A Systematic Review and Meta-Analysis of Deep Brain Stimulation for Progressive Supranuclear Palsy

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Research

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Abstract

Background: Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease and currently no effective symptomatic or neuroprotective treatment is available for PSP. Deep brain stimulation (DBS), as a neurosurgical procedure, plays an important role in a range of neurological and psychiatric disorders. However, there are no systematic investigations about the DBS in PSP patients.

Objective: We performed a systematic review and meta-analysis to evaluate the safety and efficacy of DBS for PSP.

Methods: PubMed, EMBASE, Cochrane library, Chinese National Knowledge Infrastructure and Wan Fang databases were systematically searched without time restrictions. We assessed the data between DBS-OFF and DBS-ON groups, as measured by the Unifed Parkinson Disease Rating Scale (UPDRS).

Results: Of 154 identified studies, 13 were eligible and were included in our meta-analysis (N = 36 participants). A reduction of UPDRS scores under DBS-ON conditions was observed, but the differences yielded no statistical significance.

Conclusion: Since part of PSP patients could benefit from DBS, we speculate that DBS may become a safe and promising tool for PSP in axial symptoms as well as non-motor symptoms though further investgations are needed. Our findings will provide design strategies for following clinical trials and ultimately help improve the clinical application of DBS in PSP patients.

1. Background

Progressive supranuclear palsy is one of the most common atypical parkinsonian disorders [1] with prominent four-repeat (4R-) tau neuropathology [2], and the classic phenotype termed Richardson's syndrome (PSP-RS, also known as Steele–Richardson–Olszewski syndrome) is characterized by prominent postural instability with repeated unprovoked falls, vertical supranuclear gaze palsy, akinetic-rigid parkinsonism with poor response to dopaminergic agents, and cognitive decline [3, 4]. PSP is clinically heterogeneous and several variant phenotypes have been gradually reported since PSP-RS was introduced in 1964, including PSP-parkinsonism (PSP-P) [5], progressive gait freezing (PSP-PGF, ever referred to pure akinesia with gait freezing, PAGF) [6], and other 7 rare presentations [7, 8]. PSP is a uniformly fatal disease with an average disease duration of 8 years [9] and current medical has a limited role in PSP [10]. There are still no disease-modifying treatments despite the transient benefit from levodopa therapy in early stages of some cases [11].

As a neurosurgical procedure through implanting electrodes into specific targets within the brain and delivering electricity from an implanted battery source [12], deep brain stimulation (DBS) has become an important clinical tool and has been applied to a range of neurological and psychiatric disorders mainly including Parkinson's disease (PD), essential tremor, dystonia, epilepsy, major depression [12, 13]. The subthalamic nucleus (STN) and globus pallidus interna (GPi) are common stimulating targets for treatments of PD in the clinic, especially in cases without response to medication adjustments [14, 15]. The pedunculopontine nucleus (PPN) is part of the mesencephalic locomotor region (MLR) and plays a role in the initiation and maintenance of gait and balance [16]. PPN has been proposed as a new target for DBS to treat movement disorders since the first PPN-DBS was carried out in a parkinsonian patient in 2005 [17]. Studies have proven that PD patients treated by PPN-DBS show improvements in gait disorder and falls [14, 18]. Additionally, several researches have proposed that PPN can be a potential target for PSP [19–21].

The Unifed Parkinson Disease Rating Scale (UPDRS) [22], PSP rating score (PSPRS) [23] and freezing of gait questionnaire (FOG-Q) [24] are widely used clinical rating scales for parkinsonism, among which, UPDRS part (UPDRS) is the most common objective assessment applied in DBS. Since there is contraversy about surgery benefits between different studies, herein, we carried out a meta-analysis to evaluate the curative effect and attempted to provide a comprehensive summary about DBS for PSP.

2. Methods

2.1 Information sources and search strategy

This meta-analysis has been organized according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement guidelines [25] and a protocol has been registered at the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020212628). We performed a comprehensive search of the PubMed, EMBASE, Cochrane library, Chinese National Knowledge Infrastructure (CNKI) and Wan Fang databases without time limitation, using the following terms: "progressive supranuclear palsy" or "PSP" in association with "deep brain stimulation" or "DBS". We scanned reference lists of relevant literatures for additional potential sources. All publications were restricted to the English and Chinese languages, and all study designs were included.

2.2 Study selection and data extraction

Eligible literature had to meet all of the indicated criteria: (1) Subjects: PSP clinical diagnosis. (2) Interventions: any types of DBS. (3) Clinical assessments: outcome measures at baseline and follow-up. Reviews, animal researches, repeated publications on patients and studies without complete data were excluded. Two independent investigators selected studies through reviewing the titles and abstracts in accordance with the inclusion and exclusion criteria. Disagreements between the two investigators were resolved by a third investigator.

Data were independently extracted by two investigators from each included study on: (1) study information (including the first author, year of publication, country of centers); (2) patient characteristics (including age, gender, illness duration and diagnostic criteria of PSP); (3) intervention (including surgical target for electrode implantation, proper voltage and frequency); (4) assessment of surgery effectiveness [including follow-up time, PSPRS, UPDRS scores and other outcomes].

2.3 Quality assessment and statistical analysis

Eligible articles were independently assessed by two investigators according to the Cochrane methods which were partly modified to better serve this study, and the risk of bias was categorized as high, low, or unclear on the adequacy of 7 items: random sequence generation (it refers to the accuracy of PSP diagnoses and clinical phenotypes in this meta-analysis), allocation concealment (it represents surgical operations and stimulation parameters in this meta-analysis), blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Statistical analyses were performed using Review Manager 5.3 for Windows. We assessed the effect of DBS-OFF/ON and baseline/DBS-ON treatments on UPDRS- ; PSPRS, FOG-Q and other outcomes couldn't be analyzed due to lack of enough data. Case reports are important for rare diseases and are often the primary evidence of the effectiveness of a new therapy [26], we therefore properly combined some data from case reports considering the fact that single case reports were unable to make effects in this meta-analysis. We divided the follow-up duration into two parts: short-term (< 12 months after DBS) and long-term (≥ 12 months after DBS). When I^2 was ≤ 50% or P was > 0.10, a fixed effects model was used and when I^2 was > 50% or P was < 0.10, a random effect model was used. We were unable to perform bias analysis on the studies using the funnel plot Begg and Egger considering the fact that the number of studies that we included in each meta-analysis was less than 10. To further decrease the heterogeneity and bias we performed subgroup analysis.

3. Result

3.1 Description of Studies

A total of 154 articles of interest were searched and 94 articles were identified after duplicates removed (Fig. 1). Of these, 62 articles were identified as irrelevant literatures based on their titles and abstracts and were therefore eliminated. Among 32 potentially relevant articles, 10 were excluded because they were the abstracts of poster presentations; patients from 5 articles [27–31] overlapped with those in other studies [21, 32] and these 5 articles were excluded; 4 articles [33–36] had no extracted data and were excluded. 13 articles were finally included in the analysis containing 36 PSP patients: 32 with PPN-DBS, 1 with STN-DBS, 1 with GPi-DBS, 2 with compound DBS. The basic characteristics of included studies are shown in Table 1 and the risk of bias summary and graph is shown in Fig. 2

Table 1
Baseline characteristics of the included studies

Authors and year	Sample size and Gender	Mean age, ys	Duration, ys	Clinical diagnosis	DBS target	DBS parameters			Follow-up	
						Vol. V	FrEq. Hz	Pulse width, us	Time, ms	Clinical evaluations
Bergmann et al. 2007 [37]	1 F	55	8	PSP-P	bi-STN	L2.5 R3.5	185	60	9/42	UPDRS-Ⅲ, cognitive tests and levodopa responsiveness
Brusa et al. 2009 [38]	1 M	70	3	PSP-P	uni PPN	3.4	25	NA	3/6/9	UPDRS-Ⅲ, cognitive tests and FOG-Q
Lim et al. 2009 [39]	1 F 1 M	59.5	NA	PSP	2 uni PPN	2-2.8	5–30	NA	7/10	Sleep stage distribution
Wilcox et al. 2010 [40]	1 M	69	8	PSP-PGF	bi PPN	L2.8-3.3 R3.5-3.8	35	60	2.5/5/7/10/15	FOG-Q and GF-Q
Ostrem et al. 2010 [41]	1 M	76	4	PSP-PGF	bi PPN	L4.5-5.1 R4.0-4.4	25	60	3/6/12	UPDRS and FOG-Q
Servello et al. 2014 [42]	3 M	68	NA	2 PSP-RS 1 PSP-P	2 uni PPN 1 uni PPN + bi GPi	NA	NA	NA	12/14	PSPRS-Ⅱ
Doshi et al. 2015 [19]	3 F 1 M	60.8	3	2 PSP-RS 2 PSP-P	4 bi PPN	0.7–3.5	20–45	60	6/18	PSPRS, UPDRS, PDQ-39 and adverse events
Oliveira Souza et al. 2016 [16]	1 F	74	NA	PSP-RS	bi PPN	2–4	20	60	1/3	UPDRS-Ⅲ
Mazzone et al. 2016 [21]	4 NA	NA	NA	PSP	4 PPN	4.3–6.9	NA	60	0.5	UPDRS-Ⅲ, Hoehn and Yahr
Scelzo et al. 2017 [32]	8 NA	NA	NA	PSP-RS	8 uni PPN	NA	NA	NA	6/12	PSPRS, UPDRS-Ⅱ and adverse events
Galazky et al. 2018 [20]	5 F 2 M	70	6.2	4 PSP-RS 2 PSP-PGF 1 PSP-P	6 bi PPN 1 PPN + STN	3.5	8-130	60	3/12/24	UPDRS-Ⅲ, TUG, PSP-QoL, cognitive tests and adverse events
Leimbach et al. 2019 [43]	1 F 1 M	61	5	PSP	2 uni PPN	NA	NA	NA	12	Cognitive tests

Authors and year	Sample size and Gender	Mean age, ys	Duration, ys	Clinical diagnosis	DBS target	DBS parameters			Follow-up	
						Vol. V	FrEq. Hz	Pulse width, us	Time, ms	Clinical evaluations
Orcutt et al. 2020 [44]	1 M	75	4	PSP-RS	bi GPi	L 5.3 R 4.7	130	60	12	Improvement of AEO

DBS = deep brain stimulation; PSP = progressive supranuclear palsy; PSP-P = progressive supranuclear palsy-parkinsonism; PSP-RS = progressive supranuclear palsy-Richardson Syndrome; PPN = pedunculopontine nucleus; STN = subthalamic nucleus; GPi = globus pallidus internus; UPDRS = unified Parkinson disease rating scale; PSPRS = progressive supranuclear palsy rating scale; FOG-Q = freezing of gait questionnaire; GF-Q = gait and falls questionnaire; PDQ-39 = the 39-item Parkinson's disease questionnaire; TUG = timed up and go test; AEO = apraxia of eyelid opening; PSP-QoL = progressive supranuclear palsy quality of life scale.

3.2 DBS for UPDRS of PSP patients

Available data from 6 studies were included in this meta-analysis comparing UPDRS in PSP patients under DBS-OFF and DBS-ON status (Fig. 3). The heterogeneity was high (I^2 = 75%), thus a random-effects model was selected. The UPDRS scores of patients when DBS was on were lower compared to those when DBS was off, though the differences didn't show statistical significance [11.46 (95% confidence interval, CI = -1.39 to 24.31)].

We divided the follow-up duration into two parts for subgroup analysis, named short-term and long-term. The mean differences were more obvious in the short-term group [15.47 (95% CI = -3.94 to 34.88)] compared to this in the long-term group [2.63 (95% CI = -6.72 to 11.98)], which to some degree indicated that the difference in follow-up time might impact on the UPDRS scores.

On the other hand, we carried out another analysis using data from 6 articles and we compared the UPDRS scores in PSP patients before DBS surgery (at baseline) and after surgery (DBS-ON) without the follow-up time restriction (Fig. 4). No significant differences between these two groups were observed [-3.03 (95% CI = -11.42 to 5.37)], which showed that DBS might not affect the natural progression of UPDRS in PSP patients.

3.3 DBS for UPDRS of patients with different PSP phenotypes

In total, 5 articles provided available data for this part where subgroup analysis of DBS was performed among patients presenting as different PSP clinical phenotypes: PSP-RS, PSP-P and PSP-PGF (Fig. 5). Both groups did not yield significant differences: the mean difference was 6.19 (95% CI = -3.44 to 15.83) in short-term group and 2.71 (95% CI = -0.64 to 6.06) in long-term group, respectively. The evidence suggested PSP clinical phenotypes made little effects on scores of UPDRS in PSP patients treated by DBS.

3.4 Unilateral PPN-DBS vs bilateral PPN-DBS for UPDRS of PSP patients

UPDRS of PSP patients treated by unilateral or bilateral PPN-DBS was evaluated in short-term group from 4 studies with 14 participants and in long-term group from 3 studies with 13 participants (Fig. 6). There was no statistical significance in this analysis [2.60 (95% CI = -10.94 to 16.14) in short-term group, 2.00 (95% CI = -9.52 to 13.52) in long-term group, respectively].

3.5 Other outcomes

Servello et al. followed up 3 PSP cases who underwent DBS and used PSPRS as main outcome in the long term. They observed a reduction of falls and an amelioration of postural balance in all patients, which was an encouraging result [42]. Another two studies also evaluated PSPRS in their cases and reported that there was no obvious improvement [19, 32]. In total, 3 cases from 3 studies provided available FOG-Q scores, including 1 PSP-P patients [38], 2 PSP-PGF patients [40, 41]. The FOG-Q scores among these cases averagely reduced 23.8% at the short-term follow-up visit, with a reduction of 50% in a PSP-PGF patient. However, the sample size was too small to perform statistical analysis.

One article observed a great improvement of apraxia of eyelid opening (AEO) in a PSP patient through bilateral GPi stimulations [44]. Lim and collaborators proved that PPN-DBS significantly increased nocturnal rapid eye movement (REM) sleep in 5 cases including 2 PSP patients [39], which linked PPN with sleep and extended the functions of PPN-DBS. Leimbach et al. focused on the effects of PPN-DBS on cognition through evaluating a comprehensive battery of neuropsychological assessment in 5 PD cases and 2 PSP cases. They concluded that PPN-DBS was generally safe from a cognitive perspective though there was no significant change from before to after surgery [43], which was consistent with the results from other studies on cognitive domains [37, 38].

Additionally, 3 studies mentioned the adverse events about DBS. Intraoperative bleeding is a major surgical adverse event and it occurred in 2 patients with unknown reasons [32]. Other surgical adverse events included apathy and a buccofacial apraxia, which were transient and recoverable [20]. As for stimulation-related adverse events, paraesthesia, oscillopsia, diplopia and dysarthria were observed [19, 20].

4. Discussion

The aim of this study was to summarize the efficacy of DBS in PSP patients through analyzing related articles. To our knowledge, this is the first meta-analysis of DBS for PSP despite the fact that we were only able to combine results from 13 studies. In most cases, the scores of UPDRS Ⅲ decreased under DBS-ON conditions compared to those under DBS-OFF conditions, however, we found no statistical significances. Subgroup analyses indicated that the durations of follow-up time might influence the degree of clinical scales improvement while the phenotypes of PSP and target sites of PPN-DBS made little effects. We further found DBS were associated with sleep, AEO and cognitive functions of PSP patients, in addition to improving axial symptoms like falls and gait disorders.

PPN is a new target of DBS, and several studies have supported the positive effects of PPN-DBS for PD [14, 18, 45]. Garcia-Rill et al. further concluded some possible mechanisms of how stimulation in the PPN area could improve gait [46], which mainly results from the complex anatomy and multiple projections of PPN. There are evidences that position of the electrodes could lead to the variability of clinical response [47], which to some extent, can explain why our result was highly heterogeneous. Furthermore, pathological study observed that cholinergic and noncholinergic neuronal populations in the PPN were more affected in the PSP than in the PD patients [48] and this discovery helps us to understand why the efficacy of PPN-DBS was less obvious in this meta-analysis compared to studies focusing on PD patients. Therefore, in order to optimize the curative effect of PPN-DBS for PSP, it's important to further understand the anatomy of PPN and improve the localization of the optimal targets.

The treatment of PSP is changeling since currently, no effective symptomatic or neuroprotective treatment is available for PSP [10]. DBS is a promising tool for treatment of PSP. Galazky et al. proposed that bilateral PPN-DBS resulted in frequency-dependent effects in PSP patients and they observed low frequency improved cyclic gait parameters while high frequency ameliorated hypokinesia [20], which indicates that choosing proper stimulator parameters for individualized patients is essential. One PSP case treated by double implanted GPiPPN gained better clinical outcomes [42]. Considering that basal ganglia and brainstem are generally affected in PSP patients [49], there may be an increased synergic effect existing when simultaneously stimulating different nucleus if the patient is tolerant.

Our meta-analysis has several limitations. The major limitation is the relatively small number of included studies as well as the small size of eligible participants. Second, some of included studies are case reports and the data from several studies are incomplete, which gains the bias of statistical outcomes though we combined some data from case reports to avoid unavailability. Moreover, it's an important limitation to analyze the clinical scales which were performed in different cases where there were no consistent stimulation procedures, DBS parameters, and washout periods. Finally, the outcome of our study is simple though UPDRS Ⅲ as the primary outcome was well analyzed, we really desire more motor and non-motor scales to evaluate the DBS for PSP. Thus, further well-designed researches with larger cohorts are well needed.

5. Conclusion

The results of this review and analysis support that DBS is a safe and promising clinical tool for treatments of PSP though more data are needed to evaluate the efficacy of DBS in PSP. We suggest that once comprehensively understood, DBS will play an important role in movement disorders.

Abbreviations

PSP: progressive supranuclear palsy; DBS: deep brain stimulation; UPDRS: the Unifed Parkinson Disease Rating Scale; PSP-RS: Richardson's syndrome; PSP-P: PSP-parkinsonism; PSP-PGF: progressive gait freezing; PD: Parkinson's disease; STN: subthalamic nucleus; GPi: globus pallidus interna; PPN: pedunculopontine nucleus; MLR: mesencephalic locomotor region; PSPRS: PSP rating score; FOG-Q: freezing of gait questionnaire; GF-Q: gait and falls questionnaire; PDQ-39: the 39-item Parkinson's disease questionnaire; TUG: timed up and go test; PSP-QoL: progressive supranuclear palsy quality of life scale; AEO: apraxia of eyelid opening; REM: rapid eye movement

Declarations

Author contributions

Yafei Wen searched the articles, selected and assessed the articles, extracted and analyzed the data, and drafted the manuscript; Bin Jiao made contributions to data analysis and manuscript revision; Yafang Zhou and Lu Shen contributed equally to study design, acquisition of data, assessment of articles, analysis and interpretation of data, drafting and revising the manuscript.

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Conflict of interest

The authors have no conflict of interest to report.

Availability of data and materials

All data related to this study are included in this published article

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

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Figures

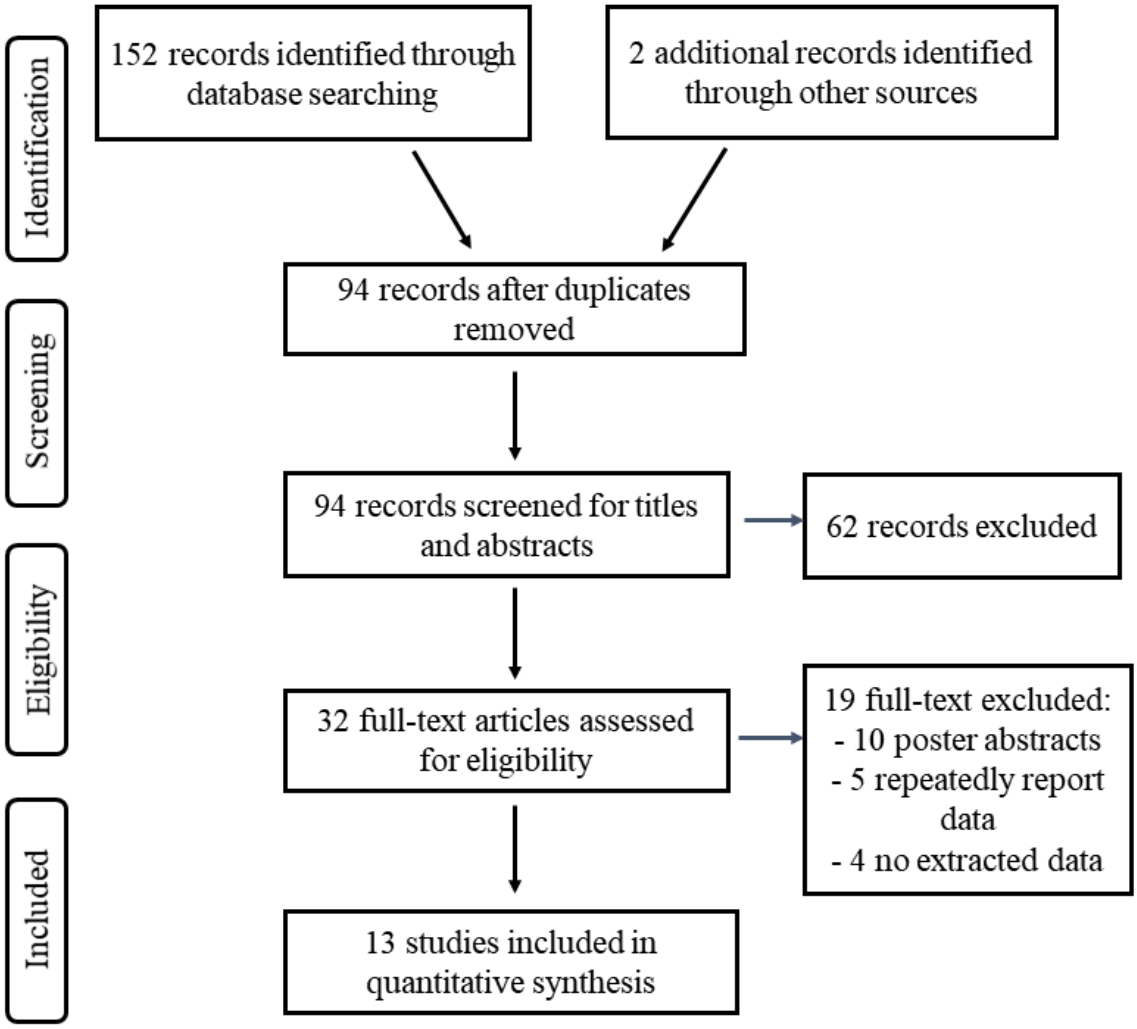
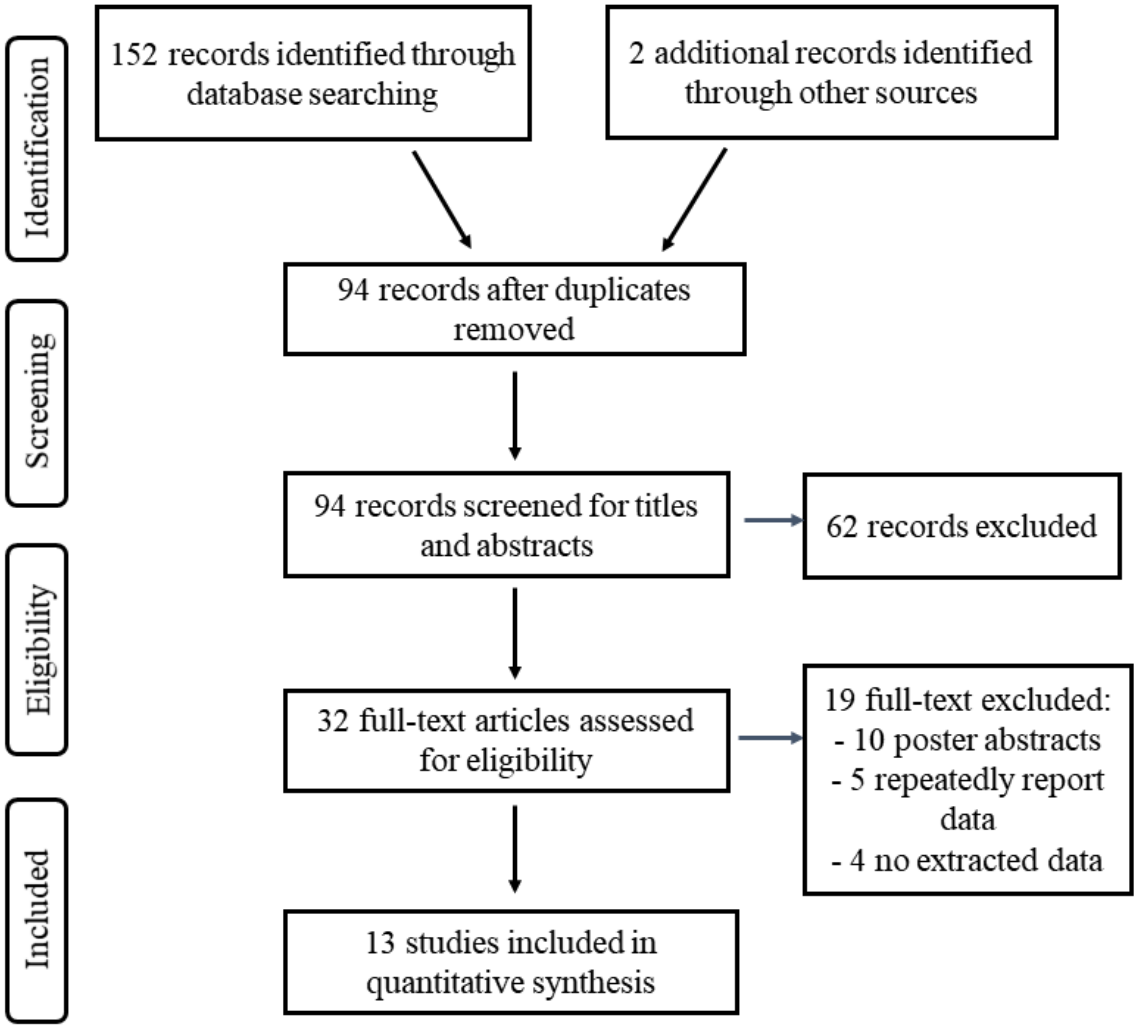


Figure 1

Flow of study information according to PRISMA statement, study selection and reasons for exclusion



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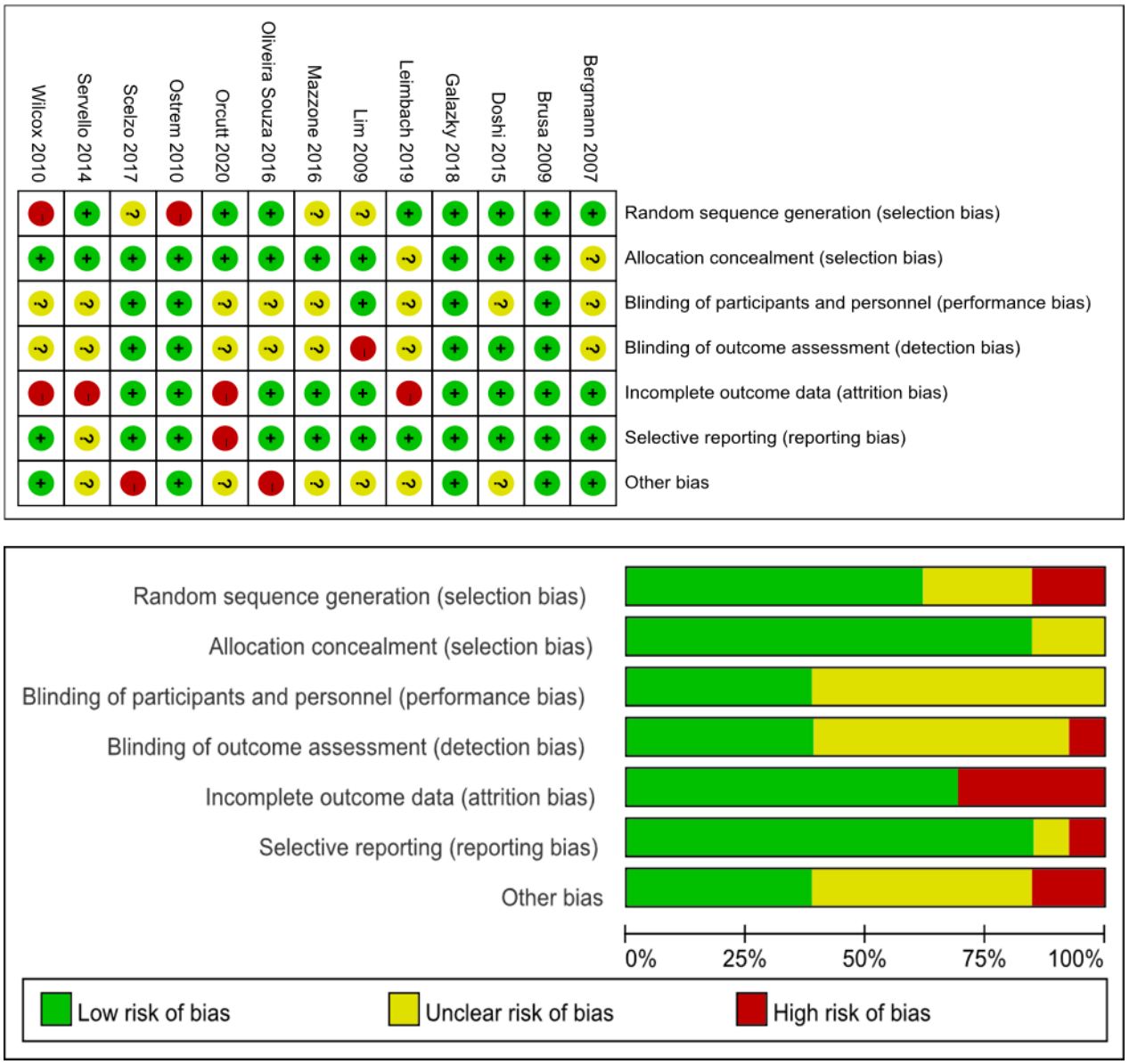
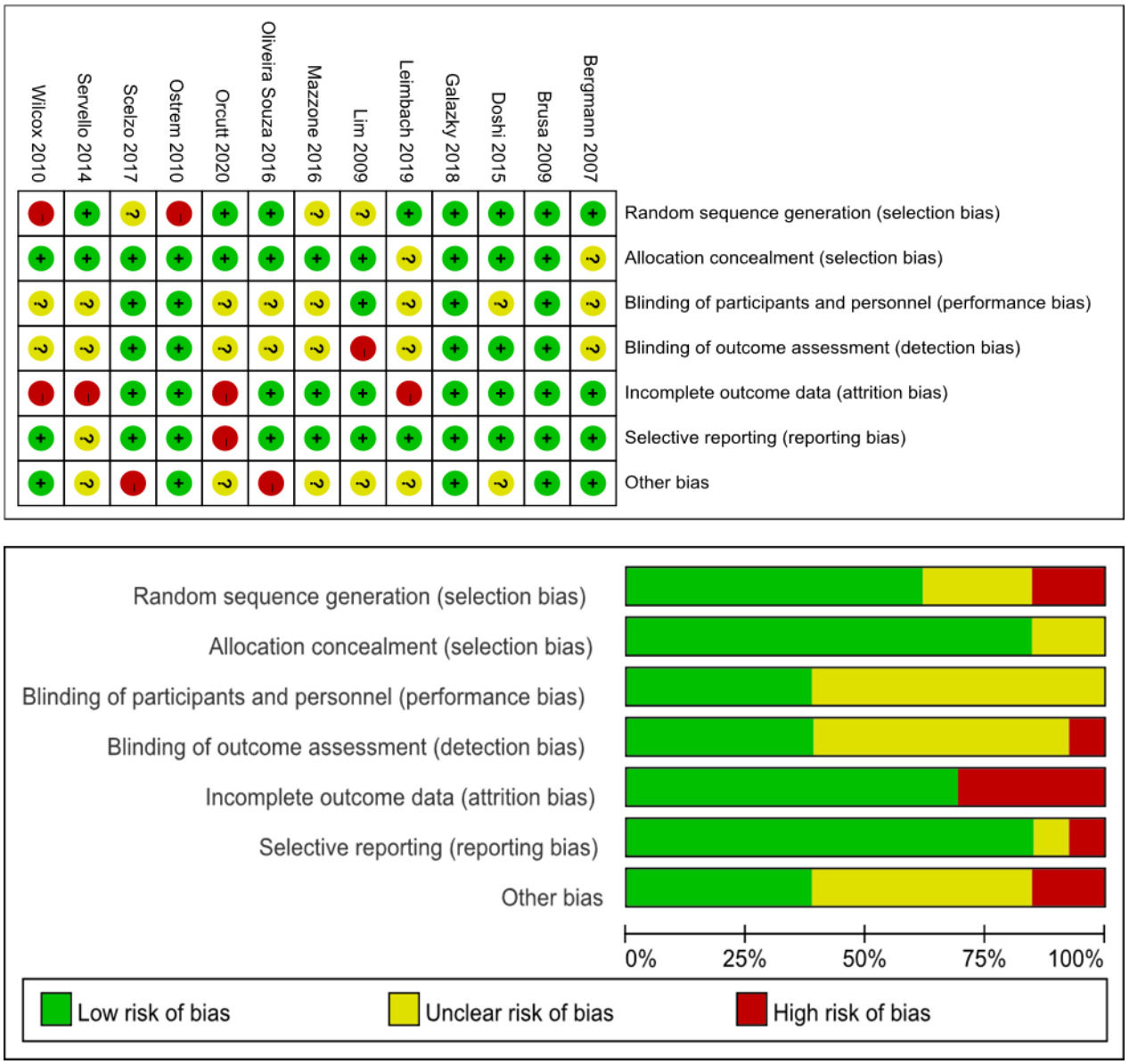


Figure 2

Risk of bias summary and graph



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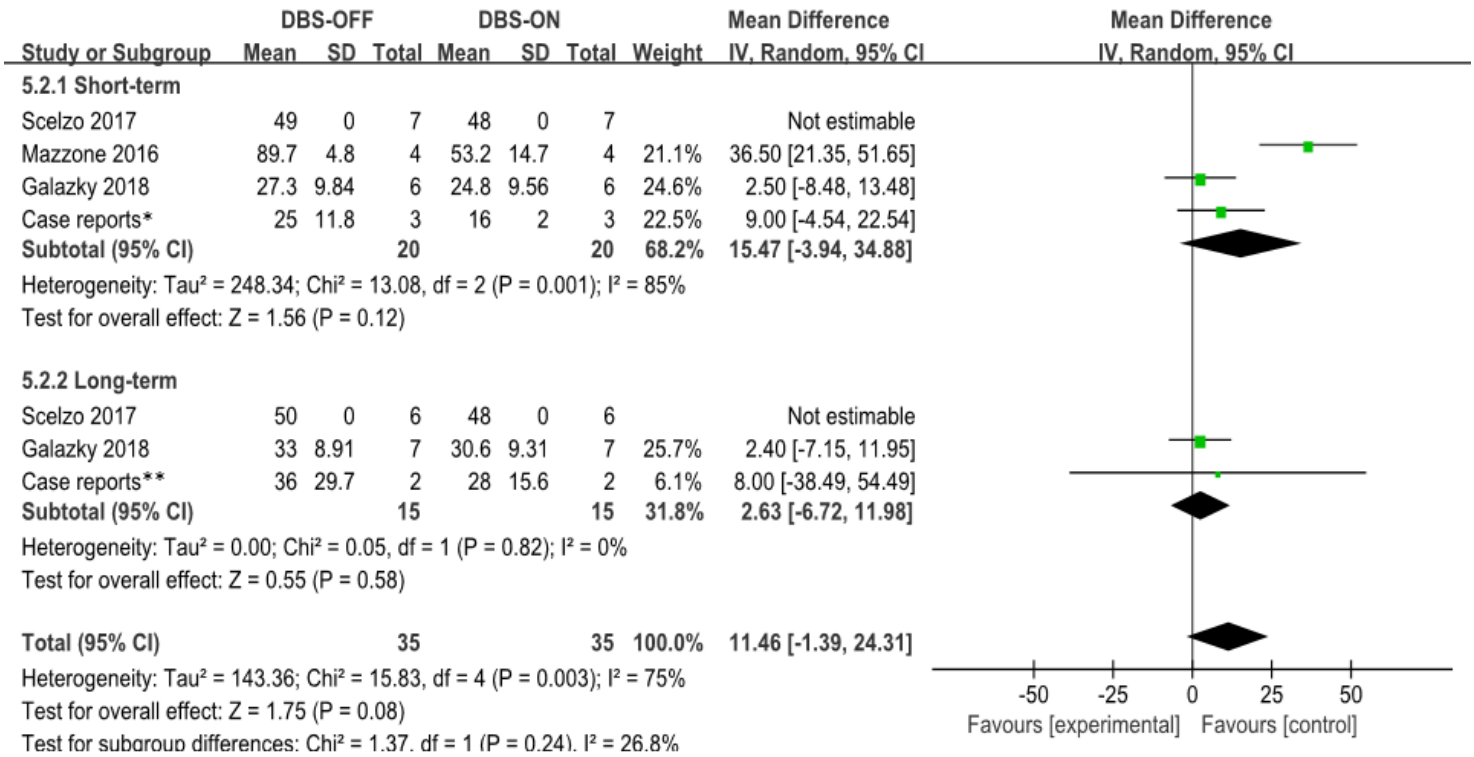
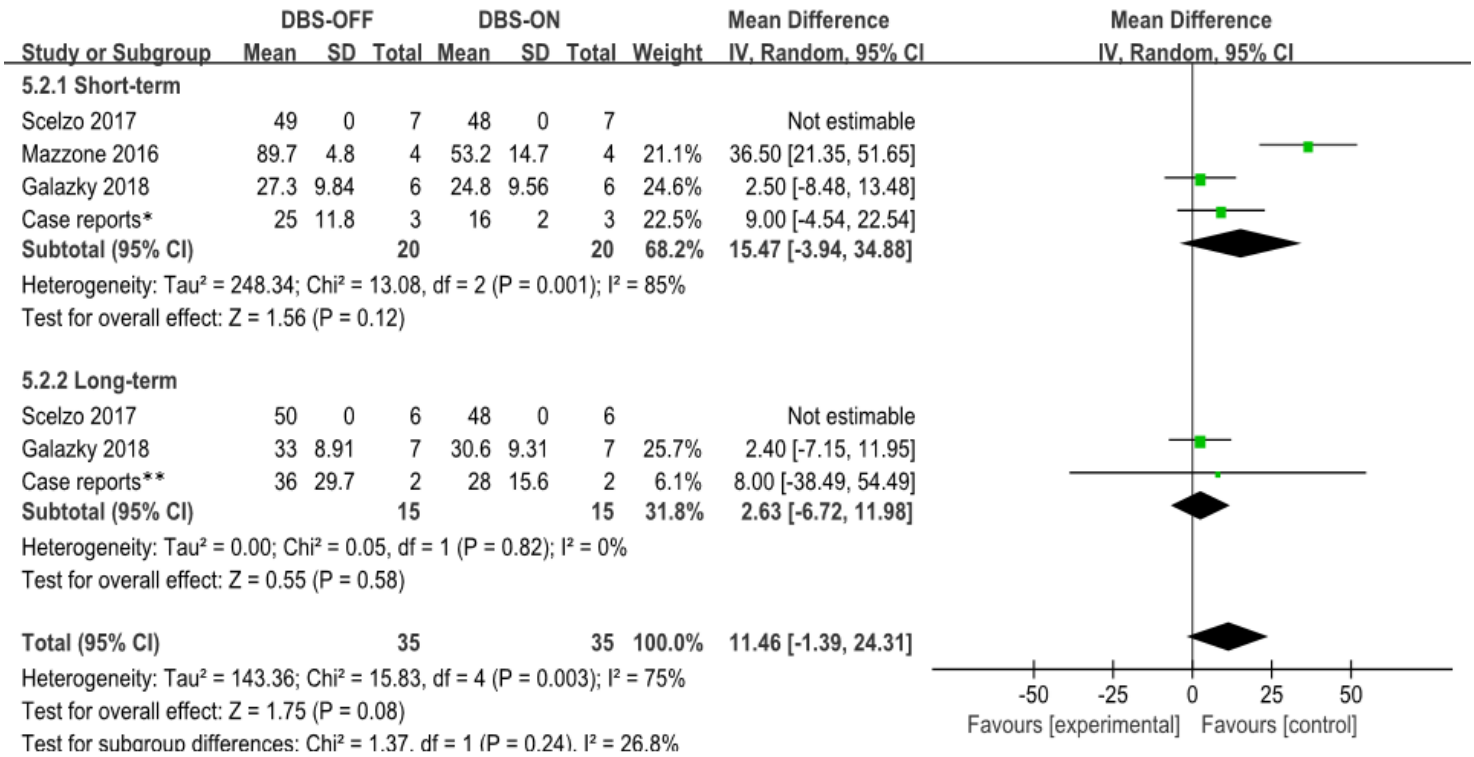


Figure 3

Subgroup analysis of DBS in PSP treatment. Forest plots of standardized mean differences in UPDRS of PSP patients under DBS-OFF and DBS-ON status. Case reports* in short-term group included the data from three case studies [37, 38, 41]; Case reports** in long-term group included the data from two case studies [37, 41]. Short-term less than 12 months after DBS, long-term more than or equal to 12 months after DBS, SD standardized mean, CI confidence interval



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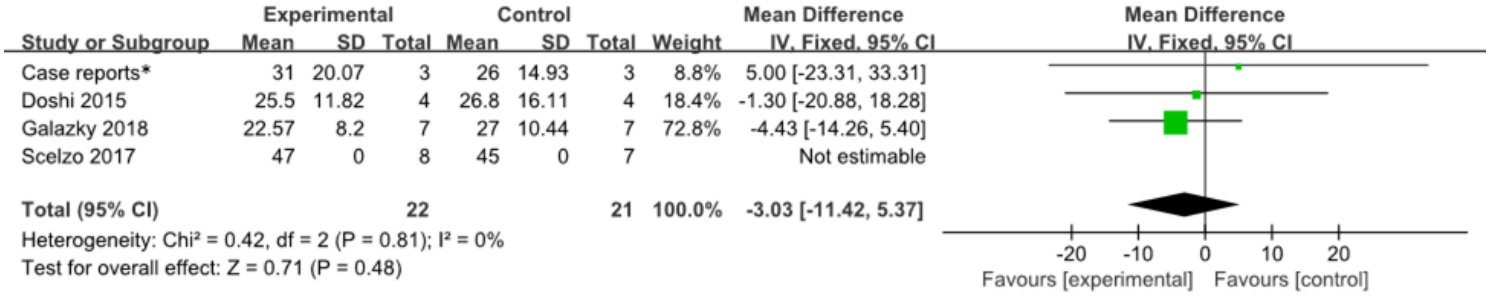

Figure 4

Analysis of DBS in PSP treatment. Forest plots of standardized mean differences in UPDRS of PSP patients under pre-operation (baseline) and post-operation (DBS-ON) status. Case reports* in this meta-analysis included the data from three case studies [16, 38, 41]. SD standardized mean, CI confidence interval

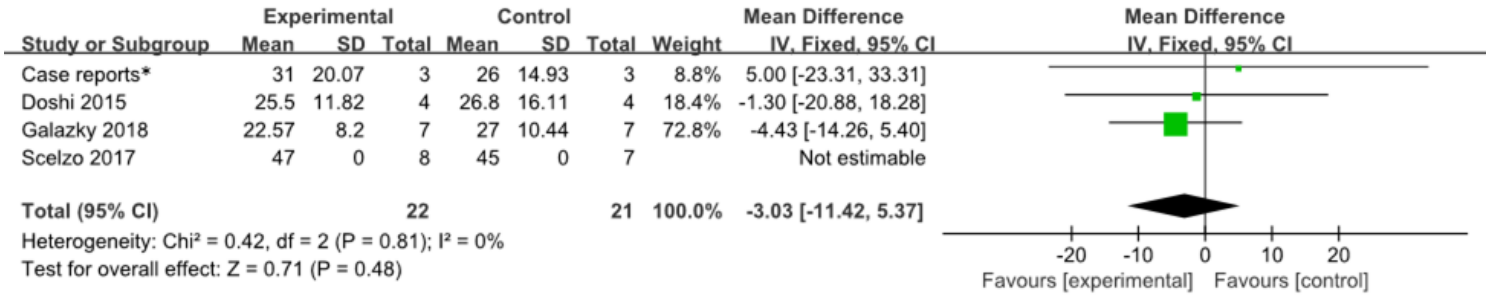

Figure 4

Analysis of DBS in PSP treatment. Forest plots of standardized mean differences in UPDRS Ⅲ of PSP patients under pre-operation (baseline) and post-operation (DBS-ON) status. Case reports* in this meta-analysis included the data from three case studies [16, 38, 41]. SD standardized mean, CI confidence interval

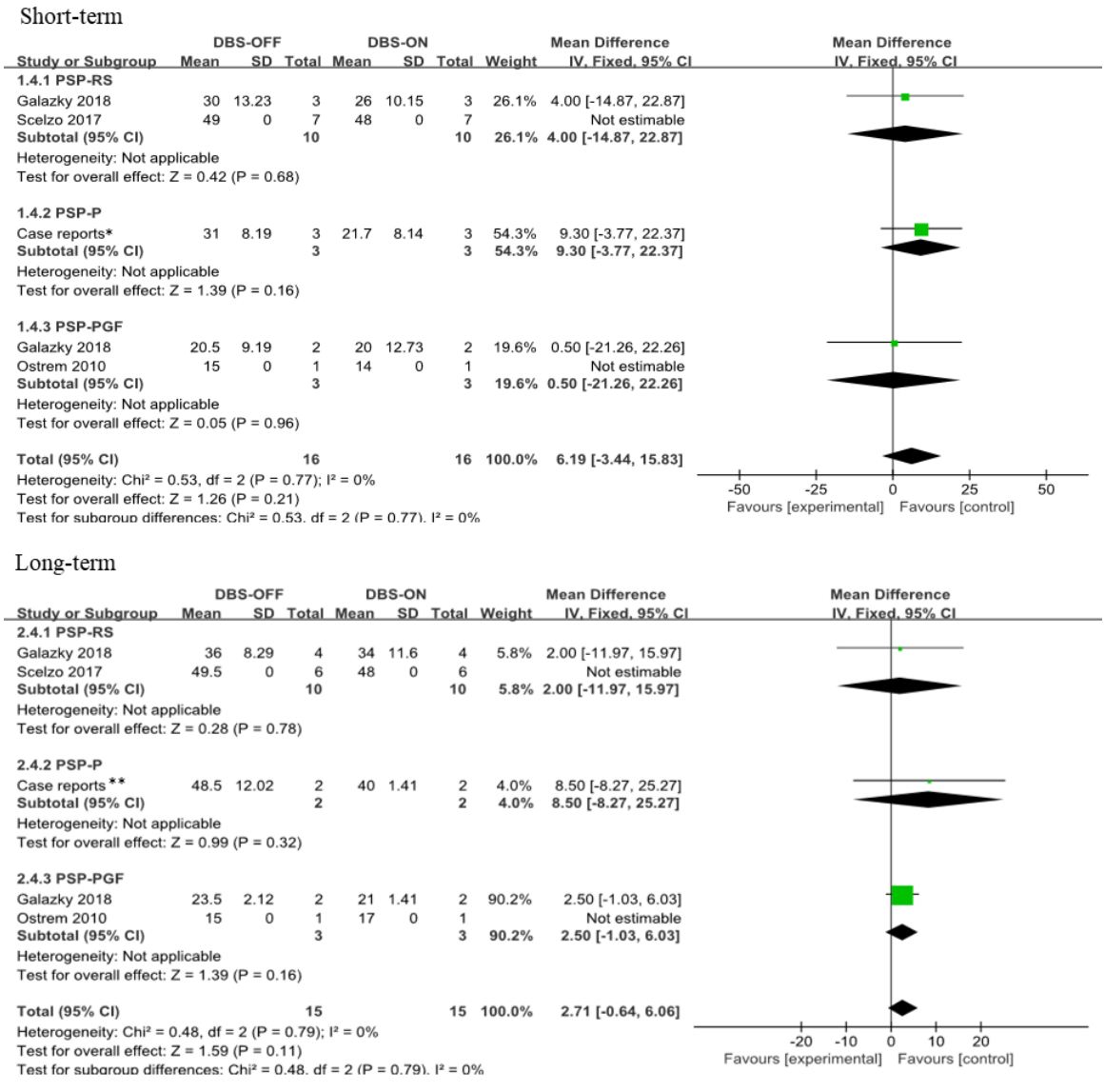

Figure 5

Analysis of DBS in PSP treatment. Forest plots of standardized mean differences in DBS for UPDRS Ⅲ of patients with different PSP phenotypes. Case reports* in short-term group included the data from three case studies [20, 37, 38]; Case reports** in long-term group

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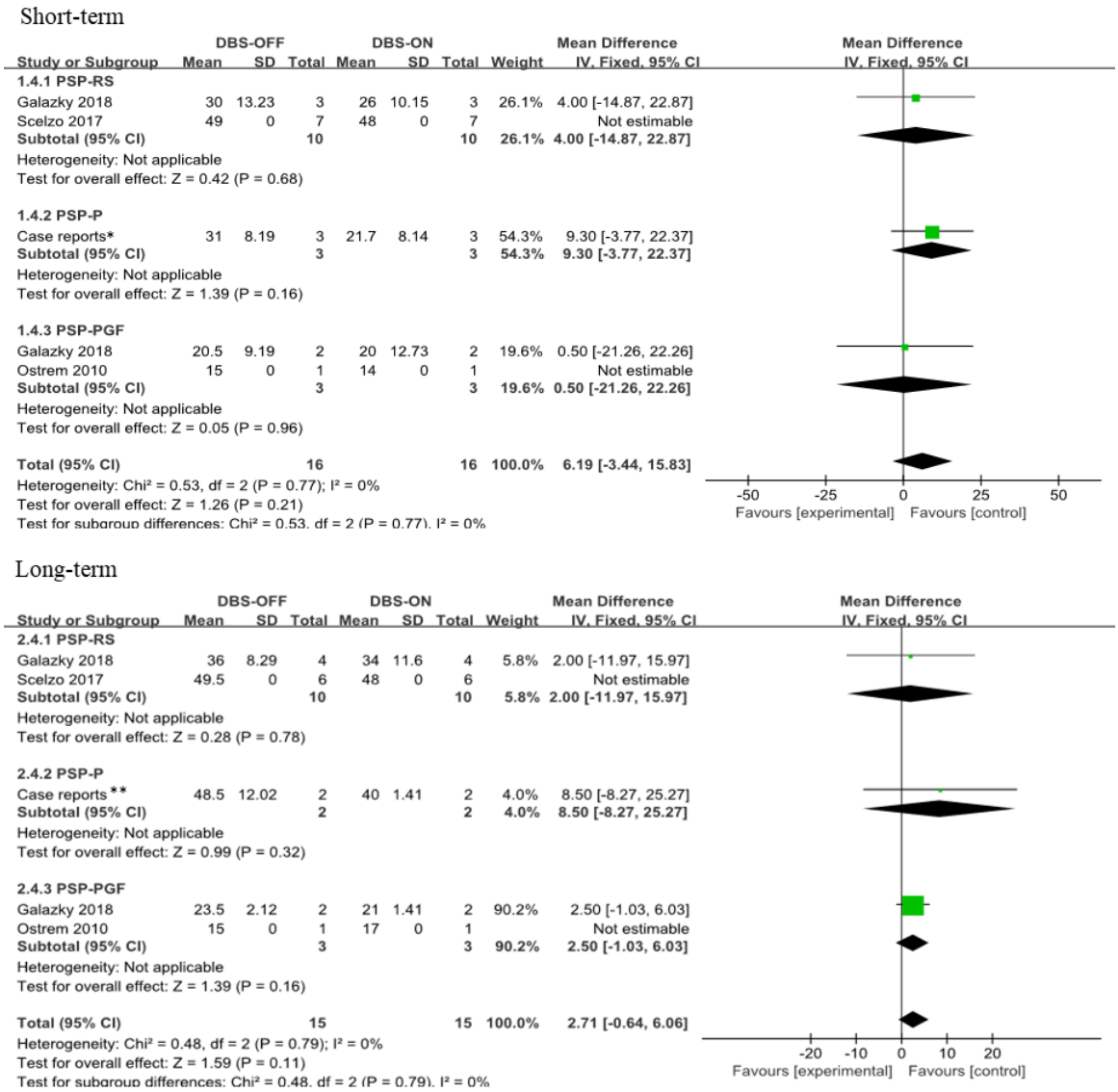

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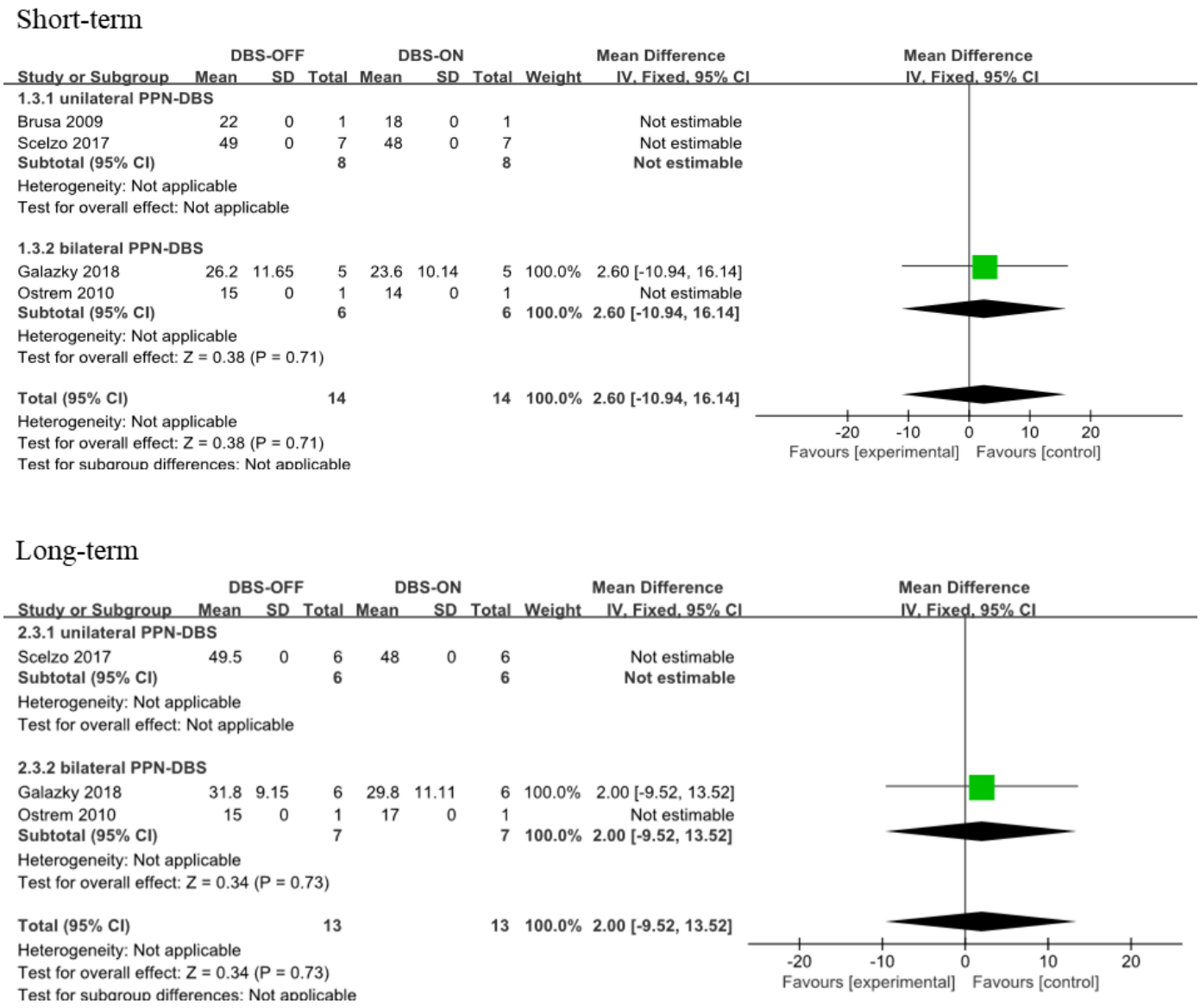
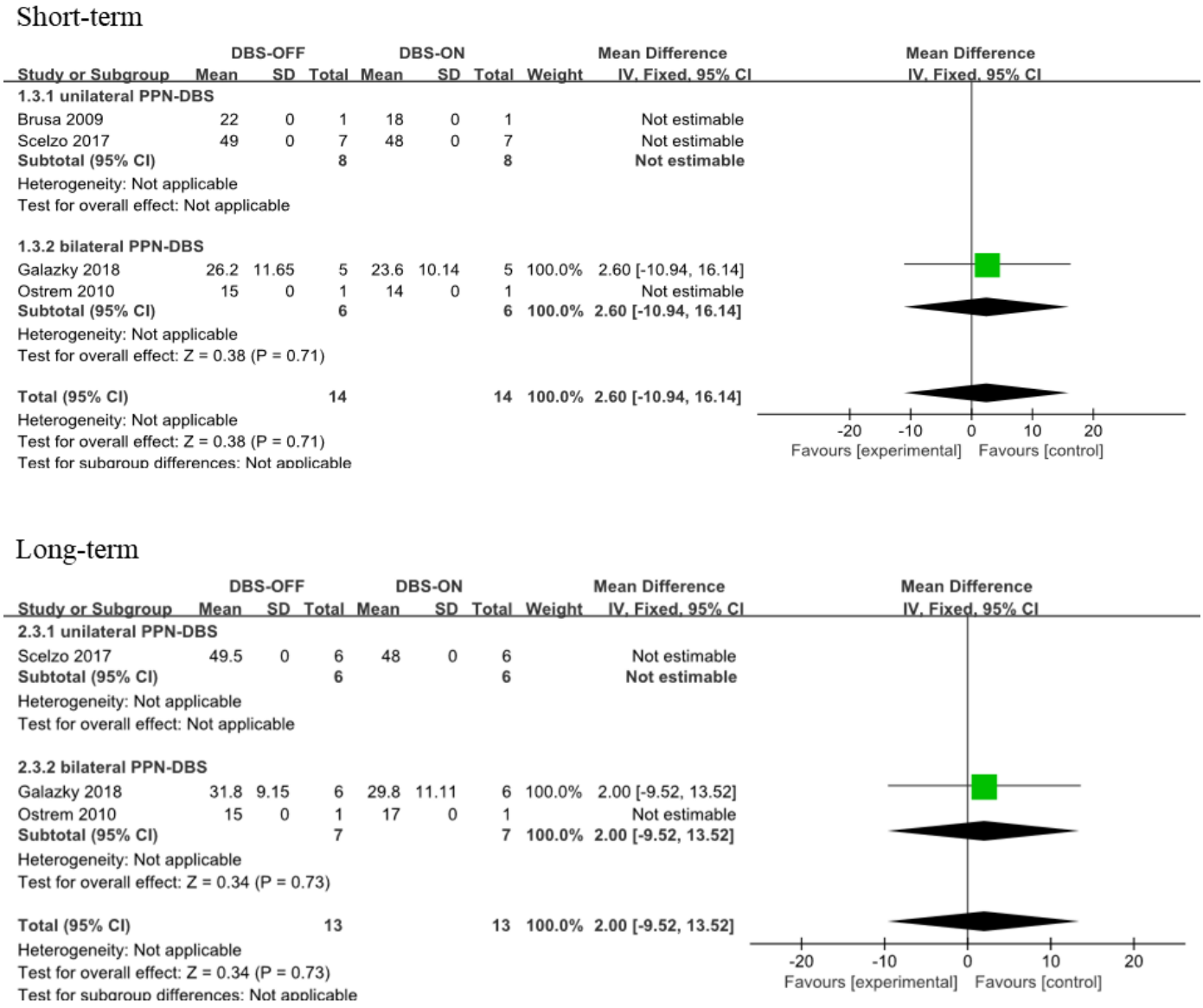


Figure 6

Analysis of DBS in PSP treatment. Forest plots of standardized mean differences in PPN-DBS for UPDRS of PSP patients. Short-term less than 12 months after DBS, long-term more than or equal to 12 months after DBS, SD standardized mean, CI confidence interval



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