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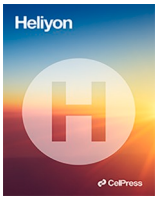

Research article

Neurocognitive changes at different follow-up times after bilateral subthalamic nucleus deep brain stimulation in patients with Parkinson's disease

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ABSTRACT

Background: Bilateral deep thalamic nucleus brain stimulation (STN-DBS) surgery is often used to treat the motor symptoms of patients with Parkinson's disease. The change of neurocognitive symptoms in patients is, however, still unclear.
Objective: We aimed at analyzing the deterioration of neurocognitive symptoms in patients with Parkinson's disease after deep brain stimulation surgery under different follow-up times.
Methods: A comprehensive literature review was conducted using Pubmed, Cochrane Library, and Web of Science to screen eligible study records, the meta-analysis was performed using an inverse variance method and a random-effects model. Additionally, the areas of analysis include five: cognition, executive function, memory capacity, and verbal fluency (phonetic fluency and semantic fluency). They were analyzed for changes at six and twelve months postoperatively compared to baseline. The Meta-analysis has been registered with PROSPERO under the registration number: CRD42022308786.
Results: In terms of overall cognitive performance, executive function, and memory capacity, the original studies show a trend of improvement in these areas at 12 months postoperatively compared with 6 months, at variance, patients did not improve or deteriorated in phonetic fluency($d = -0.42$ at both 6-month and 12-month follow-up) and semantic fluency from 6 to 12 months postoperatively.
Conclusion: In terms of most neurocognitive symptoms, including cognitive ability, executive function, and learning memory capacity, bilateral STN-DBS surgery appears to be safe at relatively long follow-up times. However, postoperative phonetic and semantic fluency changes should still not be underestimated, and clinicians should pay more attention to patients' changes in both.

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1. Introduction

Parkinson's disease （PD） is a progressive neurological disorder characterized by tremor, rigidity, and bradykinesia associated with progressive neuronal loss in the substantia nigra and other brain structures [1]. Although Parkinson's disease is primarily considered a disease that produces motor symptoms, it frequently manifests non-motor symptoms such as dementia and autonomic deficits in patients with it [2–4]. Symptomatic treatment of PD involves dopamine medications like levodopa, while surgical treatment is sometimes performed in more severe cases. Among these， deep brain stimulation (DBS) has been the most used and most efficient surgical treatment for some cardinal symptoms of PD after three decades of development [5–7]. In particular, bilateral STN has become the most commonly used target in the treatment of Parkinson's disease worldwide due to its significant improvement in major PD symptoms [8,9].

Although bilateral STN-DBS has shown notable improvement in motor symptoms and quality of life in PD patients, negative impacts on mood and cognitive function have been proposed by many studies [10]. Although this alteration is often considered mild [11], neurocognitive deterioration following bilateral STN-DBS has been consistently reported, with more significant decreases in frontal executive function, particularly verbal fluency [12–14]. Previous research has also observed a significant association between postoperative follow-up times and worsening neurocognitive symptoms, with 36% of patients developing dementia within 6 months of implantation, and although in the long term this is related to the natural history of the disease, studies suggest that this stimulation accelerates the process of cognitive decline [15]. With relatively long-term follow-up, neurocognitive changes in PD patients after STN-DBS appear to be moderate and partially reversible [16]. Symptoms initially worsen postoperatively but gradually improve over a year [17]. After bilateral STN-DBS, patients experience a significant initial decline in cognitive function, as assessed by MMSE scores, which was faster in the first 6 months after DBS than in the 6–36 month period [18]. Although the mechanisms involved remain unclear, compared to short-term follow-up, bilateral STN-DBS seems to be safer for the neurocognitive function of PD patients during relatively long-term follow-up.

For patients with neurocognitive symptoms after bilateral STN-DBS surgery, meta-analysis is often used to explore to assess the severity of these symptoms. A meta-analysis that extracted data from 28 cohort studies to investigate the effects of bilateral STN-DBS on the cognitive consequences of Parkinson's disease found small but significant decreases in executive function, verbal learning, and memory. Patients exhibited moderate decreases in semantic (Cohen's $d = 0.73$) and phonetic speech fluency (Cohen's $d = 0.51$) [14]. Another meta-analysis looked at different targets of DBS to verify that after surgery on the subthalamic nucleus and globus pallidus internal segment(GPI), both GPI-DBS and bilateral STN-DBS produced subtle cognitive decline from a neurocognitive perspective, but GPI-DBS appeared to be relatively better tolerated [13].

However, most of these meta-analyses overlook the fluctuation of psychological and cognitive symptoms in patients over time, as well as pooling effect sizes at different follow-up times from various literature sources, which obscures their important role in the process of symptom change and may limit the identification of when these symptoms occur in patients after surgery. Therefore, it is crucial to comprehensively analyze the timing of symptom onset and their trends at different follow-up times for patients undergoing deep brain stimulation. Such an examination can help clinicians to better understand the process of symptom change and to make more informed decisions regarding patient care.

The objective of this paper is to examine the neurocognitive symptoms of patients with Parkinson's disease at 6 and 12 months after bilateral STN-DBS surgery, specifically, how their cognitive symptoms change after 6 and 12 months of the surgery. Our analysis will focus on five major areas: overall cognitive profile, phonetic fluency, semantic fluency, executive ability, and memory function after bilateral STN-DBS. This analysis can inform subsequent treatment strategies and facilitate the improvement of patients' postoperative quality of life while ensuring their safety.

2. Method

2.1. Search methodology

A search of Pubmed, Cochrane Library, and Web of Science for structured electronic databases to retrieve studies published between January 2003 and January 2022 assessing neurocognitive outcomes in PD patients treated with bilateral STN-DBS. Search terms included: "bilateral STN-DBS", "deep brain stimulation", "subthalamic stimulation ", "Parkinson's disease", "cognitive dysfunction", "cognitive disturbance", "cognition", "psychocognitive", "psycho cognition", "neurocognitive", "neurocognition", "neuropsychological", "neuropsychology", "mood" and "emotional".

All duplicates in the database were excluded and the literature was screened according to the defined nadir criteria. In addition, other literature that was highly relevant to the purpose of the study was manually added to the included literature.

2.2. Eligibility criteria

The included literature was subject to the following criteria: (1) participants were patients with Parkinson's disease; (2) at least one group of patients underwent bilateral deep brain stimulation surgery in the subthalamic nucleus; (3) more than 6 case series were studied; (4) patients were recorded for a period that included 6 or 12 months postoperatively; (5) standard methods were used to measure patients' preoperative and postoperative psychological cognitive symptoms.

Excluded publications met one or more of the following criteria: (1) animal studies with non-human subjects; (2) studies with missing baseline data on patients; (3) studies in which the target of DBS was not the STN or in which patients did not receive DBS for

having Parkinson's disease; and (4) studies without data at the required follow-up points or studies in which patients' psychological cognitive symptoms were not quantified and documented. In addition, case studies, review articles, and meta-analyses were excluded.

2.3. Outcome measures

The primary outcome extracted from the original study was a scale score of neurocognitive symptoms after DBS surgery. Neuropsychological tests were divided into five cognitive domains: cognitive ability, executive function, learning memory capacity, phonetic fluency, and semantic fluency to assess changes in patients' neurocognitive symptoms compared to baseline at two major time points, 6 months postoperatively and 12 months postoperatively [19]. Although most neuropsychological measures involve multiple cognitive domains, each test is assigned to the domain of primary relevance to it. Because comparisons needed to be made between two different follow-up time points, and the scales used vary across the literature, the most frequently used scale in each neurocognitive domain was used to increase its comparability. The Simple Mental State Examination (MMSE) scores were most commonly used to assess patients' general cognitive level, while the Rey Auditory Verbal Learning Test (RAVLT) scores were used to assess patients' memory ability, and the Trail making B test to assess patients' executive function, and for patients' postoperative verbal fluency, the two main areas of focus are phonetic fluency and semantic fluency. Improvement or deterioration of symptoms was determined by subtracting the baseline score from the score at a given follow-up time.

2.4. Data coding

The literature search and screening were performed independently by two investigators, and any discrepancies were discussed and then determined. The required data were extracted using a customized data extraction form, and the following information was recorded: 1) sample size; 2) inclusion and exclusion criteria of the sample; 3) type of intervention; 4) location of electrode placement; 5) time point of assessment; 6) neurocognitive characteristics of the patient at the corresponding time point; 7) assessment measures; 8) baseline characteristics of the patient and sample (e.g., age, sex ratio, and duration of illness), and neuropsychological tests were divided into five cognitive domains: cognitive ability, executive function, learning memory capacity, and verbal fluency (phonetic fluency and semantic fluency).

Since most neuropsychological measures involve multiple cognitive domains and are prone to bias if this factor is ignored, we selected a more relevant and widely used test in the included literature for each cognitive domain of interest.

3. Data analysis

Because of the many sources of variability among the study samples, the raw data were preferentially processed using a random effects model, which adjusts the weights of each study and measurement according to the degree of heterogeneity in the study, allowing exposure effects to vary across studies, and appears to be more conservative and accurate compared to a fixed effects model (Higgins and Green, 2011), while whether a fixed effects model depends on the amount of heterogeneity in the original study, and for low heterogeneity in the original study, a fixed effects model should be used to combine the data; however, the fixed effects model may be too strict. The determining factor for using a random effects model in this analysis is that the model tends to produce more general

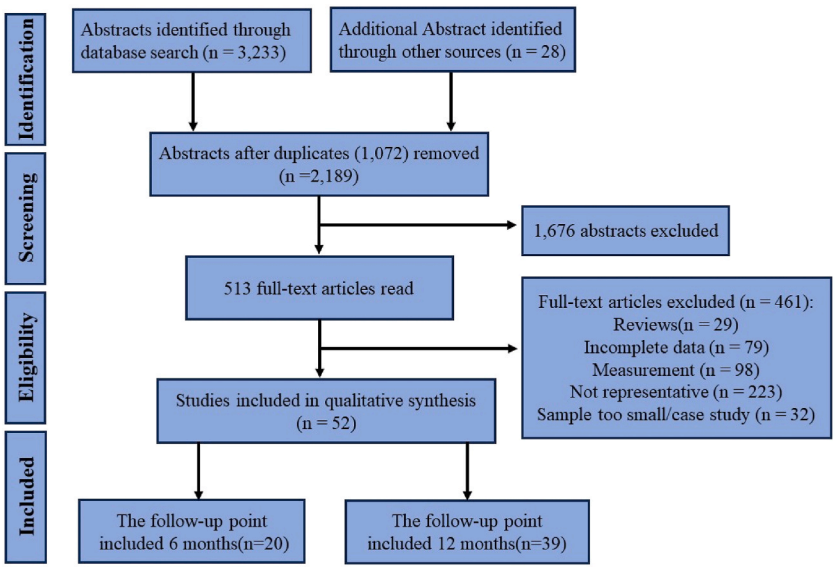

Fig. 1. Flowchart of the search and selection procedure.

parameter estimates. Heterogeneity was then evaluated using Q-statistic and I^2 to determine the appropriateness of the fixed or random effects model. Where I^2 values of 25%, 50%, and 75% indicate a low, medium, and high degree of heterogeneity, respectively [20]. Publication bias was detected by funnel plot and further confirmed by Begg's test. p-values <0.0 5 for Begg's test were considered as statistically significant publication bias and the results will be adjusted using the trim-fill method. All analyses were performed using Review Manager 5.3.

4. Results

4.1. Description of included studies

A total of 3261 documents were obtained after the search, of which 936 documents were searched by Pubmed, 2136 by Web of Science, and 161 by Cochrane Library. In addition, 28 publications were identified by manually scanning the reference list. Two researchers conducted the literature screening independently, and any discrepancies were decided through joint discussion. Of these, 1072 articles were discarded due to duplication, the remaining articles were read by title and abstract, and 1676 articles were eliminated. The resulting 513 articles were used for full-text reading and scrutinized. Ultimately, the investigators identified 52 articles that met our inclusion criteria, including 16 articles on overall cognitive status at the 6-month follow-up and 31 articles at 12 months; semantic fluency was 8 articles at 6 months and 12 articles at 12 months; phonetic fluency was 9 articles at 6 months and 13 articles at 12 months; memory capacity was 6 articles at 6 months and 6 articles at 12 months, and executive function was 6 articles at 6 months and 8 articles at 12 months.

The selection process of the literature is shown in Fig. 1. The flowchart mimics the Preferred Reporting Items for Systematic Evaluation and Meta-Analysis (PRISMA) guidelines. In addition, we conducted a quality evaluation of the included literature using the Cochrane Collaboration tool for assessing the risk of bias (Fig. 2). The baseline characteristics and demographics of patients are shown in Table 1.

4.2. Neurocognitive effects

The results of this meta-analysis suggest that bilateral STN-DBS appears to be safe in most aspects of patients' mental cognition under its long-term effects on them. However, our study also pointed out that the decline in patients' postoperative verbal fluency was general and persistent, with a moderate effect on semantic fluency and a slightly smaller effect on phonetic fluency. Although the decline in verbal fluency was not as great compared to previous studies [14], overall the pattern of change was the same (Fig. 3).

4.3. Phonetic fluency

For the aspect of patients' postoperative fluency, we focused on two main themes: phonemic fluency and semantic fluency. In our included literature, a total of 21 papers documented patients' phonetic fluency, 9 of the 21 studies recorded patients at 6 months postoperatively, and 13 recorded changes at 12 months postoperatively. 209 patients who were followed up at 6 months post-operatively showed a decrease in their phonetic fluency compared to baseline ($d = -0.42[-0.61,-0.22]$, $Z = 4.19$, $p < 0.001$), while for the 12-month follow-up 427 patients at 12 months, their speech fluency remained in decline ($d = -0.42[-0.56, -0.29]$, $Z = 6.12$, $p < 0.001$) (Fig. 4).

4.4. Semantic fluency

19 papers documented patients' postoperative semantic fluency, with eight of the 19 papers documented semantic fluency containing data on this aspect of patients' bilateral STN-DBS at 6 months postoperatively, and 12 papers documented data on patients at 12 months postoperatively. Among the 204 patients followed up at 6 months postoperatively, there was a decrease in fluency

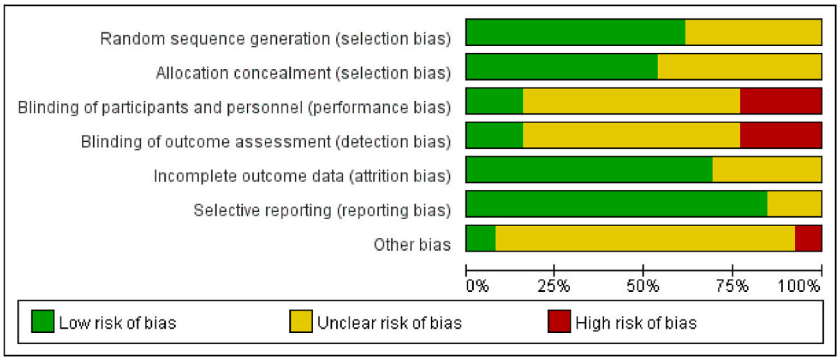

Fig. 2. Quality assessment of RCTs using Cochrane Collaboration's tool for assessing risk of bias.

Table 1
Baseline demographic characteristics and quality evaluation of included articles.

Author & Year	No.	Male sex (%)	Age (years)	Disease duration (years)	Levodopa equivalence dosage (mg)	UPDRS III "off"
Alegret 2004	9	N/A	62.9 ± 8.4	14.1 ± 3.4	1166.0 ± 486.3	N/A
Antonini 2010	21	61.9	61.0 ± 8.0	N/A	N/A	33.4 ± 11.6
Aono 2014	13	46.2	67.0 ± 7.8	8.1 ± 4.4	281.9 ± 154.4	27.8 ± 12.4
Asahi 2014	11	54.5	N/A	N/A	487.6 ± 150.5	33.4 ± 11.6
Aviles-Olmos 2014	41	65.9	56.2 ± 8.4	12.9 ± 5.8	1471.0 ± 515	50.3 ± 15.8
Balestrino 2017	32	62.5	60.0 ± 7.0	12.0 ± 4.0	1111.6 ± 396.7	43.6 ± 9.2
Boel 2016	63	69.8	60.9 ± 7.6	12.0 ± 5.3	N/A	N/A
Borden 2014	24	62.5	63.5 ± 9.5	12.0 ± 5.8	1093 ± 342	N/A
Castelli 2010	27	63.0	60.6 ± 6.7	15.3 ± 5.1	1046.1 ± 436.4	55.0 ± 11.3
Cilia 2007	20	70.0	59.1 ± 7.4	13.2 ± 3.1	951.0 ± 465.0	35.7 ± 9.4
Drapier 2006	15	66.7	59.7 ± 7.6	12.2 ± 2.8	1448.0 ± 400.0	41.6 ± 10.2
Fluchere 2013	213	70.4	61.0 ± 7.0	12.0 ± 4.0	1173 ± 495	33.6 ± 13.3
Funkiewiez 2004	77	55.8	55.0 ± 8.0	15.0 ± 5.0	N/A	N/A
Gan 2007	36	61.1	55.4 ± 8.3	12.5 ± 4.0	1228.3 ± 648.9	42.2 ± 14.6
Geraedts 2021	60	66.7	N/A	N/A	1129.0 ± 482.0	43.3 ± 11.1
Gervais-Bernard 2009	23	73.9	55.1 ± 7.2	12.9 ± 3.2	1188.0 ± 465.0	43.1 ± 14.0
Gironell 2003	8	N/A	56.6 ± 4.8	12.5 ± 4.8	1020.0 ± 490.2	59.9 ± 15.5
Heo 2008	46	39.1	58.0 ± 8.3	11.6 ± 5.6	798.9 ± 385.0	N/A
Houeto 2006	20	35.0	54.9 ± 10.3	13.7 ± 6.1	1320.0 ± 560.0	42.4 ± 15.4
Janssen 2014	26	69.2	58.0 ± 6.9	12.7 ± 5.1	824.0 ± 479.0	40.3 ± 13.8
Jiang 2020	10	70.0	55.4 ± 9.9	8.9 ± 2.1	710.6 ± 176.9	46.8 ± 6.8
Jiang 2015	10	60.0	59.4 ± 9.3	9.3 ± 2.9	660.4 ± 210.1	44.1 ± 9.8
Jost 2021	73	58.9	62.0 ± 8.3	10.3 ± 4.7	1146.2 ± 508.2	N/A
Kim 2013	36	50.0	56.8 ± 8.0	9.7 ± 4.1	1038.7 ± 473.9	36.6 ± 13.6
Lefaucheur 2012	26	N/A	57.9 ± 8.5	11.4 ± 3.5	N/A	42.8 ± 12.1
Lewis 2014	28	60.7	61.2 ± 8.9	12.4 ± 6.7	831.5 ± 425.9	41.3 ± 11.2
Lezcano 2016	69	60.9	61.3 ± 7.4	13.2 ± 5.7	919.1 ± 457.3	40.4 ± 11.1
Lilleeng 2015	16	37.5	60.0 ± 8.1	12.9 ± 5.7	960.0 ± 220.0	N/A
Author & Year	No.	Male sex (%)	Age (years)	Disease duration (years)	Levodopa equivalence dosage (mg)	UPDRS III "off"
Liu 2019	45	46.7	61.8 ± 8.1	11.9 ± 5.2	996.7 ± 398.7	48.5 ± 13.1
Odekerken 2015	56	75.0	60.3 ± 7.4	12.3 ± 5.5	N/A	N/A
Ory-Magne 2007	45	57.8	60.1 ± 8.7	13.5 ± 3.6	1466.0 ± 665.0	44.7 ± 14.5
Peak 2011	38	39.5	N/A	12.2 ± 5.3	793.4 ± 527.0	40.9 ± 13.4
Rizzone 2014	26	N/A	N/A	N/A	N/A	56.7 ± 15.8
Samura 2019	33	48.5	62.6 ± 10.9	11.9 ± 7.2	803.8 ± 254.2	30.0 ± 11.7
Schoenberg 2008	20	50.0	66.7 ± 9.4	10.9 ± 4.4	716.3 ± 334.9	57.8 ± 28.1
Smeding 2006	99	58.6	57.9 ± 8.1	13.7 ± 6.1	899.3 ± 498.0	43.6 ± 12.5
Smeding 2009	105	60.0	58.4 ± 7.8	N/A	N/A	43.7 ± 12.3
Tanaka 2019	25	72.0	65.0 ± 8.8	11.8 ± 4.1	971.1 ± 365.9	N/A
Tang 2015	27	66.7	55.5 ± 6.1	10.1 ± 3.8	N/A	43.7 ± 12.9
Tramontana 2015	15	93.3	60.0 ± 6.8	N/A	417.2 ± 306.6	25.3 ± 9.0
Tsuboi 2017	32	40.6	63.3 ± 9.1	N/A	952.0 ± 371.9	N/A
Volonté 2021	18	72.2	56.0 ± 7.0	11.0 ± 4.0	1163.8 ± 375.3	40.9 ± 11.2
Welter 2014	262	60.7	57.6 ± 8.1	12.8 ± 5.1	889.0 ± 373.0	38.7 ± 14.3
Witjas 2007	40	75.0	59.0 ± 8.0	12.4 ± 4.5	1091.9 ± 374.8	38.0 ± 10.2
Witt 2008	60	60.0	60.2 ± 7.9	13.8 ± 6.3	1203.0 ± 535.0	47.9 ± 13.1
Witt 2013	31	54.8	59.8 ± 7.5	13.3 ± 5.5	1244.0 ± 527.0	47.2 ± 12.3
Yakufujiang 2019	17	58.8	65.2 ± 5.3	13.6 ± 3.5	1022.0 ± 189.0	41.7 ± 13.8
Yakufujiang 2021	35	57.1	63.9 ± 7.4	N/A	1188.0 ± 326.0	43.0 ± 13.8
Yamamoto 2017	31	N/A	66.7 ± 0.9	11.6 ± 3.7	1065.75 ± 31.13	42.9 ± 2.2
York 2008	23	56.5	59.5 ± 11.8	12.0 ± 5.5	1009.8 ± 445.2	49.3 ± 11.3
Zangaglia 2009	32	56.3	58.8 ± 7.7	11.8 ± 5.1	617.2 ± 303.6	40.1 ± 15.5
Zibetti 2011	14	64.3	60.4 ± 6.5	17.0 ± 4.7	955.0 ± 406.0	51.3 ± 15.4

Data are shown as the mean ± SD or number.
Abbreviation: N/A: not available, UPDRS: unified Parkinson's disease rating scale, NO.: number of people participating in the study.

compared to baseline (d = −0.51[−0.70,-0.31], Z = 5.01, $p < 0.001$), while in the 432 patients followed up at 12 months, the decrease in semantic fluency was even greater than in the patients followed up at 6 months (d = −0.54[−0.68,-0.68]). 0.68, −0.41], Z = 7.81, $p < 0.001$) (Fig. 5).

Overall, the change in verbal fluency in patients after bilateral STN-DBS does not appear to be satisfactory, which contrasts with the gradual recovery observed in other symptom domains with long-term follow-up.

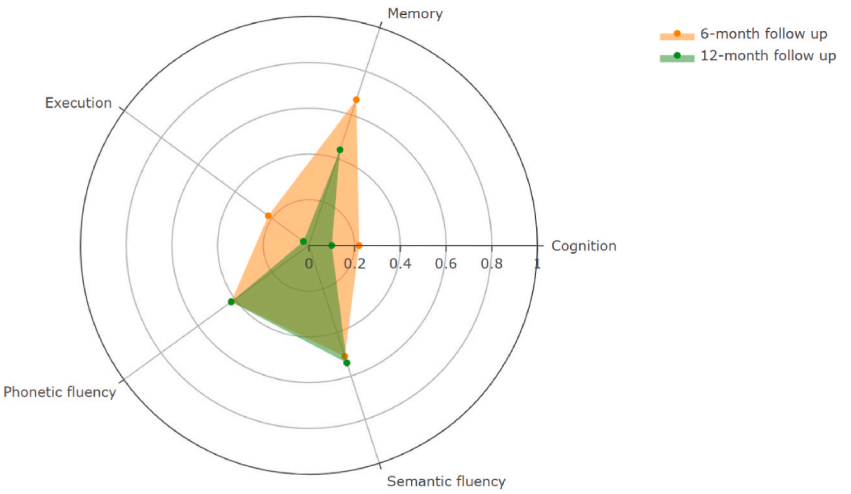

Fig. 3. Radar chart of the changes in neurocognitive symptoms at 6 and 12 months postoperatively. Each of the five axes in the graph represents its corresponding symptom, and the different colored values respectively represent their effect sizes at 6 and 12 months postoperatively. Improvement or deterioration of symptoms was determined by subtracting the baseline score from the score at a selected follow-up time.

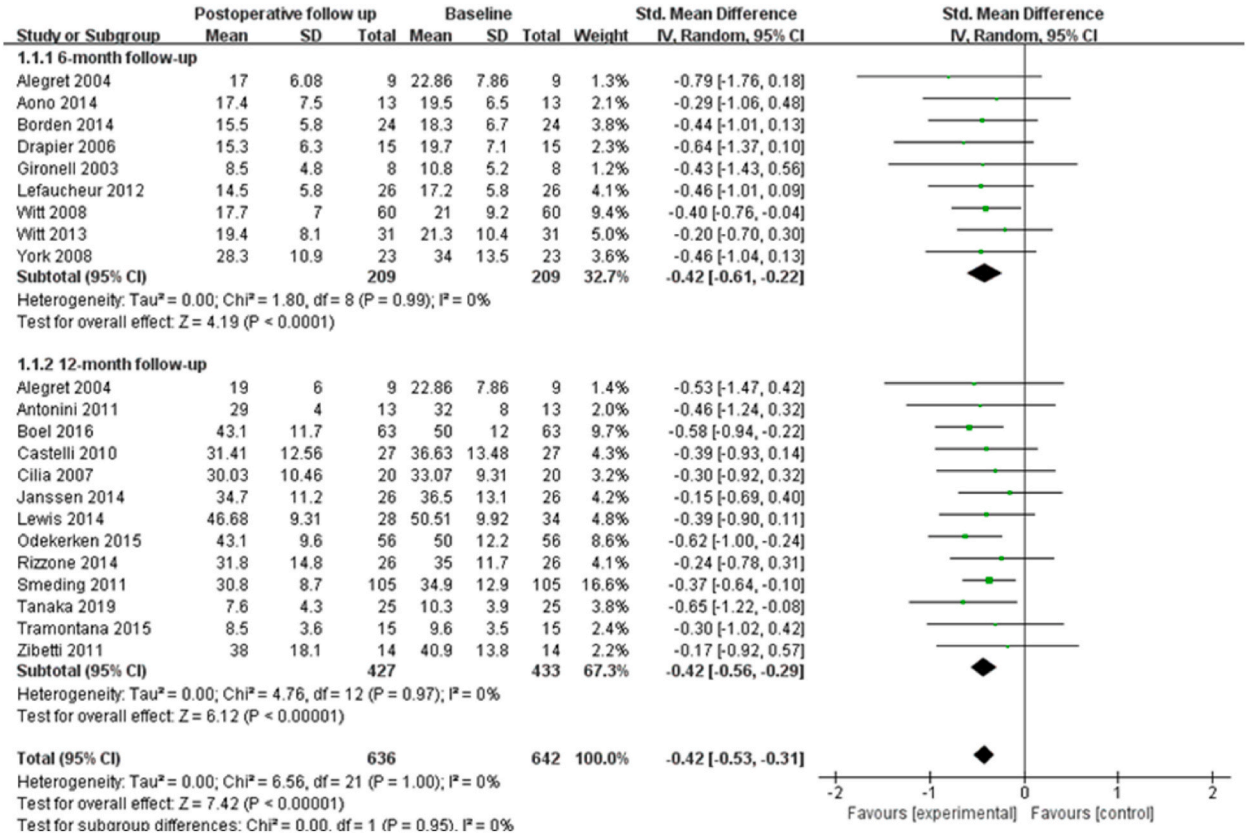

Fig. 4. Forest plot of phonetic fluency at 6-month& 12-month follow-up. The green squares indicate the mean of each study, and the error bars are the respective 95% confidence intervals. Black diamonds indicate the results of the subgrouped studies for a period of time, and the last diamond indicates the unified results of the two subgroups evaluated. IV=Initialization Vector; df = degrees of freedom.

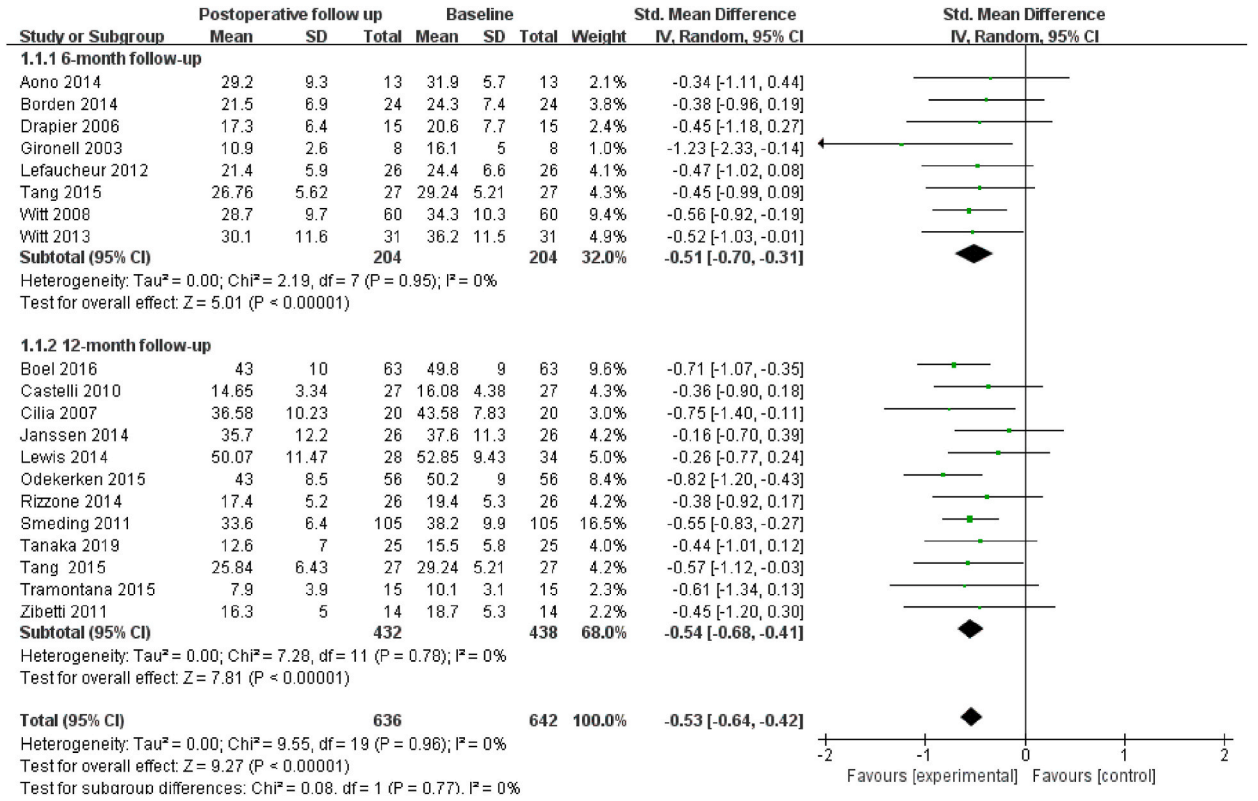

Fig. 5. Forest plot of Semantic fluency at 6-month& 12-month follow-up. The green squares indicate the mean of each study, and the error bars are the respective 95% confidence intervals. Black diamonds indicate the results of the subgrouped studies for a period of time, and the last diamond indicates the unified results of the two subgroups evaluated. IV=Initialization Vector; df = degrees of freedom.

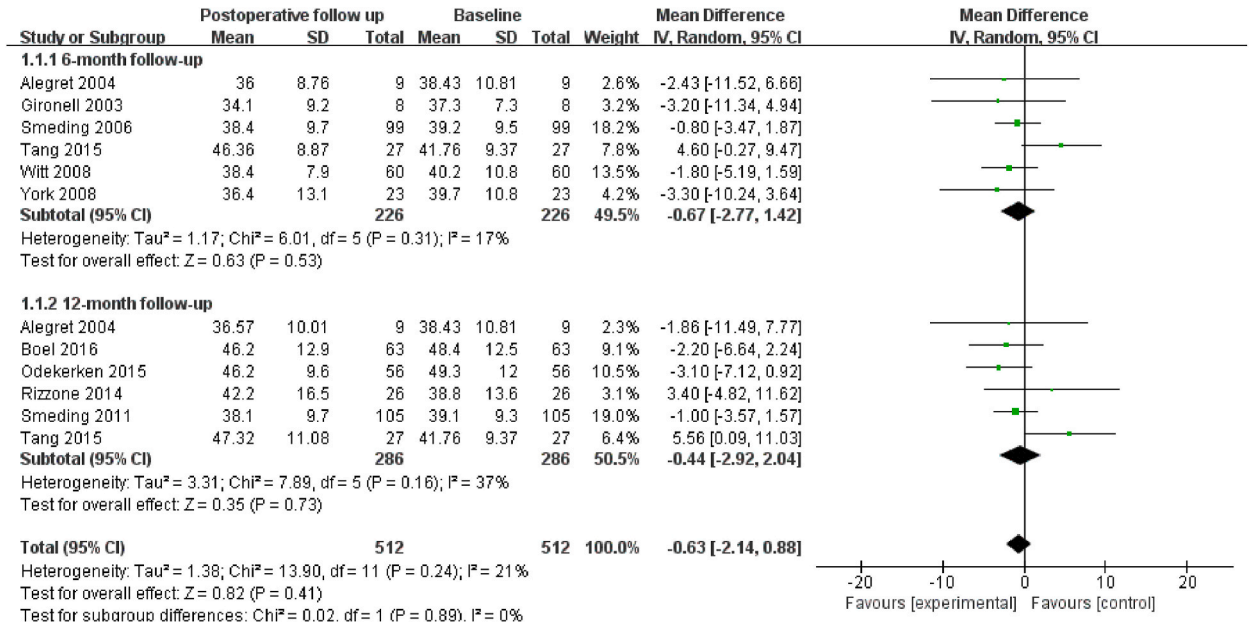

Fig. 6. Forest plot of Memory capacity at 6-month& 12-month follow-up. The green squares indicate the mean of each study, and the error bars are the respective 95% confidence intervals. Black diamonds indicate the results of the subgrouped studies for a period of time, and the last diamond indicates the unified results of the two subgroups evaluated. IV=Initialization Vector; df = degrees of freedom.

4.5. Memory capacity

A total of ten studies using the Rey Auditory Verbal Learning Test (RAVLT) to record postoperative memory capacity at follow-up were included. Of these, six papers recorded data at 6 months postoperatively and six papers recorded data at 12 months. In terms of effect size, the degree of memory decline at 6 months postoperatively (d = −0.67 [−2.77, 1.42], Z = 0.63, p = 0.530) was substantially greater than at 12 months postoperatively (d = −0.44 [−2.92,2.04], Z = 0.35, p = 0.730), but overall, the difference was not statistically significant at either 6 or 12 months postoperatively. It is suggested that there is almost no effect on the memory capacity of patients with Parkinson's disease after bilateral STN-DBS (Fig. 6).

4.6. Executive function

For patients' executive function, we selected the test Trail making B as a representative. Of our included literature, 13 documents followed and recorded data on this scale postoperatively, six of which recorded data at 6 months postoperatively and eight at 12 months postoperatively. Through analysis, it is clear that there was a slight but significant decrease in the patient's executive function at 6 months postoperatively (d = 0.22[0.01,0.42], Z = 2.06,p = 0.040), and this decrease has lost statistical significance at 12 months postoperatively (d = 0.03[−0.11,0.18], Z = 0.44,p = 0.660) (Fig. 7). Our study supported a mild effect of bilateral STN-DBS on patients' memory ability at 6 months and no effect at 12 months.

4.7. Cognition

A total of 40 publications described the overall cognitive symptoms of patients after bilateral STN-DBS, of which 16 documented the cognitive status of patients at 6 months postoperatively compared to baseline, while 31 documented the cognitive status of patients at 12 months postoperatively. For most of the literature, the Mini-mental State Examination (MMSE) was the method used to detect and record patients' cognitive status, in addition to the MDRS (Mattis dementia rating scale), the MoCA (Montreal Cognitive Assessment), and the cognitive component of the PDQ-39 (The 39-item Parkinson's Disease Questionnaire).

By and large, across all indicators, there was a decline in overall cognitive ability after DBS surgery, with a slight to moderate significant reduction in 562 patients followed up at 6 months postoperatively (d = −0.22[−0.34,-0.09], Z = 3.41, p = 0.001). At 12 months postoperatively, the cognitive decline was moderated considerably, with a slight decrease from baseline in 1505 patients at 12 months postoperative follow-up (d = −0.10[−0.18,-0.01], Z = 2.29,p = 0.020) (Fig. 2). The test of heterogeneity of the two pooled analyses showed that the heterogeneity was small (I^2 = 9% for 6 m and I^2 = 15% for 12 m, both in the category of small heterogeneity), which proves that the literature selected by our strict nadir criteria has a high homogeneity, so the results of the meta-analysis are more reliable.

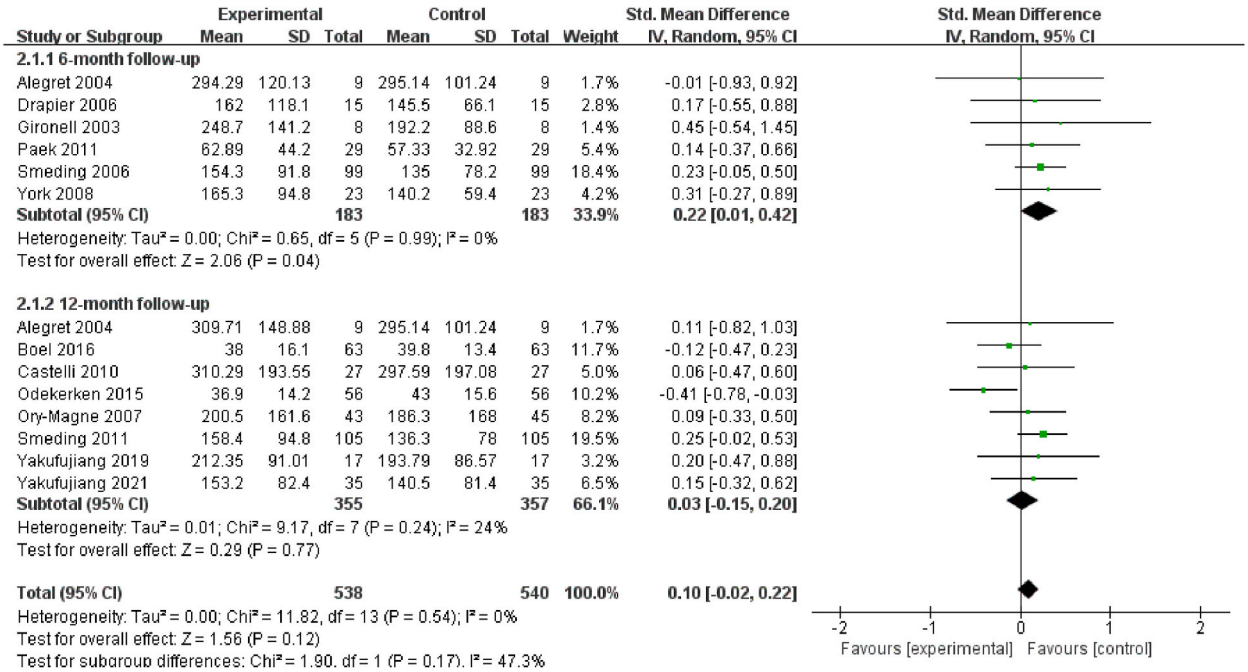

Fig. 7. Forest plot of Executive function at 6-month& 12-month follow-up. The green squares indicate the mean of each study, and the error bars are the respective 95% confidence intervals. Black diamonds indicate the results of the subgrouped studies for a period of time, and the last diamond indicates the unified results of the two subgroups evaluated. IV=Initialization Vector; df = degrees of freedom.

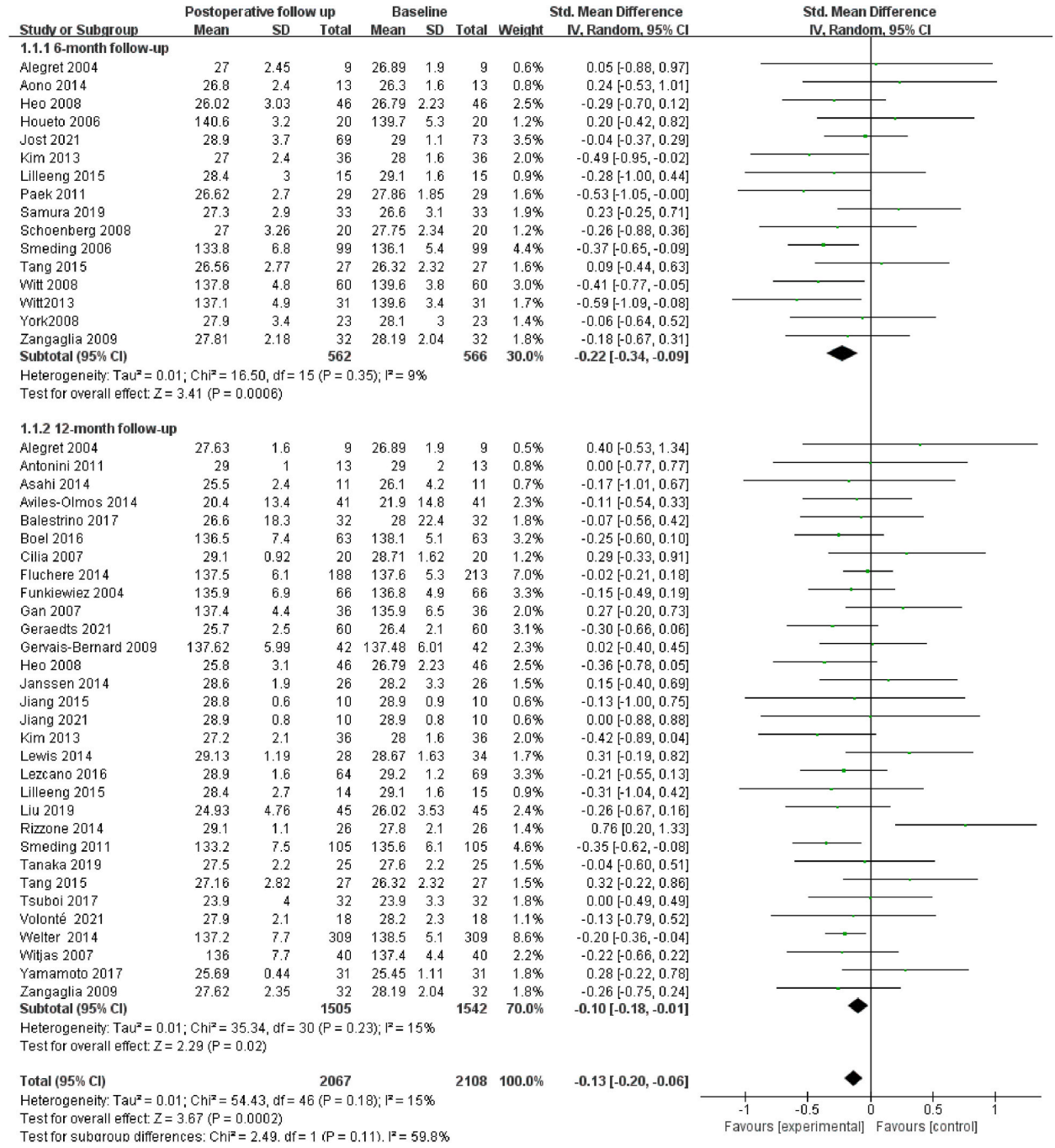

Fig. 8. Forest plot of Cognition at 6-month& 12-month follow-up. The green squares indicate the mean of each study, and the error bars are the respective 95% confidence intervals. Black diamonds indicate the results of the subgrouped studies for a period of time, and the last diamond indicates the unified results of the two subgroups evaluated. IV=Initialization Vector; df = degrees of freedom.

The above data showed that the cognitive decline was greater at 6 months after bilateral STN-DBS surgery, and relatively smaller at 12 months (Fig. 8).

5. Discussion

The aim of this meta-analysis and systematic review is to provide clinical practice with a more comprehensive overview of changes in mental cognitive status in patients with Parkinson's disease after surgery. Studies published over the past 18 years were combined

and pooled to understand the impact of bilateral STN-DBS on patients' neurocognitive aspects during relatively long-term postoperative follow-up. Generally, the results of this meta-analysis were consistent with previously published studies, especially with regard to verbal fluency.

The results indicate that postoperative bilateral STN-DBS affects various cognitive domains in patients with Parkinson's disease, but it is worth noting that compared with 6 months, patients showed improvement in all neurocognitive symptoms except for a decrease in semantic (d = 0.54) and phonetic fluency(d = 0.42) at the 1-year follow-up. Our study suggests that bilateral STN-DBS has no significant effect on patients' memory. Although patients undoubtedly experience cognitive decline after surgery, the deterioration of these symptoms does not increase linearly over time. In fact, patients included in our study at 12 months postoperative follow-up compared to those at 6 months showed an increase in overall cognition, memory capacity, and executive function were somewhat alleviated, whereas, for verbal fluency, patients' phonetic fluency and semantic fluency did not change significantly between the two time points.

Approximately 20%–50% of individuals with Parkinson's disease experience cognitive impairment as the disease progresses, and it may even manifest in the early stages [21]. These cognitive deficits tend to worsen as the disease advances, eventually leading to dementia [22]. A long-term follow-up study on newly diagnosed Parkinson's disease patients revealed that after 20 years, up to 80% of them developed dementia [23]. In comparison to the continuous decline seen in the natural progression of the disease, patients who experience bilateral STN-DBS have a relatively mild degree of neurocognitive deterioration.

In their previous study, Boel et al. found that cognitive test declines tend to be more significant in the first year following STN-DBS surgery, compared to one to three years later [24]. Another long-term study found that patients had only poor verbal fluency scores three years after STN-DBS, while deterioration in other cognitive functions was found to be transient [25]. In addition, several publications have also shown that symptoms are most pronounced in patients after STN-DBS surgery in the first six months, with a slight reduction later [26,27], and stabilize one year after surgery [25,28]. Previously meta-analyses have found that patients undergoing bilateral STN-DBS tend to experience declines in overall cognition, phonetic fluency, semantic fluency, executive ability, and memory function. However, except for verbal fluency, the magnitude of the decline is considered to be very small or minimal (d ~ 0.11–0.24) [13,14]. A long-term clinical study demonstrated that the most significant feature was a decrease in verbal fluency 5–8 years after patients after bilateral STN-DBS surgery [29]. Another controlled clinical study also noted small declines in cognitive domains other than verbal fluency in patients at 12 months of follow-up [30]. These previous findings corroborate our study and further support its accuracy.

The decline in verbal fluency presents a challenge for clinical explanation as it relies on various aspects of cognitive function, including memory extraction, executive function, and lexical retrieval [31]. Multiple factors, such as electrode location and stimulus amplitude, have been suggested to influence decreases in phonetic fluency and semantic fluency [32]. In letter language fluency tasks, the motor prefrontal cortex may be more critical, whereas in category fluency tasks, the temporal cortical areas are more important [33].

Given that dopamine affects cognitive function in patients with Parkinson's disease, excessive initial Levodopa equivalent daily dose(LEDD) reduction may be responsible for the initial rapid decline in overall cognitive function [34,35]. Furthermore, cognitive decline after it is strongly correlated with the lead trajectory of the procedure, in which damage to the caudate nucleus affects patients across cognitive domains, with one study indicating a 37-fold increase in the risk of overall cognitive decline for every 0.1 ml volume of electrode penetration within the caudate nucleus [32,36]. Mental fluctuations may be dependent on the limbic dopaminergic system, specifically, the tegmental-ventral area, and the psychiatric symptoms reported by patients may be a side effect due to current diffusion into the limbic STN area [37].

There are certain signs before surgery that can help patients to avoid some of the postoperative symptoms. Certain quantitative preoperative EEG features can provide a more accurate prediction of postoperative cognitive decline in patients undergoing bilateral STN-DBS [38]. Additionally, patients with Parkinson's disease who have GBA mutations are more likely to experience severe negative cognitive effects after surgery. Therefore, preoperative decision-making is crucial in preventing postoperative cognitive decline [39]. The absence of pre-surgical education programs is also one of the potential causes of worsening subjective outcomes after surgery [40].

Several studies have looked into the postoperative decline in patients' verbal fluency, indicating that this may not be related to long-term modulation but mainly to insertional or impairment effects caused by the surgical procedure. Okun et al. found that in patients after undergoing bilateral STN-DBS surgery, the impairment in speech fluency remained unchanged regardless of changes in the stimulus settings [41]. Since most of the decrease in verbal fluency was observed shortly after bilateral STN-DBS surgery, it has been suggested that surgical microdamage affecting the cortico-basal ganglia circuits involved in word extraction processes could be the cause [42]. Alternatively, stimulation of the STN may lead to reduced activation of the left hemisphere's inferior frontal and temporal cortices, resulting in decreased verbal fluency [43]. This appears to explain why patients continue to show a large decrease in verbal fluency despite relatively long-term postoperative follow-up. Additionally, studies show that the amplitude and frequency settings of DBS have a direct impact on speech intelligibility. This highlights the necessity of careful programming of DBS parameters to reduce speech-related side effects [44]. During ventral contact, an increase in tissue activation within the STN has been linked with a decrease in verbal fluency performance [45]. It is evident that appropriate stimulation parameters, precise targeting locations, and the correct surgical procedure play an important role in the change of the patient's postoperative fluency.

5.1. Limitations

One limitation is that a portion of the studies included in our meta-analysis were not randomized studies with a control group, this type of data is based only on preoperative and postoperative measurements of patients, and there is a section of the literature that does

not indicate relevant data on stimulation parameters and detailed locations, which limits our quest to identify the causes of postoperative neurocognitive symptom decline in patients and to further determine the relationship between cognitive decline and factors such as patient age, gender, disease duration, medication dose, and stimulation parameters.

Another potential drawback is that we did not combine data at 6 and 12 months postoperatively on the same cohort of patients, and the discontinuity of the data and the differences in cases would have some impact on the results and make it challenging to compare the statistical differences in results between the two groups with different follow-up times. Consequently, we could only analyze the symptoms of two separate cohorts of patients from a macroscopic perspective, and could not implement the 6- 6-month and 12-month follow-ups on the same cases to obtain continuous in time and participant data.

Furthermore, cognitive decline may occur during the follow-up period after 1 year postoperatively, as noted by Krack et al. in a prospective study conducted in 2003 with a 5-year follow-up, 5 of 49 patients with Parkinson's disease developed cognitive decline and, interestingly, 3 patients developed progressive dementia between the third and fifth years postoperatively rather than immediately after surgery. Such cases of progressive cognitive impairment may reflect a long-standing natural history of Parkinson's disease [46]. Therefore, additional long-term follow-up studies are needed to understand how cognitive symptoms change over a longer period after surgery.

Lastly, it is important to acknowledge that each original study included cases based on their defined nadir criteria, researchers often excluded patients with pre-existing severe cognitive impairment (e.g., dementia) before surgery to explore their cognitive phenomena in the postoperative period. Consequently, the results obtained from the studies tend to be more idealistic compared to real-world scenarios, and therefore our conclusions may not be applicable to every patient.

6. Conclusions

This study provides a comprehensive analysis of neurocognitive changes in various domains at different follow-up times after bilateral STN-DBS in Parkinson's patients. The findings demonstrate that the patients' neurocognitive deteriorations were mostly alleviated, except for verbal fluency, by the 12-month postoperative mark. Therefore, it was concluded that under relatively long-term follow-up, the neurocognitive effect of bilateral STN-DBS on patients is relatively mild, but attention should be given to changes in patients' postoperative verbal fluency.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Zhuohang Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zijian Zheng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Junwen Huang:** Writing – review & editing, Writing – original draft, Software, Investigation. **Xu Cai:** Supervision, Resources, Investigation, Data curation. **Xinjie Liu:** Writing – original draft, Resources, Data curation. **Cheng Xue:** Writing – original draft, Resources, Data curation. **Longping Yao:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **Guohui Lu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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