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Review Paper

Effect of Deep Brain Stimulation on Parkinson Disease Dementia: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Patients in the early stages of Parkinson 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 the cognitive function of PD patients. This study aimed to investigate the effect of subthalamic nucleus (STN)-DBS on the dementia of PD patients after surgery compared to medical therapy and other procedures.

Methods: We searched PubMed, Scopus, Cochrane Library, and Web of Science database on October 2020, with keywords: "Deep brain stimulation," "Parkinson disease," "dementia," and "memory." Reviews, abstracts, case presentations, and letters were excluded.

Results: In total, 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. Overall, 800 patients were included in this meta-analysis, using the Mattis dementia rating scale (MDRS) and descriptive data from the articles extracted to assess global dementia.

Conclusion: Our results suggest that the STN-DBS group showed a larger cognitive decline than the patients receiving the best medical treatment (BMT). However, comparing STN-DBS with globus pallidus interna stimulation and pallidotomy could not demonstrate a significant statistical effect on the global dementia of patients. More long-term studies with larger sample sizes are needed to validate current findings.

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Highlights

• STN-DBS can cause higher cognitive decline in PD patients compared to the medical therapy.

• There is no significant difference in the effect of STN-DBS compared to globus pallidus interna stimulation and pallidotomy methods in PD patients.

Plain Language Summary

Patients with Parkinson's disease (PD) may experience some types of cognitive deficits in the course of their disease. This cognitive decline is called Parkinson's disease dementia or PDD. As the PD advances, patients may not respond to conventional treatment such as medical therapy. In such cases, deep brain stimulation (DBS) may be offered to these patients to improve their symptoms but the actual effect of DBS on these patients is controversial in the literature. Hence, we have conducted this systematic review and meta-analysis to investigate the effect of DBS targeting the subthalamic nucleus (STN), which is the main target for patients with PD, on the PDD, and compare STN-DBS with other targets. Our results suggest that patients with STN-DBS may experience a larger cognitive decline than patients receiving the best medical treatment (BMT). However, no significant difference was found between STN-DBS and other targets.

1. Introduction

Parkinson disease (PD) is one of the most common neurodegenerative conditions, which is characterized by bradykinesia, rigidity, and tremor (Groiss et al., 2009). Patients in the early stages of PD may have subtle cognitive deficits, while overt cognitive deficits are usually manifestations of late-stage PD (Hanagasi et al., 2017). Pathologically, the cardinal features of PD are dopaminergic cell degeneration in the nigrostriatal system, aggregation of Lewy bodies in the cell cytoplasm, and Lewy neurites (Weil et al., 2017).

According to a population-based cohort study, nearly 80% of patients with PD will develop cognitive dysfunction (Aarsland et al., 2003). Mild cognitive impairment as a transition state between normal aging and dementia can be converted to Parkinson disease dementia (PDD) in about 50% of cases (Broeders et al., 2013). Furthermore, according to the Sydney multicenter study, 10 years after diagnosis of PD, dementia may develop in 75% of patients and up to 83% after 20 years (Hely et al., 2008). Although the pathogenesis of PDD is still not completely known, some studies assumed that dysfunction in memory circuits may explain PDD (Lv et al., 2018). Other studies claim that PDD can be related to the presence of Lewy bodies, amyloid plaques, and neurofibrillary tangles in the neocortex and limbic system (Delgado-Alvarado et al., 2016; Weil et al., 2017). Atrophy in the front striatal area and cholinergic structures associated with frontal executive dysfunction are also considered predictors of PDD (Sunwoo et al., 2014; Weil et al., 2017). Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus interna (GPi) has been tried for treatment of PD patients (Radhakrishnan & Goyal, 2018). 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 the progression and advancement of PDD is still unknown (Bronstein et al., 2011; Groiss et al., 2009; Kogan et al., 2019).

Appleby et al. reviewed PD patients and showed the controversial effect of DBS on PDD; while some patient's conditions improved, others worsened or remained unchanged (Appleby et al., 2007). On the other hand, a long-term follow-up of PD patients illustrated no significant changes in dementia scores compared to the baseline (Sunwoo et al., 2014).

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

2. Materials and Methods

We searched the keywords ((“DBS” OR “deep brain stimulation,”), (“PD” OR “Parkinson's disease”) AND (“memory” or “dementia”)) in PubMed, Scopus, Cochrane Library, and Web of Science database on October

22, 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.

The exclusion criteria were as follows:

- Reviews, case series or case reports, letters, Commentaries,

- Articles that were not written in English or included less than five cases,

- No randomization methods were used in the study for advocating patients into the case and control groups, and

- Articles with inadequate data for the assessment of global dementia.

Again, two separate researchers extracted the Mattis dementia rating scale (MDRS) score and descriptive characteristics of the studies, including the author's name, publication date, the stimulated targets, and the age, and sex of the patients. If any conflict was noted, the issue was discussed with a third researcher.

We used comprehensive meta-analysis version 2 to analyze the data. The raw mean difference was used as the articles studied the same questionnaire and score. A random model was used, and as the correlation coefficient (r) was not reported in the articles, 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, which was assessed using I^2 scores. The scores less than 25% were considered low, 26%-50% mild, 51%-75% high, and 75%-100% very high. The Egger test was used to assess the publication bias. Also, the sensitivity of the results to each article was assessed by excluding each study and analyzing the effect size again.

Two different analyses were conducted. The first analysis compared the best medical treatment (BMT) to subthalamic nucleus- deep brain stimulation (STN-DBS), and the second analysis was performed to compare STN-DBS with other procedures and targets.

3. Results

Study selection

In total, 491 studies were screened after removing the duplicates. The screening results yielded 81 articles to be checked for eligibility. Finally, six studies were included in this meta-analysis for synthesis. The PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart was used for other details (Figure 1).

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 the assessment of global dementia, MDRS, along with descriptive data from the articles, were extracted. Patients with Parkinson disease comprised our study population. In comparing BMT and STN, all studies followed the patients for 6 months, and 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 (GPi stimulation) and pallidotomy. It is worth mentioning that 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 shown in Table 1.

Results of analysis

In a comparison of BMT and STN stimulation, the results revealed a significant decrease in MDRS in the STN group compared to BMT (difference in means=-1.285, 95% CI, -2.24%, -0.32%; P=0.009). The publication bias was not significant in Egger test (P=0.860), and no heterogeneity was found (I^2=0.00). The forest plot of this analysis is displayed in Figure 2.

In the analysis comparing STN vs other procedures, the result was not significant, and stimulation of STN had no superior effect on dementia of patients with PD (difference in means=-1.071; 95% CI, -2.25%, 0.11%; P=0.77). Also, the Egger test was not significant (P=0.71), and no heterogeneity was observed (I^2=0.00). Other details are reported in Figure 3.

4. Discussion

Overall, our results indicated the STN-DBS group showed a larger cognitive decline than the BMT. It should be noted that these articles only followed the patients for a short period after surgery, and the 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 patients and general PD patients and confirmed that the incidence of dementia was increasing as the disease advanced in both the DBS group and general PD patients (Gruber et al., 2019; Jellinger, 2018). In two cohort studies, PD

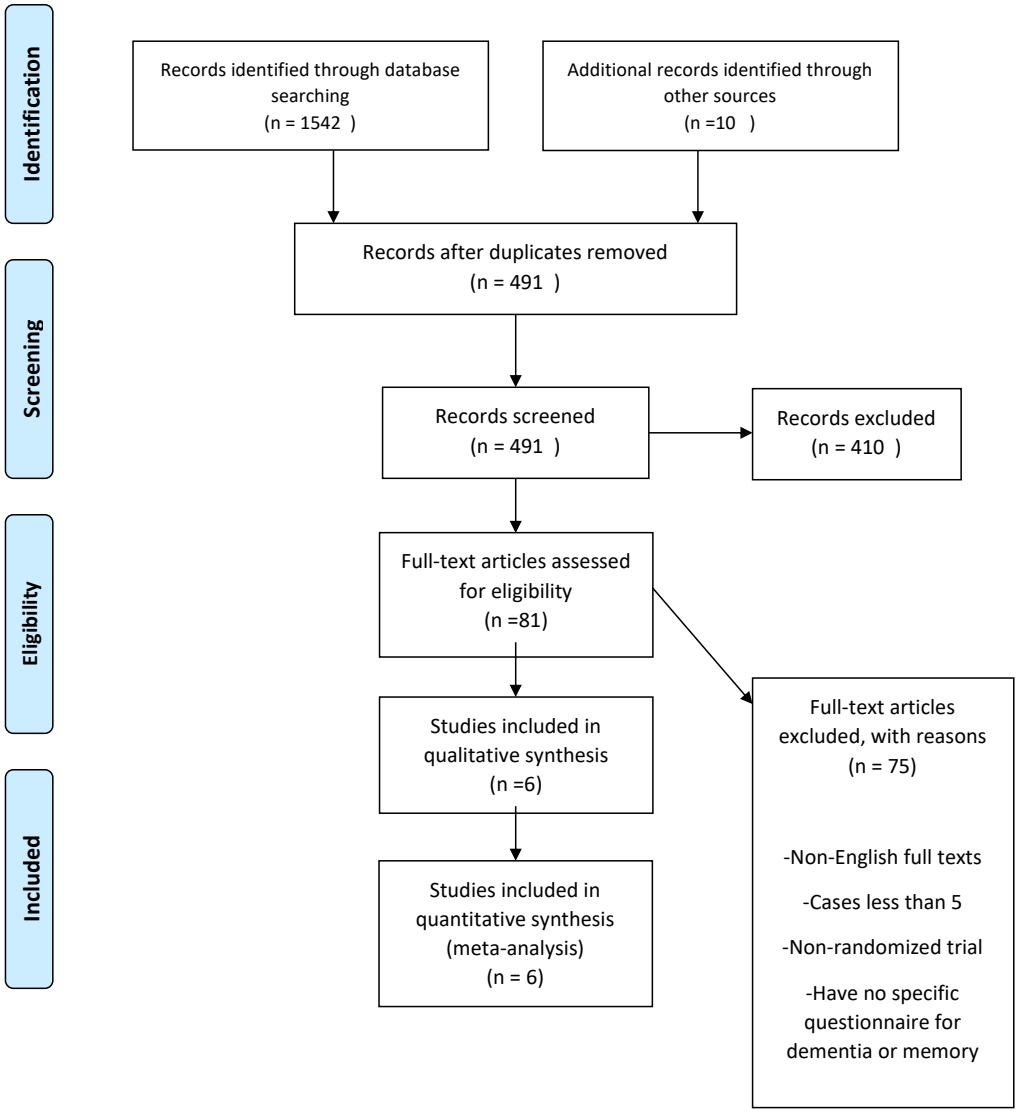

Figure 1. PRISMA flowchart for search and screenings

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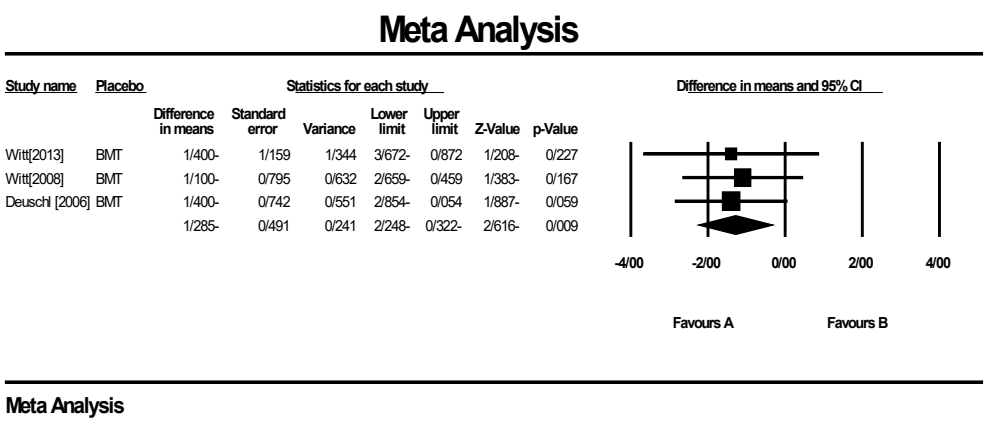

Figure 2. Forest plot comparing MDRS between BMT and STN stimulation

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Abbreviations: BMT: Best medical treatment; MDRS: Mattis dementia rating scale; STN: Subthalamic nucleus.

Table 1. Descriptive characteristics of the studies

Studies	Mean±SD Age (Intervention/ Control) (y)	Sex (Intervention/ Control) (Male/Female)	Setting	Country	Intervention Group	Control Group	Follow-up Duration (M)	Number of Patients (Intervention/Control)
BMT vs STN stimulation								
Witt et al., 2013	59.8±7.5/ 58.9±9.6	1.2/1.2	Randomized clinical trial	Germany	STN stimulation	BMT	6	31/31
Witt et al., 2008	60.2±7.9/ 59.4±7.5	1.5/1.86	Randomized clinical trial	Germany	STN stimulation	BMT	6	60/63
Deuschl et al., 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	The USA	STN stimulation	GPi stimulation	24	147/152
Boel et al., 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 et al., 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 et al., 2005	59.2±8.6/ 62.1±8.1	0.42/0/55	Randomized clinical trial	The Netherlands	STN stimulation	Pallidotomy	12	19/13
Smeding et al., 2005	59.2±8.6/ 62.1±8.1	0.42/0/55	Randomized clinical trial	The Netherlands	STN stimulation	Pallidotomy	6	19/13

Abbreviations: STN: Subthalamic nucleus; BMT: Best medical treatment; GPi: Globus pallidus interna.

patients were followed after STN-DBS implantation surgery for 3-10 years. The incidence of new-onset dementia in these two studies was approximately equal to the patients who were medically treated (Aybek et al., 2007; Bove et al., 2020). It should be considered that the onset of PD and age of DBS-implanted patients were different in these two studies and in other studies, which may lead to incongruency in the results (Bove et al., 2020).

The explanation for the short- and long-term effects of STN-DBS on dementia in PD patients is challenging. The deficit in the cholinergic output of the nucleus basalis of Meynert to the cortex is assumed to be a major

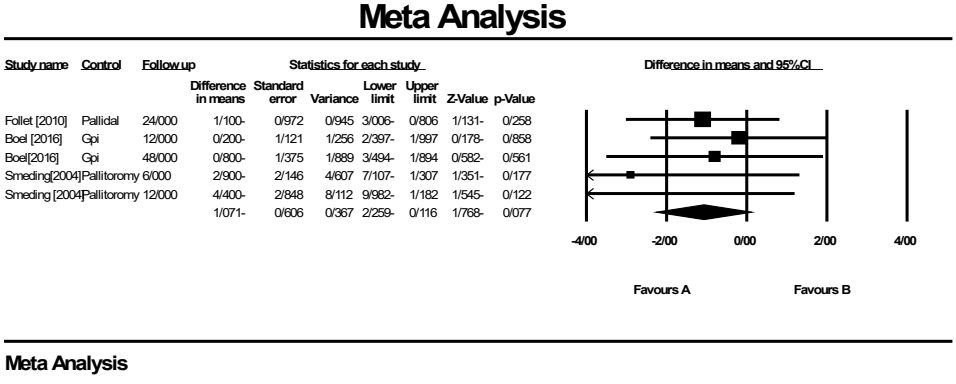

Figure 3. Forest plot comparing STN stimulation with other procedures

GPi: Globus Pallidus interna, STN: Subthalamic nucleus.

*GPi and pallidal stimulation are the same.

cause of dementia in PD (Bohnen et al., 2006). Gielow et al. (2017) conducted a study on cholinergic input and output of the forebrain. The study showed that STN had a cholinergic output to the motor cortex and ventral and lateral orbitofrontal cortices. On the other hand, DBS may inhibit the neighboring neurons (Chiken & Nambu, 2016). Based on these articles, this hypothesis might be developed that cholinergic output to the cortex will be decreased even more by the stimulation of the STN. The hypothesis mentioned above may explain the decrease in MDRS in the short term. Still, as the PD progresses, it may be assumed that the degenerative processes of the disease may worsen the situation.

Other researchers have proposed different theories about cognitive decline after DBS implantation surgery. Witt et al. (2013) discussed that physical insult, especially to the caudate nucleus during surgery, may negatively affect global cognition. Also, STN stimulation changes the cerebral blood flow of the cortex and plays a role in impairing response inhibition. Another study hypothesized that the role of DBS lead in interrupting connections in the white matter and resulting cognitive decline (Blume et al., 2017). Erasmi et al. (2018) argued that the controversial effect of hyperintense lesioning around magnetic resonance imaging (MRI) of the brain after surgery, classified as gliosis, may negatively affect cognition. The study investigated 30 patients who conducted MRIs for different reasons for hyperintense lesions around the DBS lead. Finally, 26 out of 30 patients had these lesions. In contrast, Liu et al. (2020) denied the correlation between white matter hyperintensities and cognitive decline.

5. Conclusion

To sum up, our study showed that STN-DBS may have a negative effect on the global dementia of patients with PD compared with patients receiving only BMT in a short follow-up period. However, our study could not demonstrate such an effect comparing STN-DBS with other procedures like pallidotomy or GPi stimulation.

Study limitations

The major limitation of our study was the small number of randomized clinical trial articles compared with each other. Also, the number of patients in the included trials could be more. In addition, more long-term studies with larger sample sizes are needed to validate current findings.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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