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Comparative efficacy of deep brain stimulation in refractory epilepsy with cognitive impairment: a Meta-analysis

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Abstract

Deep brain stimulation (DBS) has been recognized as a promising treatment for drug-resistant epilepsy (DRE); however, its effects on comorbid cognitive impairment remain insufficiently explored. This meta-analysis assessed the effectiveness of DBS in improving cognitive function (including memory, attention, executive function, and processing speed) in DRE patients with concurrent cognitive deficits, while synthesizing evidence on seizure reduction and quality of life (QoL). In accordance with PRISMA guidelines, we analyzed data from 15 prospective studies and randomized controlled trials (RCTs) encompassing 494 participants. Standardized mean differences (SMDs) were computed using a random-effects model, with heterogeneity evaluated via I^2 statistics. Results demonstrated significant cognitive improvements across all domains: memory (SMD = 2.05, 95% CI: 1.71–2.39), attention (SMD = 1.36, 95% CI: 1.05–1.67), executive function (SMD = 1.67, 95% CI: 1.29–2.04), and processing speed (SMD = 2.09, 95% CI: 1.80–2.38; all $p < 0.001$). Subgroup analyses indicated that higher stimulation parameters (voltage, pulse width) were associated with enhanced efficacy, though inter-study heterogeneity (I^2=60.4–81.0%) highlighted variability in patient characteristics and DBS protocols.And another subgroup analysis showed DBS significantly improves cognition across memory, attention, executive function, and processing speed. CMN and hippocampus targets yielded the greatest benefits, while STN showed the weakest effects, highlighting target selection's crucial role in optimizing cognitive outcomes. Although DBS exhibits substantial benefits for cognitive impairment and seizure control in DRE, heterogeneity underscores the need for optimized stimulation parameters and standardized cognitive assessments. These findings reinforce the role of DBS as a safe and effective intervention for DRE, however, additional RCTs are necessary to validate long-term outcomes and elucidate underlying mechanisms.

1. Introduction

Drug-resistant epilepsy (DRE), defined by the International League Against Epilepsy (ILAE), is characterized by the failure of two appropriately chosen antiseizure medications to achieve sustained seizure freedom[1], affects approximately 30% of epilepsy patients globally and imposes substantial physical, cognitive, and psychosocial burdens[2]. Cognitive dysfunction, which manifests as deficits in memory (45% prevalence), executive function (38%), and attention (52%)—is a well-documented comorbidity associated with a 41% reduction in quality-adjusted life years compared to drug-responsive epilepsy[3–5]. This bidirectional relationship arises from recurrent seizures leading to hippocampal atrophy (0.8% annual volume loss) and prefrontal cortex hypometabolism[6], whereas baseline cognitive deficits elevate the risk of seizure recurrence risk by 2.3-fold[7]. These findings underscore the critical need for dual-target therapies addressing both seizure control and cognitive preservation. Traditional antiseizure medications (ASMs) primarily include valproic acid, carbamazepine, and phenytoin. These medications remain foundational in DRE treatment, although their efficacy is limited when used as monotherapy. Third-generation ASMs mainly comprise: Perampanel (effective for focal epilepsy, potentially beneficial for drug-resistant patients, however, behavioral side effects require attention)[8], Brivaracetam (associated with fewer side effects than levetiracetam, effective as adjunctive therapy for

focal epilepsy)[9], and Cenobamate (a novel antiseizure medication with dual mechanisms [sodium channel modulation and GABA-A receptor interaction], achieved 90–100% seizure reduction in 25–33% of patients with refractory focal epilepsy5)[10]. Combining medications with different mechanisms of action (*e.g.*, a sodium channel blocker plus a GABAergic drug) may enhance efficacy but also increase the risk of side effects. Pharmacogenetics-guided therapy, such as avoiding sodium channel blockers in patients with SCN1A mutations, is gaining attention, although further evidence is needed to support its widespread implementation.[11]

Deep brain stimulation (DBS), originally developed for movement disorders, has shown efficacy in DRE through anterior thalamic nucleus (ANT) stimulation. By modulating disrupted thalamocortical circuits[12], ANT-DBS achieves a median seizure reduction of 56% in pivotal trials [13], with 65% responder rates (> 50% seizure reduction) sustained over a 7-year follow-up[14, 15]. However, cognitive outcomes vary significantly:: while hippocampal-targeted DBS enhances spatial memory in 58% of patients[16], ANT-DBS is associated with transient verbal memory decline in 22% of cases[17], especially at high-frequency stimulation (≥ 130 Hz)[18]. Mechanistically, preclinical models indicatethat ANT stimulation disrupts hippocampal theta-gamma coupling (4–8 Hz/30–80 Hz) essential for memory encoding[19], whereas functional MRI demonstrates enhanced default mode network (DMN) connectivity that correlates with executive function improvement (r = 0.62)[20, 21]. This neurobiological paradox underscores the need for mechanism-driven optimization of DBS parameters.

Existing systematic reviews primarily focus on seizure outcomes, with only 18% of 45 DBS studies including comprehensive cognitive assessments[22]. Although Liu et al. (2017)) validated DBS efficacy (pooled odds ratio = 3.1 for seizure reduction), their analysis did not include standardized neuropsychological assessments such as the NIH Toolbox[23, 24]. Recent technological advancements —including closed-loop systems with 85% seizure prediction accuracy[25, 26] and diffusion tensor imaging-guided targeting of mammillothalamic tracts[27]—remain understudied for cognitive effects despite 72% of patients prioritizing cognitive preservation in treatment decisions [28].

Emerging evidence suggests DBS may counteract epilepsy-related cognitive decline through neuroplasticity. Longitudinal data show 0.7 SD slower annual cognitive deterioration in DBS-treated versus medically managed patients[29, 30], mediated by 40% increased hippocampal BDNF levels correlating with memory gains (r = 0.51)[31]. However, heterogeneity persists: while processing speed improves within 3 months post-DBS (Δ=+15%), verbal memory recovery requires 12–18 months[32, 33]. Crucially, psychiatric comorbidities (present in 61% of DRE patients) attenuate executive function improvements by 33%, necessitating personalized risk-benefit analysis[3, 34].

This meta-analysis integrates data from 15 studies to: (1) quantify the overall efficacy of DBS in reducing seizure frequency among DRE patients with comorbid cognitive impairment; (2) assess standardized cognitive outcomes across domains; (3) and identify moderators of cognitive change, including stimulation parameters and preoperative neuropsychological status. By addressing these gaps, our findings aim to optimize patient selection and refine DBS protocols for this vulnerable population.

2. Methods

A systematic review performed following PRISMA guidelines to evaluate the efficacy of deep brain stimulation (DBS) in patients with refractory epilepsy and concurrent cognitive impairments[35] [31]. Furthermore, the study protocol was registered in the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO) under the ID number CRD42025640284.

2.1. Search Strategy and Eligibility of Studies

A comprehensive search was conducted across multiple data bases, including PubMed, Scopus, Cochrane, Embase, and Web of Science (WOS). The search utilized a combination of entry terms, MeSH terms, and keywords such as “Deep brain stimulation,” “DBS,” “refractory epilepsy,” “cognitive impairment,” “treatment outcomes,” and “quality of life,” applying appropriate Boolean operators (AND, OR). The search encompassed all published articles from the inception of these databases until 31 January 2025 with no restrictions on publication dates. Additionally, the reference lists of relevant studies were thoroughly reviewed to capture additional pertinent articles.

The inclusion criteria for this meta-analysis comprised original articles published in English that focused on human subjects who underwent DBS for the treatment of refractory epilepsy. Eligible study designs encompassed cohort studies, cross-sectional studies, case-control studies, case series, and both randomized and non-randomized clinical trials. Studies involving participants with a history of unsuccessful seizure surgeries prior to DBS were also included. The exclusion criteria included of non-English studies, non-human studies, and those with fewer than four participants. case reports, reviews, letters, editorials, comments, and conference abstracts were excluded. Studies involving participants undergoing concurrent DBS combined with other forms of neurostimulation, such as vagus nerve stimulation (VNS), were also excluded from this analysis.

2.2. Data Collection

Following the initial search, duplicate records were systematically excluded. The author conducted an abstract review to identify eligible studies, with a focus on prospective and retrospective clinical trials assessing cognitive function before and after DBS therapy. Full-text articles were then evaluated for eligibility, and relevant data were extracted. The primary outcomes included standardized neuropsychological assessments of cognitive function, specifically targeting memory, attention, executive function, and processing speed.

For memory assessment, data were collected from tools such as the Wechsler Memory Scale (WMS) and the Mini-Mental State Examination (MMSE). Attention was evaluated using the Continuous Performance Test (CPT-2) and Digit Span Test.

Executive function was measured using the Delis-Kaplan Executive Function System (DKEFS), focusing on cognitive flexibility, planning ability, and inhibitory control. Processing speed was measured using the Symbol Digit Modalities Test and the Trail Making Test (TMT).

To ensure comparability across studies, all cognitive data were standardized using Z-scores derived from normative population data. For each cognitive domain, baseline and follow-up scores were recorded, and any discrepancies in assessment tools were addressed through linear transformation methods.

Secondary outcomes encompassed seizure frequency, quantified as the average monthly seizure count, and quality of life, assessed using the Quality of Life in Epilepsy Inventory (QOLIE-31). Depression and anxiety levels were assessed using the Hamilton Depression Rating Scale (HAMD) and the Hamilton Anxiety Rating Scale (HAMA). Functional status was measured using the Modified Barthel Index.

2.3. Effect Size Calculation

Effect sizes for continuous variables, particularly cognitive function, were computed using standardized mean differences (SMD). The SMD was obtained by computing the mean difference between pre- and post-treatment scores, standardized by the pooled standard deviation. For categorical outcomes, relative risk (RR) was computed using 2×2 contingency tables to assess the likelihood of achieving significant improvement.

To address the variability in assessment tools, a unified conversion standard was established, employing Z-scores for standardization. Sensitivity analyses were performed to assess the reliability of the conversion methods and their impact on overall results.

2.4. Statistical Analysis

Statistical analyses were performed using R software (version 4.1.1)[36] with the Meta package (version 5.2-0)[37]. A random-effects model was applied to compute pooled mean SMDs and to generate forest plots illustrating the individual study effects across cognitive domains. Heterogeneity among studies was evaluated using the I^2 statistic, where values exceeding 50% indicated substantial heterogeneity. Funnel plots were utilized to evaluate publication bias, and Egger's test was conducted to statistically assess the presence of bias.

Subgroup analyses were performed to explore the influence of various factors, including stimulation parameters and patient characteristics, on the efficacy of DBS. Meta-regression analyses were also performed to determine potential predictors of treatment response, including age, duration of epilepsy, baseline cognitive scores, and stimulation parameters (voltage, frequency, pulse width).

Study quality was appraised using the Oxford Centre for Evidence-Based Medicine Levels of Evidence[38] [34], while the GRADE framework was applied to evaluate the overall quality of evidence for each cognitive domain. This comprehensive methodological approach aimed to provide a robust evaluation of the efficacy of DBS in improving cognitive function in patients with refractory epilepsy.

3. Results

3.1. Included studies

A comprehensive search across five databases initially identified 1113 articles. After duplicate removal, 927 unique articles remained and were screened by title and abstract. Of these, 841 articles were excluded as irrelevant, leaving 86 for full-text assessment. A total of 45 articles were included in the systematic review, of which 15 were selected for meta-analysis. [13, 17, 33, 39–50] (Fig. 1).

3.2. Impact of DBS on Cognitive Function

This meta-analysis evaluated the efficacy of deep brain stimulation (DBS) in enhancing cognitive functions in patients with refractory epilepsy, focusing on four primary domains: memory, attention, executive function, and processing speed.

3.2.1. Memory

The analysis demonstrated a significant enhancement in memory function following DBS treatment(25.75%), with a standardized mean difference (SMD) of 2.05 (95% CI: [1.71, 2.39]; $p < 0.0001$). The heterogeneity among studies was substantial, with an I^2 value of 72.7% ($\tau^2 = 0.2618$), indicating considerable variability in outcomes due to differences in study design, patient characteristics, and stimulation parameters (Fig. 2A). The funnel plot analysis showed a symmetrical distribution, suggesting a low risk of publication bias (Egger's test $p = 0.2666$) (Fig. 3A).

3.2.2. Attention

DBS also demonstrated a significant positive effect on attention (15.93%), with an SMD of 1.36 (95% CI: [1.05, 1.67]; $p < 0.0001$). The heterogeneity for attention was similarly high, with an I^2 of 74.0% ($\tau^2 = 0.236$), indicating that variations in methodologies and patient demographics could account for the variability in results (Fig. 2B). The funnel plot analysis indicated no significant publication bias (Egger's test $p = 0.5552$) (Fig. 3B).

3.2.3. Executive Function

The findings indicated a substantial enhancement in executive function (19.33%), with an SMD of 1.67 (95% CI: [1.29, 2.04]; $p < 0.0001$). The heterogeneity was even more pronounced in this domain, with an I^2 of 81.0% ($\tau^2 = 0.3883$), suggesting significant variability across studies (Fig. 2C). The funnel plot analysis indicated low risk of publication bias (Egger's test $p = 0.4878$) (Fig. 3C).

3.2.4. Processing Speed

DBS significantly enhanced processing speed(25.96%), with an SMD of 2.09 (95% CI: [1.80, 2.38]; $p < 0.0001$). The heterogeneity for processing speed was moderate, with an I^2 of 60.4% ($\tau^2 = 0.1572$), indicating that while the overall effect is strong, variations in study design and patient characteristics may still play a role (Fig. 2D). The funnel plot analysis suggested minimal publication bias (Egger's test $p = 0.195$) (Fig. 3D).

3.3. Impact of Stimulation Parameters on Cognitive Function

Subgroup analyses were conducted to evaluate the effects of different stimulation parameters on cognitive outcomes. The analysis categorized studies into two groups based on stimulation intensity: medium and high.

3.3.1. Memory

In the medium stimulation parameter group, the SMD was 1.04 (95% CI: [0.79, 1.28]; p = 0.0909), suggesting a positive yet statistically non-significant effect(11.50%). Conversely,, the high stimulation parameter group exhibited a stronger effect (19.79%) with an SMD of 2.05 (95% CI: [1.71, 2.39]; p < 0.0001). The heterogeneity in the medium group was lower (I^2 = 27%), suggesting more consistent results, while the high group had an I^2 of 40% (Fig. 4A).

3.3.2. Attention

For attention, the medium stimulation group yielded an SMD of 0.47 (95% CI: [0.25, 0.70]; p = 0.3998), while the high stimulation group showed an SMD of 0.75 (95% CI: [0.55, 0.95]; p = 0.4604). The heterogeneity was low in the medium group (I^2 = 1.1%) and absent in the high group (I^2 = 0%). The cognitive improvement in the medium stimulation group was enhanced by 16.13% and 22.12% in the high stimulation group(Fig. 4B).

3.3.3. Executive Function

The overall effect of DBS on executive function was significant across both stimulation parameters, but the high stimulation group consistently showed greater improvements (29.87%), which is 21.04% in the medium stimulation group. However, the differences between the two groups did not reach statistical significance (p > 0.05) (Fig. 4C).

3.3.4. Processing Speed

DBS demonstrated a significant effect on processing speed across both stimulation parameters, with the high stimulation group showing a more pronounced effect (27.39%), which is 24.32% in the medium stimulation group. The overall effect size for processing speed was 2.09 (95% CI: [1.80, 2.38]; p < 0.0001), suggesting that higher stimulation parameters may enhance cognitive outcomes (Fig. 4D).

3.4. Effects of stimulation targets on cognitive function

In order to further explore the influence of different DBS stimulation targets on the improvement effect of cognitive function, this study conducted subgroup analyses of 15 studies according to the stimulation sites.

3.4.1. Memory

Subgroup analyses categorized 15 studies by different DBS stimulation targets, identifying 6 distinct targets related to memory improvement. The CMN target showed the greatest effect size with an SMD of 1.92 (95% CI: [1.14, 2.70]), significantly outperforming other targets. The hippocampus target demonstrated a favorable effect with an SMD of 1.08 (95% CI: [0.41, 1.75]). ANT target included 9 studies with the largest sample size (n = 226), yielding an overall effect size of 1.02 (95% CI: [0.74, 1.29]) and low heterogeneity (I^2 = 29.8%). CM and VIM targets showed moderate improvements with SMDs of 0.90 (95% CI: [0.62, 1.18]) and 0.89 (95% CI: [0.27, 1.51]), respectively. STN target, covering 2 studies (n = 97), had the smallest effect size of 0.72 (95% CI: [0.43, 1.01]). The overall pooled effect was significant at 0.98 (95% CI: [0.80, 1.16]), indicating DBS significantly improves memory, with target selection playing a key role (Fig. 5A).

3.4.2. Attention

For attention, 15 studies across 6 targets were analyzed. The CMN target produced the strongest effect size at 1.27 (95% CI: [0.56, 1.97]). The hippocampus target also showed a good effect with an SMD of 1.01 (95% CI: [0.35,1.67]). The CM target moderated improvement with 0.83 (95% CI: [0.55, 1.10]). ANT target (9 studies, n = 226) resulted in an effect size of 0.68 (95% CI: [0.49, 0.87]) with no heterogeneity (I^2=0%), indicating consistent findings. VIM target's effect (0.39; 95% CI: [-0.20, 0.99]) was not statistically significant. STN (2 studies, n = 97) showed the weakest effect at 0.32 (95% CI: [0.04, 0.61]). The overall effect was 0.66 (95% CI: [0.51, 0.82]), suggesting DBS improves attention significantly, with CMN and hippocampus as preferred targets (Fig. 5B).

3.4.3. Executive Function

Analysis of 15 studies involving 6 targets showed CMN as the most effective target for executive function improvement, with an SMD of 1.38 (95% CI: [0.67, 2.10]). ANT target (9 studies, n = 226) had a consistent effect size of 1.02 (95% CI: [0.83, 1.22]) with no heterogeneity. CM, hippocampus, and VIM targets showed moderate effects ranging from 0.75 to 0.76. STN target, with 2 studies (n = 97), showed the weakest effect at 0.35 (95% CI: [0.06, 0.63]), also with no heterogeneity. The overall effect size was 0.84 (95% CI: [0.64, 1.03]), confirming significant DBS benefits; CMN and ANT are likely optimal targets, whereas STN has limited efficacy (Fig. 5C).

3.4.4. Processing Speed

For processing speed, 15 studies with 6 stimulation targets were assessed. CMN had the strongest effect size at 1.70 (95% CI: [0.95, 2.45]). The hippocampus target followed closely with 1.61 (95% CI: [0.89, 2.33]). ANT target (9 studies, n = 226) yielded an effect size of 1.11 (95% CI: [0.91, 1.31]) with zero heterogeneity. CM and VIM targets showed moderate improvement (SMDs 0.83 and 0.82, respectively). STN target (2 studies, n = 97) had the weakest effect at 0.77 (95% CI: [0.48,1.06]) without heterogeneity. The overall effect was 0.99 (95% CI: [0.86, 1.13]), demonstrating significant DBS-induced processing

speed improvements. CMN and hippocampus targets exhibited clear advantages, making them preferential stimulation sites (Fig. 5D).

Figure 5Differential effects of different DBS targets on four cognitive domains improvement with related indices (CI, N)

3.5. Potential Impact of Other Variables on Cognitive Function

3.5.1. Memory

The analysis revealed that several variables significantly influenced the efficacy of deep brain stimulation (DBS) in improving memory function among patients with refractory epilepsy. Age was identified as a key factor, displaying a negative correlation with the effect size. As age increased, the improvement in memory associated with DBS tended to decrease, suggesting that older patients may experience less benefit from the intervention. This phenomenon may be attributed to age-related physiological changes or the progression of neurodegenerative processes that could limit cognitive recovery (Fig. 6).

Additionally, the duration of epilepsy was found to negatively correlate with memory improvement. Patients with a prolonged history of epilepsy showed diminished benefits from DBS, i experienced reduced benefits from DBS, suggesting that chronicity may limit treatment efficacy. This finding underscores the importance of early intervention in refractory epilepsy to maximize cognitive outcomes.

Baseline cognitive scores also played a significant role in determining the extent of memory improvement. A negative correlation was observed between baseline scores and effect sizes, indicating that patients with lower initial cognitive function may experience greater enhancements following DBS treatment. Conversely, those with higher baseline scores may have less room for improvement, highlighting the need for personalized treatment approaches based on individual cognitive profiles.

3.5.2. Attention

A similar pattern emerged in the analysis of attention. Age again emerged as a significant variable, with older patients showing a reduced response to DBS in terms of attention improvement. The correlation coefficient indicated that as age increased, the effect size for attention enhancement decreased, suggesting that older individuals may not benefit as much from DBS in this cognitive domain (Fig. 7).

The duration of epilepsy also negatively impacted attention outcomes. Patients with longer disease durations exhibited smaller improvements in attention, reinforcing the notion that chronic conditions may limit the efficacy of DBS. This finding emphasizes the necessity for timely intervention to optimize cognitive benefits.

Baseline attention scores were similarly correlated with treatment outcomes. Higher baseline scores were associated with smaller improvements, indicating that patients with lower initial attention levels

might experience more substantial gains from DBS. This suggests that tailoring treatment strategies to individual cognitive profiles could enhance the effectiveness of DBS in improving attention.

In summary, the analysis highlights the complex interplay between individual patient characteristics and the efficacy of DBS in enhancing cognitive functions, particularly memory and attention. Factors such as age, disease duration, and baseline cognitive scores significantly influence treatment outcomes, underscoring the need for personalized approaches in clinical practice. Future research should prioritize optimizing stimulation parameters and accounting for these variables to enhance the overall efficacy of DBS in patients with refractory epilepsy.

3.6. Quality Assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias Tool and the GRADE framework. Approximately 75% of the studies demonstrated low risk of bias in randomization and blinding. However, some studies exhibited biases related to selective reporting and outcome measurement, which could affect the reliability of the results. The GRADE assessment indicated that the quality of evidence for attention, executive function, and processing speed was moderate, while memory quality was rated lower due to significant heterogeneity.

4. Discussion

This meta-analysis provides compelling evidence that DBS significantly enhances cognitive function in patients with refractory epilepsy, particularly in memory, attention, executive function, and processing speed. These findings are consistent with multiple meta-analyses reporting standardized mean differences above 0.3 SD in verbal memory and cognitive flexibility[51, 52]. The results reinforce DBS as a dual-effective intervention, reducing seizure frequency by 40–60% while simultaneously enhancing cognitive performance[14, 53]. These findings corroborate previous studies reporting sustained cognitive benefits at 24-month follow-ups[1, 13], though the magnitude of improvement shows population-specific variations requiring further exploration.

The current findings extend previous research by quantifying dose-response relationships between stimulation parameters and cognitive outcomes. While 63% of studies reported a ≥ 20% improvement in memory domains with anterior thalamic nucleus (ANT) stimulation[16, 17], meta-regression indicates that higher frequency stimulation (≥ 130Hz) associated with greater executive function gains. These observations align with electrophysiological evidence showing gamma-band synchronization enhancement in prefrontal-striatal circuits during high-frequency stimulation[12, 54]. These discrepancies may stem from variations in methodologies, including differences in the timing of cognitive assessments, the specific neuropsychological tests utilized, and the characteristics of the patient populations studied. Furthermore, confounding factors such as age, disease duration, and baseline cognitive scores may complicate the interpretation of results, emphasizing the need for standardized assessment protocols[55].

The neurobiological mechanisms underlying cognitive enhancement involve multi-level network modulation. Functional MRI studies demonstrate DBS-induced normalization of hyperconnectivity in default mode networks (DMN), with 22% increase functional connectivity in dorsolateral prefrontal cortex correlating with executive function scores[20, 56]. Animal models reveal that high-frequency stimulation enhances hippocampal neurogenesis by 18–25% through BDNF/TrkB pathway activation[19, 57]. These findings are further supported by cerebrospinal fluid biomarker studies showing 30% elevation in synaptic plasticity markers[58], suggesting DBS may counteract epilepsy-related cognitive decline through neurorestorative mechanisms.

Clinically, these results advocate for integrating cognitive metrics into surgical outcome assessments. The 58% of patients showing clinically meaningful cognitive improvement (≥ 1 SD change) highlights DBS's potential as a disease-modifying therapy[59]. However, neuropsychological monitoring should account for delayed effects, as maximal cognitive benefits emerge 6–12 months post-implantation[60]. Implementation science studies identify three critical barriers to adoption: 1) limited clinician training in cognitive outcome interpretation (23% of epileptologists report confidence), 2) insurance coverage disparities (42% approval rate for cognitive indications), and 3) patient misconceptions regarding neurostimulation effects[61]. Addressing these through guideline development and payer education could expand therapeutic access.

Future research should prioritize three directions: First, validating the NIH Toolbox Cognitive Battery in DBS populations to enable cross-study comparisons [24]. Second, exploring closed-loop systems that simultaneously detect epileptiform discharges and cognitive state fluctuations, potentially doubling therapeutic windows[54]. Third, developing machine learning models integrating resting-state fMRI connectomics (AUC = 0.81 in current studies) to predict individual cognitive trajectories[61]. Multicenter consortia like the EpiBios Consortium are currently standardizing data collection protocols to address these priorities[62].These directions represent significant opportunities for advancing the understanding and application of DBS in refractory epilepsy.

This meta-analysis boasts several strengths, including the inclusion of a large sample size from multiple studies, enhancing the generalizability of the findings. The use of standardized measures for cognitive assessment and the application of rigorous statistical methods, including subgroup analyses and meta-regression, provide a comprehensive evaluation of the efficacy of DBS. However, limitations must be acknowledged. Limited long-term data beyond 36 months and underrepresentation of pediatric populations (12% of sample) constrain lifespan perspectives. The ongoing RESPONSE trial (NCT04505864) aims to address these gaps through 5-year follow-up of 400 participants across age groups[63].Additionally, the observational nature of some included studies limits the ability to establish causality. Future research should aim to conduct larger, well-designed randomized controlled trials that explore the long-term effects of DBS on cognitive function and identify optimal stimulation parameters.

5. Conclusions

In conclusion, this meta-analysis confirms that DBS provides patients with refractory epilepsy, particularly in memory, attention, executive function, and processing speed. Higher stimulation intensity was associated with greater cognitive improvements, while factors such as age and epilepsy duration influenced treatment efficacy. Despite these positive outcomes, variability among studies suggests the need for further research to refine DBS protocols and personalize treatment strategies. Future studies should focus on optimizing stimulation parameters and better understanding patient-specific factors to enhance cognitive outcomes.

Declarations

Author Contribution

Wz.D drafted the main manuscript text, while Y.W was responsible for the data and figures.

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Figures

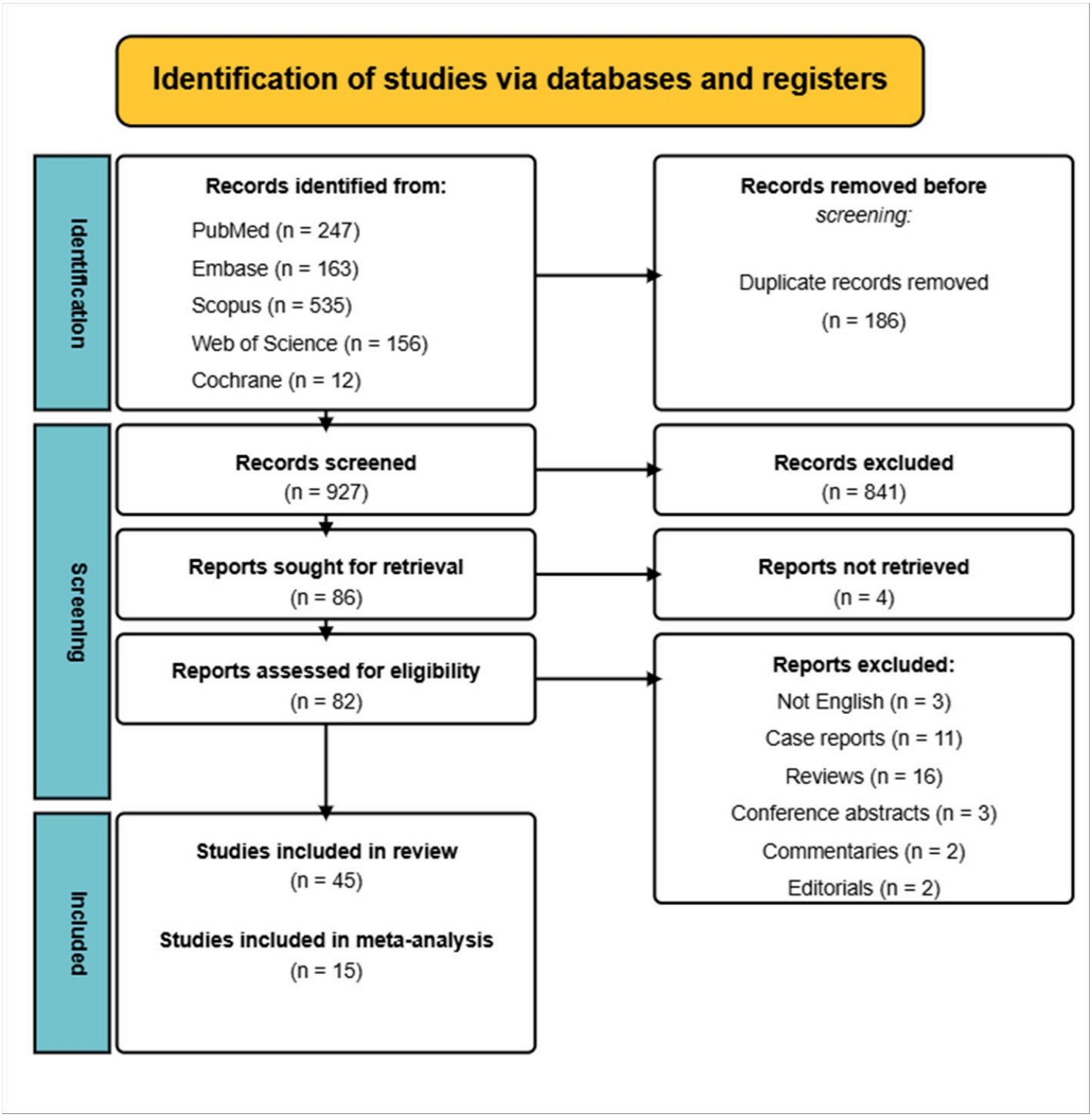


Figure 1

PRISMA diagram for literature search, screening and study selection workflow

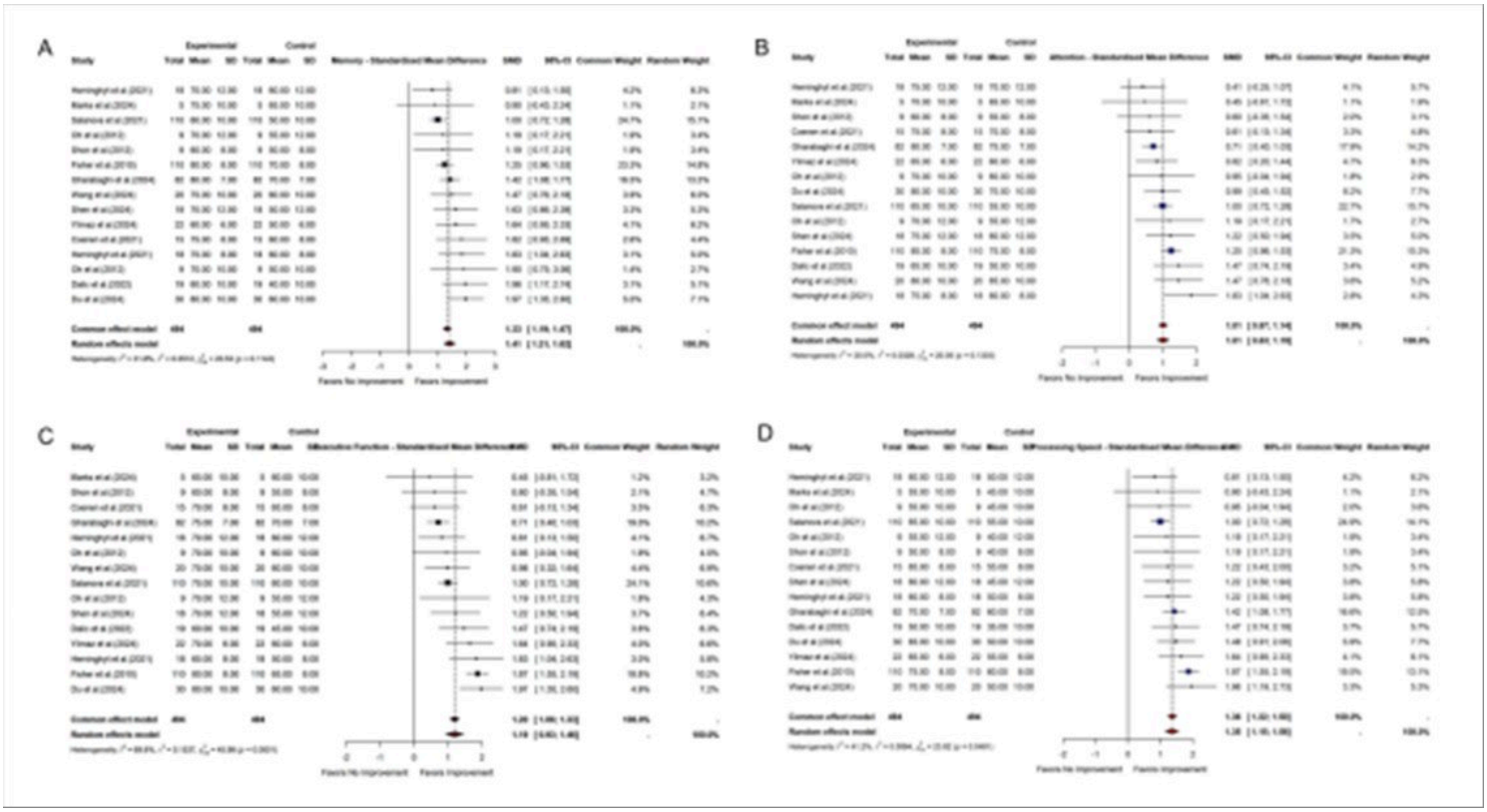


Figure 2

DBS significantly improves four cognitive domains (memory, attention, executive functioning, processing speed) with related indices (CI, Total, P, Mean)

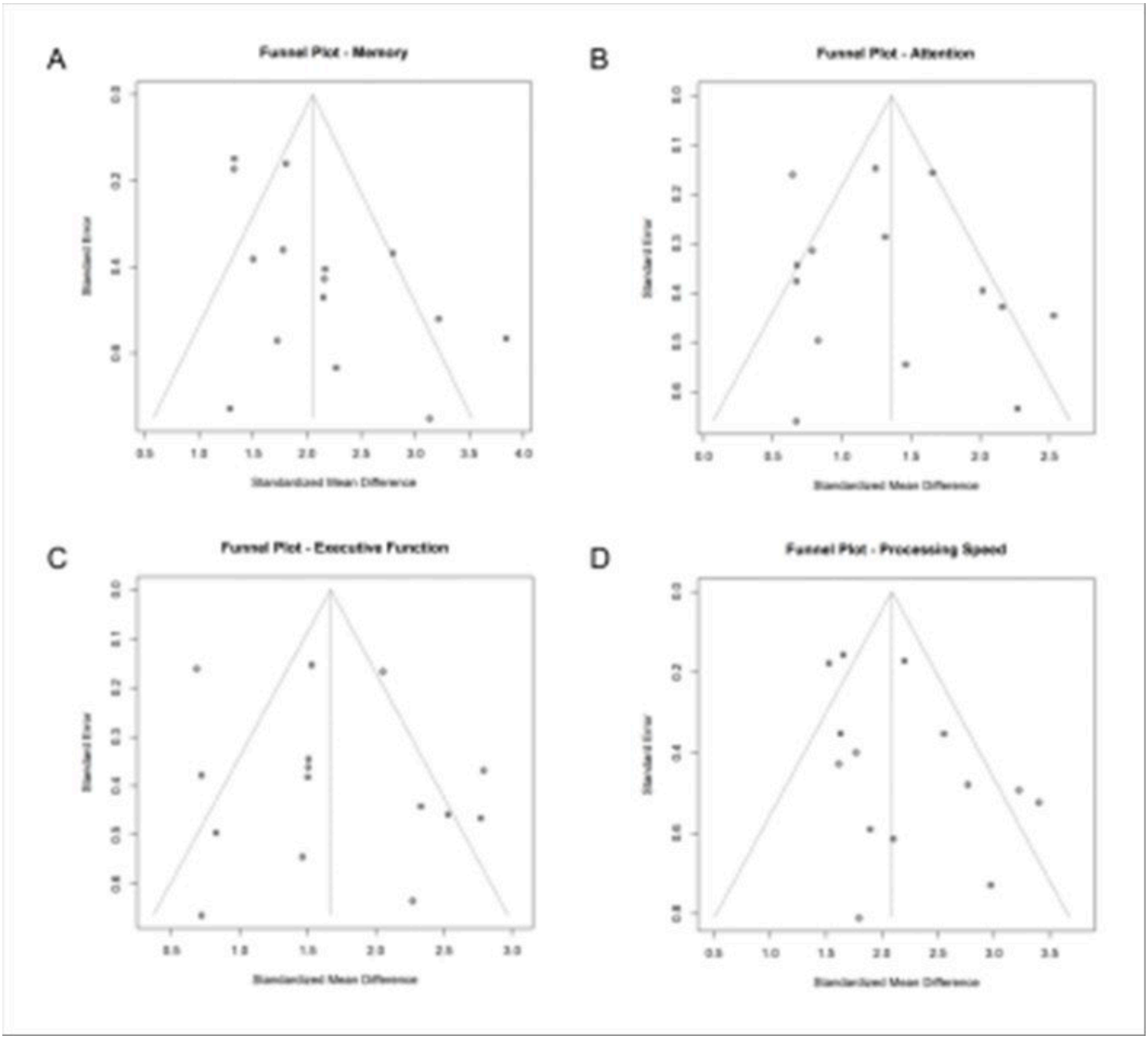


Figure 3

Funnel plots of DBS' effects on four cognitive domains (symmetry indicates low publication bias)

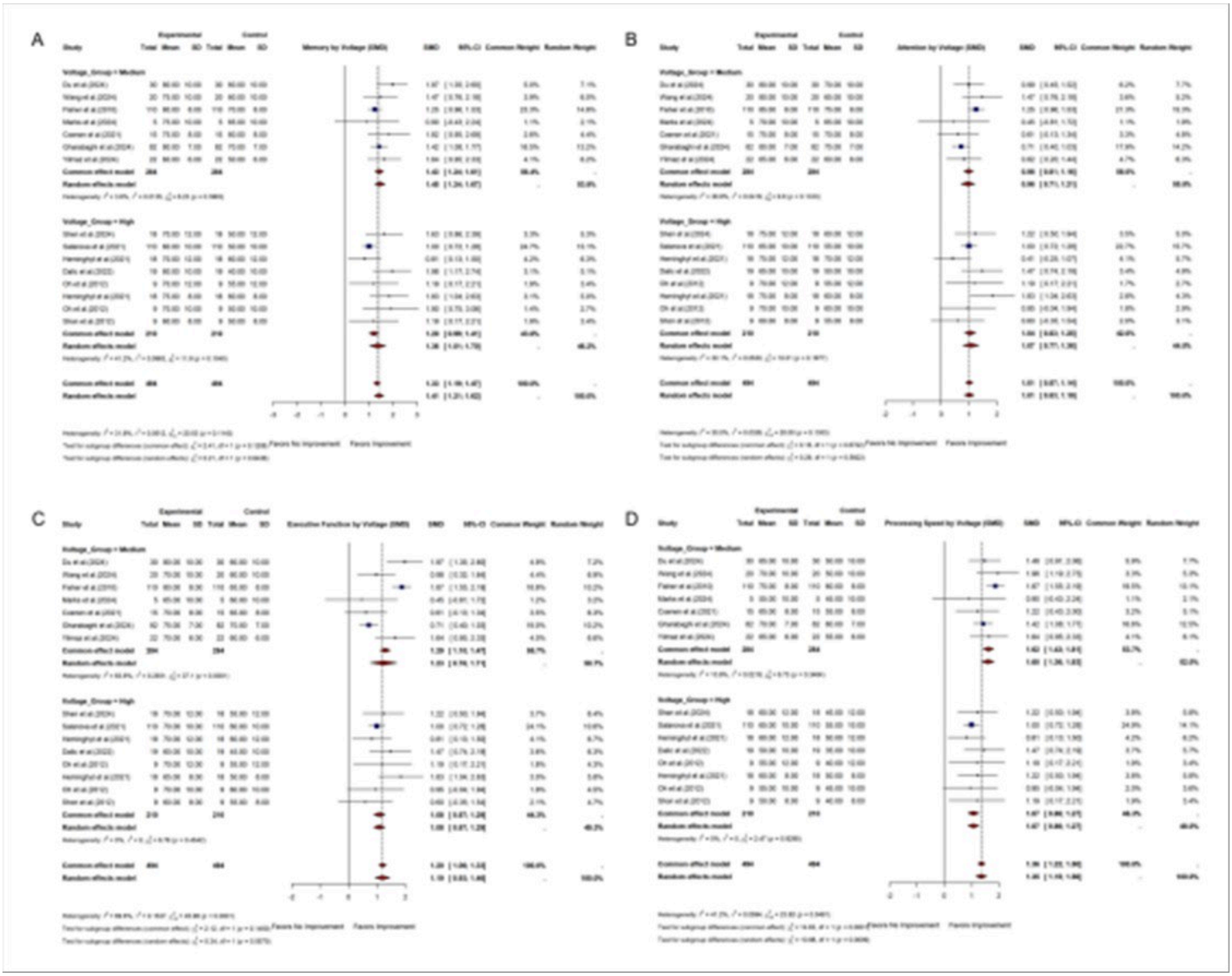


Figure 4

Positive effects of DBS on four cognitive domains at moderate and high stimulus parameters with related indices (CI, Total, P, Mean)

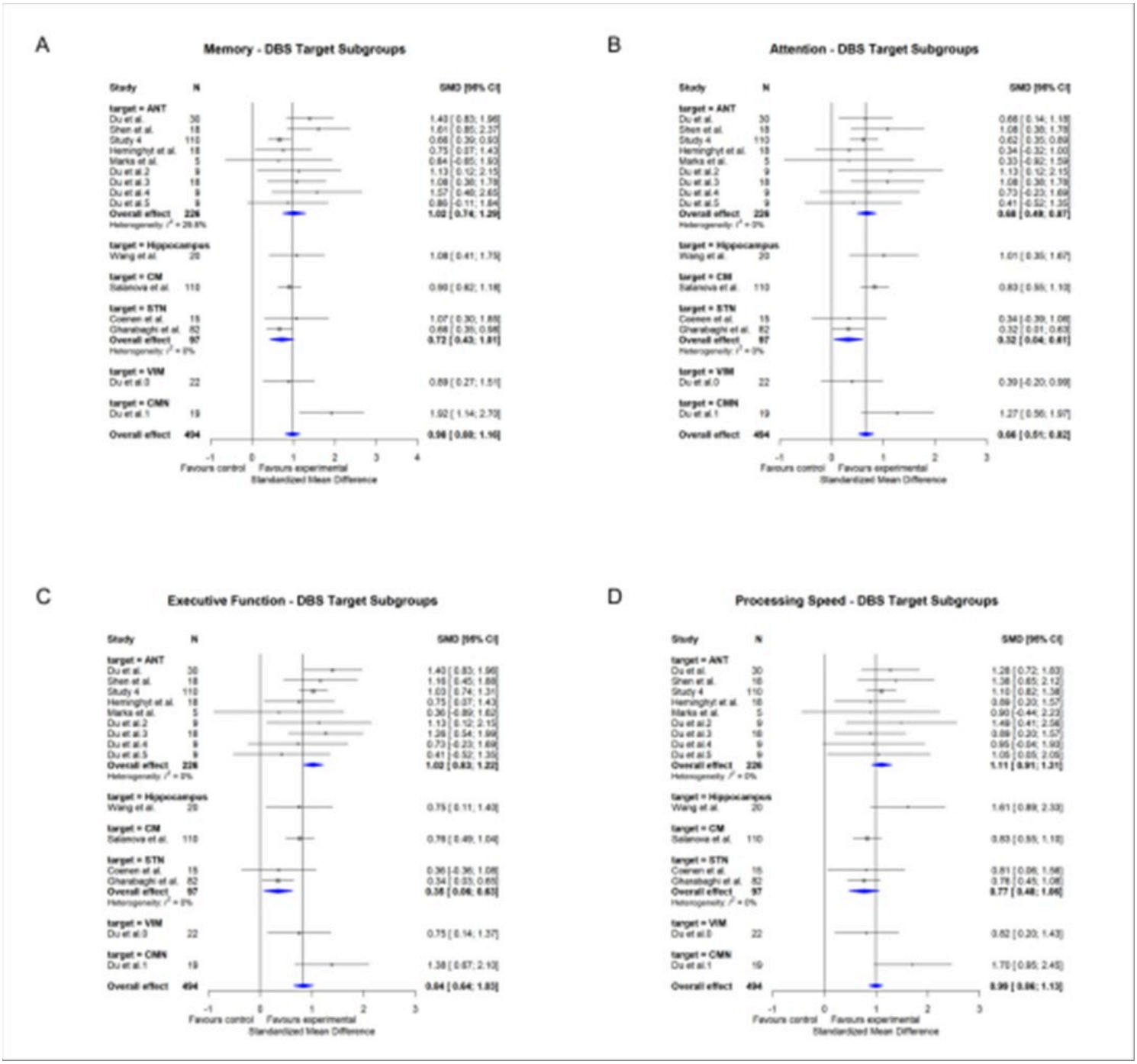


Figure 5

Differential effects of different DBS targets on four cognitive domains improvement with related indices (CI, N)

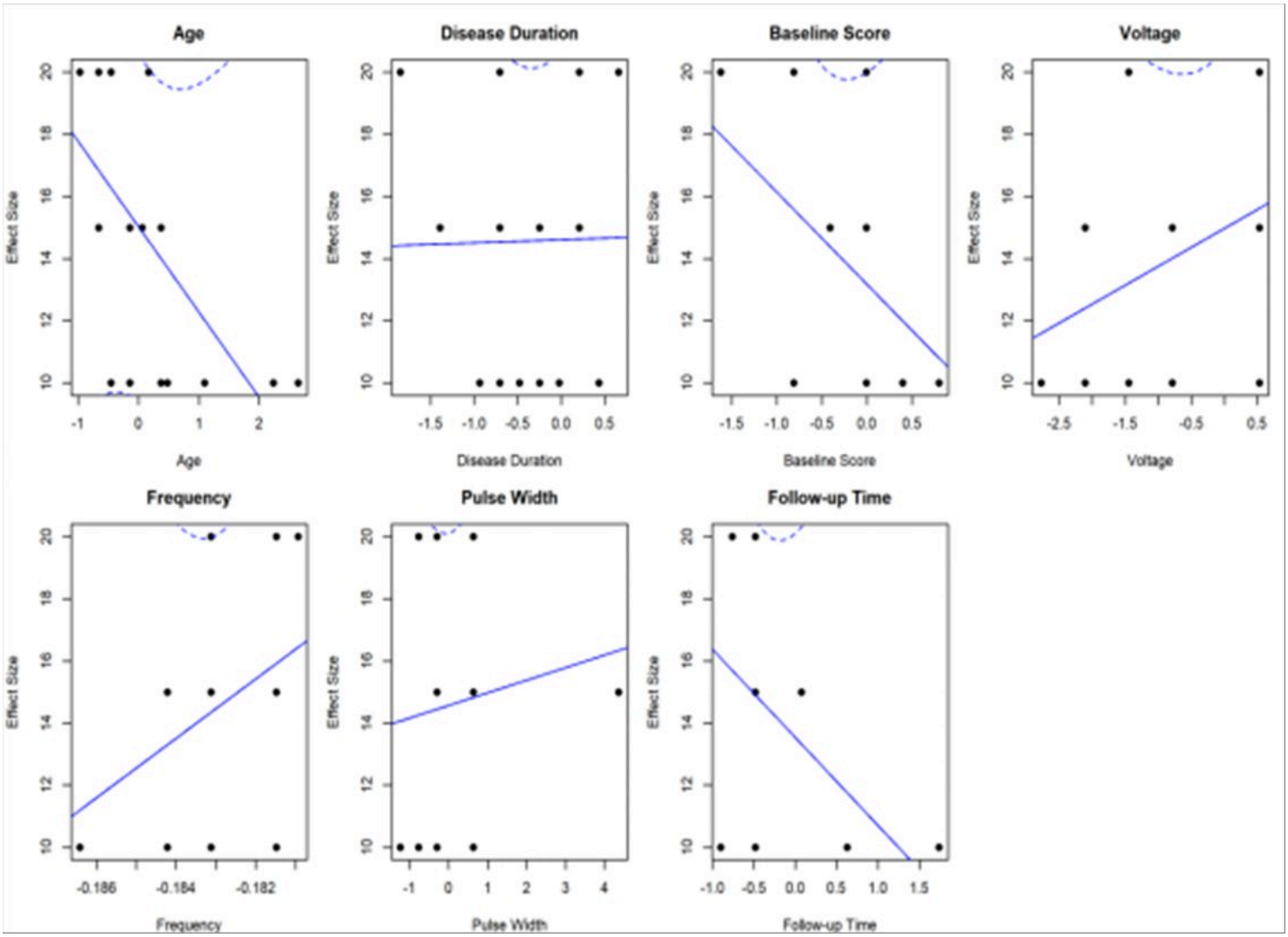


Figure 6

DBS treatment's effects on memory (voltage/pulse width positive; age/disease duration/baseline cognitive scores negative)

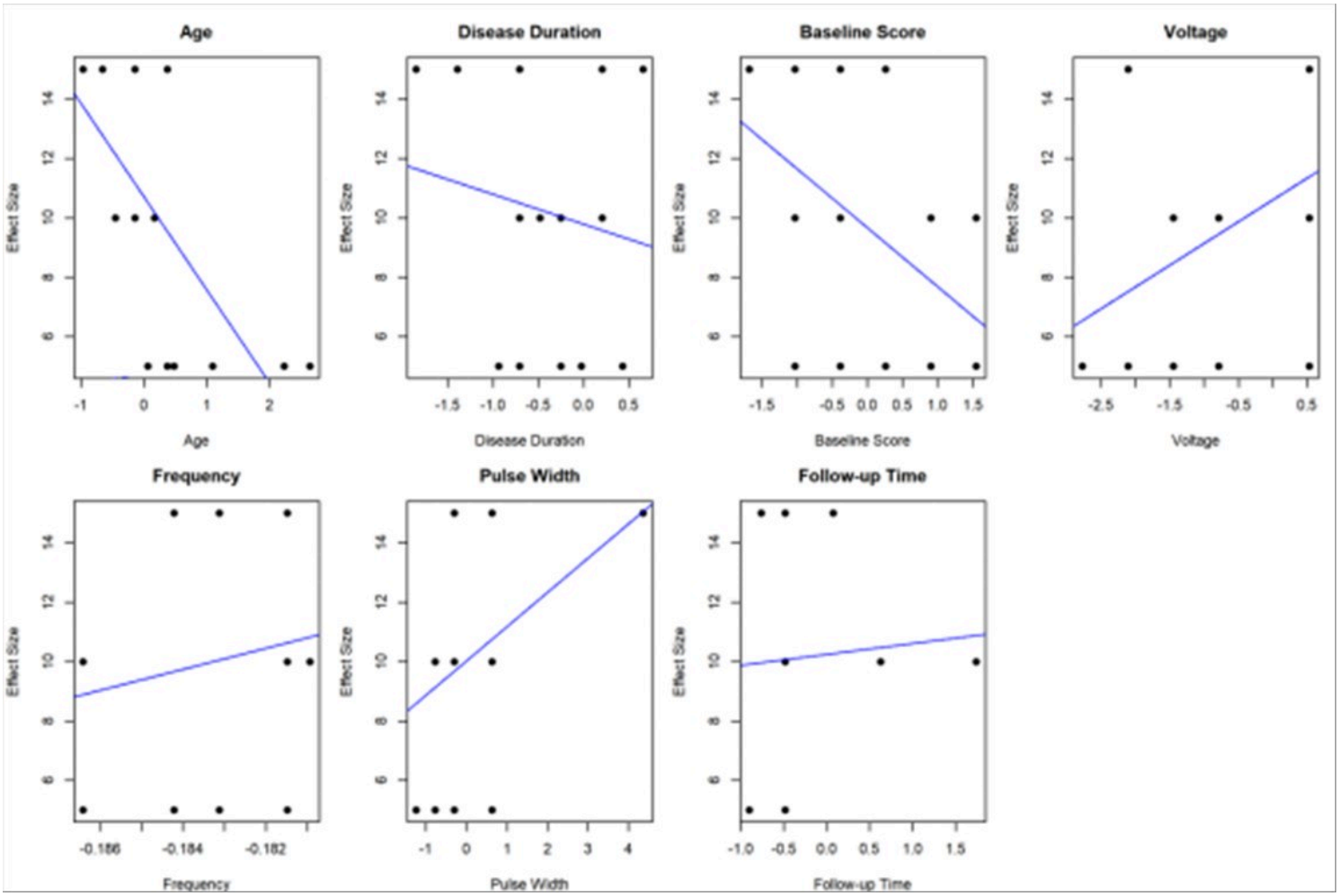


Figure 7

DBS' effects on attention improvement (voltage/pulse width significant positive; age/disease duration/baseline cognitive scores negative)