

Title: Effect of Deep Brain Stimulation on Parkinson's Disease Dementia: A Systematic Review and Meta-Analysis

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Abstract

Patients in the early stages of Parkinson's disease(PD) may have subtle cognitive deficits, while overt cognitive deficits are usually manifestations of late-stage PD. There is still a debate on the outcome of deep brain stimulation (DBS) on cognitive function of PD patients. This study aimed to investigate the effect of subthalamic nucleus(STN)-DBS on dementia of PD patients after surgery as compared to medical therapy and other procedures.

We searched PubMed, Scopus, Cochrane library and Web of Science database in 22th October 2020. The words Deep Brain stimulation, Parkinson's disease, dementia, and memory have been searched. Reviews, abstracts, case presentations and letters were excluded.

Totally, 490 studies were screened after removing the duplicates. The screening results yielded 81 articles to be screened for eligibility. Finally, 6 studies were included in this meta-analysis for synthesis. Overall, 800 patients were included in this meta-analysis, using Mattis dementia rating scale (MDRS) along with descriptive data of the articles was extracted for assessment of global dementia.

Our results indicated that STN-DBS group showed a larger cognitive decline than the best medical treatment(BMT). DBS diminished the score of Mattis dementia rating scale in PD patients more than BMT. The effect of STN-DBS vs. other procedures on dementia was not significant; our results showed that STN stimulation made no significant change in global dementia of PD patients in midterm compared to GPi, Pallidal stimulation and pallidotomy.

Keywords: Subthalamic nucleus, Parkinson's disease, deep brain stimulation, Parkinson's disease dementia

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative conditions, which is characterized by bradykinesia, rigidity, and tremor(1). Patients in the early stages of PD may have subtle cognitive deficits, while overt cognitive deficits are usually manifestations of late-stage PD(2). Pathologically, the cardinal features of PD – are dopaminergic cells degeneration in the nigrostriatal system, aggregation of lewy bodies (LBs) in the cell cytoplasm, and Lewy neurites (LNs)(3).

According to a population-based cohort study, nearly 80% of patients with PD will develop cognitive dysfunction(4). Mild cognitive impairment as a transition state between normal aging and dementia can be converted to Parkinson's Disease Dementia (PDD) in about 50% of cases.(5). Furthermore, according to the Sydney Multicenter Study, 10 years after diagnosis of PD, dementia may be developed in 75% of patients and up to 83% after 20 years (6). Although the pathogenesis of PDD is still not completely known, some studies assumed that dysfunction in memory circuits may explain PDD (7). Other studies claimed that PDD could be related to the presence of LB, amyloid plaques, and neurofibrillary tangles in the neocortex and limbic system (3, 8). Atrophy in the front striatal area and cholinergic structures associated with frontal executive dysfunction is also considered a predictor of PDD(3, 9). Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus interna (GPi) has been practiced for treatment of PD patients (10). Some of the potential contraindications for DBS include some psychiatric disorders like psychosis or depression and uncompensated personality disorders, but the role of DBS in progression and advancement of PDD is still unknown (1, 11, 12).

Appleby et al. performed a review on PD patients and showed the controversial effect of DBS on PDD; while some patient's conditions was improved, others were worsened or remained unchanged (13). On the other hand, a long-term follow-up of PD patients illustrated no significant changes in dementia scores of the patients compared to the baseline(9).

There is still a debate on the outcome of DBS on cognitive function of PD patients. Based on the above-mentioned controversy, this study aimed to investigate the effect of DBS on cognition of PD patients after surgery as compared to medical therapy and compare the effect of stimulation of different targets on PDD.

Methods

We searched (“DBS” or “Deep brain stimulation”), (“PD” or “Parkinson’s disease”) and (“Memory” or “Dementia”) in PubMed, Scopus, Cochrane library and Web of Science database in 22th October 2020. Articles were added to an endnote database and two separate researchers deleted duplicate articles and screened the studies; then, the conflicts were discussed with a third person.

Exclusion criteria:

- Reviews, case series or case reports, letters, commentary
- Not written in English
- With less than 5 cases
- No randomization methods were used for advocating patients into the case and control groups
- With inadequate data collection method for assessment of global dementia

Again, two separate researchers extracted Mattis dementia rating scale score and descriptive characteristics of the studies including the author’s name, publication date, the stimulated targets, age, and sex of the patients. In case no difference was observed, the issue was consulted with a third person.

We used comprehensive meta-analysis version 2 for analyzing the data. Raw mean difference was used as the articles studied the same questionnaire. The data were continuous, and the mean difference was calculated using unmatched group option and mean and standard deviation of each condition, number of the patients and pre/post correlation. Random model was considered and the correlation coefficient (r) was not reported in the articles, so the data were analyzed three times using $r=0.1$, 0.5 and 0.9 . The final result remained significant, so it was not affected by “ r ”. We calculated the heterogeneity of the data and it was assessed using I^2 and T^2 statistics. I^2 scores less than 25% were considered low, 26-50% mild, 51-75% high, and 75-100% very high. Egger’s test was used for assessment of the publication bias. Also, sensitivity of the results to each article was assessed by excluding each study and analyzing the effect size.

Two different analyses were conducted. The first analysis compared the best medical treatment (BMT) to (STN) and the second analysis was performed to compare STN with other procedures and targets.

Results

Study selection

Totally, 491 studies were screened after removing the duplicates. The screening results yielded 81 articles to be screened for eligibility. Finally, 6 studies were included in this meta-analysis for synthesis. The PRISMA flowchart was used for other details. (Figure 1)

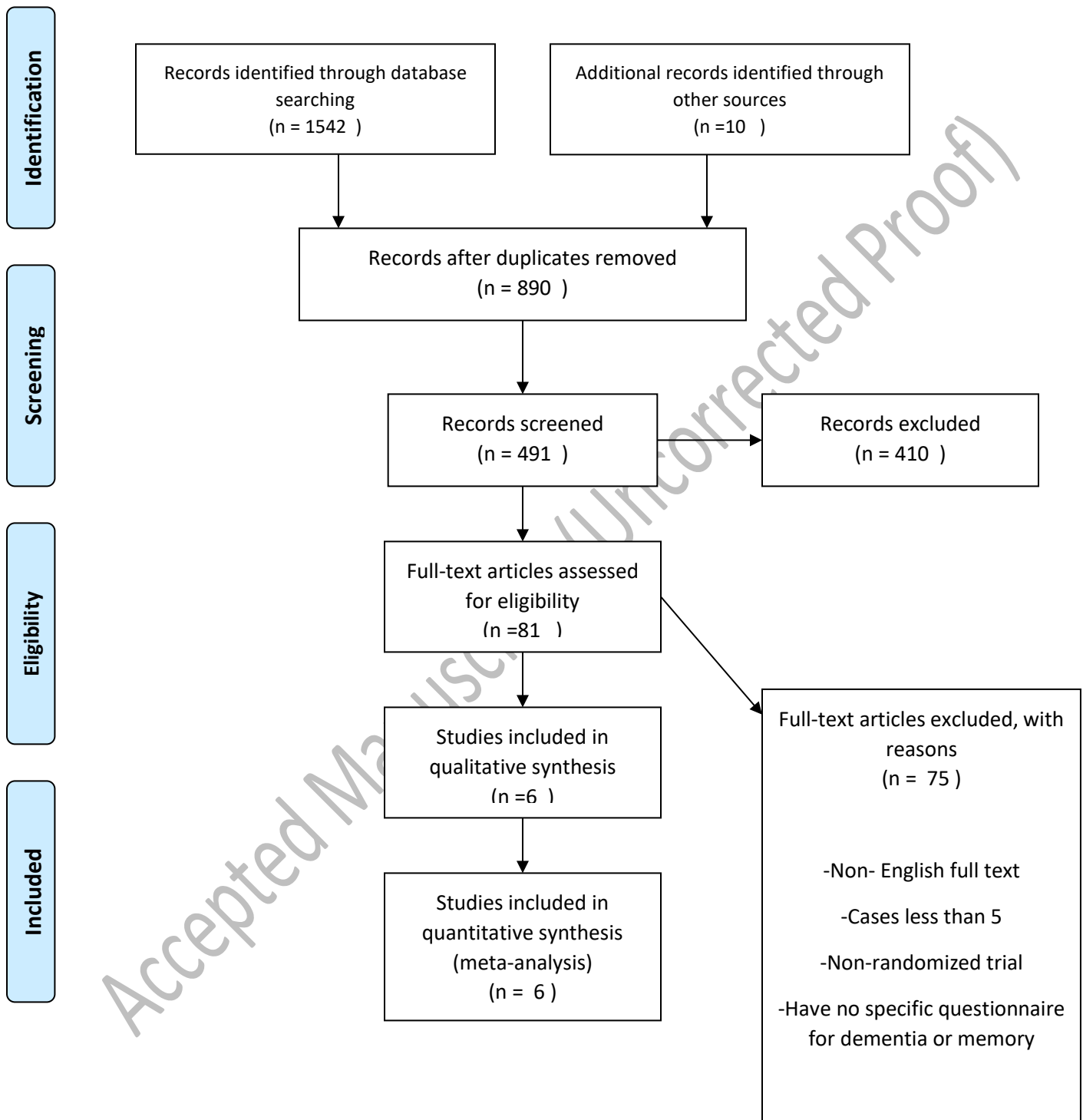


Figure1. PRISMA flowchart for search and screenings

Study characteristics

Overall, 800 patients were included in this meta-analysis (341 patients in the first analysis and 459 patients in the second one). For assessment of global dementia, Mattis dementia rating scale (MDRS) along with descriptive data of the articles were extracted. Patients with Parkinson's disease were our subject population. In comparing BMT and STN, all studies followed the patients for 6 months, but in the second analysis the follow up time varied from 6 months to 48 months. In the latter analysis, the control groups were pallidal stimulation and pallidotomy. Also, two articles were used twice as they had two different follow up times and provided adequate information for analysis. Other characteristics of these articles are show in Table 1.

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Table 1. Descriptive characteristics of the studies

Studies	Age (Intervention/ control) (year)	Sex (Intervention/ control) (Male/Female)	Setting	Country	Intervention group	Control group	Follow up duration (Months)	Number of patients (Intervention/control)
BMT vs STN stimulation								
Witt[2013]	59.8±7.5/ 58.9±9.6	1.2/1.2	Randomized clinical trial	Germany	STN stimulation	BMT	6	31/31
Witt[2008]	60.2±7.9/ 59.4±7.5	1.5/1.86	Randomized clinical trial	Germany	STN stimulation	BMT	6	60/63
Deuschl[2006]	60.5±7.4/ 60.8±7.8	1.77/1.77	Randomized clinical trial	Germany	STN stimulation	BMT	6	78/78
STN vs other procedure								
Follett [2010]	61.9±8.7/ 61.8±8.7	7/3.73	Randomized clinical trial	USA	STN stimulation	Pallidal Stimulation	24	147/152
Boel[2016]	60.9±7.6/ 59.1±7.8	2.33/2.12	Randomized clinical trial	The netherlands	STN stimulation	GPI stimulation	48	63/65
Boel[2016]	60.9±7.6/ 59.1±7.8	2.33/2.12	Randomized clinical trial	The netherlands	STN stimulation	GPI stimulation	12	63/65
Smeding[2004]	59.2±8.6/ 62.1±8.1	0.42/0/55	Randomized clinical trial	The netherlands	STN stimulation	Pallidotomy	12	19/13
Smeding[2004]	59.2±8.6/ 62.1±8.1	0.42/0/55	Randomized clinical trial	The netherlands	STN stimulation	Pallidotomy	6	19/13

Results of analysis

In comparison of BMT and STN stimulation, the results revealed a significant decrease in MDRS more in the STN group than BMT (P value 0.009 and confidence interval 95% from -2.24 to -0.32). The publication bias was not significant in Egger's test (P = 0.860) and these studies were not heterogenic (I^2 and T^2 both were 0.00). The forest plot is displayed in Figure 2.

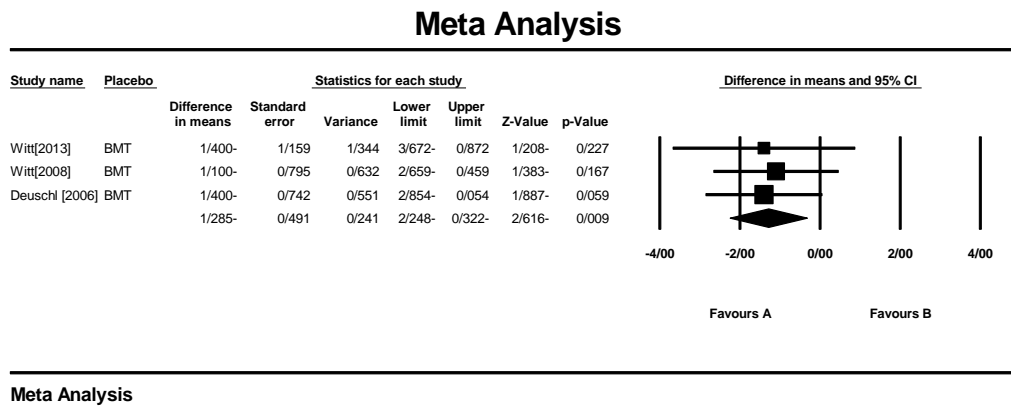


Figure 2. Forest plot comparing BMT and STN stimulation.

In the analysis comparing STN vs other procedures, the result was not significant and stimulation of STN was not superior for dementia in Parkinson's disease (P value 0.77 and confidence interval 95% from -2.25 to 0.11). Also, Egger's test was not significant (P value 0.71) and no heterogeneity was observed (I^2 and T^2 both were 0.00). Other details are reported in Figure 3.

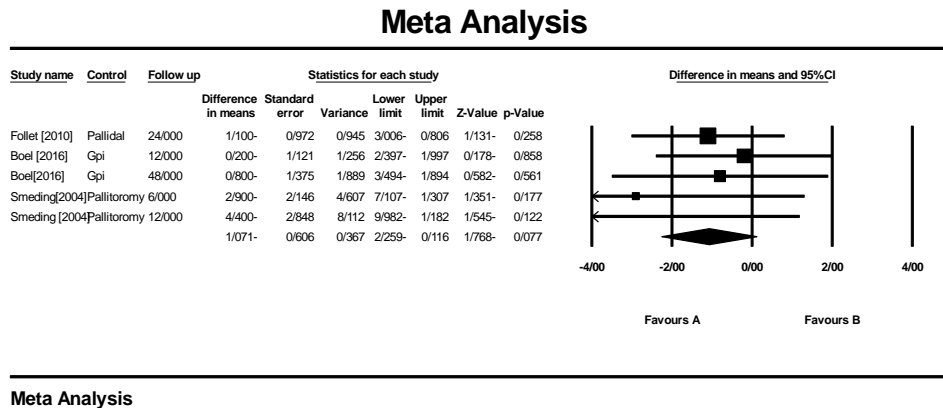


Figure 3. Forest plot comparing STN stimulation and other procedures

Discussion:

Overall, our results indicated the STN-DBS group showed a larger cognitive decline than the BMT. DBS diminished the score of MDRS in PD patients more than BMT. It should be noticed that these articles only followed the patients for a short period of time after surgery, and duration of follow up was not longer than 48 months. Long term studies have been conducted to investigate the progression of dementia in DBS-implanted group and general PD patients. All studies confirmed that the incidence of dementia was increasing as the disease advanced in both DBS group and general PD patients(14, 15). In two cohort studies, PD patients were followed after STN-DBS implantation surgery for 3 and 10 years, respectively. The incidence of new onset dementia in these two studies were both approximately equal to the patients who were medically treated (16, 17). It should be considered that the onset of PD and age of DBS implanted patients were different in not only these two studies, but also in other studies that leads to variation in the results. Also, none of these studies were conducted in a RCT setting(16).

The explanation for short- and long-term effect of STN-DBS on dementia in PD patients is challenging. Deficit in cholinergic output of the nucleus basalis of Meynret to the cortex assumed to be a major cause of dementia in PD(18). Gielow et al. conducted a study on cholinergic in- and

output of forebrain. The study showed that STN had cholinergic output to the motor cortex and ventral and lateral orbitofrontal cortices(19). On the other hand, DBS inhibits the neighbor neurons (20). Based on these articles, we can develop this hypothesis that with stimulation of the STN, cholinergic output to the cortex will be decreased even more. Although dopaminergic deficit was seen to be greater in PDD patients than the general PD population, and it is the basis of pathophysiology of PD, using dopaminergic medication does not improve cognitive impairment in these patients(21, 22). The above-mentioned hypothesis may explain the acute decrease of MDRS in acute phase, but as the PD progresses, it may be assumed that the degenerative processes of the disease will worsen the situation.

Other researchers have proposed other theories about cognitive decline after DBS implantation surgery. Witt et al. discussed the physical insult -especially to caudate nucleus-during surgery may negatively affect the global cognition. Also, STN stimulation changes the cerebral blood flow of the cortex and play a role in impairing response inhibition(23). Another study hypothesized that the role of DBS lead in interrupting connections in the white mater may result in cognitive decline(24). Erasmi et al. argued that the controversial effect of hyperintense lesioning around magnetic resonance imaging (MRI) of the brain after surgery- classified as gliosis- may have negative effects on the cognition. The study investigated 30 patients who conducted MRI for different reasons for hyperintense lesions around the DBS lead. 26 out of 30 had these lesions (25). In contrast, Liu et al. denied the correlation between white matter hyperintensities and cognitive decline(26).

In our study, the effect of STN-DBS vs. other procedures on dementia was not significant. No rational explanation was found to interpret the results. In contrast to a meta-analysis of controlled trial by Wang et al., our results showed that STN stimulation made no significant change in global dementia of PD patients in midterm compared to GPi, Pallidal stimulation and pallidotomy.

Limitation

The major limitation of our study was the small number randomized clinical trial articles to be compared with each other. Also, number of the patients in the included trials could be more.

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