Efficacy of brain stimulation therapies across psychiatric, movement, and cognitive disorders: an umbrella review synthesizing meta-analyses of randomized controlled trials

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Summary

Background Brain stimulation therapy (BST) has significant potential in treating psychiatric, movement, and cognitive disorders. Given the high prevalence of comorbidities among these disorders, we conducted an umbrella review to comprehensively assess the efficacy of BSTs in treating the core symptoms across these three categories of disorders.

Methods We systematically searched for meta-analyses and network meta-analyses of randomized controlled trials with sham controls up to September 25, 2024, from databases including PubMed, PsycINFO, Embase, and the Cochrane Library. Our primary outcome was improvements in core symptoms. We evaluated quality using 11 criteria. We calculated pooled effect estimates for core symptoms based on the largest meta-analyses, then conducted sensitivity and subgroup analyses, and assessed heterogeneity, publication bias, and small-study effects. Finally, we synthesized effect sizes from all meta-analyses to provide a comprehensive overview of BSTs' efficacy. PROSPERO registration: CRD42023439090.

Findings We included 198 articles with 108,377 patients evaluating 14 BSTs across 21 disorders. The largest meta-analysis showed a moderate standardized mean difference (SMD) of 0.56 (95% CI: 0.49, 0.64; I^2 = 70%). Subgroup analyses revealed significant SMDs for psychiatric disorders (0.60; 95% CI: 0.49, 0.71; I^2 = 66%), movement disorders (0.56; 95% CI: 0.42, 0.69; I^2 = 79%), and cognitive disorders (0.46; 95% CI: 0.32, 0.61; I^2 = 48%). SMDs were 0.44 (95% CI: 0.23, 0.65; I^2 = 70%) for follow-up ≤1 month and 0.69 (95% CI: 0.43, 0.94; I^2 = 84%) for follow-up >1 month. Compared to other conditions, BSTs show better therapeutic effects in treating depression, post-traumatic stress disorder, obsessive-compulsive disorder, pain, fibromyalgia, and post-stroke motor recovery.

Interpretation This review explored the potential of BSTs for comorbidities of the three disorders from a disorder-specific perspective, providing a roadmap for their clinical application and future research.

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Keywords: Brain stimulation therapy; Psychiatric disorders; Movement disorders; Cognitive disorders; Umbrella review

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Research in context

Evidence before this study

We conducted an investigation into psychiatric, movement, and cognitive disorders, which are common and often co-occur. As a new technique, brain stimulation therapies (BSTs) has shown good acceptance and therapeutic effects in the treatment of these disorders. While previous studies have attempted to link these three types of disorders from the perspectives of diseases or symptoms to explore new treatment strategies related to BSTs, no research to date has made such a broad attempt. Therefore, we systematically searched for meta-analyses or network meta-analyses of randomized controlled trials with sham controls up to September 25, 2024, from databases including PubMed, PsycINFO, Embase, and the Cochrane Library. Using 11 predefined criteria, we evaluated the quality of the included studies. We synthesized the largest meta-analytic findings for each BST and disorder to explore their effectiveness. Furthermore, we aggregated all relevant meta-analyses for each BST across disorders, providing a comprehensive overview to effectively guide clinical practice.

Added value of this study

This review provides the most comprehensive summary to date of the effectiveness of BSTs across psychiatric, movement, and cognitive disorders. Overall, we found that BSTs show promising therapeutic potential in all three types of disorders, particularly in an interesting brain region, the dorsolateral prefrontal cortex. Although the studies we included lacked long-term evidence, the short-term effects demonstrated a certain degree of persistence. Through a detailed analysis of each disorder, we identified beneficial effects of BSTs in conditions such as depression, post-traumatic stress disorder, obsessive-compulsive disorder, pain, fibromyalgia, post-stroke motor recovery. These higher-level syntheses serve as crucial references for future clinical applications of BSTs.

Implications of all the available evidence

For most psychiatric, movement, and cognitive disorders, pharmacotherapy remains the primary treatment. Our research provides evidence for the use of BSTs in these conditions, particularly as adjunctive therapies, and showing promising treatment prospects. Furthermore, by analyzing these disorders, we can identify potential treatment combinations, offering new insights into the clinical management of core or comorbid symptoms, improving treatment efficiency, and providing new perspectives for future cross-diagnostic experiments or reviews.

Introduction

Psychiatric disorders encompass a range of symptoms classified as positive, disorganized, or negative, which are evident in primary psychotic disorders and affective psychoses.[1] Movement disorders represent a clinically, pathologically, and genetically diverse group of neurological conditions, all sharing common features such as impaired planning, control, or execution of movement.[2,3] Cognitive disorders are characterized by a decline from previously attained levels of cognitive functioning.[4] Due to their high prevalence and poor prognosis, these disorders place a significant burden on society.[5,6]

Brain stimulation therapies (BSTs) are methods that regulate brain activity and function through electrical, magnetic, or other forms of stimulation. Since the introduction of electroconvulsive therapy (ECT) in 1938,[7] BSTs in psychiatry have evolved significantly and have been widely used to enhance emotional,[8,9] motor,[10–12] and cognitive functions[13,14] in patients. Currently, a large number of studies have explored the effectiveness of BSTs for various conditions, such as depression,[15–18] eating disorders,[19] insomnia,[20–22] schizophrenia,[23–25] Parkinson's disease (PD),[26–28] stroke,[29–31] Alzheimer's disease (AD),[32,33] and Huntington's disease.[34] Compared to traditional pharmacological or non-pharmacological treatments (such as psychotherapy or physical therapy), these techniques offer broader applicability, fewer side effects,[35,36] and higher standardization.[37] Some BSTs have been approved for certain treatments. For example, the U.S. Food and Drug Administration (FDA) has approved transcranial magnetic stimulation (TMS) for depression, obsessive-compulsive disorder (OCD), and motor cortex and language mapping.[38] Deep brain stimulation (DBS) is approved for OCD, essential tremor, and PD,[39] and trigeminal nerve stimulation is approved for pediatric Attention-Deficit/Hyperactivity Disorder (ADHD). Additionally, the UK's National Health Service is currently trialing transcranial electrical stimulation (TES) for depression.[40] Whether as a standalone treatment or as an adjunct therapy,[41] BSTs seem to be a promising new therapeutic approaches.[42,43]

Building on the exploration of BSTs for single diseases or symptoms, some researchers have attempted to broaden their focus. For example, studies have investigated the effects of non-invasive brain stimulation (NIBS) on pain, cognitive function, and psychiatric symptoms in patients with multiple sclerosis,[12] or examined its impact on core symptoms[9,44] or unique health endpoints across a range of disorders.[45] Current research also explores symptoms from a transdiagnostic perspective. One study on BSTs for depressive symptoms across psychiatric, movement, and cognitive disorders identified the left dorsolateral prefrontal cortex (DLPFC) as a transdiagnostic neural mechanism.[46] Another study on transcranial direct current

stimulation (tDCS) for treating anxiety and depression found that disorders such as OCD and post-traumatic stress disorder (PTSD) share fundamental clinical features and similar neuropathological mechanisms involving the amygdala and prefrontal cortex.[47] Additionally, research involving non-invasive, non-convulsive electrical neuromodulation found improvements in mood and sleep symptoms across diagnoses.[48] Despite many studies attempting to link various diseases from the perspectives of specific diseases or symptoms, the overall research is limited in scope and quantity. Current evidence does not provide comprehensive guidance for psychiatric, movement, and cognitive disorders.

Umbrella review is a comprehensive analysis of the highest-level evidence, namely systematic reviews and meta-analyses.[49] It helps determine whether different authors reach similar conclusions on related issues, providing clinicians with the available evidence to make informed decisions amid conflicting literature.[50] Since the scope of this work is not to elaborate on the neural mechanisms but rather to provide a quantitative synthesis to guide clinical practice and future research in this area, we chose an umbrella review approach.

We conduct a comprehensive review of the effects of brain stimulation on the treatment of core symptoms in psychiatric, movement, and cognitive disorders using an umbrella review approach. We aim to systematically review this three categories of disorders, to promote more efficient treatment of their comorbidities in clinical practice, which will also provide broader research ideas for future cross-diagnostic studies or clinical trials.

Methods

Search strategy and inclusion criteria

We searched PubMed, PsycINFO, Embase, and the Cochrane Library up to September 25, 2024. Two authors (ZZ, FC) independently performed searches, title/abstract screening, and full-text assessments. The search strategy and reasons for exclusion of full texts are provided in the Appendix (pp 1–29). Discrepancies were resolved through discussion with a third author (LY). We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[51] The systematic review did not require ethical approval or informed consent.

Meta-analyses and network meta-analyses (NMAs) of randomized controlled trials (RCTs) comparing BSTs to sham controls and reporting primary outcomes were eligible. Psychiatric disorders of interest included depressive disorder, bipolar disorder (BD), anxiety disorders (including generalized anxiety disorder (GAD), social anxiety disorder, and specific phobias), panic disorder, OCD, PTSD, ADHD, substance use disorder (SUD), autism spectrum disorder (ASD), and any other psychiatric disorders meeting the validated clinical diagnostic criteria. Movement disorders of interest included down syndrome, PD, pain, tourette syndrome (TS), essential tremor, cerebral palsy, ataxia, choreoathetosis, stereotypic movement tics, fibromyalgia, myalgia, and post-stroke movement disorders. Cognitive disorders of interest included AD, mild cognitive impairment (MCI), dementia, and post-stroke cognitive impairment (PSCI). The brain stimulation techniques involved were repetitive transcranial magnetic stimulation (rTMS), tDCS, transcranial alternating current stimulation (tACS), ECT, DBS, vagus nerve stimulation (VNS), cerebral electrotherapy stimulation (CES), transcranial random noise stimulation (tRNS), magnetic seizure therapy (MST), transcutaneous nerve stimulation (TNS), transcutaneous vagus nerve stimulation (tVNS), theta burst stimulation (TBS), and transcutaneous electrical nerve stimulation (TENS). Descriptions of each type of BST can be found in the Appendix (pp 30–31). BSTs are typically used in conjunction with other therapies (e.g., medications, behavioral therapies, or physical therapies). This umbrella review encompasses studies examining the combined use of BSTs with conventional treatments. If multiple meta-analyses met the inclusion criteria for a specific condition, all relevant studies were included.

We excluded studies involving: a) special populations (restricted by age, gender, occupation, and clearly specify comorbidity); b) combined BST interventions; c) without a sham control (e.g., no treatment, waiting list, or treatment as usual); d) reported non-core symptoms (side effects, emotional improvements related to movement disorders, inflammatory factors); e) invalid data (specific subgroups/settings for outcomes, or data that could not be effectively converted); f) BSTs in NMA with ≤3 RCTs; and g) unavailable full text.

Data synthesis

Two authors (ZZ, FC) independently conducted data extraction, capturing details such as author names, publication year, type of disorder, number of RCTs and participants, types of intervention, stimulated areas, risk of bias assessments, quality evaluations, and effect sizes (including odds ratio [OR], risk ratio [RR], hazard ratio [HR], risk difference [RD], number needed to treat [NNT], and standardized mean difference [SMD]) with corresponding 95% confidence intervals (CIs). Adverse events and dropout rates were also recorded, along with effect estimates with 95% CIs, proportions, and any relevant data.

The co-primary outcome is treatment efficacy, defined as improvement in disease-specific core symptoms (psychiatric disorders: e.g., depression, anxiety symptoms; movement disorders: e.g., upper limb function, pain intensity; cognitive disorders: global cognition), measured by SMD with 95% CIs. Secondary outcomes include the original study-defined rates (OR, RR, HR, RD, NNT, and

SMD) of clinical treatment response, remission, dropout for any reason, and any adverse events. To ensure comparability and enhance data quality, we prioritize extracted direct comparison data over indirect comparison data. Adjusted data are preferred in instances where issues such as small study effects or excessive heterogeneity are observed. Positive SMD results indicate beneficial effects of BSTs. MD will be converted to SMD using Comprehensive Meta-Analysis (CMA, Version 3). When selecting the largest meta-analysis, we will take all factors into consideration, typically choosing the one that includes the most RCTs. Further details for data extracted can be found in the Appendix (pp 32–83). A third author (MZ) reviewed and synthesized the findings.

The quality of the included meta-analyses was independently assessed by two reviewers (LY, WW) using a total of 11 assessment criteria.[11,12] These criteria included items 1–9 from the Checklist for Systematic Reviews and Research Syntheses,[49] supplemented by item 12 from AMSTAR, and an additional criterion regarding meta-analysis registration[52] (Appendix p 84). Studies with a score ≥9 were considered to indicate relatively high quality. Consensus between the two reviewers was achieved through discussion.

Our analysis consisted of two main steps. In Step 1, we presented and evaluated the largest meta-analyses for each condition, summarizing the effect sizes (SMDs) for core symptom improvement to obtain a weighted effect of BSTs across all disorders.[52,53] Subsequently, we conducted sensitivity and subgroup analyses and assessed heterogeneity, publication bias, and small-study effects,[54] as described below. In Step 2, we summarized all meta-analytic effect sizes related to each disorder, including both primary and secondary outcomes, to provide a comprehensive overview of the effects of BSTs for each disorder.[52,53] We considers an SMD of 0.2 to be small, 0.5 to be moderate, and 0.8 to be large.[52]

We performed sensitivity analyses by removing the meta-analyses with the number of patients >1000, the number of RCTs <8, quality assessment <9, I^2 > 75%, and we used a leave-one-out approach to examine the robustness of the largest meta-analysis results. We stratified the analyses by: a) follow-up duration (>1 month vs. ≤1 month); b) three types of disorders (psychiatric vs. movement vs. cognitive); c) each BST; and d) each category of disorder.

We used the I^2 statistic to assess the between-study heterogeneity. For studies with a sample size >10, funnel plots and Egger's regression were used to assess publication bias and small study effects.[55] All analyses were performed by CMA Version 3 based on SMDs and their CIs via the CMA analysis option "generic estimates".[50,52] All analyses were conducted using a random-effects model.[50] This study was registered with PROSPERO, under the registration number CRD42023439090.

Role of the funding source

The funds of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

After searching and retrieving 8267 records, 4020 articles were excluded based on titles and abstracts, leaving 742 papers for full-text screening. Ultimately, 198 articles met the inclusion criteria (Figs. 1 and 2), and 40 articles reported follow-up data. The 198 meta-analyses encompassed 3233 RCTs (range: 1–87), and involved 108,377 participants (range: 32–3750, except for 24 articles where the number of participants could not be quantified) (Appendix pp 32–83).

This umbrella review included 14 BSTs and 21 disorders (including 10 psychiatric disorders, seven movement disorders, and four cognitive disorders) (Fig. 2; Appendix p 85). Across all meta-analyses, 49.6% of the studies reported a quality assessment score ≥9; the mean number of assessment items was 8.35 ± 1.65 (range: 3–11) and did not significantly differ among the three disorders: mean number of assessment items was 8.25 ± 1.87 for psychiatric disorders, 8.42 ± 1.40 for movement disorders, and 8.53 ± 1.44 for cognitive disorders ($F_{(2)}$ = 0.484, P = 0.617).

In the largest meta-analyses, 29% showed large effects (SMD ≥ 0.8), 38% showed medium effects (0.5 ≤ SMD < 0.8), and 33% showed small effects (SMD < 0.5) compared to sham control for psychiatric disorders. For movement disorders, the percentages were 14%, 43%, and 43%, respectively. For cognitive disorders, the percentages were 25%, 13%, and 62%, respectively. Pooling the effect sizes largest meta-analyses of all disorders yielded an SMD of 0.56 (95% CI: 0.49, 0.64; I^2 = 70%), compared with sham control (Fig. 3).

Both the subgroup and sensitivity analyses reported stable results. The pooled follow-up effect sizes for BSTs were significant across all time periods (SMD: 0.44 for ≤1 month; 0.69 for >1 month), with high heterogeneity (70% and 84%, respectively). Notably, compared to sham control, the largest meta-analyses of tDCS for schizophrenia, cerebral ataxia, AD/MCI, and dementia showed non-significant SMDs (Fig. 4). Across BSTs, significant effects (SMDs) were observed, ranging from 0.47 to 0.91, except that VNS reported a non-significant SMD of 0.43. Subgroup analysis of BSTs showed small to moderate heterogeneity (Table 1; Appendix pp 86–87).

Leave-one-out analyses and sensitivity analyses based on excluding the meta-analyses with the number of RCTs <8, quality assessment score <9, the number of patients >1000, and I^2 > 75% indicated stable therapeutic effects (Table 1; Appendix pp 88–90).

Among the 44 largest analyses, 37 reported heterogeneity. We identified moderate heterogeneity (50% ≤ I^2 < 75%) in 10 analyses (27%) and high heterogeneity

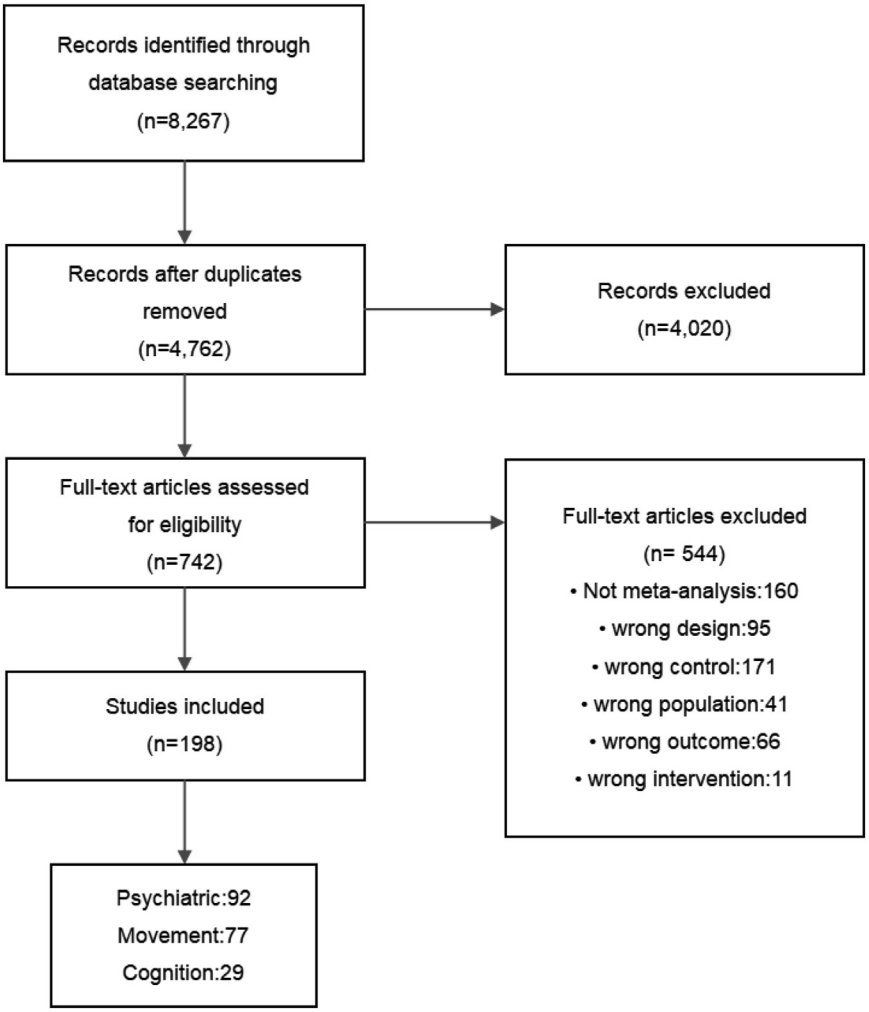

Fig. 1: **PRISMA flow chart**. n—number of study, RCT—randomized controlled trial.

($I^2 \geq 75\%$) in 10 analyses (27%), respectively. In the pooled analysis of the largest meta-analyses and the psychiatric disorder subgroup analysis, potential biases related to publication and small-study effects were identified (Appendix pp 91–92).

For psychiatric, movement, and cognitive disorders, the improvement in core symptom effect sizes ranging from small to moderate was reported (SMDs: 0.60, 0.56, and 0.46 respectively). Regarding stimulation areas, the main regions stimulated in psychiatric disorders are the prefrontal cortex, primarily the DLPFC, with other areas including the medial prefrontal cortex, inferior frontal gyrus, and orbitofrontal cortex. For movement disorders, the primary stimulation area is the motor cortex, with additional areas including the cerebellum, DLPFC, and secondary somatosensory cortices. The stimulation targets for cognitive disorders mainly involve cognitive and language-related areas, such as the DLPFC, pharyngeal/esophageal motor cortex, and Broca's and Wernicke's area. For each kind of disorder, subgroup analyses showed that the majority reported significant improvements in core symptoms (SMDs range: 0.31–1.1), except for DB and tourette. We conducted more detailed analyses of each disorder, and the result of complete analyses can be found in the Appendix (pp 93–97).

For depression, our research consistently showed that, across all meta-analytic results, BSTs demonstrated significant effects in improvement of depression symptoms, compared to sham control: rTMS (SMD range: 0.39–0.86), tDCS (SMD range: 0.31–0.97), DBS (SMD: 0.75), ECT (SMD: 0.66 and 0.91), and TBS (SMD: 1.68). Follow-up effects for rTMS (except for one study that reported an insignificant SMD of 0.29), DBS, and TBS were also significant. Dropout rates showed no significant difference compared to sham control across

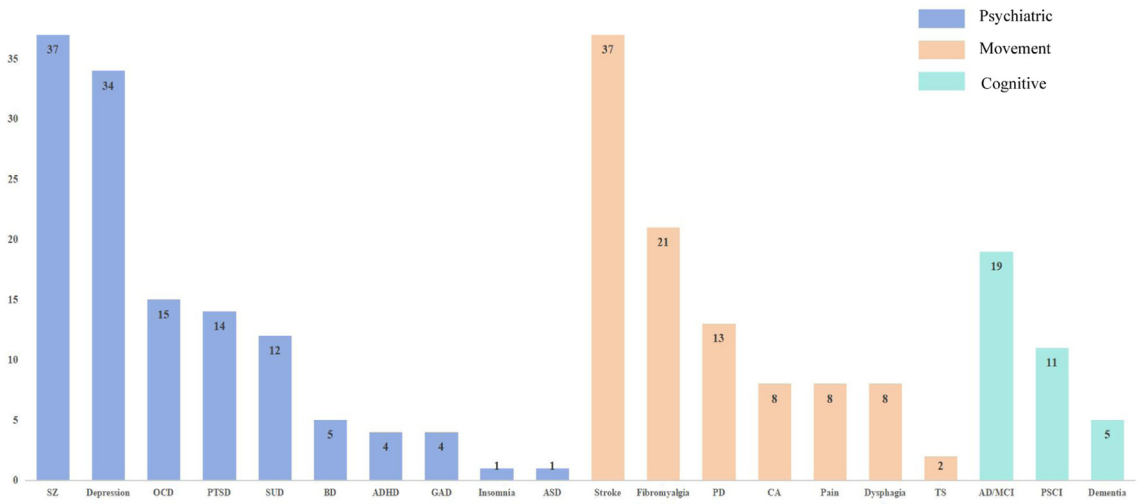

Fig. 2: **The number of studies included in each disorder.** AD—Alzheimer's disease, ADHD—attention deficit hyperactivity disorder, ASD—autism spectrum disorder, BD—bipolar disorder, CA—cerebellar ataxia, GAD—generalized anxiety disorder, MCI—mild cognitive impairment, OCD—obsessive-compulsive disorder, PD—Parkinson's disease, PSCI—post-stroke recognition impairment, PTSD—post-traumatic stress disorder, SUD—substance use disorder, SZ—schizophrenia, TS—tourette syndrome.

all BSTs. For dichotomous outcomes, the majority of studies showed significant treatment response or rTMS (OR range: 3.16–5.12) and tDCS (OR range: 1.63–4.17), as well as remission or rTMS (RR: 2.52 and 5.07) and tDCS (OR range: 1.94–2.88). For DBS, responses were not significant (RR 1.45), but became significant after 16 weeks (OR: 5.5). TBS showed significant response (RR: 2.68 and 2.4) and remission (RR: 2.59). MST also reported a significant response (OR: 5.55) in NMA.

For schizophrenia, compared to sham control, rTMS showed insignificant effects for positive symptoms (PS) (SMD range: –0.28 to 0.21). However, they were significant for negative symptoms (NS) (SMD range: 0.19–0.49), except for one study reporting a insignificant outcome (SMD: 0.41). The effect size remained significant after 4 weeks (SMD: 0.27). For auditory or verbal hallucinations (AVH), significant SMDs ranged from 0.19 to 0.88. Follow-up effect sizes were not significant, while the response rate was significant (OR: 2.94). rTMS treatment was associated with a higher likelihood of adverse events. Dropout rates varied across the studies. Regarding tDCS treatment for both PS and NS, the majority of studies did not show significant SMDs (range: 0.03–0.17 for PS; 0.17–0.63 for NS). Dropout rates were not significant as well. For AVH, the largest meta-analysis reported a significant SMD of 0.36. Overall, most effect sizes were not significant (SMD range: 0.06–0.5). Follow-up effect sizes were not significant (SMD: 0.23 for 1 week; 0.08 for 1 month). There was no significant difference in dropout rates or adverse events. TBS and tACS treatment both reported significant effects for NS (SMD: 1.3 and 0.65), but no significant effects for PS and AVH (SMD: –0.08 and 0.45 for TBS; –0.12 and 0.04 for tACS). According to an NMA, substantial heterogeneity was observed in the effect sizes of various intervention parameters for both rTMS (SMD range: –0.35 to 0.58) and tDCS (SMD range: –0.36 to 1.29). Regarding dropout rates, no significant differences were noted between tVNS, tACS, and tRNS (OR: 1, 0.88, and 3.17).

For rTMS treatment of OCD, compared to sham control, all studies reported significant improvement in obsessive symptoms (SMD range: 0.4–0.79), except for one study (SMD: 0.15) which included only three RCTs. Response rates were significant (OR: 3.15 and 3.39). Follow-up studies indicated inconsistent results (SMD range: 0.16–1.32). Dropout rates were not significant. Regarding tDCS, the SMDs were small and inconsistent (0.37 and 0.39). Two studies on DBS reported significant SMDs (0.85 and 0.90). Response was significant (RR: 2.4), and remission was not (RR: 1.3). The probabilities of an individual experiencing an adverse event or dropping out were 0.68 and 0.13, respectively.

For SUD, compared to sham control, rTMS treatment studies reported significant effect sizes for craving (SMD range: 0.61–1.53), with one study showing a insignificant SMD of 0.04. tDCS consistently showed significant effects for craving (SMD: 0.33 and 0.77). Notably, for rTMS and tDCS, the NMA showed high heterogeneity across different parameters (SMD range: 0.16–0.97) in changing smoking frequency. Gay et al. and Cha et al. analyzed 30 and 54 RCTs, respectively, and found that the therapeutic effects of rTMS and tDCS varied significantly across different types of addiction.

For PTSD, compared to sham control, rTMS treatment studies reported significant SMDs in trauma

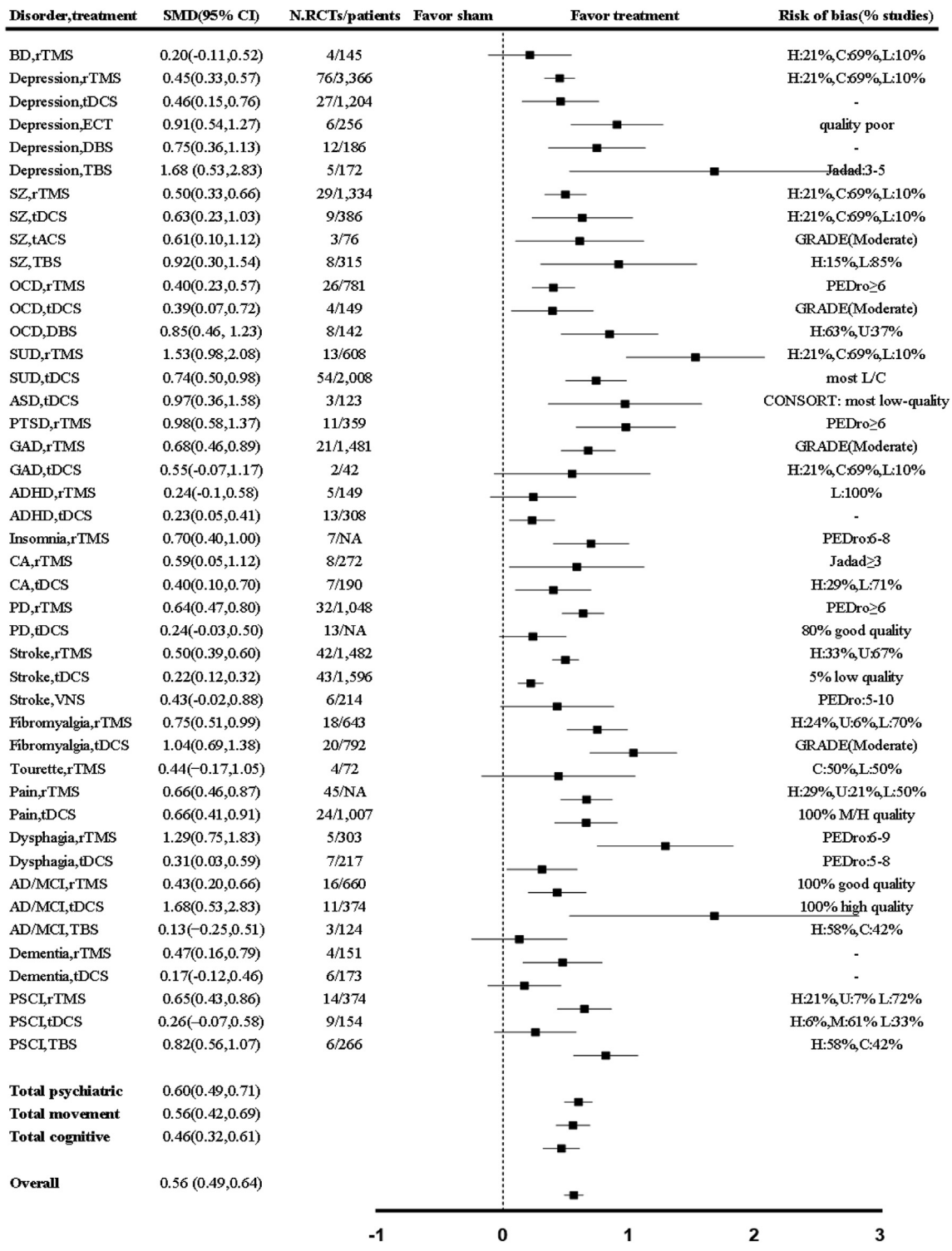

***Fig. 3*: Effect sizes in the largest meta-analyses of BSTs in comparison to sham control**. AD—Alzheimer's disease, ADHD—attention deficit hyperactivity disorder, ASD—autism spectrum disorder, BD—bipolar disorder, C—some concerns, CA—cerebellar ataxia, DBS—deep brain stimulation, ECT—electroconvulsive therapy, GAD—generalized anxiety disorder, CONSORTS—consolidated standards of reporting trials guidelines, GRADE—grading of recommendation assessment, development and evaluation, H—high risk, L—low risk, M—moderate, MCI—mild cognitive impairment, N—number of RCTs/patients, NA—not assessed or reported, OCD—obsessive-compulsive disorder, PD—Parkinson's disease,

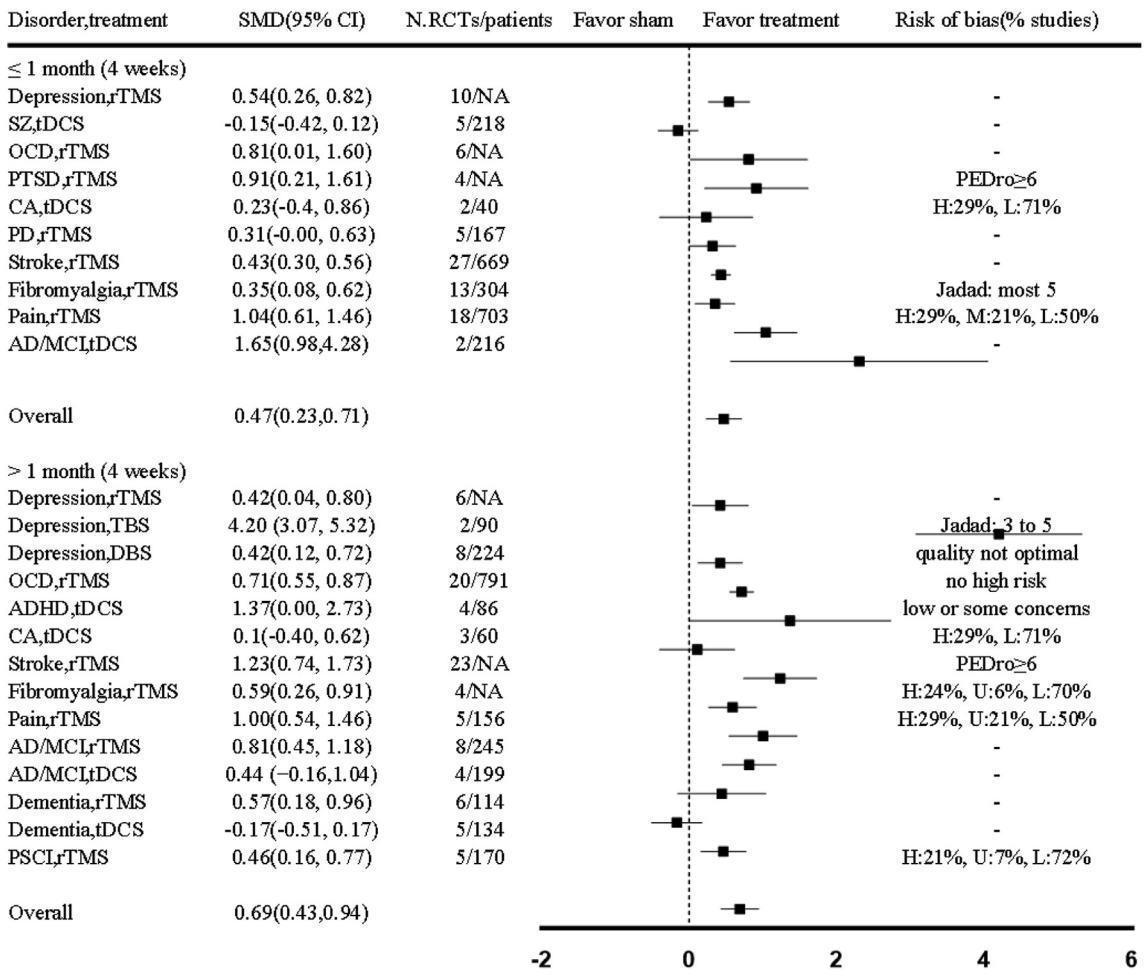

***Fig. 4:* Follow-up effect sizes in the largest meta-analyses of BSTs**. AD—Alzheimer's disease, ADHD—attention deficit hyperactivity disorder, C—some concerns, CA—cerebellar ataxia, DBS—deep brain stimulation, H—high risk, L—low risk, M—moderate, MCI—mild cognitive impairment, N—number of RCTs/patients, NA—not assessed or reported, OCD—obsessive-compulsive disorder, PD—Parkinson's disease, PEDro—physiotherapy evidence database scale, PSCI—post-stroke cognitive impairment, PTSD—post-traumatic stress disorder, rTMS—repetitive transcranial magnetic stimulation, SMD—standardized mean difference, SZ—schizophrenia, TBS—theta burst stimulation, tDCS—transcranial direct current stimulation, U—unclear.

symptom improvement (range: 0.74–2.67). The follow-up effect size at 2–4 weeks remained significant (SMD: 0.91), and the dropout rate was not significant different. An NMA reported effect sizes (SMD range: 0.26–0.71) for different rTMS parameters in the treatment of PTSD.

In rTMS studies for anxiety disorders, significant SMDs ranged from 0.68 to 1.8. There were no notable differences in adverse events or dropout rates. For tDCS studies, only one study reported a non-significant effect size (SMD: 0.55) that included two RCTs.

For ADHD, rTMS reported two insignificant effects (SMD: 0.24 and 0.5). Two articles reported tDCS treatment effects (SMD: 0.23 for immediate, and 1.37 for follow-up >3 days). For both BSTs, no significant differences were found between active stimulation and sham control.

rTMS wan effective in improving the ataxia symptoms in cerebral ataxia, with effect sizes ranging from 0.34 to 1.18 (SMD). Two studies on tDCS reported significant effects (SMD: 0.4 and 0.71). However, follow-up effect sizes were inconsistent (SMD range: 0.1–0.73). For both BSTs, no significant adverse events were reported.

PEDro—physiotherapy evidence database scale, PSCI—post-stroke cognitive impairment, PTSD—post-traumatic stress disorder, rTMS—repetitive transcranial magnetic stimulation, SMD—standardized mean difference, SUD—substance use disorder, SZ—schizophrenia, tACS—transcranial alternating current stimulation, TBS—theta burst stimulation, tDCS—transcranial direct current stimulation, U—unclear, VNS—vagus nerve stimulation.

	N	n	SMD (95% CI)	Effect size P value	Heterogeneity I^2 (%)
All disorders	44	23,702[a]	0.56 (0.49, 0.64)	P < 0.001	70%
Subgroup: three categories of disorders					
Psychiatric	22	13,590	0.60 (0.49, 0.71)	P < 0.001	66%
Movement	14	7836[a]	0.56 (0.42, 0.69)	P < 0.001	79%
Cognitive	8	2276	0.46 (0.32, 0.61)	P < 0.001	48%
Subgroup: each kind of disorder					
DB	1	145	0.20 (−0.11, 0.52)	P = 0.213	0%
Depression	5	5184	0.65 (0.41, 0.90)	P < 0.001	64%
SZ	4	2111	0.55 (0.41, 0.69)	P < 0.001	0%
OCD	3	1072	0.51 (0.26, 0.76)	P < 0.001	57%
SUD	2	2616	1.10 (0.33, 1.87)	P < 0.001	85%
ASD	1	123	0.97 (0.36, 1.58)	P = 0.002	0%
PTSD	1	359	0.98 (0.59, 1.38)	P < 0.001	0%
GAD	2	1523	0.67 (0.46, 0.87)	P < 0.001	0%
ADHD	2	457	0.23 (0.07, 0.39)	P = 0.004	0%
Insomnia	1	NA	0.70 (0.40, 1.00)	P < 0.001	0%
CA	2	462	0.45 (0.18, 0.71)	P = 0.001	0%
PD	2	1048[a]	0.45 (0.06, 0.85)	P < 0.001	84%
Stroke	3	3292	0.37 (0.14, 0.61)	P < 0.001	86%
Fibromyalgia	2	1435	0.87 (0.59, 1.15)	P < 0.001	45%
Tourette	1	72	0.44 (−0.17, 1.05)	P = 0.157	0%
Pain	2	1007[a]	0.66 (0.50, 0.82)	P < 0.001	0%
Dysphagia	2	520	0.77 (−0.19, 1.73)	P < 0.001	90%
AD/MCI	3	1158	0.58 (0.27, 0.90)	P < 0.001	57%
Dementia	2	324	0.31 (0.02, 0.61)	P = 0.005	50%
PSCI	3	794	0.48 (0.26, 0.71)	P < 0.001	50%
Subgroup: BSTs					
rTMS	19	13,228[a]	0.58 (0.49, 0.67)	P < 0.001	63%
tDCS	16	8723[a]	0.47 (0.33, 0.60)	P < 0.001	72%
TBS	4	877	0.65 (0.37, 0.94)	P = 0.001	43%
DBS	2	328	0.80 (0.53, 1.07)	P < 0.001	0%
ECT	1	256	0.91 (0.55, 1.28)	P < 0.001	0%
tACS	1	76	0.61 (0.10, 1.12)	P = 0.019	0%
VNS	1	214	0.43 (−0.02, 0.88)	P = 0.067	0%
Subgroup: month					
All	23	4449[a]	0.57 (0.40, 0.75)	P < 0.001	81%
≤1 month	10	2347[a]	0.44 (0.23, 0.65)	P < 0.001	70%
>1 month	14	2269[a]	0.69 (0.43, 0.94)	P < 0.001	84%
Sensitivity analysis (excluding)					
Quality <9	28	15,890[a]	0.55 (0.45, 0.64)	P < 0.001	71%
I^2 > 75% (exclude NA)	28	16,008[a]	0.50 (0.41, 0.58)	P < 0.001	68%
N < 8	26	20,880[a]	0.59 (0.49, 0.68)	P < 0.001	76%
n > 1000	32	9176[a]	0.59 (0.48, 0.71)	P < 0.001	69%

AD—Alzheimer's disease, ADHD—attention deficit hyperactivity disorder, ASD—autism spectrum disorder, BD—bipolar disorder, BST—brain stimulation therapy, CA—cerebellar ataxia, DBS—deep brain stimulation, ECT—electroconvulsive therapy, GAD—generalized anxiety disorder, MCI—mild cognitive impairment, N—number of RCTs, n—number of patients, NA—not available, OCD—obsessive-compulsive disorder, PD—Parkinson's disease, PTSD—post-traumatic stress disorder, PSCI—post-stroke cognitive impairment, rTMS—repetitive transcranial magnetic stimulation, SMD—standardized mean difference, SUD—substance use disorder, SZ—schizophrenia, tACS—transcranial alternating current stimulation, TBS—theta burst stimulation, tDCS—transcranial direct current stimulation, VNS—vagus nerve stimulation. [a]The data excludes meta-analysis with unextractable participant numbers.

Table 1: **Largest meta-analyses, subgroup analysis, and sensitivity analysis results.**

For PD, rTMS studies showed that improvement in movement symptoms (especially on the Unified Parkinson's Disease Rating Scale—Part III [UPDRS-III]) was significant (SMD: range 0.27–0.64). However, the effect size at the 1-month follow-up was not significant (SMD: 0.31). For tDCS treatment, effect sizes were

consistently insignificant (SMD range: 0.07–0.24). An NMA on DBS found that high-frequency stimulation was more effective for movement symptoms (UPDRS-III) than low-frequency when used alone, but low-frequency was more effective when combined with medications. Another NMA showed that high-frequency rTMS was more effective in improving movement symptoms improvement than low-frequency rTMS; tDCS was more effective on the DLPFC than on other targets; and iTBS had no significant effect.

For stroke, the majority of rTMS studies showed significant improvement in motor function (SMD range: 0.38–1.00). Effect sizes for follow-up were inconsistent (SMD: range: 0.1–1.61). For tDCS treatment, effects were inconsistent (SMD range: –0.12 to 0.83). For VNS, one study reported a non-significant effect (SMD: 0.43), and follow-up result also not significant. NMA indicated a high inconsistency (SMD range: 0.13–0.53). The NMA also reported significant SMDs for taVNS (1.2) and iTBS (0.72). Adverse events did not show any significant differences.

For fibromyalgia, in rTMS studies, all reported significant improvement in pain symptoms compared to sham control (SMD range: 0.49–1.29), except for one study (SMD: 0.86), which was based on only four RCTs. Follow-up <1 month effects were significant (SMD range: 0.35–0.7), while those >1 month were not significant (SMD: 0.14 and 0.59). Regarding tDCS, all studies reported significant SMDs (range: 0.5–1.65). The comparison of different parameters of rTMS, tDCS, TENS, and CES in two NMAs showed that TENS (SMD: 0.46 and 3.00) and CES (SMD: 0.36) treatment effects were not significant.

For pain, the majority of studies of rTMS reported significant improvement in pain symptoms for both immediate and follow-up (SMD range: 0.43–1.04). tDCS studies reported significant SMDs (range: 0.59–1.14), except for one study, which reported 0.38. For both BSTs, adverse events were not significant.

For dysphagia, rTMS showed significant improvement in swallowing function (SMD range: 0.56–1.61), while the effects of tDCS were inconsistent (SMD range: 0.31–0.54). An NMA reported insignificant effects of 0.86 for rTMS.

For AD and MCI, rTMS studies reported significant improvement in global cognition (SMD range: 0.39–2.07). Significant follow-up effects were observed (SMD range: 0.29–5.04). tDCS studies reported inconsistent SMD (range: 0.37–6.32). Follow-up data were not significant (SMD range: 0.19–1.65). Adverse events of rTMS were significant greater compared to sham control (RR: 2.29 and 2.67), while those of tDCS were not significant. An NMA report showed that tDCS and iTBS had no significant effect sizes, while rTMS demonstrated an overall significant treatment effect. There was no difference in dropout rates between the two groups.

For PSCI, including aphasia, all rTMS studies showed significant effect sizes in the improvement in global cognition (including naming) compared to sham control (SMD range: 0.25–1.04), and follow-up effects were also significant (SMD range: 0.46–0.53). Inconsistent effects were observed in tDCS studies (SMD range: 0.26–0.82). TBS reported a significant effect (SMD: 0.82). An NMA indicated rTMS interventions were effective for aphasia (SMD range: 1.03–1.93), while effects of tDCS varied significantly (SMD range: –1.2 to 0.78). Both dropout rates and adverse events did not show significant differences.

Discussion

In this umbrella review, we synthesized evidence from 198 meta-analyses and NMAs, encompassing more than 108,377 participants from 3233 RCTs. To our knowledge, this study represents the most extensive exploration of the applications of BSTs, pioneering for its inclusion of these three disorders.

Overall, this umbrella review suggests BSTs may have clinically relevant effects on these three disorders, confirming that their efficacy is comparable to conventional treatments like medication and psychotherapy.[52,56] However, moderate effect sizes indicate significant room for improvement, highlighting both the promising potential and opportunities to enhance BSTs.

From the perspective of BSTs, subgroup analyses show that research primarily focuses on three NIBS techniques: rTMS, tDCS, and TBS. These methods stimulate cortical areas of the brain directly, avoiding the need for surgery or invasive procedures. They are associated with minimal adverse effects and are more readily accepted in clinical settings.[8] Furthermore, we found that, compared to other treatment methods, rTMS demonstrates greater therapeutic potential for various disorders, including advantages such as a wide range of applicability, good efficacy, and high safety. tDCS is also a highly promising treatment modality, as its portability, safety, and cost-effectiveness highlight its clinical relevance for patients with limited treatment options.[57] TBS is a novel therapeutic approach that, compared to traditional rTMS, can achieve a similar therapeutic effect in a shorter time (typically 10% of the conventional rTMS duration).[58] A large body of research has focused on its efficacy in motor areas and the prefrontal cortex.[59] Our TBS subgroup analysis reported significant effect sizes, but its high efficiency requires further investigation. In addition, many new BSTs, such as tACS, tRNS, and CES, have demonstrated therapeutic potential, especially in improving motor symptoms.

In terms of treatment sustainability, the umbrella review indicates that BSTs have a certain degree of treatment persistence. However, due to the limited number of studies lasting more than three months, the follow-up effects need further investigation. In follow-up

studies, tDCS shows poor efficacy for schizophrenia,[60] CA,[61] AD/MCI,[13,62,63] and dementia.[64] However, when comparing these results with the largest meta-analysis, it is revealed that tDCS inherently has poor efficacy for these conditions.[13,65] Therefore, these findings should not be taken as evidence of poor continuity in BSTs.

From the perspective of these three types of disorders, disorder-type subgroup analyses indicated that BSTs were similarly effective for psychiatric, movement, and cognitive disorders. Neuroimaging studies in both resting and task states have found that DLPFC is associated with abnormalities in various disorders. It serves as a hub for processes disrupted in various neuropsychiatric disorders.[66–68] Previous studies have shown the feasibility of DLPFC in rTMS and the mechanisms for these disorders.[69] Our study builds on this foundation, and we also found that many treatments for movement disorder engage the DLPFC. Future research could consider expanding the scope of cross-diagnostic studies to explore the interactive effects of psychiatric, cognitive, and movement disorders.

Our review of BSTs for psychiatric disorders differs from a recent umbrella review.[44] First, while both affirm the safety and efficacy, our study analyzed each condition individually and aggregated effect sizes, reporting a moderate overall effect size and providing quantitative support. Second, although our findings align with previous research on conditions like depression, PTSD, and OCD, we draw different conclusions in certain areas. For instance, in schizophrenia, we found that BSTs show limited improvement in negative symptoms, with highly variable and small effects on positive symptoms, including AVH. We attribute these differences to the varying control conditions (sham vs. active control). Previous umbrella reviews noted that control conditions impact results. This finding has been confirmed in psychological and pharmacological research,[70,71] and our study suggests might also apply to BST. Additionally, in contrast to Malhi and Rosson, we believe that tDCS has greater potential in the treatment of SUD, based on an extensive literature review.[44,72] Notably, we included a recent study that analyzed 43 RCTs on tDCS for substance abuse, showing good effectiveness for various substances but poorer results for alcohol addiction.[73] Furthermore, there has been an surge in OCD research over the past two years. Compared to previous studies, our umbrella review includes many articles on non-treatment-resistant OCD, expanding upon some earlier conclusions.[74,75] Regarding BSTs for depression, particularly tDCS, our study provides a more robust conclusion than previous meta-analyses.[76] While BSTs show great potential, we believe they should be considered an adjunct treatment alongside conventional treatments.[77,78]

For most movement and cognitive disorders, higher-level evidence supporting the effectiveness of BSTs is lacking, although we have made new attempts. This umbrella review provides a comprehensive summary of BST treatment effects in these disorders, based on the latest evidence. For conditions like chronic pain, BSTs such as rTMS and tDCS are considered adjunctive options. A comprehensive analysis of all complementary and alternative medicine therapies for stroke found that inhaled cannabis, graded motor imagery, and compound kushen injection appeared to be the most promising treatment for chronic pain.[41] However, in terms of therapeutic dose standardization, rTMS, tDCS, and TENS outperform other adjunct therapies, including those listed.[41] Our umbrella review, which included a broader range of studies, found that rTMS and tDCS show promising results for stroke treatment, providing additional evidence for their clinical application. For dementia, international treatment guidelines recommend non-pharmacological interventions.[79] Our study found that BSTs, particularly rTMS, offer greater efficacy and durability compared to previously recommended treatments, such as music therapy.[14] Some BSTs are standardized and cost-effective, presenting a potentially new option for dementia patients compared to expensive multi-sensory rooms or personalized care.[14] Overall, our research supports the general claim that BSTs are beneficial for most movement and cognitive disorders. We recognize the potential in BSTs for treating pain, fibromyalgia, and post-stroke motor recovery, consistent with findings from previous reviews.[80,81] However, our inclusion of studies on tDCS for PD yielded results that differ from prior research, which suggested efficacy with anodal motor/premotor/SMA tDCS for PD movement function.[81] The difference may stem from Fregni's detailed subdivision of brain regions, suggesting a need for further exploration of regional significance. tDCS contributes to changes in regional cerebral blood flow and mitigates aberrant neural synchronization,[82] while rTMS enhances long-term potentiation (LTP) in Alzheimer's patients,[83] which may explain the improvement of core symptoms of AD observed in our study. For disorders like Alzheimer's that have not yet established effective pharmacological treatments, these results are encouraging.[33] Notably, in research on cognitive disorders, BSTs showed larger effect sizes but also higher heterogeneity compared to other conditions, likely due to our assessment of general cognitive function rather than subtype-specific functions.

There are several important limitations to this study. First, due to difficulties in blinding and randomization, we included a limited number of studies on DBS and ECT. Previous research indicates that DBS is widely used in clinical practice for treating movement disorders such as PD, dystonia, and essential tremor.[84] It has also been explored for other conditions, including depression, OCD, anorexia nervosa, and PTSD.[85] The absence of this segment may diminish the interpretive

power of the results related to DBS and ECT. Second, BSTs are often used as adjunctive treatments.[86] For most disorders, current treatment guidelines continue to recommend pharmacotherapy as the first-line treatment strategy in clinical practice.[9,87] The observed effect sizes may not fully account for the influence of concurrent medications or other interventions, which could potentially inflate our research findings.[88] Third, BSTs encompass many targets and parameters. Our study aims to provide a broad synthesis of the relevant research. As a result, we did not analyze the targets and stimulation parameters in detail. We recommend conducting more thorough research in the future. Fourth, our umbrella review results demonstrate a high level of integration and offer certain guidance and insights. However, caution is needed in clinical applications, and we recommend conducting more well-designed experimental studies in the future to validate our findings. Finally, we identified areas where specific techniques may be effective, such as rTMS for BD, ADHD, insomnia, cerebral ataxia, dysphagia, and dementia. For tDCS, potential applications include ASD, anxiety disorders, ADHD, insomnia, tourette, cerebral ataxia, dysphagia, AD, and MCI. Some promising results have been achieved in these areas,[22,89,90] but current research is limited and lack high-quality evidence. Future research should explore their optimal treatment parameters more thoroughly to draw more accurate conclusions.

In conclusion, our comprehensive analysis provides a detailed summary of the therapeutic effects of BSTs on psychiatric, movement, and cognitive disorders. This pioneering study not only aligns with current cross-diagnostic research but also provides a key foundation for clinical decision-making, enhancing BSTs' treatment efficiency and promoting the development of integrated therapies.

Contributors

ZZ, FC, XL, and KW designed the study. ZZ and FC drafted the manuscript. ZZ, FC, LY, LH, ZL, HD, and MZ contributed to the database preparation and double check. FC, NL, XX, and ZZ did data analyses. WW and LY assessed the quality of meta-analyses using predefined criteria. LM and ZZ revised the manuscript. XL and KW accessed and verified the data. All authors commented on and approved the draft and final manuscripts.

Data sharing statement

All data included in this umbrella review were extracted from publicly available systematic review. The Supplement Materials will be freely available online with the publication of this Article. Additional data can be shared upon request to the corresponding author.

Declaration of interests

All authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2024.103046.

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