J Neurol (2016) 263:1195–1203
DOI 10.1007/s00415-016-8129-9

ORIGINAL COMMUNICATION

Deep brain stimulation improves gait velocity in Parkinson's disease: a systematic review and meta-analysis

Jaimie A. Roper[1,2] · Nyeonju Kang[1] · Juliana Ben[1,2] · James H. Cauraugh[1] · Michael S. Okun[2,3,4] · Chris J. Hass[1,2]

Received: 21 December 2015 / Revised: 9 March 2016 / Accepted: 11 April 2016 / Published online: 28 April 2016

Abstract In Parkinson's disease (PD), slow gait speed is significantly related to clinical ratings of disease severity, impaired performance of daily activities, as well as increased overall disability. Conducting a meta-analysis on gait speed is an objective and quantitative technique to summarize the effectiveness of DBS and to determine the effect sizes for future studies. We conducted a systematic review and meta-analysis that analyzed the effects of deep brain stimulation (DBS) surgery on gait speed in patients with PD to gain fundamental insight into the nature of therapeutic effectiveness. A random effects model meta-analysis on 27 studies revealed a significant overall standardized mean difference medium effect size equal to 0.60 (SE = 0.06; $p < 0.0001$; $Z = 10.58$). Based on our synthesis of the 27 studies, we determined the following: (1) a significant and medium effect size indicating DBS improves gait speed; (2) DBS improved gait speed regardless of whether the patients were tested in the on or off medication state; (3) both bilateral and unilateral DBS led to gait speed improvement; (4) the effects of DBS on gait speed in the data collection sessions after surgery (DBS on vs. off) were comparable with data collection before surgery (before surgery vs. DBS after surgery); and (5) when evaluating the effects of DBS and medication on gait speed suprathreshold doses were comparable to normal dosages of medication and DBS. The current analysis provides objective evidence that both unilateral and bilateral DBS provide a therapeutic benefit on gait speed in persons with PD.

Keywords Deep brain stimulation · Parkinson's · Gait · Gait speed

✉ Jaimie A. Roper
jaimier@ufl.edu

[1] Department of Applied Physiology and Kinesiology, University of Florida, 100 Florida Gym, PO Box 118205, Gainesville, FL 32611-8205, USA

[2] Center for Movement Disorders and Neurorestoration, University of Florida, Gainesville, USA

[3] Department of Neurology, University of Florida, Gainesville, USA

[4] Department of Neurosurgery, University of Florida, Gainesville, USA

Introduction

Parkinsonian gait is characterized by slow, small shuffling steps, stooped posture, and reduced arm swing. With progression in disease severity, gait impairment becomes significantly recognizable and leads to important reductions in independence and quality of life. Of these impaired features of parkinsonian gait, gait speed has received the most attention in the gerontology literature. Recently, we [1] and others [2, 3] reported that up to 24 % of older adults had self-selected gait speeds below 0.8 m/s, a range signaling "limitations in community mobility" [4]. Indeed, slowing of gait (0.02–0.03 m/s per year [5]; 12–16 % per decade [6]) is endemic in older adults [7, 8] and is a significant predictor of poor outcomes such as increased difficulties in performing activities of daily living, higher risk of falling, hospitalization, lower quality of life, and mortality [8–10]. As a result, gait speed is often considered a clinical vital sign. In PD, gait speed declines much faster, 0.02 m/s every 6 months [11]. Slow gait speed is significantly related to clinical ratings of disease severity, impaired performance of daily activities [12] as well as increased overall disability [4] and reduced community ambulation [10]. More recently, Ellis and colleagues observed a steeper trajectory of decline in gait speed in a

large cohort of persons with PD over a 2-year period compared to other activity, Unified Parkinson's Disease Rating Scale scores, and participation measures. These findings support the importance of gait speed as a prominent marker of disability [11]. Thus, it is not surprising that individuals with PD report restoration of walking ability as a primary concern [13].

Deep brain stimulation (DBS) of basal ganglia and/or brainstem nuclei is a common therapeutic strategy for the amelioration of parkinsonian motor symptoms. The beneficial effects of DBS on appendicular symptoms such as tremor, rigidity, limb bradykinesia and dyskinesia are well established. More recent works have focused on investigating the effects of DBS on axial symptoms such as gait disturbance. While this body of literature is growing, contradictory results from individual studies cloud our understanding of the therapeutic benefit of DBS on gait performance. Further complicating our understanding is methodological differences such as the intended targeted brain nuclei, heterogeneity of presentation in the parkinsonian population, the interactive effects of DBS and medication, over-reliance on clinical scales rather than objective and sensitive biomechanical measures. Disparate findings suggest that DBS may impact certain aspects of gait dysfunction in PD but not others. Further, observed results may be biased by the influence of changing variables such as medication state, unilateral versus bilateral stimulation, and whether DBS effectiveness was compared to pre-surgical performance or just to performance with the stimulators turned off. Each of these concerns severely obscures our understanding of the therapeutic effects of DBS on gait in this population.

Thus, an appealing alternative approach that aptly integrates the varied literature and findings is a robust, systematic review and meta-analysis. We propose that conducting a meta-analysis on gait speed is an objective and quantitative technique to summarize the effectiveness of DBS and to determine standardized effect sizes. Further, given the exponential increase in studies publishing this information the field could benefit by gaining fundamental insights into the reasons for the effectiveness of DBS. We used a meta-analytic technique, to ask the critical question: Does DBS lead to improvements in gait speed?

Methods

Study inclusion and exclusion criteria

We conducted an exhaustive search for studies that analyzed gait speed in PD patients who underwent DBS and were published and listed on three common computerized database search engines (January 2000–February 2016): (a) PubMed, (b) ISI's Web of Knowledge, and (c) Cochrane Database of Systematic Reviews. Seven key words and phrases defined our search: Parkinson's disease, deep brain stimulation, electrical stimulation, gait speed, gait velocity, walking speed, walking velocity, step length, and cadence. Thus, our initial search identified 72 records. Initial inspection found three foreign language articles. However, we included only English language manuscripts in our meta-analysis.

Four predetermined inclusion and exclusion criteria follow:

1. Examining each study for quantitative evaluations on gait speed at a self-selected pace identified 41 valid comparisons. Thirty-one studies without gait speed data were excluded.
2. Relevance to the specific question of DBS and gait speed confirmed 39 studies. We discarded two non-relevant studies.
3. A third inclusion criterion involved comparison groups for DBS (i.e., on–off; pre–post; unilateral–bilateral stimulation) and each of the 39 studies qualified.
4. The fourth inclusion criterion focused on data extraction. Nine studies failed to report the necessary data required for coding and extracting gait speed.
5. We excluded three studies that did not focus on subthalamic nucleus (STN) as a DBS target area.

Three authors (JB, JR, and NK) independently coded the 27 remaining studies and extracted data. The coding system applied to each article included five categories: (a) characteristics of participants (e.g., age, gender, and sample size), (b) PD duration, (c) medication conditions (e.g., on vs. off and typical dose vs. supra-threshold dose), (d) site of DBS (e.g., DBS on bilateral vs. unilateral STN), (e) gait speed outcome measures and data. Table 1 shows the characteristics of the 27 comparison studies involving DBS, PD, and gait speed.

Outcome measures

Our global questions on DBS in PD patients and gait speed included two outcome measures: (a) self-selected gait speed: 25 studies and (b) step speed: two studies. Consistent with conventional meta-analysis techniques and in line with our research questions, we extracted data on both outcome measures from each study (see Table 2).

Data synthesis and analysis

In harmony with meta-analytic recommendations, we synthesized and analyzed our set of common studies. This procedure involved (a) describing relevant

Table 1 Characteristics of each comparison included in the present meta-analysis (studies listed alphabetically)

Study	Total *N*	Analyzed *N*	Gender	Mean age (years)	Mean PD duration (years)	Mean UPDRS score	Medication	DBS	Site
Allert et al. [47]	8	8	N/A	57.4	11.8	6.0 M	Off	BI	STN
Bastian et al. [40]	6	6	3 F, 3 M	53.5	N/A	32.3	Off	UNI	STN
Carpinella et al. [51]	10	10	N/A	52–68	8–26	N/A	On	BI	STN
Fasano et al. [52]	13	13	3 F, 10 M	63.5	15.4	N/A	Off	BI	STN
Ferrarin et al. [53]	10	10	5 F, 5 M	60.2	16.9	N/A	On[a]	BI	STN
Ferrarin et al. [54]	10	10	5 F, 5 M	52–68	16.9	13.2 M	On[a]	BI	STN
Ferrarin et al. [55]	10	10	N/A	60.2	16.9	N/A	Off	UNI	STN
Hausdorff et al. [56]	13	13	3 F, 10 M	63.6	12.9	8.5 M	On	BI	STN
Hill et al. [57]	30	30	11 F, 19 M	64.0	14.3	N/A	Off	UNI	STN
Iansek et al. [58]	14	14	5 F, 9 M	57.4	14.9	11.0 M	On	BI	STN
Johnsen et al. [59]	14	8	N/A	60.1	13.5	16.8 M	Off	BI	STN
Johnsen et al. [60]	22	10	9 F, 13 M	60.8	N/A	N/A	Off	BI	STN
Kelly et al. [23]	8	8	2 F, 6 M	51.9	10.1	23.0 M	On	UNI	STN
Krystkowiak et al. [25]	10	10	3 F, 7 M	57.0	13.0	14.0 M	On	BI	STN
Liu et al. [33]	11	11	2 F, 9 M	53.7	13.1	17.2 M	On	BI	STN
Lohnes et al. [61]	11	11	3 F, 8 M	66.6	15.6	N/A	Off	BI	STN
Lubik et al. [62]	12	12	7 F, 5 M	62.3	N/A	21 M	On[a]	BI	STN
McNeely et al. [63]	23	23	4 F, 19 M	62.0	15.0	35.5 M	Off	UNI	STN
Muniz et al. [64]	10	10	3 F, 7 M	58.1	11.9	19.9 M	Off	BI	STN
Peppe et al. [24]	5	5	5 M	57.8	16.0	33.3 M	Off	BI	STN
Rocchi et al. [65]	15	15	4 F, 11 M	61.4	11.9	20.6 M	On	BI	STN
Rochester et al. [66]	17	14	8 F, 9 M	54.9	12.5	N/A	On	BI	STN
Seri-Fainshtat et al. [67]	28	28	3 F, 25 M	61.5	13.2	13.4 M	On	BI	STN
Stolze et al. [68]	9	9	N/A	N/A	N/A	31 M	Off	BI	STN
Tabbal et al. [44]	52	45	16 F, 36 M	61.0	N/A	N/A	Off	UNI	STN
Vallabhajosula et al. [69]	19	19	3 F, 16 M	61.8	13.6	29.1	Off	BI	STN
Xie et al. [35]	10	10	5 F, 5 M	55.8	13.3	19.0 M	Off	BI	STN
Total = 400		Total = 372		$M = 59.4$ SD = 3.7	$M = 13.9$ SD = 1.9				

F female, *M* male, *BI* bilateral stimulation, *UNI* unilateral, *STN* subthalamic nucleus; *M* indicates UPDRS III subscore

[a] Indicates supra threshold dose of medication

characteristics of studies as well as comparison groups, (b) calculating standardized mean difference effect sizes for each comparison, (c) determining an overall effect size, and (d) identifying potential moderator variables [14–17]. Once potential moderator variables were identified, additional meta-analyses were conducted to measure the contributions of subgroups to effect sizes [18–20].

Further, Table 2 displays relative weight values for each DBS study. Borenstein et al. [14] and Cumming [21] define relative weight as the inverse of variance of the effect size for individual studies [14, 21]. Sample size may affect the proportion of individual weight relative to the sum of weights for all studies.

Measuring heterogeneity

Three specific tests provided critical values on the heterogeneity in our group of studies: (a) Cochrane's Q and p value, (b) Tau-squared (T^2), and (c) Higgins and Green's, I-squared (I^2). Examining and reporting both tests gave us a broad perspective on heterogeneity.

Evaluating publication bias

Three traditional statistical techniques determined the presence of potential publication bias: (a) funnel plots; (b) trim and fill procedure creating a second funnel plot with imputed values; and (c) fail-safe N analysis. Meta-

Table 2 Summary statistics for the 27 comparisons in the meta-analysis

Study	Primary outcome measure	Standardized mean difference	Confidence interval (95 %)		Weight
Allert et al. [47]	Gait speed (m/s) (after surgery: post vs. before surgery: pre) with med off	0.84	0.03	1.64	1.9
Bastian et al. [40]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.89	−0.05	1.84	1.4
Carpinella et al. [51]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.72	0.02	1.41	2.6
Fasano et al. [52]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.64	0.04	1.24	3.5
Ferrarin et al. [53]	Gait speed (%h/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.72	0.02	1.41	2.6
Ferrarin et al. [54]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.72	0.02	1.41	2.6
Ferrarin et al. [55]	Gait speed (cm/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.72	0.02	1.41	2.6
Hausdorff et al. [56]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.75	0.14	1.37	3.3
Hill et al. [57]	Gait speed (%change) (DBS OFF: pre vs. DBS ON: post) with med off	0.42	0.05	0.80	8.9
Iansek et al. [58]	Gait speed (m/min) (DBS OFF: pre vs. DBS ON: post) with med on	0.79	0.19	1.39	3.5
Johnsen et al. [59]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.84	0.03	1.64	1.9
Johnsen et al. [60]	Step speed (%change) (DBS OFF: pre vs. DBS ON: post) with med off	0.72	0.02	1.41	2.6
Kelly et al. [23]	Gait speed (m/s) (after surgery: post vs. before surgery: pre) with med on	0.13	−0.57	0.82	2.6
Krystkowiak et al. [25]	Gait speed (m/s) (after surgery: post vs. before surgery: pre) with med on	1.51	0.60	2.42	1.5
Liu et al. [33]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.67	0.02	1.33	2.9
Lohnes et al. [61]	Gait speed (not reported) (DBS OFF: pre vs. DBS ON: post) with med off	0.67	0.02	1.33	2.9
Lubik et al. [62]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.47	−0.12	1.07	3.5
McNeely et al. [63]	Gait speed (cm/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.73	0.27	1.19	5.9
Muniz et al. [64]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.72	0.02	1.41	2.6
Peppe et al. [24]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	1.31	0.11	2.50	0.9
Rocchi et al. [65]	Step speed (m/s) (after surgery: post vs. before surgery: pre) with med on	0.55	0.01	1.10	4.2
Rochester et al. [66]	Gait speed (m/s) (after surgery: post vs. before surgery: pre) with med on	0.23	−0.30	0.76	4.4
Seri-Fainshtat et al. [67]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med on	0.38	0.00	0.77	8.4
Stolze et al. [68]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.77	0.03	1.51	2.2
Tabbal et al. [44]	Gait speed (not reported) (DBS OFF: pre vs. DBS ON: post) with med off	0.56	0.25	0.87	12.6
Vallabhajosula et al. [69]	Gait speed (m/s) (DBS OFF: pre vs. DBS ON: post) with med off	0.48	0.01	0.96	5.5
Xie et al. [35]	Gait speed (m/min) (DBS OFF: pre vs. DBS ON: post) with med off	0.72	0.02	1.41	2.6

Model	Overall weighted effect size	SE	Confidence level (95 %)	*Q* statistics	I^2 (%)	T^2	Classic fail-safe *N*
Random	0.60	0.06	0.49–0.71	14.52	0	0.0	793

DBS deep brain stimulation, *Q statistics* Cochran's heterogeneity statistic, I^2 Higgins and Green's heterogeneity statistic

analytic researchers frequently report these techniques for a comprehensive perspective [14].

Results

Standardized mean difference effect

A random effects model meta-analysis on 27 qualified studies revealed a significant overall standardized mean difference effect equal to 0.60 (SE = 0.06; $p < 0.0001$; $Z = 10.58$) with a 95 % confidence interval of 0.49 to 0.71. This medium positive effect (e.g., large ≥0.80) indicated definite gait speed benefits because of deep brain stimulation [16, 22]. Table 2 shows the individual standardized mean difference for each comparison and the values ranged from 0.13 to 1.65. As displayed in the forest plot (Fig. 1), deep brain stimulation treatments improved gait speeds. Further, all our individual weighted effect sizes are positive and to the right of the zero effect vertical line. This further confirms the statistically robust deep brain stimulation effect on gait speed.

Moreover, three comparisons [23–25] were considered as outlier scores because the three effect sizes (0.13;

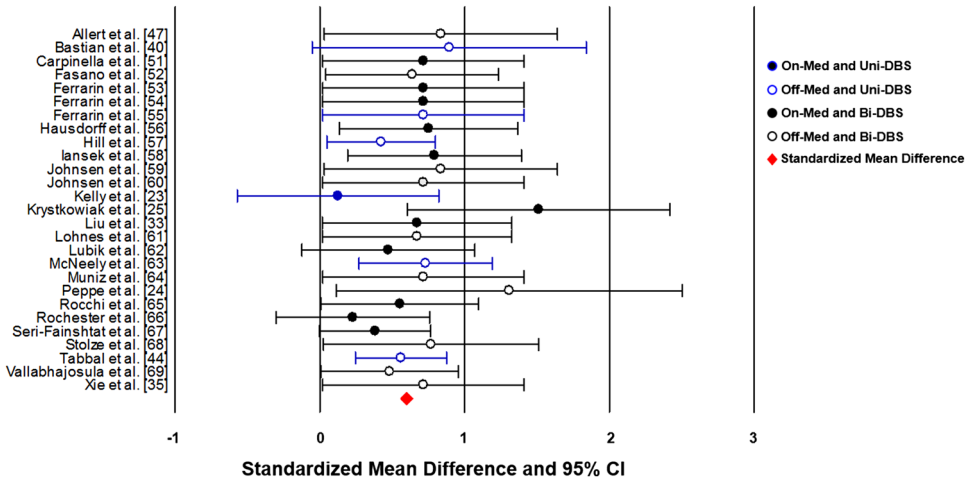

Fig. 1 *Forest plot* of the effects of DBS on gait speed in PD. Data derived from a random effects model meta-analysis. Each *line* and *tick mark* represents an individual effect size

1.31; 1.51) were greater than two standard deviations beyond the standardized mean effect size. Thus, we conducted a subsequent analysis after removing the three outliers, and the overall effect was still nearly the same medium value (ES = 0.59; SE = 0.06; $p < 0.0001$; $Z = 10.17$).

Heterogeneity

Three heterogeneity tests revealed: (a) Cochrane's $Q = 14.52$ and $p = 0.97$, (b) Tau-squared (T^2) = 0.00, and (c) Higgins and Green's, *I*-squared (I^2) = 0.00 %. According to Higgins et al. [26], variability in groups of study comparisons should ideally approach zero dispersion. Three heterogeneity results, as found in the current meta-analysis, indicates no observed heterogeneity in the comparison studies. The overall weighted effect size =0.60 is robust across the comparisons and outcome measures [14, 27].

Publication bias and fail-safe analysis

The funnel plot shown in Fig. 2 displays each treatment effect size as a function of standard error. Visual inspection indicates that our set of DBS articles is mildly asymmetrical. Even though the two sides of the DBS funnel are slightly different, mild asymmetry contributes minimally to publication bias. Consistent with conventional meta-analysis techniques we only analyzed gait speed data from each DBS study. This conventional approach minimizes data biasing effects [15, 28, 29].

Applying Duval and Tweedie's trim and fill technique to the original funnel plot produced a second funnel plot shown in Fig. 3 [30]. The technique involves imputed values in creating an ideal symmetry of standardized mean difference (individual effect sizes) and standard error. Eight individual values on the lower right side are imputed on the left side for complete symmetry [30]). Each solid black circle represents a balanced study with a generated effect size plotted as a function of standard error, achieving relatively perfect symmetry. The *x*-axis displays the original effect size (white diamond) and the recalculated overall effect (black diamond) given the imputed scores on the left side. Importantly, the two overall medium positive effect values at the base of the trim and fill funnel plot are nearly identical.

A third technique, classic fail-safe *N* analysis, provided additional information supporting our conclusion of only minor bias. The fail-safe analysis determined that 793 null effect findings were required to lower our cumulative effect size of 0.60 to an insignificant level (Table 2). Such a large *N* clearly indicates a distinct DBS benefit on gait speed. Taken together, the near symmetrical original funnel plot, slightly adjusted imputed plot, and classic fail-safe *N*, we are confident in stating that publication bias was not a serious concern for the 27 comparison studies [14, 31].

Moderator variable analyses

Further analysis of the identified cumulative positive effect of DBS on walking included four moderator variable analyses. The first moderator variable analysis compared studies that tested gait speed while participants were on medication versus off medication. Analysis of the 12 studies that tested participants on medication showed an overall effect of 0.56 (SE = 0.09; $p < 0.0001$; $Z = 6.37$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.39 and 0.73). Analysis of the 15 off medication studies revealed a significant medium effect size (ES = 0.63; SE = 0.08; $p < 0.0001$; $Z = 8.46$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.49 and 0.78). Importantly, regardless of being on or off medication, DBS benefited gait speed.

A second subgroup moderator variable analysis, investigated gait speed performances of participants who

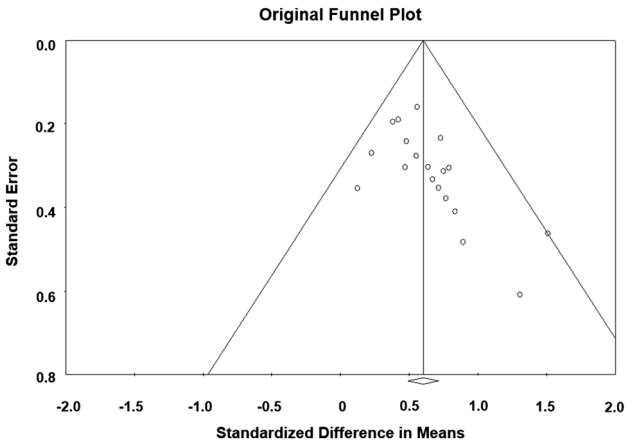

Fig. 2 *Funnel plot* of the comparisons for our random effects model. The *x*-axis represents the standardized mean difference and the *y*-axis indicates the standard error associated with each comparison

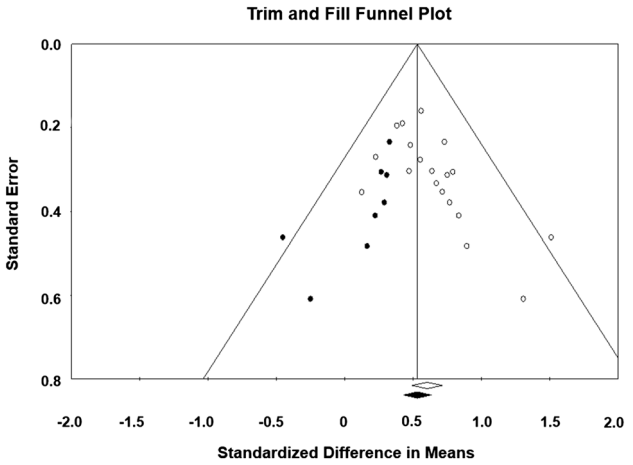

Fig. 3 Best estimate *funnel plot* of a symmetrical and unbiased distribution after conducting the trim and fill technique. The *white circles* and *white diamond* indicate our original 27 comparison studies while the *black circles* and *black diamond* represent imputed comparisons

received unilateral DBS versus bilateral DBS. Six studies provided unilateral stimulation, and the analysis indicated a significant ES = 0.55 (SE = 0.10; $p < 0.0001$; $Z = 5.59$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.36 and 0.74). Analysis of the 21 bilateral DBS studies revealed a slightly larger significant standardized effect = 0.63 (SE = 0.07; $p < 0.0001$; $Z = 9.00$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.49 and 0.77). Thus, DBS provided simultaneously to both hemispheres shows a slightly higher *ES*.

The third moderator variable analysis compared the gait speeds in two subsets of DBS studies: (a) data collection before surgery ($N = 5$) and (b) data collection after surgery ($N = 22$). Both subgroup analyses indicated significant standardized mean effects: (a) pre-surgery data collection (ES = 0.57; SE = 0.21; $p = 0.007$; $Z = 2.69$; $T^2 = 0.10$; $I^2 = 47.37$; 95 % CIs = 0.15 and 0.98), and (b) post-surgery data collection only (ES = 0.62; SE = 0.06; $p < 0.0001$; $Z = 10.01$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.50 and 0.74). Thus, the effects of DBS on gait speed were slightly higher in data collection after surgery (DBS on vs. off) than data collection before surgery (before surgery vs. DBS on after surgery).

The fourth moderator variable analysis compared two medication doses in 12 studies: (a) normal dose ($N = 9$) and (b) supra threshold dose ($N = 3$). Both subgroup analyses indicated significant standardized mean effects: (a) normal dose (ES = 0.56; SE = 0.11; $p < 0.0001$; $Z = 5.16$; $T^2 = 0.01$; $I^2 = 13.80$; 95 % CIs = 0.35 and 0.77), and (b) supra threshold dose (ES = 0.62; SE = 0.19; $p = 0.001$; $Z = 3.19$; $T^2 = 0.00$; $I^2 = 0.00$; 95 % CIs = 0.24 and 1.00). The supra threshold dose of medication revealed a greater effect of DBS on gait speed than normal dose of medication.

Discussion

Gross motor improvement is frequently observed following PD DBS. However, lack of uniformity in methodology and measured outcomes has clouded the interpretation of DBS benefits across the motor domain and especially related to gait functions. Herein, we focused on the principal outcome measure of gait speed because of the nearly universal recognition that walking speed is an important gerontological marker of morbidity and mortality. Our prospective and robust meta-analysis included critical evaluation of 27 studies leading to five primary findings: (1) a significant and medium effect size indicating DBS improves gait speed; (2) DBS improved gait speed regardless of whether the patients were tested in the OFF or ON medication state; (3) both bilateral and unilateral DBS led to gait speed improvement; (4) the effects of DBS on gait speed in the data collection sessions after surgery (DBS on vs. off) were comparable with data collection before surgery (before surgery vs. DBS after surgery); and (5) when evaluating the effects of DBS and medication on gait speed supra-threshold doses were comparable to normal dosages of medication and DBS.

Our results indicate that gait speed is improved following DBS surgery, regardless if the patient undergoing gait analysis is on or off medication, indicating a specific and independent benefit of gait speed that is provided by DBS. This finding is consistent with Piper and colleagues [32], who observed that DBS surgery significantly improved gait speed in both on and off medication states. Moreover, previous studies [33–35] reported that DBS when combined with levodopa increased walking speed by 1.5–3.4 times compared to off medication/off stimulation

walking speeds. Although optimal treatment of PD symptoms is typically achieved using a combination of stimulation and medication, we observed that stimulation alone was comparable to medication when specifically focusing on the variable of improvement of gait speed. Additionally, normal and suprathreshold dosages of medication both produced a moderate effect on gait speed improvement when combined with DBS. Finally, gait speed did not change after surgery in the off stimulation state when compared to before surgery. This suggests that the improvement of gait speed is in part because of the stimulation, and not a result of the lesional effect created by implantation of the leads. Again, these findings highlight the unique benefit stimulation offers on gait speed. This observation may be explained by the electrical, chemical, and additional neural-network effects on brain tissue that DBS provides [36].

Parkinson's patients who undergo DBS may receive either bilateral or unilateral lead implantation, with bilateral implantation being the most frequent approach [37, 38]. Typically, the purpose for implanting a second DBS lead is to address persisting motor symptoms that are not resolved with a unilateral implantation [39] and to address selective symptoms that are potentially responsive to DBS therapy. The most common reason for patients receiving only one implant is asymmetric but potentially DBS responsive symptoms. Many of the patients who require only unilateral therapy also have low UPDRS motor scores that are reflective of less severe disease. Further, in a staged approach, successful relief of motor symptoms, which may also yield bilateral benefits [37, 38] may preclude the implant of a second lead. Many studies have suggested bilateral stimulation as an appropriate treatment for improving aspects of gait [40–44]. For example, Bastian and colleagues [40] observed different relative effects of unilateral versus bilateral STN stimulation on walking in patients that received bilateral DBS. In this study, four of the six patients exhibited improvements in walking speed and stride length with unilateral stimulation, while two required bilateral stimulation to improve walking speed. In addition, an additive effect (of bilateral stimulation) was observed in the patients who improved walking speed with unilateral stimulation, as they improved walking speed even more with bilateral stimulation. Yet in our analyses, gait speed was improved with bilateral DBS and unilateral DBS. Our findings highlight the power of meta-analytical techniques such that the results in the literature are not solely biased by studies where the patients had undergone bilateral surgery, but are tested in a unilateral state. While unilateral DBS may offer less risk compared to bilateral procedures, we conclude that both unilateral and bilateral DBS are comparable in improving gait speed in patients with PD.

Unfortunately, we were unable to perform a brain target site analyses between STN, globus pallidus interna (GPi) and pedunculopontine tegmental nucleus (PPN). The studies included in our analysis only included STN stimulation, as only 2 GPi and 1 PPN stimulation study met the rigid inclusion criteria for our study. The small sample size did not allow us to use these studies in our meta-analysis. STN DBS is the most common DBS approach used worldwide for treatment of PD, and lesional studies of this brain target have shown similar improvements [45]. Additionally, STN DBS has proven to be more advantageous in medication reduction as compared to GPi targets [46]. Additional DBS target sites have included GPi, PPN, the centro-median thalamic nucleus, and the zona incerta [32, 47–50]. Due to the low number of studies that have investigated GPi and PPN as target sites for DBS in PD, future research should aim to examine the effectiveness of stimulation on these target sites using objective and sensitive measures of gait performance. Further understanding the differences between targets (GPi, STN, PPN, etc.) will require more scrutiny with regard to their effects on gait performance, and will be important to guide clinicians when selecting a target site for stimulation.

Compliance with ethical standards

Conflict of interest Full financial disclosure for the past 12 months: JAR, NK, JB, JHC, and CJH do not have any disclosures. MSO serves as a consultant for the National Parkinson Foundation, and has received research Grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. Dr. Okun has previously received honoraria, but in the past >60 months has received no support from industry. Dr. Okun has received royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge (movement disorders books). Dr. Okun is an associate editor for New England Journal of Medicine Journal Watch Neurology. Dr. Okun has participated in CME and educational activities on movement disorders (in the last 36) months sponsored by PeerView, Prime, Quantia, Henry Stewart, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic, Abbvie, and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.

Ethical standards The manuscript does not contain clinical studies or patient data.

References

1. Hass CJ, Malczak P, Nocera J, Stegemöller EL, Wagle Shukla A, Malaty I, Jacobson IV CE, Okun MS, McFarland N (2012) Quantitative normative gait data in a large cohort of ambulatory persons with Parkinson's disease. PLoS One. doi:10.1371/journal.pone.0042337

2. Plummer-D'Amato P, Altmann LJ, Reilly K (2011) Dual-task effects of spontaneous speech and executive function on gait in aging: exaggerated effects in slow walkers. Gait Posture. doi:10.1016/j.gaitpost.2010.11.011
3. Hollman JH, McDade EM, Petersen RC (2011) Normative spatiotemporal gait parameters in older adults. Gait Posture. doi:10.1016/j.gaitpost.2011.03.024
4. Brusse KJ, Zimdars S, Zalewski KR, Steffen TM (2005) Testing functional performance in people with Parkinson disease. Phys Ther 85:134–141
5. Himann JE, Cunningham DA, Rechnitzer PA, Paterson DH (1988) Age-related changes in speed of walking. Med Sci Sports Exerc 20:161–166
6. White DK, Neogi T, Nevitt MC, Peloquin CE, Zhu Y, Boudreau RM, Cauley JA, Ferrucci L, Harris TB, Satterfield SM, Simonsick EM, Strotmeyer ES, Zhang Y (2013) Trajectories of gait speed predict mortality in well-functioning older adults: the Health Aging and Body Composition study. J Gerontol A Biol Sci Med Sci. doi:10.1093/gerona/gls197
7. Lim LI, van Wegen EE, de Goede CJ, Jones D, Rochester L, Hetherington V, Nieuwboer A, Willems AM, Kwakkel G (2005) Measuring gait and gait-related activities in Parkinson's patients own home environment: a reliability, responsiveness and feasibility study. Parkinsonism Relat Disord 11:19–24
8. Morris ME, Matyas TA, Iansek R, Summers JJ (1996) Temporal stability of gait in Parkinson's disease. Phys Ther 76:763–777
9. Studenski S, Perera S, Wallace D, Chandler JM, Duncan PW, Rooney E, Fox M, Guralnik JM (2003) Physical performance measures in the clinical setting. J Am Geriatr Soc 51:314–322
10. Elbers RG, van Wegen EE, Verhoef J, Kwakkel G (2013) Is gait speed a valid measure to predict community ambulation in patients with Parkinson's disease? J Rehabil Med. doi:10.2340/16501977-1123
11. Ellis TD, Cavanaugh JT, Earhart GM, Ford MP, Foreman KB, Thackeray A, Thiese MS, Dibble LE (2016) Identifying clinical measures that most accurately reflect the progression of disability in Parkinson disease. Parkinsonism Relat Disord 25:65–71
12. Tan D, Danoudis M, McGinley J, Morris ME (2012) Relationships between motor aspects of gait impairments and activity limitations in people with Parkinson's disease: a systematic review. Parkinsonism Relat Disord. doi:10.1016/j.parkreldis.2011.07.014
13. Nisenzon AN, Robinson ME, Bowers D, Banou E, Malaty I, Okun MS (2011) Measurement of patient-centered outcomes in Parkinson's disease: what do patients really want from their treatment? Parkinsonism Relat Disord. doi:10.1016/j.parkreldis.2010.09.005
14. Borenstein M (2009) Introduction to meta-analysis. Wiley, Chichester
15. Rosenthal R (1995) Writing meta-analytic reviews. Psychol Bull 118:183–192
16. Rosenthal R, DiMatteo MR (2001) Meta-analysis: recent developments in quantitative methods for literature reviews. Annu Rev Psychol. doi:10.1146/annurev.psych.52.1.59
17. Rosenthal R, Hiller JB, Bornstein RF, Berry DT, Brunell-Neuleib S (2001) Meta-analytic methods, the Rorschach, and the MMPI. Psychol Assess 13:449–451
18. Borenstein M, Hedges LV, Higgins JP, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. doi:10.1002/jrsm.12
19. Hedges LV, Olkin I (1985) Statistical methods for meta-analysis. Academic Press, Orlando
20. Sutton AJ (2000) Methods for meta-analysis in medical research. Wiley, Chichester
21. Cumming G, Fidler F, Kalinowski P, Lai J (2012) The statistical recommendations of the american psychological association publication manual: effect sizes, confidence intervals, and meta-analysis. Aust J Psychol 64:138–146. doi:10.1111/j.1742-9536.2011.00037.x
22. Cohen J (1988) Statistical power analysis for the behavioral sciences. L. Erlbaum Associates, Hillsdale
23. Kelly VE, Israel SM, Samii A, Slimp JC, Goodkin R, Shumway-Cook A (2010) Assessing the effects of subthalamic nucleus stimulation on gait and mobility in people with Parkinson disease. Disabil Rehabil. doi:10.3109/09638280903374139
24. Peppe A, Pierantozzi M, Chiavalon C, Marchetti F, Caltagirone C, Musicco M, Stanzione P, Stefani A (2010) Deep brain stimulation of the pedunculopontine tegmentum and subthalamic nucleus: effects on gait in Parkinson's disease. Gait Posture. doi:10.1016/j.gaitpost.2010.07.012
25. Krystkowiak P, Blatt JL, Bourriez JL, Duhamel A, Perina M, Blond S, Guieu JD, Destee A, Defebvre L (2003) Effects of subthalamic nucleus stimulation and levodopa treatment on gait abnormalities in Parkinson disease. Arch Neurol 60:80–84
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ. doi:10.1136/bmj.327.7414.557
27. Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions. Wiley, New Jersey
28. Fanelli D (2009) How many scientists fabricate and falsify research? A systematic review and meta-analysis of survey data. PLoS ONE. doi:10.1371/journal.pone.0005738
29. Sterne JA, Egger M, Smith GD (2001) Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. BMJ 323:101–105
30. Duval S, Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56:455–463
31. Rothstein H, Sutton AJ, Borenstein M (2005) Publication bias in meta-analysis: prevention, assessment and adjustments. Wiley, Hoboken, NJ
32. Piper M, Abrams GM, Marks Jr WJ (2005) Deep brain stimulation for the treatment of Parkinson's disease: overview and impact on gait and mobility. NeuroRehabilitation
33. Liu W, McIntire K, Kim SH, Zhang J, Dascalos S, Lyons KE, Pahwa R (2005) Quantitative assessments of the effect of bilateral subthalamic stimulation on multiple aspects of sensorimotor function for patients with Parkinson's disease. Parkinsonism Relat Disord 11:503–508
34. Faist M, Xie J, Kurz D, Berger W, Maurer C, Pollak P, Lucking CH (2001) Effect of bilateral subthalamic nucleus stimulation on gait in Parkinson's disease. Brain 124:1590–1600
35. Xie J, Krack P, Benabid AL, Pollak P (2001) Effect of bilateral subthalamic nucleus stimulation on parkinsonian gait. J Neurol 248:1068–1072
36. Okun MS (2012) Deep-brain stimulation for Parkinson's disease. N Engl J Med. doi:10.1056/NEJMct1208070
37. Alberts JL, Hass CJ, Vitek JL, Okun MS (2008) Are two leads always better than one: an emerging case for unilateral subthalamic deep brain stimulation in Parkinson's disease. Exp Neurol. doi:10.1016/j.expneurol.2008.07.019
38. Taba HA, Wu SS, Foote KD, Hass CJ, Fernandez HH, Malaty IA, Rodriguez RL, Dai Y, Zeilman PR, Jacobson CE, Okun MS (2010) A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. J Neurosurg. doi:10.3171/2010.8.JNS10312
39. Okun MS, Foote KD (2010) Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. Expert Rev Neurother 10:1847–1857
40. Bastian AJ, Kelly VE, Revilla FJ, Perlmutter JS, Mink JW (2003) Different effects of unilateral versus bilateral subthalamic nucleus stimulation on walking and reaching in Parkinson's disease. Mov Disord. doi:10.1002/mds.10493

41. Chung SJ, Jeon SR, Kim SR, Sung YH, Lee MC (2006) Bilateral effects of unilateral subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Eur Neurol 56:127–132
42. Germano IM, Gracies JM, Weisz DJ, Tse W, Koller WC, Olanow CW (2004) Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double-blind 12-month evaluation study. J Neurosurg. doi:10.3171/jns.2004.101.1.0036
43. Kumar R, Lozano AM, Sime E, Halket E, Lang AE (1999) Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology 53:561–566
44. Tabbal SD, Ushe M, Mink JW, Revilla FJ, Wernle AR, Hong M, Karimi M, Perlmutter JS (2008) Unilateral subthalamic nucleus stimulation has a measurable ipsilateral effect on rigidity and bradykinesia in Parkinson disease. Exp Neurol. doi:10.1016/j.expneurol.2008.01.024
45. Bergman H, Wichmann T, DeLong MR (1990) Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 249:1436–1438
46. Benabid AL, Chabardes S, Mitrofanis J, Pollak P (2009) Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol. doi:10.1016/S1474-4422(08)70291-6
47. Allert N, Volkmann J, Dotse S, Hefter H, Sturm V, Freund HJ (2001) Effects of bilateral pallidal or subthalamic stimulation on gait in advanced Parkinson's disease. Mov Disord. doi:10.1002/mds.1222
48. Goff LK, Jouve L, Melon C, Salin P (2009) Rationale for targeting the thalamic centre-median parafascicular complex in the surgical treatment of Parkinson's disease. Parkinsonism Relat Disord. doi:10.1016/S1353-8020(09)70807-7
49. Plaha P, Khan S, Gill SS (2008) Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry. **(jnnp.2006.112334 [pii])**
50. Mazzone P, Paoloni M, Mangone M, Santilli V, Insola A, Fini M, Scarnati E (2014) Unilateral deep brain stimulation of the pedunculopontine tegmental nucleus in idiopathic Parkinson's disease: effects on gait initiation and performance. Gait Posture. doi:10.1016/j.gaitpost.2014.05.002

References marked with an asterisk indicate studies included in the meta-analysis. Asterisks do not precede the in-text citations to studies

51. *Carpinella I, Crenna P, Marzegan A, Rabuffetti M, Rizzone M, Lopiano L, Ferrarin M (2007) Effect of L-dopa and subthalamic nucleus stimulation on arm and leg swing during gait in Parkinson's Disease. Conf Proc IEEE Eng Med Biol Soc. doi:10.1109/IEMBS.2007.4353888
52. *Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R, Volkmann J, Deuschl G (2011) Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord. doi:10.1002/mds.23583
53. *Ferrarin M, Rizzone M, Lopiano L, Recalcati M, Pedotti A (2004) Effects of subthalamic nucleus stimulation and L-dopa in trunk kinematics of patients with Parkinson's disease. Gait Posture. doi:10.1016/S0966-6362(03)00058-4
54. *Ferrarin M, Rizzone M, Bergamasco B, Lanotte M, Recalcati M, Pedotti A, Lopiano L (2005) Effects of bilateral subthalamic stimulation on gait kinematics and kinetics in Parkinson's disease. Exp Brain Res. doi:10.1007/s00221-004-2036-5
55. *Ferrarin M, Carpinella I, Rabuffetti M, Rizzone M, Lopiano L, Crenna P (2007) Unilateral and bilateral subthalamic nucleus stimulation in Parkinson's disease: effects on EMG signals of lower limb muscles during walking. IEEE Trans Neural Syst Rehabil Eng. doi:10.1109/TNSRE.2007.897000
56. *Hausdorff JM, Gruendlinger L, Scollins L, O'Herron S, Tarsy D (2009) Deep brain stimulation effects on gait variability in Parkinson's disease. Mov Disord. doi:10.1002/mds.22554
57. *Hill KK, Campbell MC, McNeely ME, Karimi M, Ushe M, Tabbal SD, Hershey T, Flores HP, Hartlein JM, Lugar HM, Revilla FJ, Videen TO, Earhart GM, Perlmutter JS (2013) Cerebral blood flow responses to dorsal and ventral STN DBS correlate with gait and balance responses in Parkinson's disease. Exp Neurol. doi:10.1016/j.expneurol.2012.12.003
58. * Iansek R, Rosenfeld JV, Huxham FE (2002) Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Med J Aust. **(ian10553_fm [pii])**
59. *Johnsen EL, Mogensen PH, Sunde NA, Ostergaard K (2009) Improved asymmetry of gait in Parkinson's disease with DBS: gait and postural instability in Parkinson's disease treated with bilateral deep brain stimulation in the subthalamic nucleus. Mov Disord. doi:10.1002/mds.22419
60. *Johnsen EL, Sunde N, Mogensen PH, Ostergaard K (2010) MRI verified STN stimulation site–gait improvement and clinical outcome. Eur J Neurol. doi:10.1111/j.1468-1331.2010.02962.x
61. *Lohnes CA, Earhart GM (2012) Effect of subthalamic deep brain stimulation on turning kinematics and related saccadic eye movements in Parkinson disease. Exp Neurol. doi:10.1016/j.expneurol.2012.05.001
62. *Lubik S, Fogel W, Tronnier V, Krause M, Konig J, Jost WH (2006) Gait analysis in patients with advanced Parkinson disease: different or additive effects on gait induced by levodopa and chronic STN stimulation. J Neural Transm. doi:10.1007/s00702-005-0310-8
63. *McNeely ME, Hershey T, Campbell MC, Tabbal SD, Karimi M, Hartlein JM, Lugar HM, Revilla FJ, Perlmutter JS, Earhart GM (2011) Effects of deep brain stimulation of dorsal versus ventral subthalamic nucleus regions on gait and balance in Parkinson's disease. J Neurol Neurosurg Psychiatry. doi:10.1136/jnnp.2010.232900
64. *Muniz AM, Liu H, Lyons KE, Pahwa R, Liu W, Nadal J (2010) Quantitative evaluation of the effects of subthalamic stimulation on gait in Parkinson's disease patients using principal component analysis. Int J Neurosci. doi:10.3109/00207454.2010.504904
65. *Rocchi L, Carlson-Kuhta P, Chiari L, Burchiel KJ, Hogarth P, Horak FB (2012) Effects of deep brain stimulation in the subthalamic nucleus or globus pallidus internus on step initiation in Parkinson disease: laboratory investigation. J Neurosurg. doi:10.3171/2012.8.JNS112006
66. *Rochester L, Chastin SF, Lord S, Baker K, Burn DJ (2012) Understanding the impact of deep brain stimulation on ambulatory activity in advanced Parkinson's disease. J Neurol. doi:10.1007/s00415-011-6301-9
67. *Seri-Fainshtat E, Israel Z, Weiss A, Hausdorff JM (2013) Impact of sub-thalamic nucleus deep brain stimulation on dual tasking gait in Parkinson's disease. J Neuroeng Rehabil. doi:10.1186/1743-0003-10-38
68. *Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, Schrader B, Raethjen J, Wenzelburger R, Mehdorn HM, Deuschl G, Krack P (2001) Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. Neurology
69. Vallabhajosula S, Haq IU, Hwynn N, Oyama G, Okun M, Tillman MD, Hass CJ (2015) Low-frequency versus high-frequency subthalamic nucleus deep brain stimulation on postural control and gait in Parkinson's disease: a quantitative study. Brain Stimul 8:64–75. doi:10.1016/j.brs.2014.10.011