

SYSTEMATIC REVIEW



Effects of deep brain stimulation on cognitive functioning in treatment-resistant depression: a systematic review and meta-analysis

N. Runia ^{1,2,3,4}✉, G. J. J. Mol ^{1,2,4}, T. Hillenius ^{1,4}, Z. Hassanzadeh ¹, D. A. J. P. Denys ^{1,2,3} and I. O. Bergfeld ^{1,2,3}

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Deep brain stimulation (DBS) is a promising intervention for treatment-resistant depression (TRD). Effects on cognitive functioning are unclear since they have been studied in small samples. We aim to estimate the impact of DBS on cognitive functioning in TRD with a systematic review and meta-analyses. After systematically searching PubMed we included 10 studies which compared standardized neuropsychological tests before and after DBS or between active and sham DBS in TRD. Different random-effects meta-analyses were done for different cognitive (sub-)domains and for different follow-up time windows (<6 months, 6–18 months, and >18 months). We found no significant differences in cognitive functioning up to 6 months of DBS. After 6–18 months of DBS small to moderate improvements were found in verbal memory (Hedge's $g = 0.22$, 95% CI = [0.01–0.43], $p = 0.04$), visual memory (Hedge's $g = 0.37$, 95% CI = [0.03–0.71], $p = 0.04$), attention/psychomotor speed (Hedge's $g = 0.26$, 95% CI = [0.02–0.50], $p = 0.04$) and executive functioning (Hedge's $g = 0.37$, 95% CI = [0.15–0.59], $p = 0.001$). Not enough studies could be retrieved for a meta-analysis of effects after >18 months of DBS or for the comparison of active and sham DBS. Qualitatively, generally no differences in cognitive functioning between active and sham DBS were found. No cognitive decline was found in this meta-analysis up to 18 months of DBS in patients with TRD. Results even suggest small positive effects of DBS on cognitive functioning in TRD, although this should be interpreted with caution due to lack of controlled data.

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INTRODUCTION

Major depressive disorder (MDD) is one of the largest contributors to disability worldwide, with a lifetime prevalence of 14.6% in high-income countries [1, 2]. MDD is characterized by a depressed mood and/or loss of interest or experiencing pleasure and may lead to cognitive dysfunction in several domains, such as memory, attention, and executive functions [3, 4]. Despite adequate treatment with pharmacological interventions, 30% of patients with MDD do not achieve remission and are referred to as suffering from an advanced stage of treatment-resistant depression (TRD) [5, 6]. For this population, deep brain stimulation (DBS) is a promising solution [7].

DBS is a holistic treatment requiring neurosurgical, psychiatric and psychological expertise. One part consists of a surgical intervention during which electrodes are stereotactically implanted in specific areas of the brain [8]. The electrodes are subcutaneously connected to a pulse generator in the pectoral region which continuously stimulates the brain target [8]. For TRD, the most extensively studied targets are the subcallosal cingulate cortex (SCC), the ventral capsule surrounding the ventral striatum (VC/VS), and the medial forebrain bundle (MFB) [9]. Approximately half of all included patients show a clinical response ($\geq 50\%$ symptom reduction) after one year of open-label neurostimulation

[7]. Although results from randomized, sham-controlled trials have been inconsistent, active DBS shows significantly better antidepressant effects compared to sham DBS in recent meta-analyses [7, 10, 11].

Despite its invasive nature, DBS is considered a safe and well-tolerated treatment for TRD [7]. Nevertheless, extensive research on DBS of the subthalamic nucleus in patients with Parkinson's Disease has shown cognitive decline in several domains including general cognition, visuospatial reasoning and memory, processing speed, executive functions, verbal fluency, and verbal memory [12–14]. Whether such cognitive decline also occur in TRD patients treated with DBS in different target regions compared to Parkinson's Disease, is subject of ongoing research. Several studies have examined the effects of DBS in TRD on cognitive domains including memory, attention, psychomotor speed, executive functions, visuospatial functioning, language, motor skills, visual and verbal fluency, general functioning, and intelligence [15–19]. Outcomes between these studies vary, with some suggesting adverse effects and others suggesting positive effects in specific cognitive domains. However, these studies lack power due to small sample sizes.

Therefore, we aim to investigate the effects of DBS on cognitive functions in patients with TRD by means of a systematic review

¹Department of Psychiatry, Amsterdam UMC location University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands. ²Amsterdam Neuroscience, Amsterdam, The Netherlands. ³Amsterdam Brain and Cognition, Amsterdam, The Netherlands. ⁴These authors contributed equally: N. Runia, G. J. J. Mol, T. Hillenius.

✉email: n.runia@amsterdamumc.nl

and meta-analyses, examining both longitudinal change in cognitive function and potential differences between active and sham stimulation.

METHODS

Details of the protocol for this systematic review and meta-analysis were registered in the PROSPERO International Prospective Register of Systematic Reviews with registration number CRD42022333129. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [20].

Search strategy and eligibility criteria

The PubMed/MEDLINE online database was systematically searched using terms related to DBS combined with terms related to cognitive functions on August 16, 2021 and was repeated on March 16, 2022 (See the Supplementary Materials for full search strategy). Reference lists of the included studies were also examined for additional eligible studies.

Articles were included if they were original studies published in English or Dutch in a peer-reviewed journal. The studies included human adults (≥ 18 years of age) diagnosed with MDD who were being treated with DBS. To reduce the risk of an overly stringent study selection we also included studies with samples with a maximum of 15% bipolar disorder (BP) diagnoses. All studies used neuropsychological tests to measure cognitive function at one pre-DBS baseline assessment and at least one post-DBS follow-up assessment or after active and sham stimulation. Exclusion criteria were studies involving patients with comorbid neurological or psychotic disorders, case studies, or series with four participants or less.

Study selection and quality assessment

Titles and abstracts of the articles that resulted from the initial electronic search on August 16, 2021 were screened and scrutinized by two reviewers (ZH and TH) independently. Articles that clearly did not fulfill the eligibility criteria were excluded. Next, the full texts of the remaining articles were reviewed and ineligible studies were excluded. Additional articles that were identified after the repeated search on March 16, 2022 were similarly reviewed by two reviewers (GM and NR). Any persisting disagreements on eligibility were resolved with the help of a third reviewer (IB). One reviewer (TH) critically appraised all included studies with The Joanna Briggs Institute Critical Appraisal checklist for Case Control studies [21].

Data extraction and outcome measures

Data was extracted by one reviewer (TH) and verified by another reviewer (NR). All data were collected in an SQLite database [22]. The following descriptive variables were extracted from the included studies: author, year, number of included patients (full sample), patient characteristics (age and sex) and stimulation target. If reported, the name of the neuropsychological test, the number of patients taking the test and the outcome (mean and standard deviation (SD)) were extracted for each test assessing cognitive functioning at each individual assessment. Neuropsychological tests were categorized into cognitive domains and subdomains based on generally accepted domains [23], large factor analytical studies [24], or descriptions of the tests in the included articles. The primary outcomes were pre- and post-DBS (baseline vs. follow-up) cognitive functioning. For this, each follow-up assessment was categorized into three follow-up time windows: short-term (< 6 months postoperatively), medium-term (6–18 months postoperatively), or long-term (> 18 months postoperatively). We based these time windows on the different stages of the DBS treatment: during the first 6 months DBS parameters are frequently adapted to optimize effect and cognitive

functioning may be subject to fluctuations. In the 6–18 month range optimization is usually finished and can be considered the initial stabilization phase. The > 18 -month range can be regarded as the maintenance phase and results as long-term effects. If two or more assessments from one study fell into the same follow-up time window, only the longest follow-up assessment was included. The secondary outcome was cognitive functioning during active- compared to sham stimulation.

Statistical analysis

Meta-analyses were performed (baseline vs. short-term follow-up, baseline vs. medium-term follow-up, baseline vs. long-term follow-up and active vs. sham) for all cognitive domains and subdomains tested by at least three different studies. Studies and cognitive domains that were not included in the meta-analyses were reviewed qualitatively. When a study reported on multiple outcome measures belonging to the same cognitive subdomain, or the same domain in case a domain had no subdomains, we included the test outcome that we considered the best fit for that (sub)domain. If a lower score represents a better outcome (e.g., reaction time or the total number of errors), these values were multiplied by -1.0 ensuring a positive effect size always translates into cognitive improvement after DBS. Meta-analyses were performed using random-effects models to account for small sample sizes and expected statistical heterogeneity across studies [25]. As the studies in the quantitative analysis used different neuropsychological tests, a standardized mean difference was computed as Hedges g . Weights of the individual effect sizes were computed using the inverse variance method and the respective 95% CIs were computed using Jackson's method. All analyses were performed using R Statistical Software, version 4.1.0 with the "meta" package [26–28]. The 'Trim-and-Fill' function was used to estimate and adjust the meta-analyses results for publication bias. Forest and funnel plots were generated to visualize the meta-analyses results and publication bias estimates respectively. We considered $p < 0.05$ as significant and effect sizes of 0–0.19 as negligible, 0.2–0.49 as small, 0.5–0.79 as medium and > 0.8 as large effects.

RESULTS

A total of 620 articles were identified of which 20 were potentially eligible for inclusion. After subsequent full-text screening ten articles met the inclusion criteria and were included in the meta-analysis/review. The study selection process is shown in a PRISMA flow diagram (Fig. 1).

The following cognitive domains and their respective subdomains were assessed in the included articles: verbal memory (subdomains: immediate recall, immediate recognition, delayed recall, and delayed recognition), visual memory (subdomains: immediate recall, delayed recall, immediate recognition, and delayed recognition), executive functioning (subdomains: cognitive flexibility, cognitive inhibition, decision making, and planning), verbal fluency (subdomains: general, letter and categorical fluency), visual fluency, working memory, attention/psychomotor speed, visuospatial functioning, language, motor skills, general functioning, concentration and intelligence. For a list of neuropsychological tests included in each study see Supplementary Table 1.

Study and patient characteristics

Study characteristics are summarized in Table 1. The included studies reported on 137 patients (64 male, 73 female) with TRD who received active ($n = 125$) or only sham ($n = 12$) DBS. Across all meta-analyses, 87 unique patients were included (86 MDD/1 BP). The mean age in included studies varied from 40.0 to 53.4 years. Four studies targeted the SCC, two the Nucleus Accumbens (NAcc), two the superolateral branch of the medial forebrain

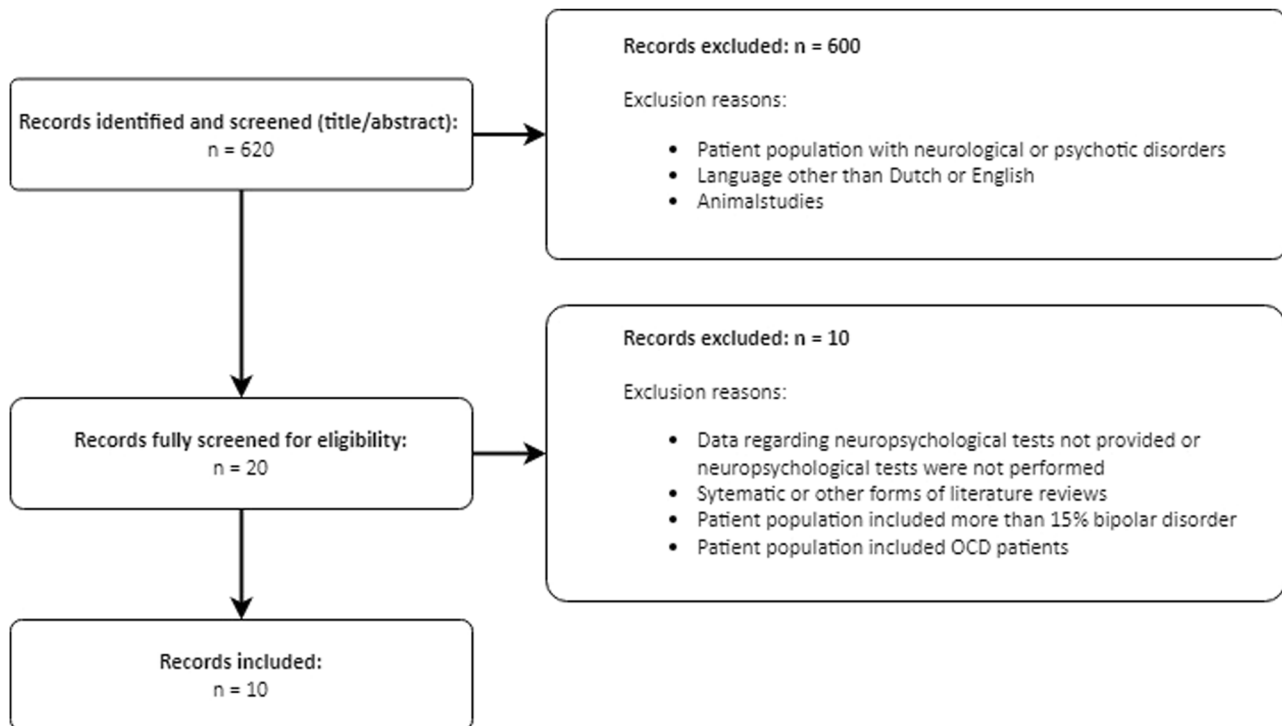


Fig. 1 Flowchart of study selection process. PRISMA flow diagram showing the article screening and study selection process, including reasons for excluding articles.

bundle (sIMFB), one the ventral anterior limb of the internal capsule (vALIC), and one the VC/VS.

Critical appraisal

Quality assessment of the included studies, according to The Joanna Briggs Institute Critical Appraisal checklist for Case Control studies [21], is provided in Supplementary Table 2.

Baseline vs. follow-up

Meta-analyses. All effect sizes, computed for the short-term (<6 months) and medium-term (6–18 months) assessments on cognitive functioning, are summarized in Table 2. Only one study reported a long-term assessment (>18 months) of cognitive functioning. Therefore, no meta-analyses were performed for this follow-up time window. An overview of the forest and funnel plots of each meta-analysis is provided in the Supplementary Materials.

Short-term vs Baseline (<6 months): For the short-term assessment only two domains were reported on by at least three studies. Both verbal memory and executive functioning did not change significantly after up to 6 months of DBS with negligible to small effect sizes ($p > 0.05$).

Medium-term vs Baseline (6–18 months): For the medium-term assessment eight domains were reported on by at least three studies. A small, significant improvement was found for the verbal memory domain (Hedges' $g = 0.22$, 95% CI = [0.01–0.43], $p = 0.04$; Fig. 2). Trim-and-fill in the overall verbal memory domain did not alter results (Hedges' $g = 0.22$, 95% CI = [0.01–0.43], $p = 0.04$). Zooming in into subdomains, we found a small, significant improvement in delayed recall (Hedges' $g = 0.45$, 95% CI = [0.05–0.86], $p = 0.03$) and negligible to small, non-significant effects in the other subdomains ($p > 0.05$).

A small and significant improvement was found for visual memory (Hedges' $g = 0.37$, 95% CI = [0.03–0.71], $p = 0.04$; Fig. 3). With trim-and-fill the effect increased and remained significant

(Hedges' $g = 0.46$, 95% CI = [0.13–0.79], $p = 0.006$). A moderate and significant improvement in the subdomain immediate recall was found (Hedges' $g = 0.57$, 95% CI = [0.10–1.05], $p = 0.02$). All other subdomains showed non-significant effects.

A small and significant improvement was found for executive functioning (Hedges' $g = 0.37$, 95% CI = [0.15–0.59], $p = 0.001$; Fig. 4). With trim-and-fill the effect slightly increased and remained significant (Hedges' $g = 0.40$, 95% CI = [0.18–0.61], $p < 0.001$). A moderate and significant improvement was found for the subdomain planning (Hedges' $g = 0.54$, 95% CI = [0.09–0.99], $p = 0.02$). Small improvements were found for subdomains cognitive flexibility ($p = 0.05$) and cognitive inhibition ($p = 0.07$), which trended towards significance. Decision making showed a negligible and non-significant change.

All other domains showed negligible to small, non-significant changes (working memory, attention/psychomotor speed, language, verbal fluency, and intelligence).

Qualitative review. For the short-term assessment the following domains were reported on by less than three studies: visual memory ($k = 2$), verbal fluency ($k = 1$), visual fluency ($k = 1$), working memory ($k = 1$), visuospatial functioning ($k = 1$), attention/psychomotor speed ($k = 2$), language ($k = 1$), concentration ($k = 1$), general functioning ($k = 1$), and intelligence ($k = 1$). They reported no statistical tests to assess changes after DBS. Based on the reported means and SDs by Coenen et al. [29], Moreines et al. [30], and McNeely et al. [31], generally no substantial changes in cognitive functioning in the above mentioned domains up to 6 months of DBS were observed, though a minor decline in verbal fluency was found by Coenen et al. [29].

For the medium-term assessment the following domains were reported on by less than three studies: motor skills ($k = 2$), visual fluency ($k = 2$), visuospatial functioning ($k = 2$), and general functioning ($k = 2$). McInerney et al. [32] and Fenoy et al. [33] reported no significant differences in motor skills after 12 months of DBS. Grubert et al. [17] reported significant improvements in

Table 1. Study characteristics of studies included in the meta-analyses and qualitative review.

Study	n ^a	Sex, (n) ^a	Mean age at Inclusion (SD) ^a	Target
Bergfeld et al. [15]	25	Male (8)/Female (17)	53.1 (8.4)	vALIC
Bewernick et al. [34]	11	Male (7)/Female (4)	48.4 (11.1)	NACC
Coenen et al. [29]	Active→ 8 ^b	Male (5)/Female (3)	Active: 53.4 (8.4)	sIMFB
	Sham lead-in→ 8	Male (5)/Female (3)	Sham: 49.9 (11.9)	
Fenoy et al. [33]	6	Male (2)/Female (4)	50.2 (10.2)	sIMFB
Grubert et al. [17]	10	Male (6)/Female(4)	48.6 (11.7)	NACC
Kubu et al. [19]	Active→ 13	Male (5)/Female (8)	Active: 47.1 (14.0)	VC/VS
	Sham→ 12	Male (9)/Female (3)	Sham: 49.9 (8.4)	
McInerney et al. [32]	20	Male (9)/Female (11)	47.4 (10.4)	SCC
McNeely et al. [31]	6	Male (3)/Female (3)	46.0 (8.0)	SCC
Moreines et al. [30]	10	Male (3)/Female (7)	40.0 (9.3)	SCC
Serra-Blasco et al. [36]	8	Male (2)/Female (6)	46.0 (11.6)	SCC

SD standard deviation, vALIC ventral anterior limb of the internal capsule, sIMFB superolateral branch of the medial forebrain bundle, VC/VS ventral capsule/ventral striatum, SCC subcallosal cingulate.

^aRefers to the entire included sample. If reported, the sample size for each individual neuropsychological test at each assessment is provided in the forest plots of each meta-analysis. If not reported, the full sample size was assumed for neuropsychological assessments.

^bIncludes one patient with bipolar disorder.

Table 2. Effect sizes (Hedges' G) comparing cognitive functions up to 6 months and between 6 to 18 months of DBS with baseline.

Domain and Subdomains	<6 months				6–18 months			
	k	Hedges' g	95% CI	p value	k	Hedges' g	95% CI	p value
Verbal Memory	3	-0.15	[-0.60; 0.30]	0.50	7	0.22	[0.01; 0.43]	0.04
Immediate Recall	3	-0.10	[-0.68; 0.47]	0.73	6	0.20	[-0.14; 0.55]	0.25
Delayed Recall	1	N/A			5	0.45	[0.05; 0.86]	0.03
Immediate Recognition	1	N/A			2	N/A		
Delayed Recognition	0	N/A			3	0.15	[-0.31; 0.62]	0.52
Visual Memory	2	N/A			4	0.37	[0.03; 0.71]	0.04
Immediate Recall	1	N/A			3	0.57	[0.10; 1.05]	0.02
Delayed Recall	1	N/A			3	0.30	[-0.33; 0.94]	0.35
Immediate Recognition	0	N/A			0	N/A		
Delayed Recognition	0	N/A			2	-0.12	[-0.93; 0.69]	0.77
Working Memory	1	N/A			3	-0.05	[-0.63; 0.53]	0.87
Attention/Psychomotor Speed	2	N/A			6	0.30	[-0.19; 0.80]	0.23
Executive Functioning	3	0.26	[-0.07; 0.59]	0.12	7	0.37	[0.15; 0.59]	0.001
Cognitive Flexibility	3	0.36	[-0.22; 0.94]	0.22	6	0.34	[-0.004; 0.68]	0.05
Cognitive Inhibition	3	0.22	[-0.36; 0.80]	0.45	4	0.43	[-0.04; 0.91]	0.07
Planning	1	N/A			4	0.54	[0.09; 0.99]	0.02
Decision Making	2	N/A			3	0.05	[-0.56; 0.66]	0.88
Language	1	N/A			4	0.22	[-0.21; 0.64]	0.32
Verbal Fluency	1	N/A			3	-0.13	[-0.58; 0.32]	0.57
General	1	N/A			0	N/A		
Category	0	N/A			2	N/A		
Letter	0	N/A			3	-0.13	[-0.68; 0.42]	0.65
Intelligence	1	N/A			3	0.39	[-0.38; 1.16]	0.32

CI confidence interval.

Significant results are indicated in bold.

visual fluency and visuospatial functioning after 12 months of DBS whereas Fenoy et al. [33] found no differences in these domains. Additionally, Grubert et al. [17] and Fenoy et al. [33] found no significant difference in general functioning.

Only one study reported a long-term assessment (>18 months) of cognitive functioning. Bewernick et al. [34] reported no significant differences in cognitive functioning after 24 to 36 months of DBS, except for a significant improvement in visual fluency.

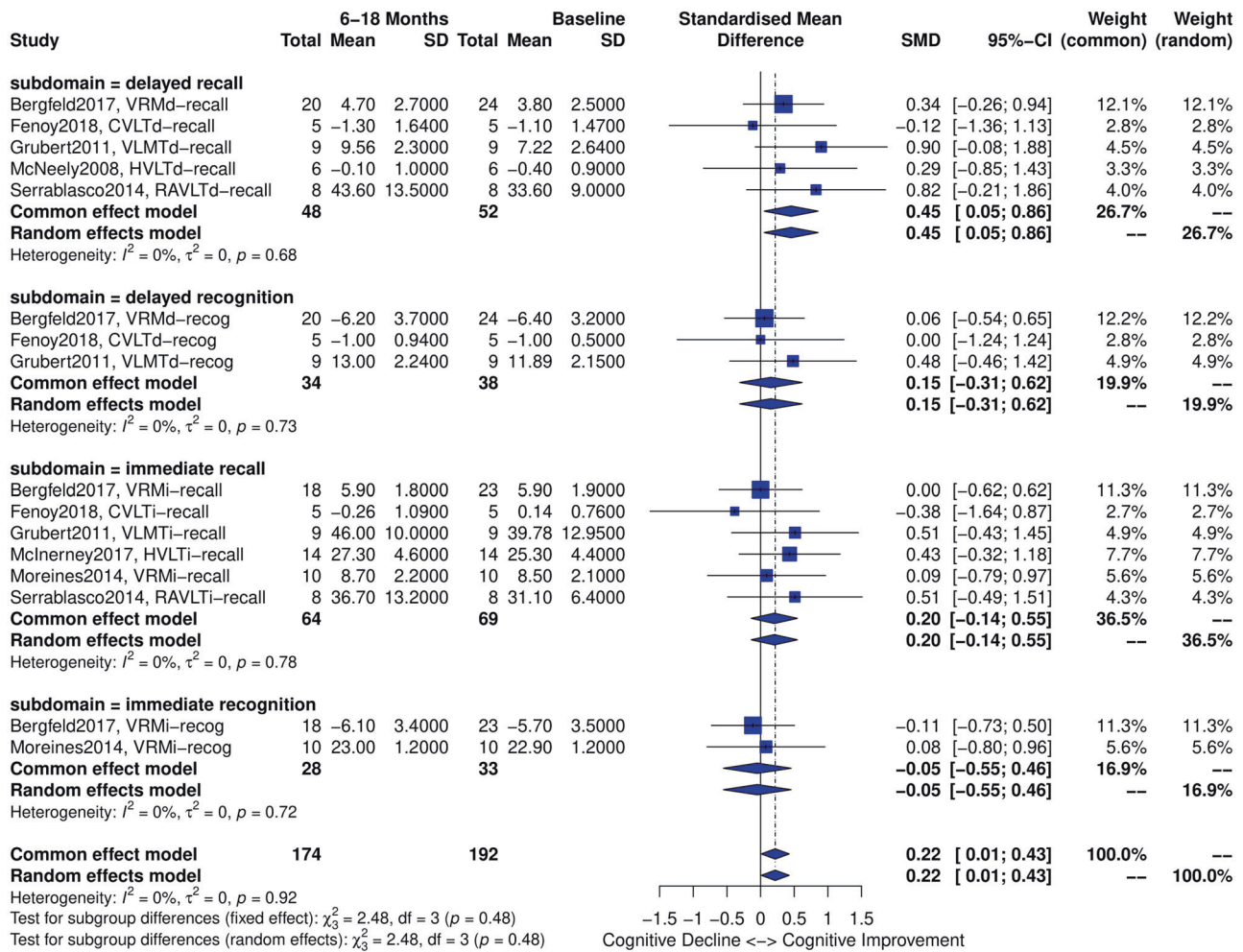


Fig. 2 Meta-analysis forest plot depicting changes in cognitive domain Verbal Memory after 6–18 months of DBS. A small, significant, positive effect was found for the overall domain ($p = 0.04$) comprised of a small, significant, positive effect in the subdomain of delayed recall ($p = 0.027$) and a small, non-significant, positive effect in immediate recall ($p > 0.05$). Abbreviations: SD standard deviation, SMD standardized mean difference (Hedges' g), CI confidence interval, VLMT Verbal Learning and Memory Test, HVL Hopkins Verbal Learning Test, VRM Verbal Recognition Memory, CVLT California Verbal Learning Test, RAVLT Rey Auditory Verbal learning Test, recog recognition, i immediate, d delayed.

Active vs. sham DBS

Three studies compared cognitive functioning during active vs. sham stimulation [15, 19, 29]. Due to differences in study design, outcome measures, follow-up- and stimulation time, data was too heterogeneous for meta-analyses. Therefore, available evidence was reviewed qualitatively per neurocognitive (sub)domain. Studies compared outcomes in the domains of general functioning ($k = 1$), verbal memory ($k = 3$), visual memory ($k = 3$), working memory ($k = 2$), attention/psychomotor speed ($k = 3$), executive functioning ($k = 3$), visual fluency ($k = 1$), verbal fluency ($k = 1$), visuospatial functioning ($k = 1$), language ($k = 1$), intelligence ($k = 2$) and motor skills ($k = 1$).

Bergfeld et al. [15] randomized 16 patients with vALIC DBS to a 12-week cross-over phase during which patients received 6 weeks of active and six weeks of sham stimulation. No significant differences in cognitive functioning after active vs. sham stimulation were found for any of the assessed domains. However, a trend (defined as $0.01 < p < 0.05$) was reported towards better functioning in the domains of language and attention/psychomotor speed after active stimulation. Domains of executive functioning and visual memory and verbal memory showed no significant differences.

Kubu et al. [19] randomized 25 participants to active ($n = 13$) vs. sham ($n = 12$) stimulation for 16 weeks in a double-blind study.

None of the tests assessing verbal, visual and working memory, attention/psychomotor speed, verbal fluency, motor skills or intelligence showed significant differences between the active and sham groups over time. A measure assessing executive functioning (cognitive flexibility and cognitive inhibition) did show a trend towards decline in the active group compared to the sham group, but this did not survive multiple comparisons correction.

Coenen et al. [29] had a single-blind, randomized sham lead-in phase during which eight of their participants received sham stimulation and eight others received active stimulation. Over a period of eight weeks, no significant differences were found between groups for any of the cognitive domains (general functioning, executive functioning, verbal-, visual-, or working memory, attention/psychomotor speed, visual fluency, visuospatial functioning, language or intelligence).

In conclusion, none of the included studies found statistically significant differences in cognitive functioning between active and sham stimulation.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis aiming assessing the effect of DBS on cognitive outcomes in patients suffering from TRD. Our meta-analyses showed

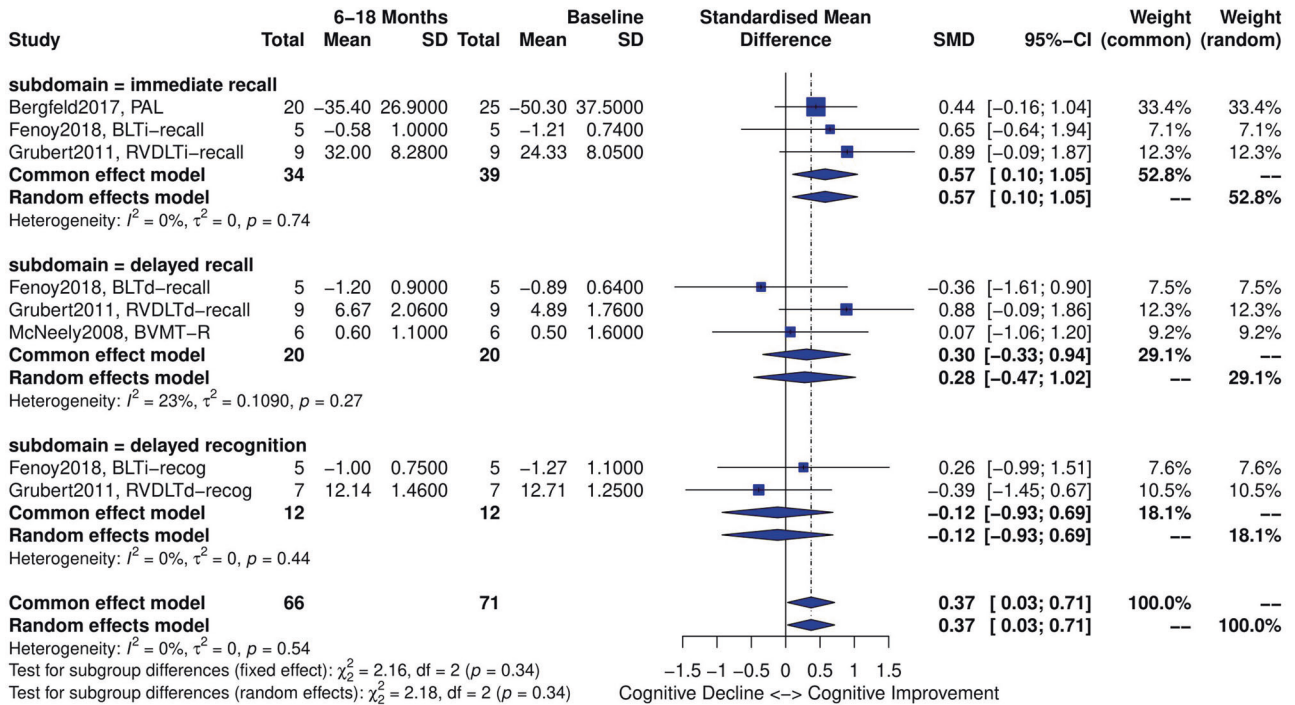


Fig. 3 Meta-analysis forest plot depicting changes in cognitive domain Visual Memory after 6–18 months of DBS. A small, significant, positive effect was observed for the overall domain ($p = 0.035$) comprised of a moderate, significant, positive effect in the subdomain immediate recall ($p = 0.018$), and a small, non-significant, positive effect for subdomain delayed recall ($p > 0.05$). Abbreviations: SD standard deviation, SMD standardized mean difference (Hedges' g), CI confidence interval, PAL Paired Associates Learning, BLT Brown Location Test, RVDLT Rey Visual Design Learning Test, BVMT-R Brief Visual Memory test Revised, i immediate, d delayed, recog recognition.

significant, small improvements in verbal memory (predominantly delayed recall), visual memory (predominantly immediate recall), and executive functioning (predominantly planning) after 6–18 months of stimulation. The short term (<6 months) meta-analysis did not yield any significant changes, but only two domains were assessed. One study with a follow-up of over 18 months was available, which did not find cognitive decline. Additionally, studies comparing sham versus active DBS did not show significant differences in cognitive functioning.

These results are reassuring for clinical practice as they provide further support for DBS as a safe treatment for TRD. Concerns of cognitive decline following DBS [14] should be attenuated in patients with TRD since no indication for decline was found in any of the cognitive domains. Moreover, our meta-analysis shows a significant improvement in verbal memory, visual memory, and executive functioning, further substantiating the safety of DBS for TRD. These improvements may be observed secondary to a depressive symptom decrease as a direct result of DBS. However, multiple studies found no correlation between cognitive improvement and symptom improvement [17, 19, 32]. This might suggest that the cognitive improvement may be a direct effect of DBS and partly independent of symptom improvement. On the other hand, these cognitive improvements can likely be explained by practice effects, a phenomenon that is observed across tests of many cognitive domains, including verbal memory, visual memory, and executive functioning [35]. Indeed, the significant cognitive improvements after DBS that were found in the two included studies that did incorporate a (healthy) control group found the same improvements in the control group [15, 36]. Future studies should incorporate (healthy) control groups and compare cognitive changes in responders with non-responders to differentiate cognitive improvement from practice effects and symptom improvement.

Our findings are in contrast with the cognitive decline on some domains in patients with Parkinson's disease after DBS, which is

the main source of concern for cognitive decline following DBS [12–14]. This difference may be explained by three inherent population and treatment characteristics that could potentially coincide. First, cognitive decline in DBS studies on Parkinson's could include more degenerative effects related to aging compared to our study [37]. Mean age at diagnosis of Parkinson's Disease is 70 years [38] whereas studies included in our meta-analysis report substantially lower average ages between 40 and 50 years. Additionally, advancing age is a risk factor for postoperative cognitive decline in Parkinson's Disease [39–41], further substantiating the role of age related differences. Second, Parkinson's Disease is a progressive, neurodegenerative movement disorder known to cause cognitive decline and even dementia in later stages of the disease [42–44]. Conversely, MDD has been associated with moderate dysfunction in several cognitive domains, but is not typically associated with a faster cognitive decline over time [45, 46]. Cognitive dysfunction in MDD may lead to an earlier cross of the threshold for clinical dementia due to lower cognitive reserve [37, 45, 46], but this association is predominantly found in late onset depression (>60 years) [45, 46]. Finally, the difference in cognitive changes following DBS may be related to the stimulation site. Target regions for Parkinson's Disease are located in the motor circuitry of the basal ganglia, the subthalamic nucleus or globus pallidus internus [47, 48], whereas targets for TRD typically reside in distributed frontolimbic networks associated with the processing of emotion and reward [49–53]. Although little is known about the exact mechanisms behind cognitive effects following DBS, stimulation induced engagement of (pre)frontal regions [53–57] may contribute to the observed cognitive improvement following DBS in targets for TRD [32, 55].

In this regard, it would be interesting to consider possible differences between various DBS targets or exact stimulation sites. The limited number of existing studies does not justify a formal meta-regression with DBS targets as a predictor. However, existing

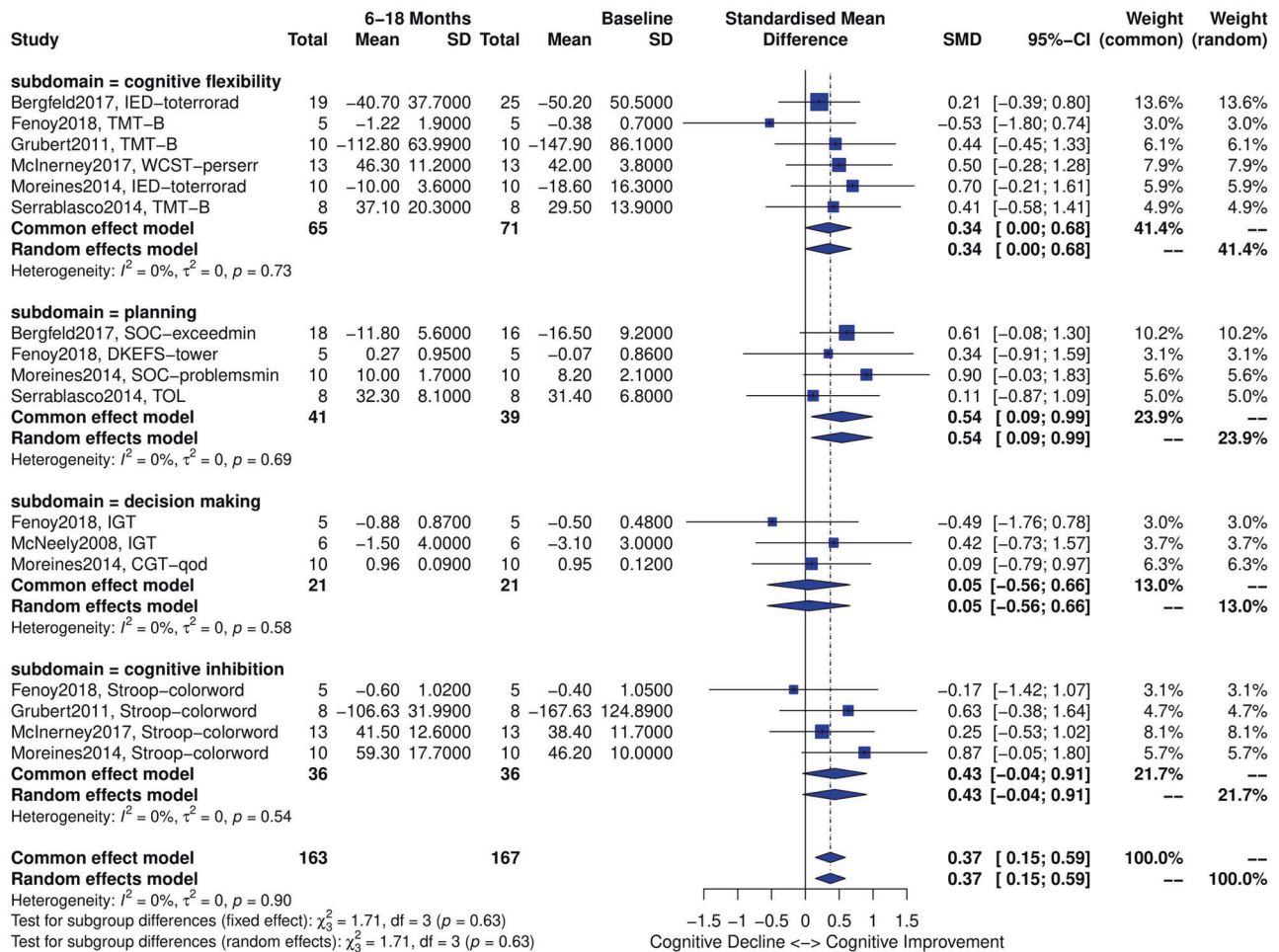


Fig. 4 Meta-analysis forest plot depicting changes in cognitive domain Executive Functioning after 6-18 months of DBS. A small, significant, positive effect was found for the overall domain ($p = 0.001$) comprised of a moderate, significant, positive effect for the subdomain planning ($p = 0.019$) and small, non-significant, positive effects for subdomains cognitive flexibility ($p = 0.053$) and cognitive inhibition ($p = 0.073$). Abbreviations: SD standard deviation, SMD standardized mean difference (Hedges' g), CI confidence interval, TMT Trail Making Test, WCST-perserr Wisconsin Card-Sorting Test – perseverative errors, OA Object Alternation, IED-toterrorad Intra/Extradimensional Shift – total errors, adjusted, IGT Iowa Gambling task, CGT-qod Cambridge Gambling Test – quality of decision making, SOC-problemsmin/exceedmin Stockings of Cambridge – problems solved in minimal moves/number of moves exceeding the minimum needed to solve the exercises, DKEFS-tower Delis-Kaplan Executive Function System – tower test, TOL Tower of London.

data could be used to explore whether stimulation of specific tracts are associated with changes in specific cognitive domains. A similar approach has resulted in specification of bundles that result in more symptom improvement [58-60].

Our study has several limitations. First, due to the relatively small patient samples included in our analyses there is limited statistical power. Therefore, it is not possible to draw definitive conclusions. After pooling all available data, only 87 unique patients were included for formal meta-analyses and effect sizes should, therefore, be regarded as preliminary. Second, as discussed above, since most studies did not include a (healthy) control group, it is difficult to differentiate between actual cognitive improvements due to DBS and practice effects. Finally, we defined rather liberal time windows for our meta-analyses. Our main findings come from studies with a follow-up assessment between 6-18 months of DBS. However, the effect of DBS on cognitive functioning at 6 months may be different compared to 18 months. Future research should expand on our meta-analysis with more narrow time windows in order to draw specific conclusions on the timing of the effects on cognitive functioning following DBS.

In conclusion, no cognitive decline was found in our meta-analyses after 6-18 months of DBS in patients with TRD. This provides further support for DBS as a safe treatment for TRD. Notably, our analysis did show small, significant positive effects after 6-18 months of DBS in the cognitive domains of verbal memory, visual memory, and executive functioning. It currently remains difficult to conclude whether these improvements are due to practice effects, a direct effect of DBS, or a secondary to depressive symptom improvement. Future studies with larger sample sizes and (healthy) control groups are necessary to corroborate these preliminary results, identify potential differences between target sites and control for depressive symptom improvement and practice effects.

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AUTHOR CONTRIBUTIONS

NR, GM, and TH: these authors contributed equally to this work. Conceptualization: TH and IB. Investigation: NR, GM, TH, ZH, and IB. Project administration: IB.

Methodology: NR, GM, TH, and IB. Formal analysis: NR and TH. Writing—original draft and visualization: NR, GM, and TH. Supervision: DD and IB. Writing—review & editing: all authors.

COMPETING INTERESTS

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Correspondence and requests for materials should be addressed to N. Runia.

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