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Verbal Fluency in Parkinson's Patients with and without Bilateral Deep Brain Stimulation of the Subthalamic Nucleus: A Meta-analysis

Kathryn A. Wyman-Chick
Pacific University, Hillsboro, Oregon

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Abstract

Objectives: Patients with Parkinson's disease often experience significant decline in verbal fluency over time; however, deep brain stimulation of the subthalamic nucleus (STN-DBS) is also associated with post-surgical declines in verbal fluency. The purpose of this study was to determine if Parkinson's patients who have undergone bilateral STN-DBS have greater impairment in verbal fluency compared to Parkinson's patients treated by medication only. **Methods:** A literature search yielded over 140 articles and 10 articles met inclusion criteria. A total of 439 patients with Parkinson's disease who underwent bilateral STN-DBS and 392 non-surgical patients were included. Cohen's *d*, a measure of effect size, was calculated using a random effects model to compare post-treatment verbal fluency in patients with Parkinson's disease who underwent STN-DBS *versus* those in the non-surgical comparison group. **Results:** The random effects model demonstrated a medium effect size for letter fluency ($d = -0.47$) and a small effect size for category fluency ($d = -0.31$), indicating individuals with bilateral STN-DBS had significantly worse verbal fluency performance than the non-surgical comparison group. **Conclusions:** Individuals with Parkinson's disease who have undergone bilateral STN-DBS experience greater deficits in letter and category verbal fluency compared to a non-surgical group. (*JINS*, 2016, *22*, 478–485)

Keywords: Letter fluency, Category fluency, Disease comparison group, STN, Movement disorders, DBS

INTRODUCTION

Deep brain stimulation (DBS) is a Federal Drug Administration-approved treatment for motor symptoms of Parkinson's disease (PD; Bronstein et al., 2011). Individuals who have undergone DBS of the subthalamic nucleus (STN-DBS) often experience improvement in dyskinesia and motor symptoms (Kleiner-Fisman et al., 2006); however, post-surgical declines in verbal fluency have been a consistent finding across studies on cognition and STN-DBS in patients with PD (Mikos et al., 2011; Parsons, Rogers, Braaten, Woods, & Troster, 2006; Witt et al., 2008). Authors of a meta-analysis published in 2006 examined cognition associated with STN-DBS in PD patients pre-surgery and post-surgery. They found that STN-DBS was associated with declines in verbal fluency, which were not related to patient age or length of disease duration (Parsons et al., 2006).

Executive dysfunction is common among patients with PD (Bronnick, 2005). Lezak, Howieson, Bigler, and Tranel (2012) have argued that verbal fluency requires the "ability to think flexibly, switch response sets, and self-regulate and self-monitor" (p. 693), which are aspects of executive functioning. Various verbal fluency tasks, such as letter fluency and category fluency, appear to be impacted by damage to different brain regions; for example, impaired letter fluency has been found in individuals with damage to the frontal lobes and impaired category fluency has been identified in individuals with temporal lobe damage (Lezak et al., 2012).

Several studies have examined letter fluency and category fluency performance in patients with PD. In a 2004 meta-analysis of 68 studies, Henry and Crawford found category fluency performance was significantly more impaired than letter fluency performance in non-surgical patients with PD. The authors argued executive dysfunction, semantic memory deficits, and difficulty with cognitive set-shifting may be related to verbal fluency deficits within this population (Henry & Crawford, 2004). Parsons et al. (2006) also found greater declines in category fluency than letter fluency in PD

Correspondence and reprint requests to: Kathryn A. Wyman-Chick, Pacific University, 190 SE 8th Avenue, Hillsboro, OR 97123. E-mail: kwyman@pacificu.edu

patients who underwent STN-DBS. This study design did not include a disease control group, which is an important limitation as PD is associated with a decline in verbal fluency as a result of the disease process (Henry & Crawford, 2004).

The long-term cognitive outcomes associated with STN-DBS are largely unknown; however, declines in letter fluency among individuals with bilateral STN-DBS are evident up to 5 years post-surgery (Contarino et al., 2007). In a 12-month study, Heo and colleagues (2008) found that bilateral STN-DBS was associated with decline in verbal fluency, but was not associated with global cognitive decline. In contrast, a study by Williams and colleagues (2011) compared cognition in 19 STN-DBS participants with 18 PD patients managed by medication and found that 32% of the STN-DBS participants converted to dementia within 24-months compared to 16% of the PD group. The differences in conversion rates were not statistically significant, but this may have been due to lack of power due to a small sample size.

Although performance on verbal fluency and executive tasks (e.g., Wisconsin Card Sorting Task) initially declined after bilateral STN-DBS, performance improved 6-months post-surgery. After 36-months, the same STN-DBS group demonstrated declines in verbal fluency and the STN-DBS group had worse verbal fluency performance compared to individuals in a PD comparison group treated by medication (Zangaglia et al., 2009). Examining the long-term cognitive effects associated with STN-DBS should continue to be a focus for neuropsychologists.

Medication such as levodopa has been found to influence verbal fluency performance in patients with PD who have not undergone DBS. Gotham, Brown, and Marsden (1988) found verbal fluency in participants with PD on Levodopa did not differ from healthy controls while taking Levodopa; however, verbal fluency was significantly worse in the participants with PD in the off medication condition compared to healthy controls. This is an important consideration, as patients who have undergone STN-DBS are typically able to significantly reduce their PD medication dosage (Kleiner-Fisman et al., 2006).

The effects of medication on cognition in STN-DBS have been examined in numerous studies; authors of a 2006 meta-analysis on STN-DBS did not find a relationship between verbal fluency and medication or a relationship between declines in verbal fluency (Parsons et al., 2006). A recent study compared verbal fluency performance in a bilateral STN-DBS group as well as a non-surgical PD group treated with medication only. The authors argued that both the DBS group and PD group had lower verbal fluency production than healthy controls, and, therefore, the "independence from the medication status suggests a disease-related origin of this deficit" (Ehlen et al., 2013; p. e79247).

Researchers have not demonstrated a relationship between the effects of DBS stimulation parameters (e.g., pulse width values, rate, and voltage) and declines in verbal fluency (Parsons et al., 2006). There is evidence to suggest that the decrease in verbal fluency following DBS surgery is related to the surgical procedure to implant the electrode, rather than an effect of stimulation, as individuals who have undergone surgery, but have not had their stimulators turned on exhibit declines in their performance (Okun et al., 2009, 2012). Furthermore, there is a greater risk of cognitive impairment in STN-DBS if the caudate nucleus is disturbed during the procedure (Witt et al., 2013). Evidence from SPECT imaging reflects that the decline in verbal fluency after STN-DBS is associated with decreased perfusion in the prefrontal cortex, anterior cingulate cortex, and the ventral caudate nucleus (Cilia et al., 2007). Taken together, there is evidence to suggest the caudate nucleus is involved with the production of verbal fluency in patients with PD.

In addition to examining the role of the caudate nucleus in verbal fluency, researchers have also studied the effects of location of stimulation within the STN. Witt and colleagues (2013) demonstrated that target location within the STN may influence verbal fluency, as those with stable verbal fluency performance had bilateral STN-DBS electrodes in a different location within the STN than those who had declines in verbal fluency performance. Similarly, Mikos and colleagues (2011) reported stimulation within the ventral associative region of the STN was associated with worse verbal fluency performance than stimulation of the dorsolateral sensorimotor area in a small sample of unilateral DBS patients. Given this information, there may be methods of minimizing the risk of verbal fluency deficits associated with STN-DBS to treat motor symptoms of PD.

Several studies have examined cognition among individuals with unilateral DBS *versus* bilateral DBS. In a study examining staged STN-DBS, there was no significant difference between verbal fluency performance after the first and second surgeries (Rothlind, Cockshott, Starr, & Marks, 2007). When individuals with unilateral DBS are compared with a PD control group, unilateral left-sided surgery was found to be associated with semantic fluency declines (Zahodne et al., 2009). However, authors of a small study published in 2012 examined the effects of unilateral left-sided stimulation compared to bilateral stimulation and found that bilateral stimulation is associated with greater declines in verbal fluency compared to unilateral DBS of the dominant language hemisphere after 1.5 years. The authors highlighted individuals who have undergone unilateral DBS typically have less disease progression and fewer motor symptoms than those who have undergone bilateral surgery (Sjoberg et al., 2012).

Bilateral DBS surgery may be conducted simultaneously or in two separate, staged procedures. To date, there are no studies explicitly examining cognition in staged STN-DBS surgery. In research based on staged bilateral DBS of the globus pallidus, individuals experienced declines, although non-significant, in verbal fluency after the first surgery and experienced "apparent recovery after the second procedure" (Fields, Troster, Wilkinson, Rahwa, & Koller, 1999; p. 184).

Given the previous research findings on decreased verbal fluency after bilateral STN-DBS, the purpose of this study was to determine if bilateral STN-DBS in patients with PD is associated with greater impairment in verbal fluency when compared to a group of PD patients managed by medication only, as previous studies have not included a disease comparison group.

METHODS

Data included in this meta-analysis were obtained in compliance with the institutional review board regulations at the author's primary institution. The search was conducted for articles published between 2000 and 2014 using computerized databases including *PsychInfo*, *MEDLINE-OVID*, and *Web of Science.* Furthermore, a search of specific journals, including *Journal of the International Neuropsychological Society, Movement Disorders, Clinical Neuropsychologist, Neurology,* and *Parkinsonism & Related Disorders*, was conducted. Reference lists from obtained studies were also analyzed to identify additional studies.

Search terms included keywords: bilateral, deep brain stimulation, DBS, high frequency stimulation, Parkinson's disease, subthalamic nucleus, verbal fluency, letter fluency, category fluency, semantic fluency, phonemic fluency, Controlled Oral Word Association test, cognition, neuropsychological testing, and combinations of the key words. Boolean search phrases were used and wildcard search terms were also used to find studies for inclusion (e.g., random* was used to find studies using terms randomization and randomized; Parkinson* was used to find studies using terms Parkinson's and Parkinson). Specifically, only studies that were published in English in peer-reviewed journals, focused on bilateral STN-DBS, included pre-test and post-test verbal fluency data, and included a comparison group of non-surgical patients with PD were accepted for use in the current meta-analysis. Bilateral stimulation was required to avoid the confounding variable of hemispheric dominance for language found in unilateral DBS studies.

Studies that met the inclusion criteria, but did not include precise data to enable the calculation of the effect size *d,* were not included in the present analysis. Studies with dual publication were identified and the article with the publication with the greatest length of time between baseline and follow up was selected for inclusion. A literature search conducted in June 2014 yielded over 140 articles and 10 articles met inclusion criteria (see Table 1). A total of 439 patients with Parkinson's disease who underwent bilateral STN-DBS surgery and 392 non-surgical patients with Parkinson's disease were included in the analysis.

To ensure accuracy of the data gathered for the current study, a reliability analysis was conducted before conducting any statistical analyses. Two individuals (including the primary author) reviewed the studies selected for inclusion to obtain relevant information (e.g., length of time between pre-test and post-test, means/standard deviations of verbal fluency performance) and the inter-rater agreement across studies was 100%. For this study, effect sizes were pooled for letter verbal fluency and category verbal fluency, and Hedge's correction for small sample size bias was calculated before descriptive analyses were conducted.

An analysis of heterogeneity of the effects was conducted and the homogeneity statistic (Q), the standard deviation of the random effects model, and the 95% confidence intervals within which random effects can be expected to fall was conducted. A non-significant Q statistic indicates that when sampling error has been removed, there are no significant differences between the mean of the verbal fluency performance in studies included in the analysis. Cohen's d was calculated as a measure of the magnitude and direction of the effect size comparing the means and standard deviations for verbal fluency performance between participants with PD who underwent bilateral STN-DBS surgery and those treated with medication using a random effects model. The National Research Council (1992) recommends random effects models because they are less likely than fixed effects models to result in a Type I error, as the between-study variability is added to the sampling error variability. The present meta-analysis measured scores between the two groups only after treatment, as some of the included studies (e.g., Ehlens et al., 2013) did not measure baseline data. According to Cohen (1988), a Cohen's d value of .2 is considered a small effect size, .5 is considered a medium effect size, and .8 is considered a large effect size.

The present study only included published articles; therefore, Orwin's fail-safe N was calculated to estimate the number of unpublished studies with null results needed to reduce the effect size across studies to non-significant levels (Orwin, 1983). Orwin's method was chosen, as it was adapted from Rosenthal's method to be used with the standard mean difference effect size (Lipsey & Wilson, 2000). Finally, the potential influence of demographic variables on effect sizes was examined using separate weighted regression analysis for each variable. The analysis was conducted by weighting each effect size by the inverse of its variance. Demographic variables used in the analysis included the participant's age at baseline, disease duration, and length of time between STN-DBS surgery and data collection.

RESULTS

The distribution of effect sizes for the 10 studies was analyzed to determine if participants in the STN-DBS group experience greater deficits in verbal fluency than participants in the medication only group.

Letter Fluency

Analyses were performed only on those effect sizes where letter fluency was the dependent variable. There were a total of nine effect sizes and the minimum and maximum effect sizes were –0.99 and –0.11, respectively. Analyses were conducted to examine the descriptive statistics and frequency distribution for the effect sizes before aggregating at the study level. The average effect size before aggregating was –0.53 (SD = 0.30) with a minimum effect size of –0.99 and a maximum effect size of –0.11. The distribution was mesokurtic and normally distributed. Hoaglin and Iglewicz's

Table 1. Summary of studies included in the meta-analysis

Study	Subjects	Age *M (SD)*	Electrode placement verification	Disease duration in years at baseline *M (SD)*	Simultaneous or staged DBS surgery	Time between surgery and data collection	Baseline cognitive screening measure scores *M (SD)*	Letter Fluency raw scores M *(SD)*	Letter Fluency adjusted effect size	Category Fluency raw scores *M (SD)*	Category Fluency adjusted effect size
Castelli et al. (2010)	27 DBS 31 MED	60.6 (6.7) 60.2 (6.6)	Yes	15.3 (5.1) 15.6 (5.2)	Simultaneous	12 months	Not reported	31.4 (12.6) 45.62 (12.1)	−0.65	14.65 (3.3) 18.88 (6.9)	−0.23
Ehlen et al. (2013)	21 DBS 26 MED	64.7 (8.6) 67.3 (8.2)	Yes	14.1 (4.5) 11.2 (6.2)	Not reported	Not reported	17.5 (3.3) 18.0 (3.1) PANDA	18.3 (7.6) 22.6 (6.1)	−0.92	14.9 (5.3) 16.1 (4.4)	−0.41
Marshall et. al. (2012)	23 DBS 20 MED	59.8 (11.7) 65.7 (7.6)	Not Reported	9.2 (6.2) 6.6 (4.3)	Simultaneous	6 months	Not reported	9.9 (4.6) 11.2 (3.6)	−0.33	10.3 (4.5) 11.1 (3.9)	−0.21
Morrison et al. (2004)	17 DBS 11 MED	59.9 (7.7) 62.7 (11.5)	In some cases	10.8 (3.4) 10.0 (3.0)	Staged and simultaneous	13.3 (7.8) weeks	137.8 (5.6) 136.8 (4.2) DRS	Not Reported	−0.11	Not reported	−0.50
Rinehardt et al. (2010)	20 DBS 20 MED	66.7 (9.4) 69.3 (6.5)	Yes	9.4 (5.1) 7.5 (5.9)	Simultaneous	3–4 months	27.8 (2.3) 26.8 (2.9) MMSE	N/A	N/A	14.8 (3.6) 14.4 (4.9)	0.07
Smeding et al. (2006)	99 DBS 36 MED	57.9 (8.1) 63.0 (9.1)	No	13.7 (6.1) 10.4 (4.6)	Not reported	6 months	136.1 (5.4) 137.0 (5.4) DRS	30.9 (8.8) 36.4 (9.3)	−0.31	33.3 (6.7) 39.7 (6.7)	−0.51
Weaver et al. (2009)	60 DBS 134 MED	62.4 (8.8)[a] 62.3(9.0)	Not Reported	10.8 (5.4)[a] 12.6 (5.6)	Staged and simultaneous	6 months	136.7 (4.8) 136.6 (5.8) DRS	Not reported	−0.29	Not reported	−0.11
Williams et al. (2011)	19 DBS 18 MED	62.1 (10.3) 66.6 (9.0)	Not Reported	10.1 (6.2) 7.5 (4.2)	Not reported	24 months	27.9 (3.41) 28.7 (1.19) MMSE	24.5 (11.4) 35.6 (11.6)	−0.99	13.6 (5.2) 14.7 (5.6)	−0.23
Witt et al. (2008)	60 DBS 63 MED	60.2 (7.9) 54.9 (7.5)	Not Reported	13.8 (6.3) 14.0 (6.1)	Simultaneous	6 months	139.6 (3.8) 140.0 (3.5) DRS	17.7 (7.0) 21.7 (6.6)	−0.51	28.7 (9.7) 35.1 (10.1)	−0.41
Zangaglia et al. (2009)	32 DBS 33 MED	58.84 (7.7) 62.52 (6.8)	Yes	11.8 (5.1) 10.0 (4.9)	Simultaneous	36 months	28.19 (2.0) 28.24 (1.7) MMSE	25.68 (11.2) 32.62 (9.5)	−0.69	N/A	N/A

[a]The age and education demographics for the DBS group also included data from 61 patients who underwent bilateral DBS of the globus pallidus; however, the verbal fluency outcome measures were reported separately for the subthalamic nucleus group and the globus pallidus group and were separated in the outcome analysis.
DBS = Patients with bilateral deep brain stimulation of the subthalamic nucleus; MED = non-surgical comparison group treated with medication; DRS = Mattis Dementia Rating Scale; MMSE = Mini Mental Status Examination; PANDA = Parkinson Neuropsychometric Dementia Assessment.

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Table 2. Summary of findings of random effects model

Verbal Fluency condition	DBS *n*	MED *n*	k	Cohens *d*	*p*	95% CI	*Q*	Df	*p*
Letter	419	372	9	–0.47	<.001	–0.63 to –0.31	9.27	8	0.32
Category	407	359	9	–0.31	<.001	–0.47 to –0.16	8.75	8	0.36

DBS = Patients with bilateral deep brain stimulation of the subthalamic nucleus; MED = non-surgical comparison group treated with medication; *n* = number of participants; k = number of studies.

method (1987) was used to determine if outliers existed in the distribution of effect sizes based on the upper and lower quartile ranges. The lower quartile (i.e., 25th percentile score) value was –0.81 and the upper quartile (i.e., 75th percentile score) value was –0.30. None of the effect sizes in this sample were outside of the upper or lower bounds, thus there were no outliers. A homogeneity analysis was conducted and the resulting *Q*-value of 9.27 with eight degrees of freedom was not statistically significant ($p = .32$) indicating a homogenous distribution.

The mean effect size for the sample of studies under the random effects model was –0.47 ($SE = 0.08$) and was statistically significant ($z = -5.67$; $p < .001$), indicating participants who underwent STN-DBS have greater deficits in letter fluency than participants treated with medication only. The 95% confidence interval around the mean effect size, reported in Table 2, did not include zero and reflects the relevant precision of estimate of the mean effect size.

A weighted regression analysis tested the ability of the continuous variables, disease duration, age, and time between surgery and data collection to explain the excess effect size variability in letter fluency performance (see Table 3). For the random effects model, the regression coefficient was not significantly different from zero for disease duration, age, or time between surgery and data collection. Additionally, the weighted sum-of-squares and the predictor variables were not statistically different from zero, and thus the three predictor variables do not contribute significantly to variability across effect sizes.

Category Fluency

Analyses were repeated for effect sizes where category fluency was the dependent variable. There were a total of nine effect sizes and the results of the analysis are included in Table 2. Analyses were conducted to examine the descriptive statistics and frequency distribution for the effect sizes before aggregating at the study level. The average effect size before aggregating was –0.28 ($SD = 0.19$) with a minimum effect size of –0.51 and a maximum effect size of 0.07. The distribution was mesokurtic and normally distributed. Hoaglin and Iglewicz's method (1987) was again used to determine if outliers existed in the distribution of effect sizes for category fluency. The lower quartile value was –0.45 and the upper quartile value was –0.16. None of the effect sizes in this sample were outside of the upper or lower bounds, thus there were no outliers. A test for homogeneity was conducted and the resulting *Q*-value was not statistically significant indicating a homogenous distribution.

The mean effect size for the sample of studies under the random effects model was –0.31 ($SE = 0.08$) and was statistically significant ($z = -3.91$; $p < .001$), indicating participants who underwent STN-DBS also have greater deficits in category fluency than participants treated with medication only. The 95% confidence interval around the mean effect size, reported in Table 2, did not include zero and reveals the relevant precision of estimate of the mean effect size.

A weighted univariate meta-regression analysis tested the ability of the continuous variables, disease duration, age, and time between surgery and data collection to explain the excess effect size variability in category fluency performance (see Table 3). For the random effects model, the regression coefficient and predictor variables were not significantly different from zero for disease duration or time between surgery and data collection; however, the regression coefficient and predictor indicated age was a significant moderator for category fluency.

Table 3. Summary of findings of meta-regression analysis for moderators of Verbal Fluency performance

	Q model	df	*p*	*Q* resid	df	*p*	B	*SE*	95% CI	*z*	*p*
Letter Fluency											
Age	0.67	1	0.41	7.14	7	.41	–0.04	0.05	–0.13 to 0.05	–0.82	.41
Disease duration	0.13	1	0.72	9.13	7	.24	–0.02	0.05	–0.12 to 0.08	–0.36	.72
Time between	3.73	1	0.05	3.08	7	.80	–0.02	0.01	–0.03 to 0.00	–1.93	.05
Category Fluency											
Age	6.64*	1	0.01	2.11	7	.95	0.06*	0.02	0.01 to 0.11	2.58	.01
Disease duration	3.16	1	0.08	5.59	7	.59	–0.07	0.04	–0.14 to 0.01	–1.78	.08
Time between	0.10	1	0.76	4.80	7	.57	0.01	0.02	–0.03 to 0.04	0.31	.76

Time Between = time between surgery and data collection.
*$p \geq .5$.

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Additional Analyses

Based upon the Orwin's fail-safe N calculation using a minimum effect size of 0.2, 12 studies would be needed to reduce effect size to non-significance for letter fluency, while five studies would be needed for the category fluency condition.

CONCLUSIONS

Previous meta-analyses have been conducted with DBS patients and verbal fluency; however, the studies did not include a comparison group of patients with PD. This is a limitation of previous studies, as patients with PD often experience a decline in cognition, including verbal fluency, as part of the disease process (Henry & Crawford, 2004).

The results of the current meta-analysis indicate that patients with PD who underwent bilateral STN-DBS surgery have statistically significant deficits in verbal fluency compared to patients with PD who are treated with medication only. Furthermore, deficits in letter fluency were greater than deficits in category fluency. A medium effect size was observed for letter fluency and a small effect size was observed for category fluency. Of interest, two previous meta-analyses on verbal fluency in patients with PD, including one meta-analysis in STN-DBS patients, found category fluency was more impaired than letter fluency (Henry & Crawford, 2004; Parsons et al., 2006). The results of the current analysis suggest letter fluency deficits, although present in non-surgical PD groups, are greater than category fluency deficits among individuals who have undergone bilateral STN-DBS. It is possible the deficits in letter fluency are related to disruption of the fronto-subcortical circuits during surgery (Okun et al., 2009; Witt et al., 2013), as research has demonstrated that letter fluency is mediated by the frontal lobes and semantic fluency is more widely mediated by temporal regions of the brain (Birn et al., 2010; Lezak et al., 2012).

The inclusion of a disease comparison group to control for the effects of maturation is a marked strength of this study. Although post-treatment comparisons were made, neither disease duration, nor post-operative interval were significant predictors of verbal fluency performance. The present meta-analysis included only published articles; therefore, a calculation was performed to address the possibility of publication bias. Many of the included studies contained small sample sizes; therefore, a correction was calculated to address this before conducting the statistical analyses. Limitations of the current study include limited statistical power, as there were only 10 studies included in this meta-analysis.

The present study attempted to restrict the research question to bilateral stimulation of the STN to increase the generalizability of findings to other individuals who have undergone or are considering bilateral STN-DBS. However, there are very few studies to date that have been published on verbal fluency in STN-DBS participants that included a PD comparison group, which has been a limitation of previous meta-analyses. Combining studies on DBS and PD poses several challenges as individuals with PD are not a homogenous group and there are often differences in medication dosage and severity of motor symptoms between individuals who have undergone DBS and those who are managed by medication (Fields, 2015).

Furthermore, when conducting meta-analyses, it is important to consider the continuum of methodological quality of the studies included in the analysis. When the inclusion criteria for studies in a meta-analysis are too lenient, it can weaken the confidence placed in the findings. The studies published on this topic vary widely in their methodology, ranging from randomized control trials (Weaver et al., 2009; Witt et al., 2008) to convenience samples (Rinehardt et al., 2010), which did not match subjects on important disease-related factors such as severity of motor symptoms, "off" time, and dyskinesias. The lack of randomization or matched samples is an important limitation, as patients who are candidates for DBS often have more severe motor dysfunction and longer symptom duration (Zahodne et al., 2009). It should be noted that one of the studies in the current analysis (Morrison et al., 2004) included two DBS patients with a history of right-sided pallidotomy, which weakens the generalizability of the current findings. Another consideration is that across studies, the participants varied in their baseline cognitive scores, which likely impacted the magnitude of the effect sizes in the respective studies.

The majority of the studies included in the present analysis reported verification of electrode placement *via* imaging, but the improvement in motor symptoms and effectiveness of treatment was not specifically addressed in this analysis. Although all of the included studies involved bilateral DBS, the studies varied in the surgical procedures as the DBS implantation was conducted bilaterally during the same procedure (simultaneous) in most, but not all, studies. The current meta-analysis did not control for the effects of simultaneous *versus* staged surgical procedures, as some of the studies did not report these details (Ehlen et al., 2013; Williams et al., 2011) and other studies only used staged surgical procedures in a small number of individuals if the participant had significant fatigue or if there were technical issues (Weaver et al., 2009). Research has demonstrated the location of stimulation within the STN can also influence verbal fluency performance (Mikos et al., 2011) and this information was not available for analysis in the present study.

While the results of this meta-analysis reflect statistically significant differences in verbal fluency between patients who have undergone STN-DBS and those managed with medication only, the clinical impact of these findings is unclear. There is some evidence to suggest that performance on tests of verbal fluency has ecological validity for daily verbal communication skills (Doesborgh et al., 2002). However, cognitive changes, including a decline verbal fluency, have not been found to have a significant impact on quality of life in patients with PD (Contarino et al., 2007; Muslimovic, Post, Speelman, Schmand, & de Haan, 2008). Furthermore, up to 98% of individuals who have undergone STN-DBS report improvement or stability in quality of life post-surgery (Floden, Cooper, Griffith, & Machado, 2014). Therefore, the benefits of motor symptom improvement after DBS may outweigh any risk associated with decreased verbal fluency.

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