van Someren, R.M. de Bie, et al., A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor, *N. Engl. J. Med.* 342 (7) (2000) 461–468.

[6] M.I. Hariz, P. Krack, F. Alesch, L.E. Augustinsson, A. Bosch, R. Ekberg, et al., Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6 year follow-up, *J. Neurol. Neurosurg. Psychiatry* 79 (6) (2008) 694–699.

[7] G.M. Hariz, A.T. Bergenheim, M.I. Hariz, M. Lindberg, Assessment of ability/disability in patients treated with chronic thalamic stimulation for tremor, *Mov. Disord.: Off. J. Movement Disord. Soc.* 13 (1) (1998) 78–83.

[8] J.L. Houeto, P.B. Bejjani, P. Damier, C. Staedler, A.M. Bonnet, B. Pidoux, et al., Failure of long-term pallidal stimulation corrected by subthalamic stimulation in PD, *Neurology* 55 (5) (2000) 728–730.

[9] P. Krack, P. Pollak, P. Limousin, D. Hoffmann, J. Xie, A. Benazzouz, et al., Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease, *Brain: J. Neurol.* 121 (Pt 3) (1998) 451–457.

[10] J. Volkmann, A. Albanese, J. Kulisevsky, A.L. Tornqvist, J.L. Houeto, B. Pidoux, et al., Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease, *Mov. Disord.: Off. J. Movement Disord. Soc.* 24 (8) (2009) 1154–1161.

[11] M.S. Okun, K.D. Foote, Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return? *Arch. Neurol.* 62 (4) (2005) 533–536.

[12] M. Tagliati, Turning tables: should GPI become the preferred DBS target for Parkinson disease? *Neurology* 79 (1) (2012) 19–20.

[13] F.M. Weaver, K.A. Follett, M. Stern, P. Luo, C.L. Harris, K. Hur, et al., Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes,

- Neurology 79 (1) (2012) 55–65.
- [14] V.J. Odekerken, T. van Laar, M.J. Staal, A. Mosch, C.F. Hoffmann, P.C. Nijssen, et al., Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial, *Lancet Neurol.* 12 (1) (2013) 37–44.
- [15] V.C. Anderson, K.J. Burchiel, P. Hogarth, J. Favre, J.P. Hammerstad, Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease, *Arch. Neurol.* 62 (4) (2005) 554–560.
- [16] M.S. Okun, H.H. Fernandez, S.S. Wu, L. Kirsch-Darrow, D. Bowers, F. Bova, et al., Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial, *Ann. Neurol.* 65 (5) (2009) 586–595.
- [17] G. Deep-Brain Stimulation for Parkinson's Disease Study, J.A. Obeso, C.W. Olanow, M.C. Rodriguez-Oroz, P. Krack, R. Kumar, et al., Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease, *N. Engl. J. Med.* 345 (13) (2001) 956–963.
- [18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, *J. Clin. Epidemiol.* 62 (10) (2009) 1006–1012.
- [19] M. Borenstein, L.V. Hedges, J.P.T. Higgins, H. Rothstein, *Introduction to Meta-analysis*, Wiley & Sons, Chichester, West Sussex, United Kingdom, 2009.
- [20] J.P. Higgins, S.G. Thompson, D.J. Spiegelhalter, A re-evaluation of random-effects meta-analysis, *J. R. Stat. Soc. - Ser. A Stat. Soc.* 172 (1) (2009) 137–159.
- [21] M. Borenstein, J.P. Higgins, Meta-analysis and subgroups, *Prev. Res. Off. J. Soc. Prev. Res.* 14 (2) (2013) 134–143.
- [22] S. Duval, R. Tweedie, Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis, *Biometrics* 56 (2) (2000) 455–463.
- [23] V.J. Odekerken, J.A. Boel, B.A. Schmand, R.J. de Haan, M. Figeë, P. van den Munckhof, et al., GPi vs STN deep brain stimulation for Parkinson disease: three-year follow-up, *Neurology* 86 (8) (2016) 755–761.
- [24] E.D. Louis, D.G. Machado, Tremor-related quality of life: a comparison of essential tremor vs. Parkinson's disease patients, *Park. Relat. Disord.* 21 (7) (2015) 729–735.
- [25] E.D. Louis, G. Levy, H. Mejia-Santana, L. Cote, H. Andrews, J. Harris, et al., Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD, *Neurology* 61 (7) (2003) 931–936.
- [26] P.H. Kraus, M.R. Lemke, H. Reichmann, Kinetic tremor in Parkinson's disease—an underrated symptom, *J. Neural. Transm.* 113 (7) (2006) 845–853.
- [27] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, *Neurology* 17 (5) (1967) 427–442.
- [28] A.J. Hughes, Y. Ben-Shlomo, S.E. Daniel, A.J. Lees, What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study, *Neurology* 42 (6) (1992) 1142–1146.
- [29] A.H. Rajput, B. Rozdilsky, L. Ang, Occurrence of resting tremor in Parkinson's disease, *Neurology* 41 (8) (1991) 1298–1299.
- [30] H. Cagnan, S. Little, T. Foltynie, P. Limousin, L. Zrinzo, M. Hariz, et al., The nature of tremor circuits in parkinsonian and essential tremor, *Brain: J. Neurol.* 137 (Pt 12) (2014) 3223–3234.
- [31] F. Xu, W. Ma, Y. Huang, Z. Qiu, L. Sun, Deep brain stimulation of pallidal versus subthalamic for patients with Parkinson's disease: a meta-analysis of controlled clinical trials, *Neuropsychiatric Dis. Treat.* 12 (2016) 1435–1444.
- [32] H. Xu, F. Zheng, B. Krischek, W. Ding, C. Xiong, X. Wang, et al., Subthalamic nucleus and globus pallidus internus stimulation for the treatment of Parkinson's disease: a systematic review, *J. Int. Med. Res.* 45 (5) (2017) 1602–1612.
- [33] C.L. Xie, B. Shao, J. Chen, Y. Zhou, S.Y. Lin, W.W. Wang, Effects of neurostimulation for advanced Parkinson's disease patients on motor symptoms: a multiple-treatments meta-analysis of randomized controlled trials, *Sci. Rep.* 6 (2016) 25285.
- [34] W. Sako, Y. Miyazaki, Y. Izumi, R. Kaji, Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation, *J. Neurol. Neurosurg. Psychiatr.* 85 (9) (2014) 982–986.
- [35] A. Mansouri, S. Taslimi, J.H. Badhiwala, C.D. Witiw, F. Nassiri, V.J.J. Odekerken, et al., Deep brain stimulation for Parkinson's disease: meta-analysis of results of randomized trials at varying lengths of follow-up, *J. Neurosurg.* (2017) 1–15.
- [36] Y. Liu, W. Li, C. Tan, X. Liu, X. Wang, Y. Gui, et al., Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease, *J. Neurosurg.* 121 (3) (2014) 709–718.
- [37] Z.G. Tan, Q. Zhou, T. Huang, Y. Jiang, Efficacies of globus pallidus stimulation and subthalamic nucleus stimulation for advanced Parkinson's disease: a meta-analysis of randomized controlled trials, *Clin. Interv. Aging* 11 (2016) 777–786.
- [38] A. Ramirez-Zamora, J.L. Ostrem, Globus pallidus interna or subthalamic nucleus deep brain stimulation for Parkinson disease: a review, *JAMA Neurol.* 75 (3) (2018) 367–372.