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REVIEW ARTICLE

# Neuropsychological performance changes following subthalamic versus pallidal deep brain stimulation in Parkinson's disease: a systematic review and metaanalysis

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**Background.** Studies comparing subthalamus (STN) and globus pallidus internus (GPi) deep brain stimulation (DBS) for the management of Parkinson's disease in terms of neuropsychological performance are scarce and heterogeneous. Therefore, we performed a systematic review and metaanalysis to compare neuropsychological outcomes following STN DBS versus GPi DBS.

**Methods.** A computer literature search of PubMed, the Web of Science, and Cochrane Central was conducted. Records were screened for eligible studies, and data were extracted and synthesized using Review Manager (v. 5.3 for Windows).

**Results.** Seven studies were included in the qualitative synthesis. Of them, four randomized controlled trials ($n$ = 345 patients) were pooled in the metaanalysis models. The standardized mean difference (SMD) of change in the Stroop color-naming test favored the GPi DBS group ($SMD = -0.31$, $p = 0.009$). However, other neuropsychological outcomes did not favor either of the two groups (Stroop word-reading: $SMD = -0.21$, $p = 0.08$; the Wechsler Adult Intelligence Scale (WAIS) digits forward: $SMD = 0.08$, $p = 0.47$; Trail Making Test Part A: $SMD = -0.05$, $p = 0.65$; WAIS–R digit symbol: $SMD = -0.16$, $p = 0.29$; Trail Making Test Part B: $SMD = -0.14$, $p = 0.23$; Stroop color–word interference: $SMD = -0.16$, $p = 0.18$; phonemic verbal fluency: bilateral DBS $SMD = -0.04$, $p = 0.73$, and unilateral DBS $SMD = -0.05$, $p = 0.83$; semantic verbal fluency: bilateral DBS $SMD = -0.09$, $p = 0.37$, and unilateral DBS $SMD = -0.29$, $p = 0.22$; Boston Naming Test: $SMD = -0.11$, $p = 0.33$; Beck Depression Inventory: bilateral DBS $SMD = 0.15$, $p = 0.31$, and unilateral DBS $SMD = 0.36$, $p = 0.11$).

**Conclusions.** There was no statistically significant difference in most of the neuropsychological outcomes. The present evidence does not favor any of the targets in terms of neuropsychological performance.

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**Key words**: Parkinson's disease, deep brain stimulation, subthalamus, globus pallidus, neuropsychological performance.

## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% of the population above 60 years of age. PD is characterized by bradykinesia, rigidity, tremor, and postural instability.[1] The cardinal pathological features of PD are loss of dopaminergic fibers of the basal ganglia and the presence of Lewy bodies.

PD patients do not respond optimally to pharmacological treatment. In advanced PD, patients experience severe motor fluctuations and dyskinesia despite optimal

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pharmacological treatment. These complications limit the efficacy of pharmacological treatment and affect the quality of life of PD patients. Deep brain stimulation (DBS), an effective surgical treatment for PD, can improve the cardinal symptoms of PD with fewer complications. The subthalamic nucleus and globus pallidus internus are two common targets for DBS in PD.[2,3]

The motor effects of DBS mimic those of dopaminergic therapies, which suggests that DBS may act similarly in terms of neuropsychological effects. However, controversy remains about neuropsychological performance changes after DBS and the relative advantages of treatment at the GPi and STN targets. STN DBS is presumed to directly affect cognitive function due to its effect on anatomical data, which play an important role in cognitive and limbic functions,[4,5] and suboptimal lead placement might be associated with irritation of nearby circuits responsible for neuropsychological functions.[6] Other factors that have been considered to contribute to neuropsychological performance changes include the reduction in doses of dopaminergic medications that frequently occurs after surgery,[7] advanced age, and impaired cognitive function at baseline.[8] Aside from motor functions and quality of life, the neuropsychological performance of PD patients should be assessed as an important outcome of DBS surgery because mood and cognitive functions impact quality of life. Therefore, it is important to predict cognitive deterioration after DBS in order to help choose a suitable DBS target in PD patients.

Multiple reports have shown that DBS is associated with mild improvements in mood and mild cognitive declines in verbal associative fluency, working memory, and learning and recall efficiency.[9,10] In the study by Troster *et al.*,[11] unilateral GPi DBS in nine patients caused a decline in verbal fluency and in visuoconstructional test scores. Studies have reported more cognitive problems after STN compared to GPi DBS and PD controls.[12] In the study by Ardouin *et al.*,[13] there was no significant change in memory or executive functions 3–6 months after DBS in a series of 62 patients with PD treated with bilateral STN or GPi stimulation. The study by Odekerken *et al.*[14] showed no difference between STN DBS and GPi DBS in composite cognition, mood, and behavior scores. Due to the heterogeneous results of the abovementioned studies and the previously published clinical trials comparing STN DBS and GPI DBS, we performed a systematic review and metaanalysis to precisely compare the two targets in terms of neuropsychological performance.

## Methods

We followed the PRISMA statement guidelines during preparation of this review and metaanalysis.

### Criteria for considering studies for this review

We used the following inclusion criteria: (1) studies that were randomized controlled trials (RCTs) or quasiexperimental studies; (2) studies where the intervention was either unilateral or bilateral subthalamic deep brain stimulation (STN DBS) compared to unilateral or bilateral globus pallidus deep brain stimulation (GPi DBS); (3) studies reporting on patients with idiopathic Parkinson's disease suffering from motor fluctuations and not showing an optimal response to pharmacological PD treatments; and (4) studies reporting on such neuropsychological functions as attention, working memory, executive functions, language, and verbal fluency. Studies were excluded if they were not written in the English language or were theses or conference abstracts. In the case of multiple reports, we analyzed data from the most complete dataset. For the quantitative evidence synthesis, only RCTs were pooled in the metaanalysis models to get a more precise effect estimate.

### Search strategy

We searched the following medical electronic databases: PubMed, Cochrane CENTRAL Register of Controlled Trials, and the Web of Science, all through October 2015. We employed the following keywords: ("Deep brain stimulation" AND "Parkinson's disease").

### Selection of studies

Three authors screened the titles and abstracts of retrieved records for eligibility. We then retrieved the full texts of the eligible abstracts, and they were screened for eligibility for our systematic review and metaanalysis.

### Data extraction

Three authors extracted the raw data (mean and standard deviation [SD] for each group) independently using a standardized online data extraction form. The extracted data included the following: (1) study design characteristics, (2) characteristics of the study population, (3) risk of bias domains, and (4) study outcomes, including changes in attention and working memory, executive functions, language, verbal function, and depression. Another author (AN) resolved disagreements.

### Assessment of risk of bias in included studies

Two authors (AE and AN) independently assessed the quality of each included study in strict accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (v. 5.1.0, updated March 2011). We utilized the quality assessment table provided in Chapter 8.5, Part 2, of the *Handbook*.

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### Outcome measurement

Multiple tests were employed to assess neuropsychological performance in PD patients. These tests are grouped into the relevant domains in Table 1.

### Dealing with missing data

When the SD of change in outcomes was not provided, we calculated it from the standard error (*SE*) or 95% confidence interval ($CI_{95\%}$) according to Altman.[15]

### Data synthesis

We used Review Manager (RevMan, v 5.3 for Windows). Mean changes from baseline in neuropsychological test scores were pooled as standardized mean differences (SMDs) between the two groups from baseline to the endpoint in the metaanalysis models using the inverse variance method. Because the results in the previous literature are not consistent, we assumed a random-effect model of the SMD as the main analysis model. Additional confirmatory analysis was conducted in two other scenarios. In the first scenario, we shifted from a random-effect model to a fixed-effect model, and in the second scenario, we shifted from SMD to crude mean difference. Only data from the main analysis are provided in this manuscript.

For all outcomes, a value of Cronbach's alpha (α) below 0.05 was considered statistically significant. Given the small effect size of neuropsychological decrements reported in previous studies, we considered an α level below 0.1 to indicate a trend toward one of the two groups.

**TABLE 1. Outcome measures of different neuropsychological domains**

| Domain | Test (outcome measure) |
|---|---|
| Attention and working memory | Wechsler Adult Intelligence Scale–Revised Digits (forward) |
| | Wechsler Adult Intelligence Scale–Revised Digits (backward) |
| | Wechsler Adult Intelligence Scale (arithmetic) |
| Executive function | Trail Making Test Part B |
| | Stroop color and word interference |
| Processing speed | Trail Making Test Part A |
| | Wechsler Adult Intelligence Scale–Revised (digit symbol) |
| | Stroop–word reading |
| | Stroop–color naming |
| Phonemic verbal fluency | F/A/S |
| Semantic verbal fluency | Animals/supermarket |
| Language | Boston Naming Test |
| Depression | Beck Depression Inventory |
| Verbal and visual memory | Rey Auditory Verbal Learning Test (immediate recall) |
| | Rey Auditory Verbal Learning Test (delayed recall) |
| | Rey Auditory Verbal Learning Test (Total 1–5) |
| | Rivermead Behavioural Memory Test (immediate recall) |
| | Rivermead Behavioural Memory Test (delayed recall) |
| | Brief Visuospatial Memory Test–Revised (total 1–3) |
| | Brief Visuospatial Memory Test–Revised (delay) |
| | Hopkins Verbal Learning Test (trials 1–3 total) |
| | Wechsler Adult Intelligence Scale (matrix reasoning) |

### Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plots and measured by the $I^2$ and chi-square ($\chi^2$) tests. The $\chi^2$ test was used to test the existence of significant heterogeneity, while the $I^2$ test was utilized to quantify the present heterogeneity, if present. The $I^2$ test was interpreted according to recommendations of the *Cochrane Handbook* with regard to metaanalysis (0–40% = might not be important, 30–60% = may represent moderate heterogeneity, 50–90% = may represent substantial heterogeneity, and 75–100% = considerable heterogeneity). For testing statistical heterogeneity, a value of α (for the $\chi^2$ test) below 0.1 was considered to represent significant heterogeneity, as recommended by the *Cochrane Handbook* (Part 2, Chapter 9).

### Subgroup analysis

Because some studies reported on unilateral DBS and others reported on bilateral DBS, we conducted subgroup analysis whenever possible. The difference in effect size between unilateral and bilateral DBS was tested by the $\chi^2$ test (test for subgroup difference). A value of α below 0.05 for this test was considered to represent a significant difference.

### Publication bias

According to Egger and colleagues,[16,17] publication bias assessment is not reliable for less than 10 pooled studies. Therefore, in the present study, we could not assess the existence of publication bias by Egger's test for funnel plot asymmetry.

## Results

Our search retrieved 579 unique citations. Of these, 49 full-text articles were retrieved and screened for eligibility. Finally, 42 articles were excluded and 7 unique studies ($n$ = 555 patients) were included in our study.[6,8,13,18–21] Of the seven studies included in our systematic review, four[8,19–21] were RCTs and were therefore pooled in the metaanalysis (see the PRISMA flow diagram in Figure 1). The reasons for study exclusion are shown in supplementary file 1 ("Reasons for Excluded Studies").

Out of the seven included studies, four were described as RCTs,[8,19–21] and three were quasiexperimental studies.[6,13,18] A summary of included studies, their design, and their main results is given in Table 2, and the baseline characteristics of their populations are presented in Table 3.

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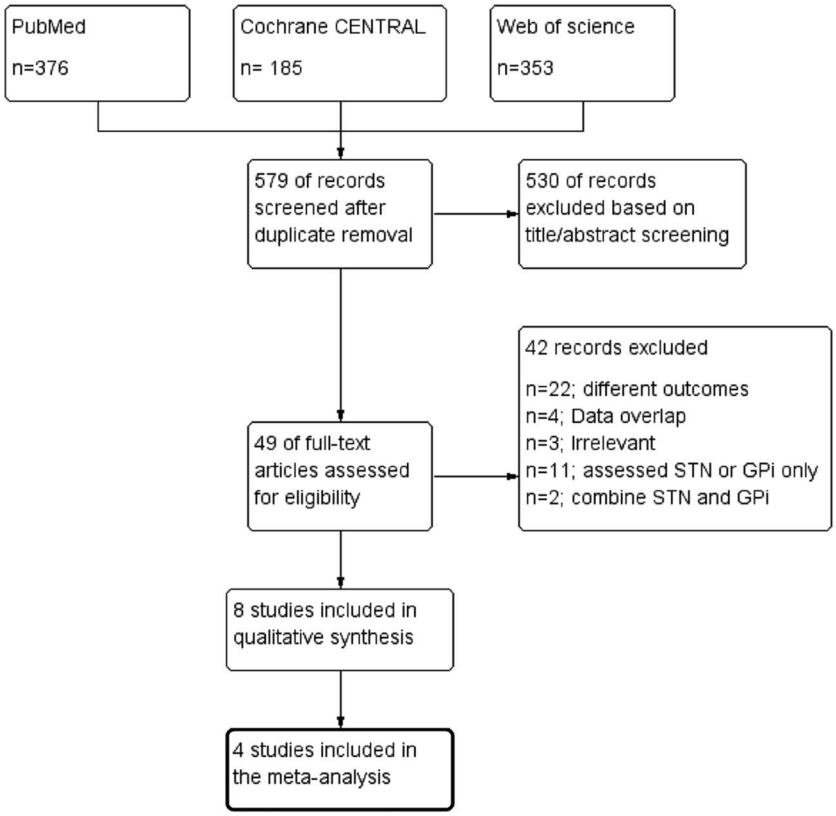


**FIGURE 1.** PRISMA flow diagram of studies' screening and selection.

The quality of the included studies was rated as from moderate to high quality according to the Cochrane Risk of Bias tool. A summary of the quality assessment domains of the four RCTs is depicted in Figure 2. The authors' judgment with justifications are presented in supplementary files 2 and 3. Quasi-randomized studies were deemed as being at high risk of bias due to a lack of the items described in the assessment tool.

Trépanier *et al.*[18] reported an increase in the risk of cognitive decline following STN DBS in comparison with GPi DBS. However, the low sample size ($n = 13$), the lack of randomization, and the lack of blinding all limit the credibility of these results.

Rothlind *et al.*[8] reported a statistically significant reduction in many cognitive domains following unilateral and bilateral DBS, but no significant difference was noted between the STN DBS and GPi DBS groups.[8]

None of the other included studies[6,13,19–21] reported a significant difference in cognitive function following STN DBS or GPi DBS.

### Attention and working memory

In terms of attention, the following outcomes did not favor either of the two groups: the Wechsler Adult Intelligence Scale (WAIS) digits forward ($SMD = 0.08$, $CI_{95\%} = [-0.14, 0.31]$, $p = 0.47$); the WAIS digits back-ward ($SMD = 0.31$, $CI_{95\%} = [-0.25, 0.87]$, $p = 0.28$); and the WAIS arithmetic ($SMD = -0.06$, $CI_{95\%} = [-0.55, 0.42]$, $p = 0.79$, Figure 3).

### Psychomotor speed

The pooled effect size did not favor either of the two groups as the Trail Making Test Part A (TMTA), the WAIS–R digit symbol, Stroop word-reading, and Stroop color-naming tests did not favor either of the two groups ($SMD = -0.04$, $CI_{95\%} = [-0.30, 0.22]$, $p = 0.78$; $SMD = -0.16$, $CI_{95\%} = [-0.45, 0.13]$, $p = 0.29$; $SMD = -0.21$, $CI_{95\%} = [-0.61, 0.18]$, $p = 0.29$; $SMD = -0.31$, $CI_{95\%} = [-0.67, 0.04]$, $p = 0.09$; respectively; see Figure 4).

### Executive function

In terms of executive functions, the pooled SMD of change on the Trail Making Test Part B (TMTB) and Stroop color–word interference did not favor either of the two groups ($SMD = -0.11$, $CI_{95\%} = [-0.47, 0.24]$, $p = 0.53$; and $SMD = -0.16$, $CI_{95\%} = [-0.38, 0.07]$, $p = 0.18$; respectively; Figure 5). The pooled studies were homogeneous ($p > 0.1$).

### Verbal fluency

The pooled SMD of change in phonemic verbal fluency did not favor either of the two groups (bilateral

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**TABLE 2. Summary of included studies**

| Study ID | Design | Blinding | Type of intervention | Condition | Sample size | Follow-up duration in months | Results |
|---|---|---|---|---|---|---|---|
| Odekerken *et al.*, 2015[20] | RCT | Double blinded | Bilateral STN DBS and GPi DBS | Patients with idiopathic PD without (DRS) score of 120 or lower (out of 144), or active psychosis. | 128 | 12 | No clinical differences in neuropsychological outcome between GPi DBS and STN DBS have been found, baseline patient characteristics cannot form the base for choice of either GPi DBS or STN DBS. |
| Rothlind *et al.*, 2015[19] | RCT | Single blinded | Bilateral STN DBS and GPi DBS | Patients with idiopathic PD without clear evidence of dementia (MMSE <25 or (DRS) >2*SD* below the mean of healthy Age-matched peers). | 182 | 6 | No significant differences in neuropsychological test change overall between GPi DBS and STN DBS have been found. |
| Rothlind *et al.*, 2007[8] | RCT | Open-label | Staged bilateral STN DBS and GPi DBS | Patients with idiopathic PD without major psychiatric disorder or dementia that would interfere with their ability to comply with follow-up for stimulator programming and assessment | 42 | 6 | Unilateral treatment resulted in small but statistically significant reductions in performance on several measures, including verbal fluency and working memory. A similar pattern was observed after bilateral treatment. Supplementary analyses suggested that decrements in select neuropsychological domains following DBS are unrelated to age or postsurgical reduction in dopaminergic medication dose. |
| Okun *et al.*, 2009[21] | RCT | Double-blinded | Unilateral STN DBS and GPi DBS | Patients with idiopathic PD | 52 | 7 | No significant difference between the mood, cognitive and motor effects of U–STN versus U–GPi DBS; however, STN had a worsened verbal fluency on the letter task, and overall also had an increased amount of mood/cognitive/ surgical adverse events |
| Pillon *et al.*, 2000[6] | Nonrandomized | Open-label | Bilateral STN DBS and GPi DBS | Patients with idiopathic PD without significant cognitive or mood impairment before surgery | 76 | 12 | DBS does not appear to affect the cognitive performance of patients with PD 12 months later, except for a mild deficit in lexical fluency, There was no differential effect of STN or GPi stimulation. |
| Trépanier *et al.*, 1999[18] | Nonrandomized | Open-label | Bilateral STN DBS and GPi DBS | Patients with idiopathic PD without dementia, other neurological or unstable medical disorders | 13 | 12 | STN DBS increases the risk of significant cognitive and behavioral decline in older patients. GPi DBS may be safer, but participants were too few to draw a conclusion. |
| Ardouin *et al.*, 1999[13] | Nonrandomized | Open-label | Bilateral STN DBS and GPi DBS | Patients with idiopathic PD without significant cognitive or mood impairment before surgery | 62 | 6 | No significant cognitive impairment after DBS with no great effect on functioning of subcortico-frontal loops involved in cognition in humans, mild literal fluency deficit observed under STN, but not under GPi. |

DRS = Disease Rating Scale; GPi DBS = unilateral globus pallidus deep brain stimulation; MMSE = Mini–Mental State Examination; PD = Parkinson's disease; RCT = randomized controlled trial; STN DBS = subthalamic deep brain stimulation.

**TABLE 3. Baseline characteristics of the population**

| Study ID | Group | Age (years) Mean (*SD*) | Gender male *n* (%) | Education, years Mean (*SD*) | Years on PD medication Mean (*SD*) | Disease duration (years) Mean (*SD*) | DRS Mean (*SD*) | Levodopa equivalence dosage (mg) Mean (*SD*) |
|---|---|---|---|---|---|---|---|---|
| Rothlind *et al.*, 2007[8] | STN DBS | 61.4 (10.11) | 15 (79) | 15.2 (3.21) | NA | 12.9 (4.3) | 140.4 (2.87) | 1925.9 (968.5) |
| | GPi DBS | 60.2 (8.83) | 18 (78) | 15.6 (2.22) | NA | 13.3 (6.4) | 139.4 (3.98) | 1655.7 (874.4) |
| Rothlind *et al.*, 2015[19] | STN DBS | 61.3 (8.5) | 153 (84) | 15.2 (3.3) | 10.1 (4.4) | 11.0 (5.0) | | 1291.5 (549.8) |
| | GPi DBS | 61.3 (8.9) | | 14.3 (3.1) | 10.4 (4.6) | 11.0 (4.7) | | 1284.0 (490.7) |
| Odekerken *et al.*, 2015[20] | STN DBS | 60.3 (7.4) | 42 (75) | 12.4 (3.4) | 9 (6–12.75)* | 12.3 (5.5) | 138.3 (5.3) | 1,200 (900–1428.8)* |
| | GPi DBS | 59.2 (7.7) | 40 (69) | 11.5 (2.8) | 8 (6.5–12)* | 10.9 (4.0) | 138.5 (3.8) | 1,226 (892.5–1655)* |
| Trépanier *et al.*, 1999[18] | STN DBS | 67.4 (7.5) | NA | 14 (4.9) | NA | 14.3 (3.5) | | 1497 (659) |
| | GPi DBS | 56 (10.9) | NA | 11 (1.2) | NA | 15 (5.3) | | 1457 (261) |
| Okun *et al.*, 2009[21] | STN DBS | 59.8 (10) | 15 (69) | NA | NA | 13.3 (4.0) | 136.5 (7) | 935.9 (373.9) |
| | GPi DBS | 60.2 (6.2) | 15 (65) | NA | NA | 12.5 (3.6) | 138.8 (4.4) | 1168.3 (611.8) |
| Pillon *et al.*, 2000[6] | STN DBS | 55.7 (7.5) | 37 (59) | 12.4 (3.8) | NA | 15.0 (4.9) | 137 (4.7) | 1110 (570) |
| | GPi DBS | 52.5 (6.5) | 9 (69) | 13.0 (3.9) | NA | 16.3 (3.4) | 137.3 (5.3) | 744 (264) |
| Ardouin *et al.*, 1999[13] | STN DBS | 54.9 (7.6) | 24 (49) | 12.3 (3.8) | NA | 15.0 (5.2) | 137.2 (4.7) | 1,112 (580) |
| | GPi DBS | 51.5 (6.5) | 9 (69) | 13.0 (3.9) | NA | 16.2 (3.4) | 137.2 (5.3) | 1,125 (454) |

* Data presented in median and interquartile range.

DBS: $SMD = -0.04$, $CI_{95\%} = [-0.26, 0.19]$, $p = 0.73$; and unilateral DBS: $SMD = -0.05$, $CI_{95\%} = [-0.47, 0.38]$, $p = 0.83$; Figure 6). The pooled studies were homogeneous ($p > 0.1$).

In terms of semantic verbal fluency, the SMD of change between the two groups did not favor either of the two groups (bilateral DBS: $SMD = -0.09$, $CI_{95\%} = [-0.27, 0.10]$, $p = 0.37$; and unilateral DBS: $SMD = -0.23$, $CI_{95\%} = [-1.29, 0.63]$, $p = 0.60$; Figure 7). The pooled studies of bilateral DBS were homogeneous ($p > 0.1$), but for unilateral DBS, the two pooled studies (Okun *et al.*[21] and Rothlind *et al.*[8]) were not homogeneous ($p > 0.07$).

### *Language*

The pooled SMD of change on the Boston Naming Test (BNT) did not favor either of the two groups ($SMD = -0.11$, $CI_{95\%} = [-0.34, 0.11]$, $p = 0.33$; Figure 8). The pooled studies were homogeneous ($p > 0.1$).

### *Severity of depression*

The pooled SMD of change in the severity of depression score did not significantly favor either of the two groups but tended to favor STN DBS (bilateral DBS: $SMD = 0.32$, $CI_{95\%} = [-0.37, 1.02]$, $p = 0.36$; and unilateral DBS: $SMD = 0.36$, $CI_{95\%} = [-0.08, 0.79]$, $p = 0.11$; Figure 9).

When we assumed a fixed-effect model for all outcomes, the Stroop word-reading and Stroop color-naming tests showed a trend toward more decline with STN DBS than with GPi DBS ($p = 0.08$ and 0.09, respectively; data not shown). When we changed the effect size to mean difference (MD) instead of SMD, the TMTB and Stroop color-naming tests significantly favored GPi DBS over STN DBS, which indicates more decline in the STN DBS group ($p = 0.03$ and 0.04, respectively; data not shown).

## Discussion

This metaanalysis provides a direct comparison between STN DBS and GPi DBS in terms of neuropsychological performance. Because the recent evidence showed no difference between the two targets in terms of motor functions, the assessment of nonmotor outcomes is gaining more attention as a basis for selecting patients for appropriate DBS targets. The effects of DBS surgery on neuropsychological performance is not consistent throughout the literature, and nearly all significant findings have a small effect size. Our metaanalysis showed no statistically significant difference between STN DBS and GPi DBS in most neuropsychological domains. Only psychomotor processing speed showed a trend to favor the GPi DBS group as measured by the Stroop color-naming test. Most studies reported more decline in semantic verbal fluency in the STN DBS group (compared to GPi DBS), but the effect size was not significant. Our additional analyses showed a trend toward more decline in the STN DBS group in terms of the Stroop word-reading test and the TMTB. The low sample size of the pooled analysis may justify this nonsignificance. In addition, this implies that the differences between STN DBS and GPi DBS are of small effect size and thus not likely to be of clinical significance.

### *Attention and working memory*

Four studies reported better attention and working memory with GPi DBS than with STN DBS. In addition,

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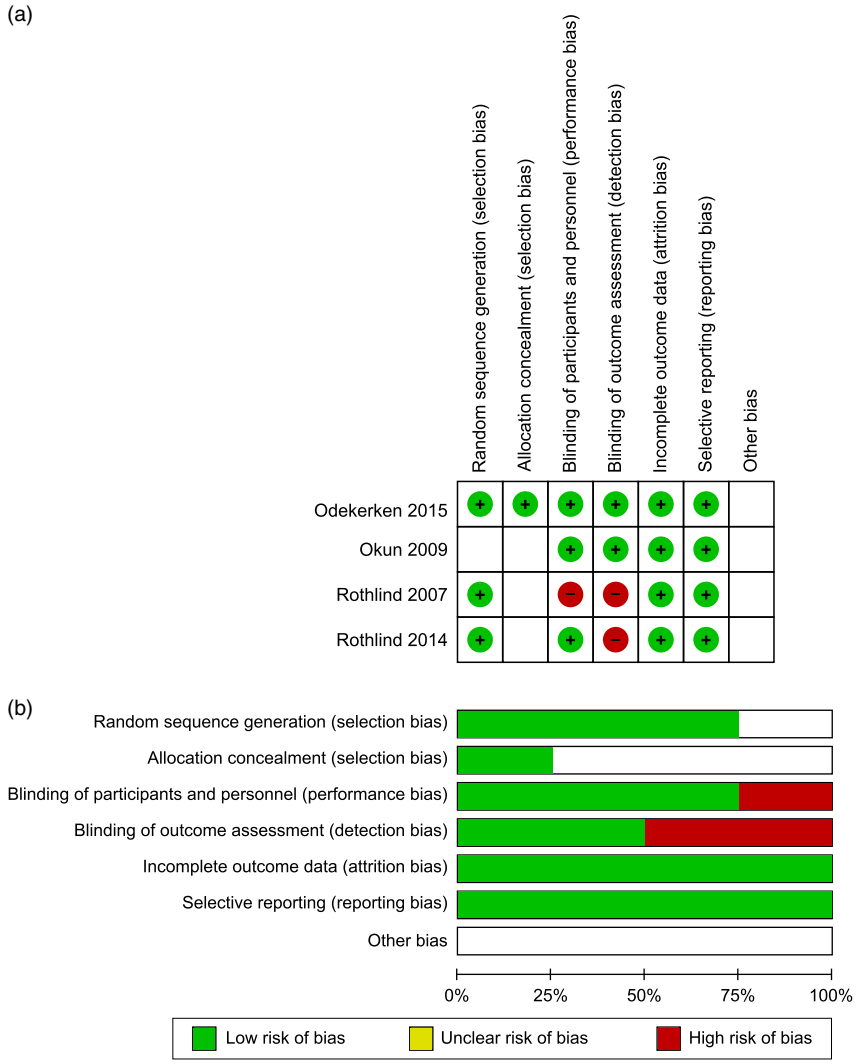


**FIGURE 2.** The risk of bias summary and risk of bias graph according to Cochrane Risk of Bias assessment tool.

Odekerken *et al.*[18] reported significant differences on Stroop word-reading, Stroop color-naming, TMTB, and WAIS similarities, with STN DBS showing a greater negative change than GPi DBS. In contrast, Pillon *et al.*[6] reported a trend toward improved working memory in the STN DBS group. Our pooled analysis showed no statistically significant difference between the two groups in WAIS digits forward, WAIS digits backward, and WAIS arithmetic.

A previous study by Kim *et al.*[24] showed that bilateral STN DBS did not affect working memory. However, another study[25] showed that unilateral STN DBS is associated with impairment in the most affected side of the brain.

### *Executive functions*

Odekerken *et al.*[20] reported a significant difference between the STN DBS and GPi DBS groups. The decline on the TMTB was greater with STN DBS than with GPi DBS (*MD* = −6.1 vs. −0.7). In addition, the STN DBS groups in Rothlind *et al.*[8,19] and Odekerken *et al.*[20] demonstrated a greater decline in the Stroop color–word interference test than the GPi DBS groups. However, our pooled analysis of the TMTB and Stroop color–word interference tests showed no significant between-group differences.

The literature suggests that STN DBS has a negative impact on the executive functions of PD patients.[22–27] Saint-Cyr *et al.*[28] reported a decline in the executive functions of PD patients after DBS. This worsening began 3 to 6 months after DBS surgery and continued beyond the duration of follow-up. They reported that patients who did not have STN DBS were not suffering from this problem.[28] Auclair-Ouellet *et al.*[29] and Funkiewiez *et al.*[7] reported a significant worsening of executive functions in PD patients who underwent STN DBS.

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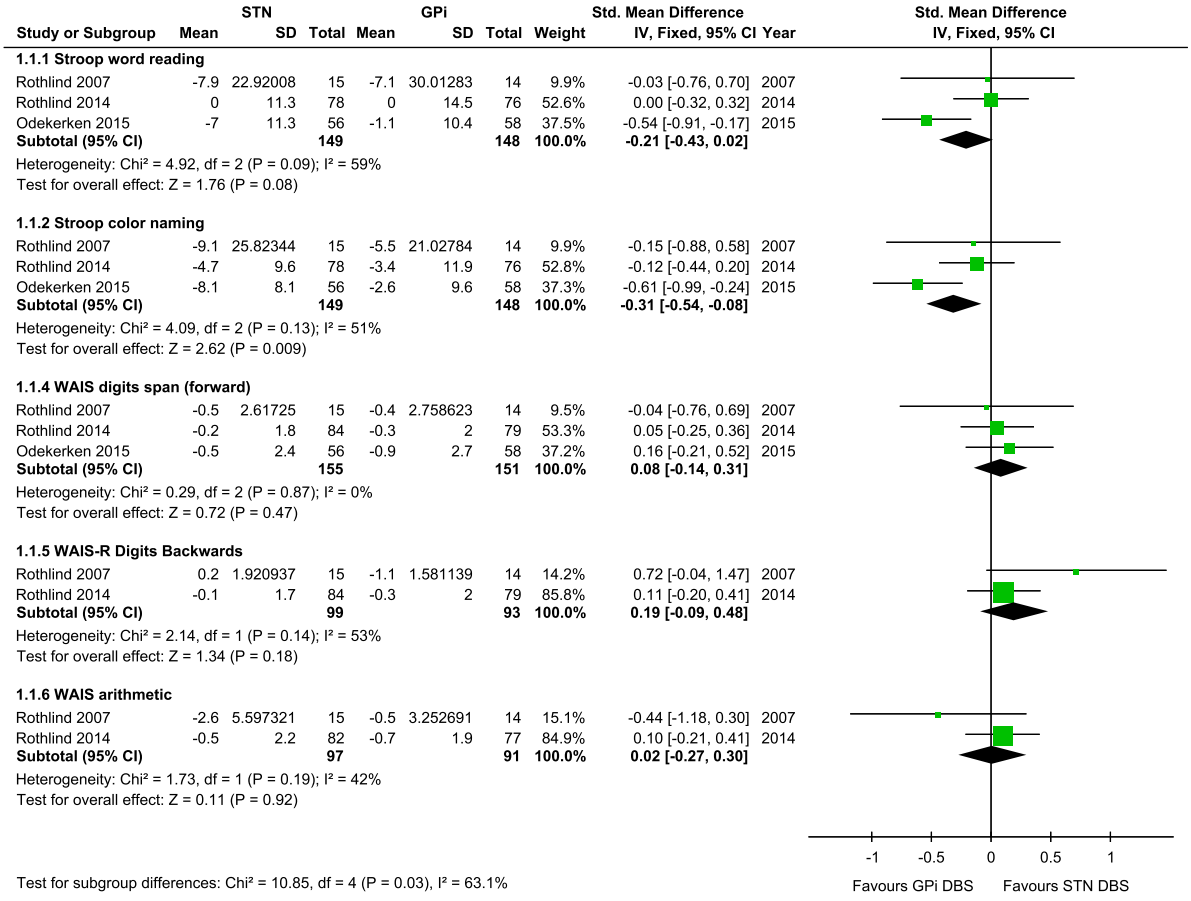


**FIGURE 3.** Forest plots of standardized mean difference in WAIS digits forward, WAIS digits backward, and WAIS arithmetic. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

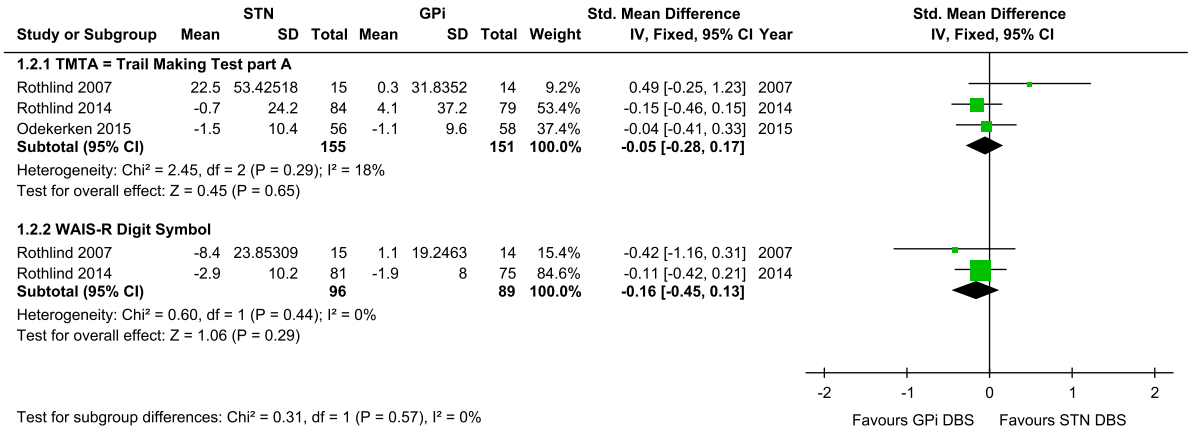


**FIGURE 4.** Forest plots of standardized mean difference in Stroop word reading, Stroop color naming, Trail Making Test Part A, and WAIS–R digit symbol. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

When it comes to GPi DBS, the cognitive outcome is more likely to be different from that of STN stimulation. Fields *et al.*[30] found no significant worsening in the executive functions of PD patients with bilateral GPi DBS. Some studies proposed that unilateral pallidal stimulation in PD patients has no significant negative influence on executive functioning except in patients of older age who took higher doses of levodopa preoperatively.[31] Other studies also reported that the negative effect of DBS on executive functioning is more significant in bilateral STN stimulation than in unilateral pallidotomy.[32]

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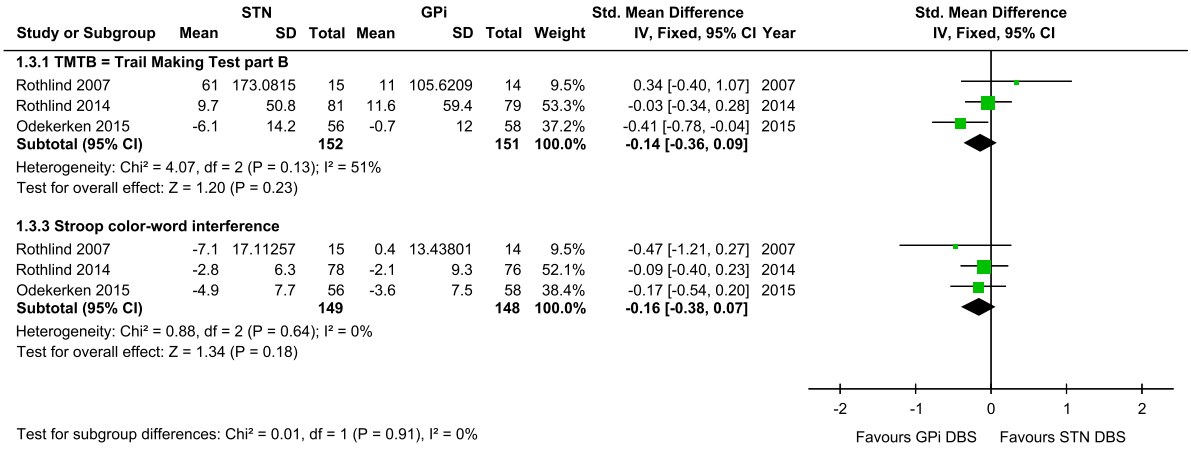


**FIGURE 5.** Forest plots of standardized mean difference in Trail Making Test Part B and Stroop color–word interference. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.


**FIGURE 6.** Forest plots of standardized mean difference in phonemic verbal fluency (bilateral DBS and unilateral DBS). CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

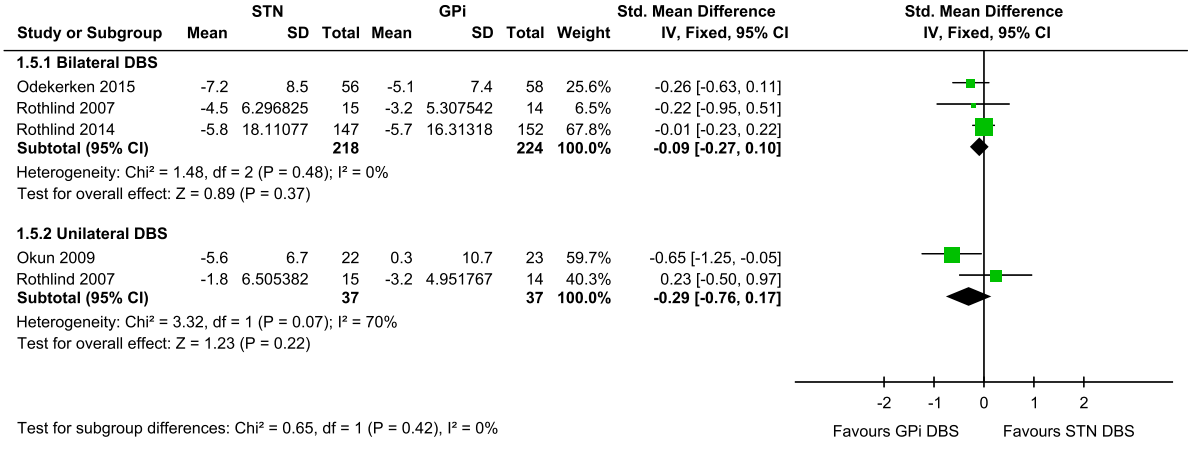


**FIGURE 7.** Forest plots of standardized mean difference in phonemic verbal fluency (bilateral DBS and unilateral DBS). CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

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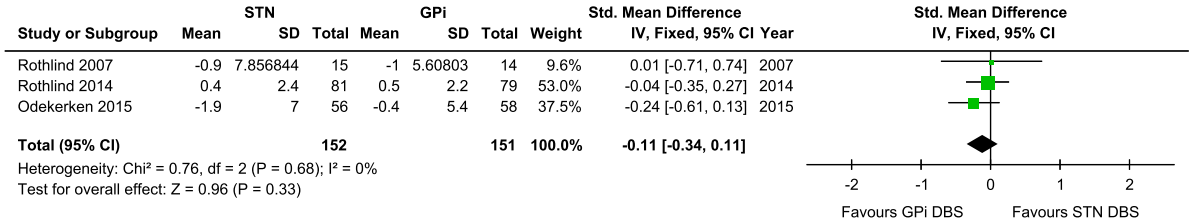


**FIGURE 8.** Forest plots of standardized mean difference in Boston Naming Test. CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

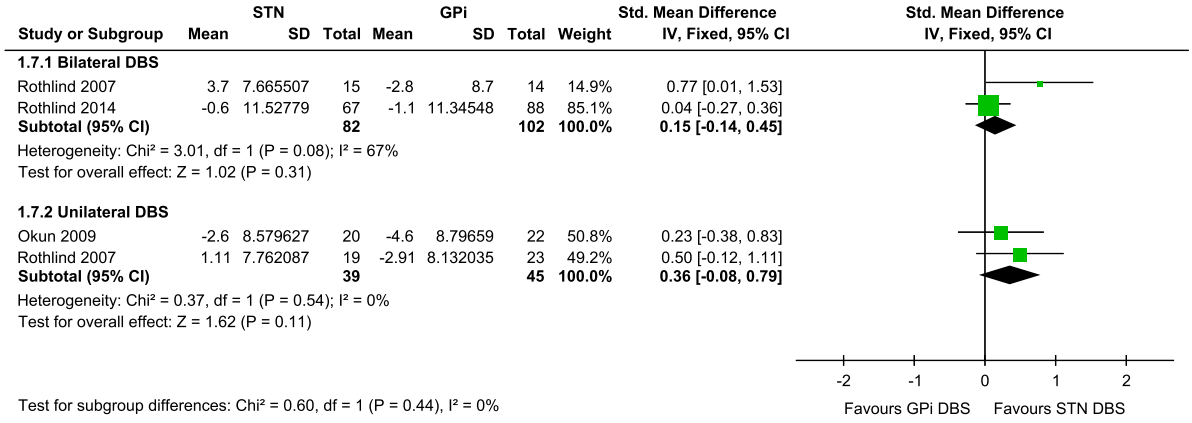


**FIGURE 9.** Forest plots of standardized mean difference in Beck Depression Inventory (bilateral DBS and unilateral DBS). CI = confidence interval; IV = inverse variance; SMD = standardized mean difference.

Certain risk factors have been correlated with this worsening of executive function. Age is a considerable predictor of decline in executive function. Older patients are more susceptible to postoperative neuropsychological complications. Other risk factors include levodopa equivalence dosage (LED) and axial subscore on the Unified Parkinson's Disease Rating Scale (UPDRS) in the off-medication state at baseline.[7,28,33] Yamanaka *et al.*[34] found an association between deterioration of executive functions following STN DBS and reduced dosages of dopaminergic medications after the operation.[34]

### *Psychomotor speed*

The TMTA and WAIS-R digit symbol tests tended to favor GPi DBS over STN DBS in Odekerken *et al.*[20] and Rothlind *et al.*[19] Our pooled analysis did not show a statistically significant difference between the STN DBS and GPi DBS groups.

Previous studies have showed that DBS has a negative impact on processing speed compared to the best practices medical therapy.[19] Bilateral STN DBS tends to cause a more significant decline in processing speed and in other cognitive domains than unilateral STN DBS.[27] This may be due to the greater reduction in dopaminergic medications after STN stimulation compared to post-GPi stimulation.[19]

### *Verbal fluency*

The STN DBS group showed a decline in verbal fluency in the studies conducted by Okun *et al.*,[21] Ardouin *et al.*,[13] and Pillon *et al.*,[6] while such a decline was not found in the GPi DBS group of the same studies. However, our pooled analysis failed to show a statistically significant difference between the two groups.

Multiple reports described a significant decline in both phonemic and semantic verbal fluency in patients with chronic bilateral STN stimulation.[24,28,35,36]

In addition, previous studies found that preoperative apathy and depressive mode were associated with an increased probability of verbal fluency decline after STN DBS surgery.[37,38] Other studies found a correlation between increasing age of PD patients and declines in verbal fluency following STN DBS.[39] Disturbed verbal fluency was also associated with left-sided DBS.[40–42]

In terms of GPi DBS, the literature suggests that verbal fluency might not be affected as it is with STN DBS. Miyawaki *et al.*[43] reported the case of a PD patient who had surgery with pallidal stimulation as a part of treatment and who showed both improved phonemic and semantic verbal fluency.

### *Verbal and visual memory*

Verbal and visual memory were measured by the Rey Auditory Verbal Learning Test (RAVLT), the Rivermead

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Behavioural Memory Test (RMBT), the Hopkins Verbal Learning Test (HVLT), the Brief Visuospatial Memory Test (BVMT), and the WAIS. The data gathered with these measures were available from two RCTs (Rothlind *et al.*,[8] Odekerken *et al.*[20]), and none of them reported a statistically significant difference between the two groups.

### Language

Language was assessed by the BNT in three RCTs (Rothlind *et al.*,[8,22] and Odekerken *et al.*[20]). The pooled effect size showed no significant difference between the two groups, which was concordant with the results from the three RCTs.

### Severity of depression

Rothlind *et al.*[22] reported no difference between the two groups in terms of severity of depression. Ardouin and colleagues[13] described a series of cases in which 62 patients were assigned to either STN DBS or GPi DBS. Postoperative evaluation of mood by the Beck Depression Inventory (BDI) showed a slight improvement in both the STN DBS and GPi DBS groups. Rothlind *et al.*[8] reported improving depression in the STN DBS group and worsening depression in the GPi DBS group. Okun *et al.*[21] (reported later by Zahodne *et al.*[44]) found a decline in BDI scores in both groups (STN –2.6 vs. GPi –4.6). However, none of these differences were statistically significant. In addition, our pooled analysis did not show any significant differences between the two groups.

Previous studies have reported heterogeneous effects of DBS in terms of mood. Some research suggested an ameliorating effect on mood with both STN DBS and GPi DBS.[45,46] In addition, Lhommée and colleagues[47] found improved mood, anxiety, and fatigue in the STN DBS group compared to the medical therapy group. The amelioration found in some studies might be explained by the improvement in motor symptoms, which improves patients' functioning in daily activities, which ameliorates their mood.[48]

Other reports have reported that STN DBS does not affect depression in PD patients.[28,49–52] However, transient mood improvement has been reported for an elderly group of patients, but it did not last for long during the first year of follow-up.[28]

In contrast, the work of York *et al.*[53] found mood worsening after STN DBS in some patients. They explained this with the suboptimal location of DBS electrodes within the STN, especially those in the lateral and inferior aspects of the left hemisphere.

### Agreements and disagreements with previous reviews

To the best of the present authors' knowledge, this is the first metaanalysis to compare neuropsychological performance between STN DBS and GPi DBS. In a recent metaanalysis, Combs and colleagues[54] assessed neuropsychological performance after GPi DBS and STN DBS separately, with no direct comparison between the two groups. In contrary to Combs *et al.*, we directly compared the two targets to provide more precise estimates. We included studies that were RCTs or quasiexperimental that directly compared STN DBS to GPi DBS; however, only RCTs were included in the metaanalysis models. According to the *Cochrane Handbook*, randomization is the only way to prevent systematic differences between the baseline characteristics of participants, and empirical evidence suggests that potential biases are likely to be greater with nonrandomized compared to randomized trials.[55] In addition, including single-arm studies would lead to unadjusted indirect synthesis of evidence. Unadjusted indirect comparisons ignore the within-trial comparison and may increase the liability of bias and overprecise estimates.[56] The STN DBS group demonstrated moderate to mild decrements in multiple neuropsychological domains, including verbal fluency ($d = -0.398$), attention ($d = -0.123$), processing speed ($d = -0.162$), learning and memory ($d = -0.115$), and executive function ($d = -0.134$). On the other hand, in the GPi DBS group, only verbal fluency ($d = -0.220$) and attention ($d = -0.185$) showed mild significant declines. These findings are consistent with our systematic review and metaanalysis. The current evidence suggests a trend toward a greater decline in verbal fluency and processing speed (Stroop color-naming test) in the STN DBS group than in the GPi DBS group.

### Completeness of evidence

Of the total of 404 patients allocated to STN DBS or GPi DBS in the four RCTs, there were 50 (~12.3%) discontinuations. We think that this percentage of discontinuations is quite high, and we consider it a limitation of our metaanalysis. Discontinuations are high since the two largest datasets—of Odekerken *et al.*[20] ($n = 128$) and Rothlind *et al.*[22] ($n = 182$)[22]—were secondary evaluations from two large primary RCTs,[14,57] while the two other studies—Okun *et al.*,[21] Rothlind *et al.*[8]—were performed primarily to assess the neuropsychological performance of DBS.

Although analysis of all the studies was conducted with an intention-to-treat approach, Odekerken *et al.*[20] did not perform an intention-to-treat analysis. Reasons for discontinuations were specified and described in detail in all studies except Odekerken *et al.*,[20] where some discontinuations were not clearly explained. However, these losses were balanced between the two groups.

In addition, the patients studied by Rothlind *et al.*[8] underwent a staged bilateral DBS. Of the 42 patients

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who underwent unilateral implantation, 13 did not undergo a contralateral implantation and were not included in the final analysis. For our study, we considered the final endpoint (after bilateral DBS; $n = 29$) in all outcomes except in depression and verbal fluency. We presented the data on both conditions in two subgroups (unilateral and bilateral) to allow indirect comparison between unilateral and bilateral DBS. However, none of the comparisons yielded a significant difference ($\chi^2$, $p > 0.05$).

## Recommendations for Future Research

Based on the present findings and given the low statistical power of the pooled analysis, we recommend further RCTs comparing STN DBS and GPi DBS in terms of neuropsychological performance with standardized outcome measures to allow comparison with other reports. In addition, some investigators have noted that the neuropsychological decline can be attributed to specific population characteristics (such as age, baseline levodopa dose, and preoperative verbal fluency). A better description of factors associated with neuropsychological decline would help to enhance selection of DBS targets for patients and would allow us to synthesize a prediction model (nomogram) for the expected risks of DBS surgery.

## Limitations and Strengths of the Study

The limitations of our study include the small number of studies in our sample and the unavailability of full neuropsychological assessment in all studies. For example, some outcomes were assessed by two studies only, which limited the statistical power of the metaanalysis models. We did not pool nonrandomized studies because they were published before 2000, and their neuropsychological measures have been revised or substituted in recent studies, and pooling tests or versions of different accuracy and reliability would have affected the quality of our metaanalysis models.

The strengths of our study are as follows: (1) this is the first metaanalytic study that presents a direct neuropsychological comparison between STN DBS and GPi DBS; (2) the search strategy included multiple medical electronic databases; (3) our eligibility criteria were well-defined; (4) our analysis was conducted in multiple scenarios assuming both random- and fixed-effect models, and we also reported any trend toward either of the two groups; (5) all steps were performed by at least two authors independently to avoid possible errors; (6) we followed the PRISMA statement guidelines during preparation of the study; and 7) we performed all steps in strict accordance with the *Cochrane Handbook*.

## Conclusions

We found no difference in most of the neuropsychological outcomes. The current evidence shows slight improvement among the GPi DBS group in terms of psychomotor speed and verbal fluency. However, these findings should be confirmed by further large RCTs with standard outcome measures and a description of outcome predictors.

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## Conflicts of Interest

All the authors certify that they have no affiliations or involvement with any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers bureaus, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

## Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and/or the national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards.

## Informed Consent

This article does not contain any studies with human participants or animals performed by any of the authors.

## Disclosures

Ahmed Elgebaly, Mohamed Elfil, Attia Attia, Mayar Magdy, and Ahmed Negida do not have anything to disclose.

## Supplementary Material

To view supplementary materials for this article, please visit https://doi.org/10.1017/S1092852917000062.

## REFERENCES:

1. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol.* 1999; **56**(1): 33–39.
2. Limousin P, Krack P, Pollak P, *et al.* Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* 1998; **339**(16): 1105–1111. http://www.nejm.org/doi/full/10.1056/NEJM199810153391603#t=articleResults. Accessed February 1, 2017.

3. Iacono RP, Lonser RR, Maeda G, *et al*. Chronic anterior pallidal stimulation for Parkinson's disease. *Acta Neurochir (Wien)*. 1995; **137**(1–2): 106–112.
4. Baunez C, Robbins TW. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. *Eur J Neurosci*. 1997; **9**(10): 2086–2099.
5. Temel Y, Blokland A, Steinbusch HWM, Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Prog Neurobiol*. 2005; **76**(6): 393–413. Epub ahead of print Oct 24.
6. Pillon B, Ardouin C, Damier P, *et al*. Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. *Neurology*. 2000; **55**(3): 411–418.
7. Funkiewiez A, Ardouin C, Caputo E, *et al*. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004; **75**(6): 834–839. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1739075/pdf/v075p00834.pdf. Accessed February 1, 2017.
8. Rothlind JC, Cockshott RW, Starr PA, Marks WJ. Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease. *J Int Neuropsychol Soc*. 2007; **13**(1): 68–79.
9. Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol*. 2004; **3**(5): 309–316.
10. Lang AE, Obeso JA. Time to move beyond nigrostriatal dopamine deficiency in Parkinson's disease. *Ann Neurol*. 2004; **55**(6): 761–765.
11. Troster AI, Fields JA, Wilkinson SB, *et al*. Unilateral pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. *Neurology*. 1997; **49**(4): 1078–1083.
12. Smeding HMM, Speelman JD, Huizenga HM, Schuurman PR, Schmand B. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2011; **82**(7): 754–760; Epub ahead of print May 21, 2009.
13. Ardouin C, Pillon B, Peiffer E, *et al*. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. *Ann Neurol*. 1999; **46**(2): 217–223.
14. Odekerken VJJ, van Laar T, Staal MJ, *et al*. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS Study): a randomised controlled trial. *Lancet Neurol*. 2013; **12**(1): 37–44. Epub ahead of print Nov 16, 2012.
15. Altman DG, Bland JM. Standard deviations and standard errors. *BMJ*. 2005; **331**(7521): 903. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1255808/. Accessed February 1, 2017.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; **315**(7109): 629–634. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2127453/. Accessed February 1, 2017.
17. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. *Stat Med*. 2003; **22**(13): 2113–2126; Erratum in *Stat Med*. 2005; **24**(5): 825–826.
18. Trépanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. *Brain Cogn*. 2000; **42**(3): 324–347.
19. Rothlind JC, York MK, Carlson K, *et al*. Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: comparisons of treatment at pallidal and subthalamic targets versus best medical therapy. *J Neurol Neurosurg Psychiatry*. 2015; **86**(6): 622–629; Epub ahead of print Sep 2, 2014.
20. Odekerken VJ, Boel JA, Geurtsen GJ, Schmand BA, de Haan RJ, Schuurman PR. Neuropsychological outcome after deep brain stimulation for Parkinson disease. *Neurology*. 2015; **84**: 1355–1361.
21. Okun MS, Fernandez HH, Wu SS, *et al*. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE Trial. *Ann Neurol*. 2009; **65**(5): 586–595. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2692580/. Accessed February 1, 2017.
22. Perozzo P, Rizzone M, Bergamasco B, *et al*. Deep brain stimulation of subthalamic nucleus: behavioural modifications and familiar relations. *Neurol Sci*. 2001; **22**(1): 81–82.
23. Lopiano L, Rizzone M, Bergamasco B, *et al*. Deep brain stimulation of the subthalamic nucleus: clinical effectiveness and safety. *Neurology*. 2001; **56**(4): 552–554.
24. Kim HJ, Jeon BS, Paek SH, *et al*. Long-term cognitive outcome of bilateral subthalamic deep brain stimulation in Parkinson's disease. 2014; **261**(6): 1090–1096; Epub ahead of print Apr 1.
25. Aono M, Iga J, Ueno S, Agawa M, Tsuda T, Ohmori T. Neuropsychological and psychiatric assessments following bilateral deep brain stimulation of the subthalamic nucleus in Japanese patients with Parkinson's disease. *J Clin Neurosci*. 2014; **21**(9): 1595–1598; Epub ahead of print May 1.
26. Kleiner-Fisman G, Lin Liang GS, Moberg PJ, *et al*. Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg*. 2007; **107**(1): 29–36.
27. Alberts JL, Voelcker-Rehage C, Hallahan K, Vitek M, Bamzai R, Vitek JL. Bilateral subthalamic stimulation impairs cognitive–motor performance in Parkinson's disease patients. *Brain*. 2008; **131**(Pt 12): 3348–3360. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2639204/. Accessed February 1, 2017.
28. Saint-Cyr JA, Trépanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain*. 2000; **123**(Pt 10): 2091–2108.
29. Auclair-Ouellet N, Chantal S, Cantin L, Prud'homme M, Langlois M, Macoir J. Transient executive dysfunction following STN DBS in Parkinson's disease. *Can J Neurol Sci*. 2011; **38**(2): 360–363.
30. Fields JA, Troster AI, Wilkinson SB, Pahwa R, Koller WC. Cognitive outcome following staged bilateral pallidal stimulation for the treatment of Parkinson's disease. *Clin Neurol Neurosurg*. 1999; **101**(3): 182–188.
31. Vingerhoets G, van der Linden C, Lannoo E, *et al*. Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1999; **66**(3): 297–304. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1736258/. Accessed February 1, 2017.
32. Smeding HM, Esselink RA. J, Schmand B, *et al*. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a comparison of neuropsychological effects. *J Neurol*. 2005; **252**(2): 176–182.
33. Daniels C, Krack P, Volkmann J, *et al*. Risk factors for executive dysfunction after subthalamic nucleus stimulation in Parkinson's disease. *Mov Disord*. 2010; **25**(11): 1583–1589.
34. Yamanaka T, Ishii F, Umemura A, *et al*. Temporary deterioration of executive function after subthalamic deep brain stimulation in Parkinson's disease. *Clin Neurol Neurosurg*. 2012; **114**(4): 347–351; Epub ahead of print Dec 15, 2011.
35. Moretti R, Torre P, Antonello RM, *et al*. Neuropsychological changes after subthalamic nucleus stimulation: a 12-month follow-up in nine patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2003; **10**(2): 73–79.
36. Gironell A, Kulisevsky J, Rami L, Fortuny N, Garcia-Sanchez C, Pascual-Sedano B. Effects of pallidotomy and bilateral subthalamic stimulation on cognitive function in Parkinson disease: a controlled comparative study. *J Neurol*. 2003; **250**(8): 917–923.

37. Marshall DF, Strutt AM, Williams AE, Simpson RK, Jankovic J, York MK. Alternating verbal fluency performance following bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease. *Eur J Neurol*. 2012; **19**(12): 1525–1531. Epub ahead of print May 26.
38. De Gaspari D, Siri C, Di Gioia M, *et al*. Clinical correlates and cognitive underpinnings of verbal fluency impairment after chronic subthalamic stimulation in Parkinson's disease. *Parkinsonism Relat Disord*. 2006; **12**(5): 289–295. Epub ahead of print Mar 22.
39. Smith KM, O'Connor M, Papavassiliou E, Tarsy D, Shih LC. Phonemic verbal fluency decline after subthalamic nucleus deep brain stimulation does not depend on number of microelectrode recordings or lead tip placement. *Parkinsonism Relat Disord*. 2014; **20**(4): 400–404. Epub ahead of print Jan 20.
40. Harati A, Müller T. Neuropsychological effects of deep brain stimulation for Parkinson's disease. *Surg Neurol Int*. 2013; **4**(Suppl 6): S443–S447. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858804/. Accessed February 1, 2017.
41. Zangaglia R, Pacchetti C, Pasotti C, *et al*. Deep brain stimulation and cognitive functions in Parkinson's disease: a three-year controlled study. *Mov Disord*. 2009; **24**(11): 1621–1628.
42. Zahodne LB, Okun MS, Foote KD, *et al*. Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *Clin Neuropsychol*. 2009; **23**(3): 385–405; Epub ahead of print Sep 23, 2008. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3045862/. Accessed February 1, 2017.
43. Miyawaki E, Perlmutter JS, Troster AI, Videen TO, Koller WC. The behavioral complications of pallidal stimulation: a case report. *Brain Cogn*. 2000; **42**(3): 417–434.
44. Zahodne LB, Okun MS, Foote KD, *et al*. Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. *J Neurol*. 2009; **256**(8): 1321–1329; Epub ahead of print Apr 12, 2009. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3045861/. Accessed February 1, 2017.
45. Woods SP, Fields JA, Troster AI. Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a critical review. *Neuropsychol Rev*. 2002; **12**(2): 111–126.
46. Witt K, Daniels C, Reiff J, *et al*. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. *Lancet Neurol.*. 2008; **7**(7): 605–614. Epub ahead of print Jun 4.
47. Lhommée E, Klinger H, Thobois S, *et al*. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. *Brain*. 2012; **135**(5): 1463–1477. Epub ahead of print Apr 15. https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/aws078. Accessed February 1, 2017.
48. Heo JH, Lee KM, Paek SH, *et al*. The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. *J Neurol Sci*. 2008; **273**(1–2): 19–24.
49. Rizzone MG, Fasano A, Daniele A, *et al*. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord*. 2014; **20**(4): 376–381; Epub ahead of print Jan 23.
50. Krack P, Batir A, Van Blercom N, *et al*. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med*. 2003; **349**(20): 1925–1934. http://www.nejm.org/doi/full/10.1056/NEJMoa035275#t=articleTop. Accessed February 1, 2017.
51. Fasano A, Romito LM, Daniele A, *et al*. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain*. 2010; **133**(9): 2664–2676. https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awq221. Accessed February 1, 2017.
52. Kaiser I, Kryspin-Exner I, Brucke T, Volc D, Alesch F. Long-term effects of STN DBS on mood: psychosocial profiles remain stable in a 3-year follow-up. *BMC Neurol*. 2008; **8**: 43. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2596774/. Accessed February 1, 2017.
53. York MK, Wilde EA., Simpson R, Jankovic J. Relationship between neuropsychological outcome and DBS surgical trajectory and electrode location. *J Neurol Sci*. 2009; **287**(1–2): 159–171. Epub ahead of print Sep 19. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2783787/. Accessed February 1, 2017.
54. Combs HL, Folley BS, Berry DTR, *et al*. Cognition and depression following deep brain stimulation of the subthalamic nucleus and globus pallidus pars internus in Parkinson's disease: a meta-analysis. *Neuropsychol Rev*. 2015; **25**(4): 439–454. Epub ahead of print Oct 12.
55. Higgins JP, Green S. eds. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*. New York: John Wiley & Sons; 2008. http://onlinelibrary.wiley.com/book/10.1002/9780470712184. Accessed February 1, 2017.
56. Glenny AM, Altman DG, Song F, *et al*. Indirect comparisons of competing interventions. *Health Technol Assess*. 2005; **9**(26): 1–134; iii–iv. https://www.journalslibrary.nihr.ac.uk/hta/hta9260#/abstract. Accessed February 1, 2017.
57. Follett KA, Weaver FM, Stern M, *et al*. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010; **362**(22): 2077–2091. http://www.nejm.org/doi/full/10.1056/NEJMoa0907083#t=articleTop. Accessed February 1, 2017.