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Efficacy and Safety of Non-Invasive Brain Stimulation for Patients with Parkinson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT:

Background: Non-invasive brain stimulation (NIBS) is a promising adjunct for Parkinson's disease (PD), but variation in modality, target, stimulation dose, outcome selection, and safety reporting has produced uncertain estimates of benefit and risk.

Objective: To evaluate the efficacy and safety of sham-controlled NIBS for adults with PD.

Methods: PubMed/MEDLINE, Embase, Web of Science, and CENTRAL were searched for randomized parallel-group trials published from 2011 through August 2026. The primary outcome was immediate post-intervention motor impairment. Standardized effects were expressed as Hedges' g, with negative values favoring active NIBS. Random-effects synthesis used restricted maximum likelihood estimation and Hartung–Knapp confidence intervals. Heterogeneity, prediction intervals, target subgroups, leave-one-out analyses, extreme-effect exclusion, funnel-plot asymmetry, and arm-level safety reporting were examined.

Results: Eighteen studies involving 579 participants were included; 17 motor comparisons (n = 561) entered the primary synthesis. Active NIBS improved motor outcomes compared with sham stimulation (g = −0.94, 95% CI [−1.57, −0.30], p = .006), although heterogeneity was substantial

(I^2 = 83.6%; 95% prediction interval, −3.36 to 1.49). The magnetic-stimulation-only estimate was similar (g = −1.01, 95% CI [−1.66, −0.35]). Excluding two extreme effects attenuated the estimate (g = −0.61, 95% CI [−0.97, −0.26]) without changing its direction. All leave-one-out estimates favored active stimulation. One small study supported a mood effect. Safety data were incomplete: trials with complete counts reported no serious adverse events or adverse-event-related withdrawals, but missing arm-level reporting prevented comparative pooling.

Conclusions: NIBS, particularly magnetic stimulation, produced an average short-term motor benefit in PD, but marked heterogeneity and incomplete safety reporting limit certainty about effect size, durability, target superiority, and comparative safety.

1. INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder with various non-motor symptoms such as alterations in cognition, mood, sleep, autonomic dysfunction and quality of life (QoL) which are heterogeneous and clinically PD is defined by parkinsonism (bradykinesia associated with rest tremor, rigidity or both) (Bloem et al., 2021; Postuma et al., 2015).

Its burden is quickly growing: According to the estimates from the Global Burden of Disease 2021, there were approximately 11.77 million people living with PD worldwide in 2021; the prevalence and incidence of which have been increasing over the past 3 decades, as well as the disability burden (Luo et al., 2025). The trend's clinical and societal implications include progressive disability, falls, communication problems, neuropsychiatric manifestations, caregiver burden and need for long-term multidisciplinary care (Armstrong & Okun, 2020; Bloem et al., 2021).

The management is currently mostly symptomatic. Dopaminergic drugs still play a key role in the management of bradykinesia and rigidity, and exercise programs and physical therapy, occupational therapy and speech and language therapy help people achieve mobility and independence in everyday life (Armstrong & Okun, 2020). However, treatment with medication can also be challenging due to wearing-off, dyskinesia, hallucinations or suboptimal control over axial and non-motor symptoms as the disease progresses (Armstrong & Okun, 2020; Bloem et al., 2021). Although DBS can be beneficial in selected patients with medication-responsive symptoms and motor complications, it is limited by its invasive nature, requirements for eligibility, cost and the perioperative requirements that limit the applicability of DBS at the population level (Bloem et al., 2021). These limitations maintain the interest in adjunctive interventions that can be used to modulate dysfunctional motor and non-motor

networks, while avoiding surgery.

Non-invasive brain stimulation (NIBS) includes methods that apply magnetic or electric fields externally to modify the way the brain's cortex becomes more or less excitable and/or how its networks work. Repetitive transcranial magnetic stimulation (rTMS) can be applied as a train of magnetic pulses, such as the conventional low- and high-frequency TMS, intermittent or continuous theta-burst stimulation and deep-TMS protocols using specific coils.

Transcranial direct current stimulation (tDCS) involves the stimulation of the brain with a weak direct current administered via electrodes placed on the scalp, which alters the polarization of the cell membranes and the likelihood of neuronal firing, but does not directly stimulate the neurons to produce action potentials (Antal et al., 2017; Lefaucheur et al., 2020). In PD, these methods are biologically plausible as motor, supplementary motor, prefrontal and cerebellar regions are involved in distributed basal ganglia–thalamo–cortical networks that are involved in motor execution, gait, cognition, and affect (Madrid & Benninger, 2021). The beneficial impact of NIBS is not only likely to be modality-dependent, but also likely to be dose-dependent. The frequency, intensity, target, montage (coil or electrodes), dose (number of pulses), number and spacing of sessions, state of medication, and severity of the disease may all affect the direction and persistence of the response (Lefaucheur et al., 2020; Madrid & Benninger, 2021).

Most research on high-frequency rTMS has focused on motor dysfunction and gait output after rTMS of the primary motor cortex and/or supplementary motor area, and rTMS over the dorsolateral prefrontal cortex for depressive and cognitive symptoms. Most of the studies on tDCS have focused on motor areas, prefrontal areas, or cerebellar areas, often in addition to gait or dual task training (Duan & Zhang, 2024; Nguyen et al., 2024). Such diversity is beneficial to clinical personalization, and also represents significant methodological heterogeneity.

Safety is also critical, as NIBS is often administered over multiple sessions, to older adults with potentially multiple health conditions and a number of medications. Modern TMS guidelines highlight the importance of systematic recording of minor adverse events and serious adverse events, structured screening, trained supervision and protocol-specific intensity limits; if recommended guidelines and precautions are followed seizures are rare (Rossi et al., 2021). Most commonly reported adverse events of conventional low-intensity tDCS are transient local sensations, discomfort, headache, or fatigue, albeit the ascertainment and reporting of adverse events are variable across trials (Antal et al., 2017). Therefore, a judgement of “safe” should not be based on the absence of reported events, the denominators for the arms should be reported, definitions of the terms should be explicit, and absence of events should be distinguished from not reported.

Based on current trials and reviews, there is some evidence that NIBS can benefit certain PD outcomes, but the extent of this benefit and how certain this is, remains to be confirmed.

Although the average motor effects of rTMS are generally favorable, the number of trials is in some cases small, with different rTMS protocols for stimulating motor-network targets (Lu et al., 2026; Zhang et al., 2022).

Recent tDCS syntheses, however, have yielded mixed or null average effects for global motor outcomes, with potential outcome and/or patient-specific responses and large prediction intervals (Duan & Zhang, 2024; Nguyen et al., 2024). Mixing clinical domains, double-counting sham groups, applying crossover data without paired variances, and assuming that little or no safety data is complete safety data are additional ways that conclusions can be skewed.

Based on this, we aimed to perform a systematic review and meta-analysis of NIBS efficacy and safety in adults with PD in sham-controlled trials, operationally defined as rTMS (theta-burst and deep-TMS) and tDCS. The main goal was to assess the effect of the intervention in the immediate post-intervention period focusing on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) or Movement Disorder Society revision (MDS-UPDRS-III).

Secondary aims were to combine gait, freezing, mood, cognition, and adverse-event outcomes where data were sufficiently comparable and to investigate whether there were differences in effects based on the modality of stimulation, target, frequency, session dose, medication state, or if there were concomitant rehabilitation.

2. LITERATURE REVIEW

NIBS research in PD has evolved from single small physiological and proof-of-concept trials to randomized trials, which have been done across several cortical targets and stimulation protocols. A preliminary cross-modality synthesis revealed that both

rTMS and transcranial electrical stimulation may yield small enhancements in performance in either the motor or cognitive domain, but also showed methodological variation, small sample sizes and few studies (Goodwill et al., 2017).

However, a more recent systematic review found that NIBS was not yet considered a standard of care due to the lack of harmonization in the stimulation parameters, clinical phenotypes, medication states, outcomes, and follow-up periods (Madrid & Benninger, 2021). Key to this evolution is the fact that the more trials conducted, the more confidence is gained, but that does not mean that the more trials the more the differences between what was stimulated, how, and which PD domain was measured, are resolved.

The signal of motor-network rTMS is the most consistent. Various targets have been tested including primary motor cortex, supplementary motor area, bilateral motor representations, combined motor and prefrontal targets, cerebellum and deeper or broader fields. In a parallel early trial, intermittent TBS over motor and prefrontal areas did not provide a consistent effect, while TBS over supplementary motor area and subsequent high-frequency TBS showed beneficial effects on specific motor and/or gait outcomes (Benninger et al., 2011; Mi et al., 2019; Shirota et al., 2013). It may also be important to combine stimulation with task-specific rehabilitation: In one randomized study, rTMS combined with gait training resulted in clinically relevant gains, as is hypothesized for stimulation to facilitate learning-dependent plasticity, rather than to be used as a stand-alone symptomatic treatment (Chung et al., 2020).

There is evidence of target and protocol modifying efficacy. New evidence-based rTMS guidelines concluded that high-frequency (>5 Hz) bilateral motor-cortex stimulation was likely effective for PD motor impairment, and left dorsolateral prefrontal stimulation was likely effective for depression in PD; however, it was noted that although rTMS may be statistically effective, this does not necessarily imply clinically meaningful benefit for all patients (Lefaucheur et al., 2020). Studies using target-based logic have further sought to extend this approach using randomized multifocal and deep-TMS, stimulating motor and/or prefrontal circuits alone or in combination, but the findings have not converged on a single, optimal configuration (Brys et al., 2016; Spagnolo et al., 2021). A subsequent meta-analysis, without any selection criteria other than that the studies were randomized trials, reported an average motor benefit of rTMS, a potential antidepressant effect, and sparse evidence for cognition, but also limited evidence for site and frequency (Zhang et al., 2022).

The latest large rTMS synthesis also confirms efficacy, but is a good example of the need for updated, "carefully set boundaries" analysis. Lu et al. (2026) incorporated 45 RCTs and demonstrated beneficial pooled effects on UPDRS-III, and selected non-motor outcomes, with subgroups varying with different areas of the supplementary motor area, primary motor cortex, and dorsolateral prefrontal cortex. But, the extensive inclusion of years, protocols, outcomes and statistical formats can lead to high clinical heterogeneity and site-specific estimates may be driven by a small number of trials. A modern review must thus differentiate between the constructs of motor, mood, select no more than one of several correlated outcomes from the same group of subjects without making adjustments, and differentiate between exploratory patterns within subgroups and confirmatory evidence.

The literature about tDCS is less clear. Target choice and combination with rehabilitation remain uncertain, as seen in a pilot randomized trial of motor-cortex tDCS in combination with dual-task gait training that did not clearly demonstrate an additive effect on the target of the study, motor-speed (Schabrun et al., 2016). Some evidence exists for motor benefits of tDCS in PD, but the conclusions of a 2021 meta-analysis suggest insufficient evidence (de Oliveira et al., 2021).

Recent syntheses have yielded more complex conclusions, however, with Nguyen et al. (2024) reporting mixed results on various domains of gait and balance and Duan and Zhang (2024) included 12 sham-controlled RCTs and reported a null average effect on global motor function, gait, and some cognitive domains, with large prediction intervals. These discrepancies may be due to a different selection of outcomes, different participants, different sessions, different montage and/or different training methods (e.g., the use of tDCS alone or in combination).

The measurement of outcomes also contributes towards inconsistencies. UPDRS-III and MDS-UPDRS-III are accepted motor-examination tools, but should not be converted from one to the other unless properly standardized, and trials might involve different medication states (Goetz et al., 2008). Even though all are continuous outcomes, they are fundamentally different constructs, and should not be combined in one omnibus effect, as this would simply be a sum of their individual effects.

Likewise, pooling an immediate post-treatment effect with a follow-up effect (also without a prespecified hierarchy) violates

the independence and interpretability of the pooled effect. Safety information has been generally reassuring, although there is less that is complete as compared to efficacy information. TMS trials generally show that side-effects reported during TMS are mild and transient including headache, scalp discomfort, dizziness, tinnitus and fatigue; serious events are rare with protocols in compliance with guidelines (Rossi et al., 2021). Most commonly observed side effects of tDCS experiments are temporary tingling, burning, itching, fatigue or headache (Antal et al., 2017). However, many PD trials do not report on each arm the number of participants affected, or report on only the number of events, or completely miss reporting numbers of adverse events. Treating such data as if there were no facts (no cells reported) for this risk and setting the number to 0 would bias the risk estimation toward safety. A strict synthesis therefore should keep 'not reported' evidence as missing, pool only compatible evidence at the participant level and keep double-zero evidence and/or evidence for which allocation was not clear narratively.

As a whole, the evidence indicates the need to perform a targeted NIBS synthesis which is sensitive to modality-specific mechanisms and outcome domains. This current review focuses on dependent comparisons, incompatible crossover statistics, heterogeneous outcome timing and incomplete reporting of adverse events using small-sample-corrected random-effects inference and choosing one immediate motor comparison per study.

3. METHODS

3.1 Protocol and Reporting Standards

The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020) and relevant methodological guidance in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2024; Page et al., 2021). No prospective protocol registration was available.

3.2 Eligibility Criteria

Eligibility was determined with the population, intervention, comparator, outcome and study-design (PICOS) framework.

Studies were eligible if they included adults with a clinically diagnosed idiopathic PD (according to accepted diagnostic criteria) and evaluated at least one eligible NIBS protocol, with otherwise balanced co-interventions; had a randomized parallel-group design; were published as full, peer-reviewed articles between 1 January 2011 and 29 August 2026; and reported sufficient numerical data for an eligible efficacy or safety outcome.

Conventional rTMS, intermittent or continuous theta-burst stimulation, deep rTMS and tDCS were the operational NIBS modalities. Single-pulse diagnostic TMS, invasive stimulation, ECT, transcranial alternating current stimulation, peripheral stimulation, focused ultrasound or noncranial stimulation were not in scope. Table 1 shows the operational inclusion/exclusion criteria that were used during screening.

Table 1. Operational PICOS eligibility criteria

Domain	Include	Exclude
Population	Adults with idiopathic Parkinson's disease	Atypical/secondary parkinsonism; non-human studies
Intervention	rTMS, iTBS/cTBS, deep rTMS, or tDCS	Diagnostic TMS, invasive stimulation, other excluded modalities
Comparator	Sham stimulation; balanced rehabilitation or usual-care co-intervention	Uncontrolled, active-only, or materially unbalanced comparator
Outcomes	Motor, gait/freezing, mood, cognition, quality of life, or participant-level adverse events	No extractable eligible outcome
Design/report	Peer-reviewed randomized parallel-group trial, 2011–2026	Nonrandomized; abstract only; crossover without paired variance or usable first-period data

A crossover trial was included only if a paired analysis was possible, based on a reported within-participant variance or an uncontaminated first period comparison. For multi-arm trials with a shared sham arm, the active arm with the greatest sample size, eligible immediate motor outcome and compatible with the subgroup was selected using prespecified hierarchy.

Alternative arms were only used if the comparator was split, or where dependence was modelled. A nonsignificant efficacy result alone was not an exclusion reason.

3.3 Information Sources and Search Strategy

The electronic search included PubMed/MEDLINE, Embase, Web of Science Core Collection and The Cochrane Central Register of Controlled Trials (CENTRAL) from 1 January 2011 to 29 August 2026. The eligible trials and relevant systematic reviews were screened in reference lists. Controlled vocabulary and free-text terms were combined to create concepts for PD, NIBS modality and random/sham-controlled study design. Outcome terms were not used as the use of varying outcome indexing may compromise sensitivity. The search structures for the databases were the following:

PubMed/MEDLINE: (Parkinson Disease[MeSH] OR Parkinson*[tiab]) AND (Transcranial Magnetic Stimulation[MeSH] OR rTMS[tiab] OR theta burst[tiab] OR transcranial direct current stimulation[tiab] OR tDCS[tiab]) AND (random*[tiab] OR sham[tiab] OR randomized controlled trial[pt]).

Embase: ('parkinson disease'/exp OR parkinson*:ti,ab) AND ('transcranial magnetic stimulation'/exp OR rtms:ti,ab OR 'theta burst':ti,ab OR 'transcranial direct current stimulation'/exp OR tdcs:ti,ab) AND (random*:ti,ab OR sham:ti,ab).

Web of Science: TS=(Parkinson* AND (rTMS OR "repetitive transcranial magnetic stimulation" OR "theta burst" OR tDCS OR "transcranial direct current stimulation") AND (random* OR sham)).

CENTRAL: Parkinson* AND (rTMS OR TMS OR theta-burst OR tDCS OR "transcranial direct current stimulation").

Search outputs were merged and deduplicated using DOI, PMID, trial registration number, title, author, and year. Complete platform-specific syntax was retained for reproducibility, and the record flow was reported in accordance with PRISMA 2020 (Page et al., 2021).

3.4 Study Selection

The titles and abstracts were screened and then potentially eligible full texts were retrieved and evaluated by the prespecified eligibility criteria. Where more than one publication was available for the same cohort, these were considered to be a single study with the most detailed publication selected as the primary study and completeness of the methods and safety information in companion publications were reviewed. A mutually-exclusive hierarchy for assigning full-text exclusion reasons was implemented and captured at report-level. Records, reports and studies were differentiated in the PRISMA flow diagram (Page et al., 2021).

3.5 Data Extraction and Management

Study and participant characteristics, as well as diagnosis, duration and severity of illness, medication status, intervention and sham parameters, target, dose, number of sessions, co-interventions, outcomes, time points, sample sizes, means, standard deviations, change scores, and number of adverse events were extracted. When supplements, registries and corrections were available, these values were cross-checked. Standard errors and confidence intervals were transformed into standard deviations using the equations proposed by Cochrane (Higgins et al., 2024). Standard errors were never inputted as standard deviations.

3.6 Outcomes and Time-Point Hierarchy

The main efficacy measure was motor impairment at immediate post-intervention using UPDRS-III or MDS-UPDRS-III for which there is a standardized scoring distribution and which assess motor examination, though versions or different scoring distributions need to be pooled separately (Goetz et al., 2008). If a study included both ON and OFF medication assessments, then the medication state that was most consistent with the prespecified endpoint of the trial was used and the other state assessed separately.

Secondary outcomes were gait and mobility, freezing of gait, depressive symptoms, cognition, activities of daily living and quality of life. Results were aggregated only at the conceptually coherent domains. Immediate post-treatment, short-term follow-up (up to 4 weeks) and long-term follow-up (over 4 weeks) were analyzed separately.

Safety outcomes included the number of participants who had at least one adverse event, at least one serious adverse event and withdrawal due to an adverse event. The descriptions of the events were tabulated according to modality and stimulation

arm. A blank cell or "not reported" was never converted to 0, and was left as missing. If event allocation was unclear, then the event was used to contribute to narrative synthesis but not an arm-level risk estimate. The safety population used was specified by the study or, if not, the number of participants who were exposed to at least one assigned session.

3.7 Risk-of-Bias Domains

Methodological appraisal was organised by the five domains of the Cochrane Risk of Bias 2 framework and included: the randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result (Sterne et al., 2019). The credibility of sham stimulation, participant and assessor blinding, attrition, and selective reporting were especially emphasized as they may be issues for masking given sensory differences between active and sham NIBS. Risk-of-bias domains were not used to convert into a numerical quality score, but were used to interpret the heterogeneity and the strength of the conclusions.

3.8 Effect Measures and Statistical Synthesis

Continuous outcomes measured with different instruments were summarized with Hedges' g and 95% confidence intervals, using the pooled within-group standard deviation and a small sample correction. Outcomes for which improvement was indicated by a higher score were multiplied by

−1 prior to pooling. If the same instrument and scale were used in all studies, differences in means were preferred.

The primary analysis was based on scores at post-intervention and change scores were synthesized separately unless a valid correlation between pre- and post-intervention scores was available to enable compatible standardization of change scores. Note that each participant only contributed once to each outcome and time-point synthesis.

Because of clinical and methodological diversity, and the primary model was random-effects. Restricted maximum likelihood was used to estimate between-study variance (τ^2) and the pooled confidence interval was adjusted for the Hartung–Knapp adjustment as recommended for meta-analyses with small studies (Higgins et al., 2024; IntHout et al., 2014). τ^2, I^2, Cochran's Q and 95% prediction interval were used to report heterogeneity. An estimator sensitivity analysis, a DerSimonian–Laird random-effects model, was calculated.

P values of <.05, two-sided, were used as cutoff values for statistical significance; and the subgroup and small-study analyses were considered exploratory.

Only arm-specific risk ratios were planned when there were compatible numbers of participants and at least one event considered dichotomous in nature was available. A double-zero study was kept as evidence of a study that reported an absence of an event, but it was not coerced into a relative-risk estimate. Due to the limited availability, variable definitions of available safety information and an absence of arm-level counts, safety information was summarized descriptively, rather than an artificial pooled rate being calculated. "Not reported" was treated as "missing" rather than "zero".

3.9 Subgroup, Sensitivity, and Small-Study Analyses

Estimates for motor-cortex or multifocal stimulation and for supplementary motor area stimulation were calculated, in these groups because there were sufficient independent comparisons to meaningfully pool them. Between-target contrast was explored as an interaction. To perform sensitivity analyses, the data were only analyzed for rTMS/TBS/deep-TMS trials, standardized effects were only analyzed if absolute values were less than 2.5, and one study was removed at a time.

Small-study effects were explored using funnel-plot inspection and Egger regression, but acknowledging the lack of specificity in the presence of high heterogeneity (Higgins et al., 2024).

Study-Selection Flow

The searches identified 3,195 records. After removal of 1,370 duplicates, 1,825 titles and abstracts were screened; 1,694 records were excluded. All 131 reports sought for retrieval were obtained and assessed at full text. A further 113 reports were excluded according to the eligibility and quantitative synthesis criteria, leaving 18 independent studies in the review: 17 motor comparisons and one mood comparison. The study-selection process is presented in Figure 1.

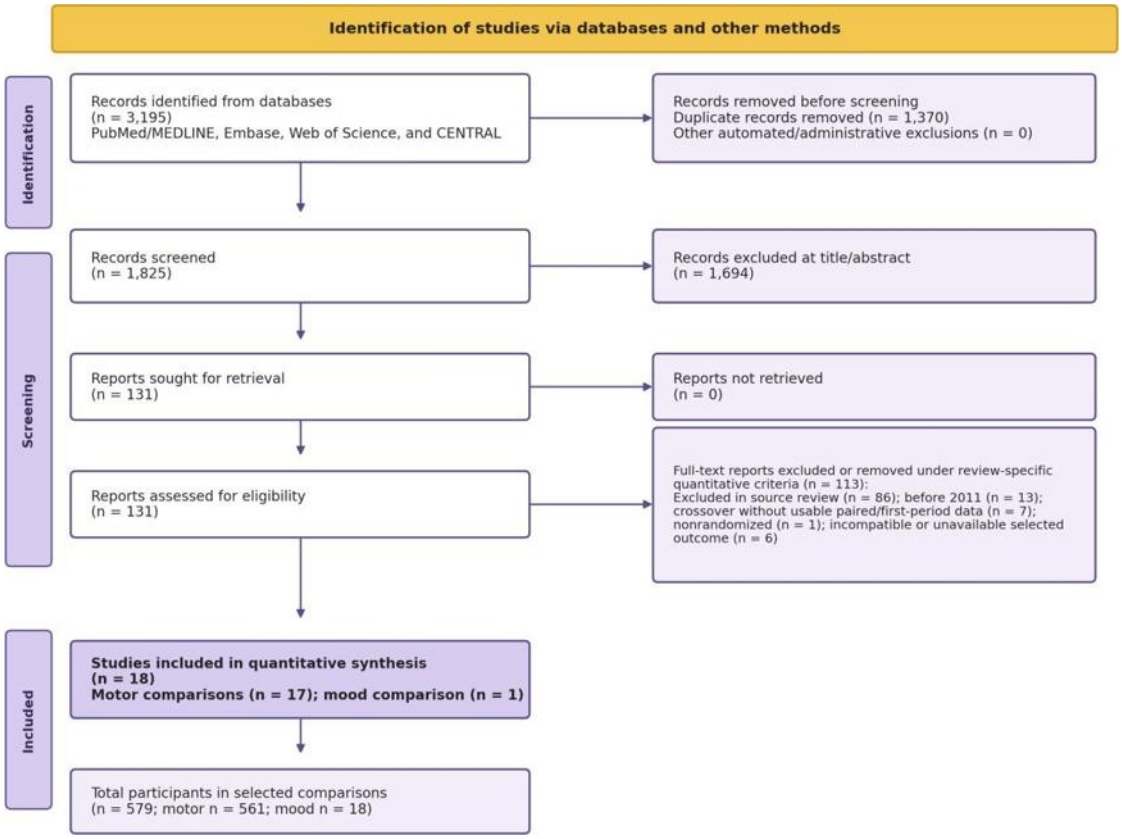

Figure 1. PRISMA 2020 flow diagram for study identification, screening, eligibility, and inclusion.

RESULTS

3.10 Study Selection and Characteristics

A total of 18 independent sham-controlled studies fulfilled the eligibility criteria and were included in the analysis a total of 579 participants (323 in the active stimulation group and 256 in the sham stimulation group) from the 2011–2024 publication period. The sizes of the comparisons included ranged from 16 to 68 (median 29.5) participants, showing that the evidence base was predominantly small trials. The 17 studies examined the effect of magnetic stimulation (either conventional rTMS, TBS, or deep rTMS) and one examined tDCS.

There were 17 studies that provided an immediate post-intervention motor comparison (n = 561) and one study provided an immediate post-intervention mood comparison (n = 18). Motor protocols included a primary motor cortex, a supplementary motor area, a dorsolateral prefrontal cortex, a cerebellum and multimodal motor and prefrontal.

3.11 Primary Motor Efficacy

Across 17 motor comparisons, random-effects meta-analysis showed lower post-intervention motor impairment after active NIBS than after sham stimulation (Hedges' g = −0.94, 95% CI [−1.57, −0.30], p = .006; Figure 2). Between-study heterogeneity was substantial, Q(16) = 97.56,

$p < .001$, $\tau^2 = 1.20$, $I^2 = 83.6\%$. The 95% prediction interval ranged from −3.36 to 1.49, indicating that the effect expected in a new comparable setting could range from a large benefit to no benefit or possible harm.

Thus, the average effect favored active NIBS, but the dispersion of true effects limited the generalizability of that mean estimate.

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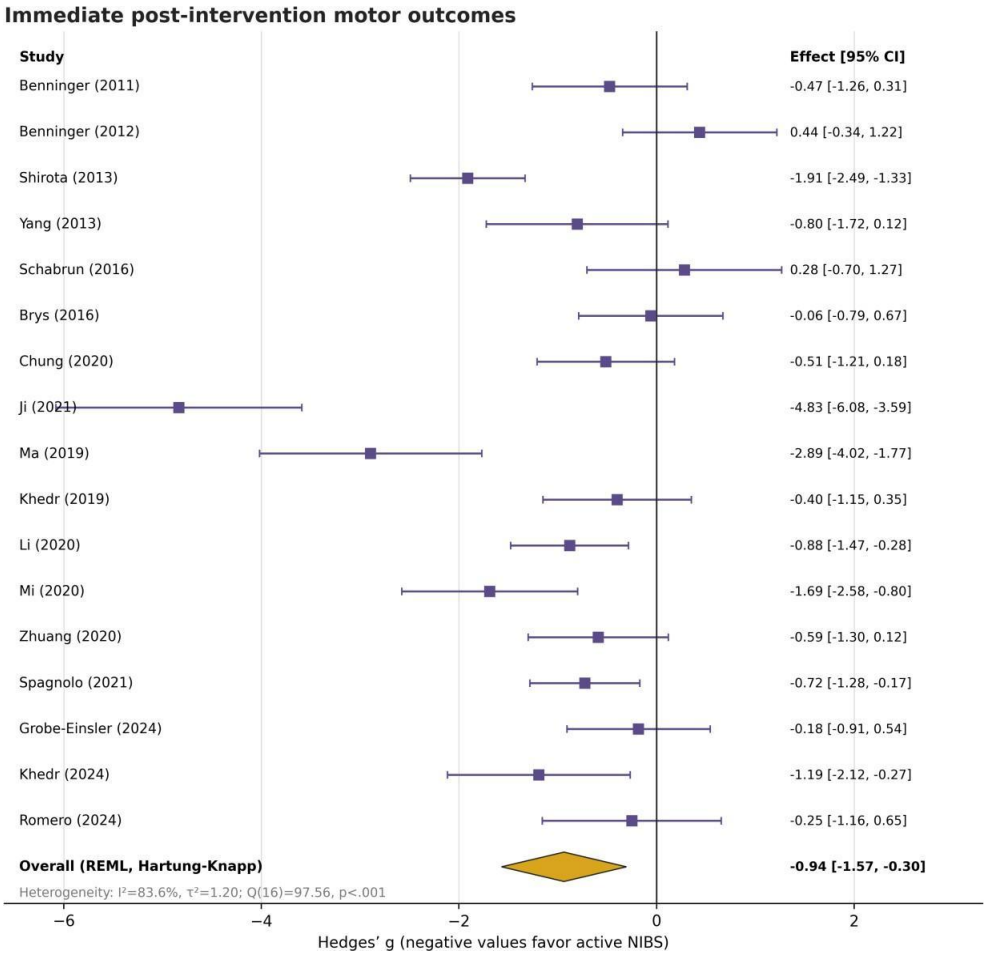

Figure 2. Forest plot of immediate post-intervention motor efficacy. Negative Hedges' g values favor active NIBS; the diamond represents the REML random-effects estimate with Hartung–Knapp confidence limits.

3.12 Subgroup and Sensitivity Analyses

The magnetic-stimulation-only analysis was consistent with the primary result (16 studies; n = 545; g = −1.01, 95% CI [−1.66, −0.35], p = .005), although heterogeneity remained high (I^2 = 83.8%). Motor-cortex or multifocal stimulation produced a smaller and more consistent estimate (11 studies; n = 330; g = −0.45, 95% CI [−0.76, −0.13], p = .010; I^2 = 30.5%).

Supplementary motor area stimulation produced a larger pooled estimate (4 studies; n = 168; g =

−2.77, 95% CI [−5.01, −0.52], p = .029), but heterogeneity was considerable (I^2 = 85.4%) and its

prediction interval crossed zero. The exploratory between-target contrast was statistically significant (difference = −2.33, p < .001), but the small SMA subgroup and extreme estimates make this contrast unsuitable for a definitive ranking of targets.

Excluding two comparisons with |g| greater than 2.5 attenuated the pooled effect to −0.61 (15 studies; n = 491; 95% CI [−0.97, −0.26], p = .003) and reduced I^2 to 66.6%, while retaining statistical significance. Excluding the non-UPDRS motor measure yielded g = −1.01 (95% CI [−1.66, −0.35]). The DerSimonian–Laird model also favored active stimulation (g = −0.92, 95%

CI [−1.39, −0.46]).

Leave-one-out estimates ranged from −1.02 to −0.72, and every confidence interval remained below zero, showing that no single trial determined the direction of the primary result. Table 2 consolidates the primary, subgroup, sensitivity, and mood estimates for direct comparison.

Table 2. Random-effects efficacy analyses.

Analysis	k	n	Hedges' g (95% CI)	I^2 (%)	95% prediction interval
Overall motor outcome	17	561	−0.94 (−1.57, −0.30)	83.6	−3.36 to 1.49
rTMS/TBS/deep TMS only	16	545	−1.01 (−1.66, −0.35)	83.8	−3.45 to 1.43
Motor cortex/multifocal	11	330	−0.45 (−0.76, −0.13)	30.5	−1.08 to 0.19
Supplementary motor area	4	168	−2.77 (−5.01, −0.52)	85.4	−9.11 to 3.58
Excluding |g| > 2.5	15	491	−0.61 (−0.97, −0.26)	66.6	−1.80 to 0.57
Excluding non-UPDRS outcome	16	545	−1.01 (−1.66, −0.35)	83.8	−3.45 to 1.43
Mood outcome (single study)	1	18	−1.09 (−2.11, −0.08)	—	—

The estimates in Table 2 show that statistical significance was retained in the overall, magnetic-only, motor-cortex/multifocal, SMA, extreme-effect-exclusion, and outcome-restricted analyses, but their precision and prediction intervals differed substantially. Figure 3 visualizes these differences in magnitude and uncertainty, making the contrast between the comparatively stable motor-cortex/multifocal result and the imprecise SMA result especially clear.

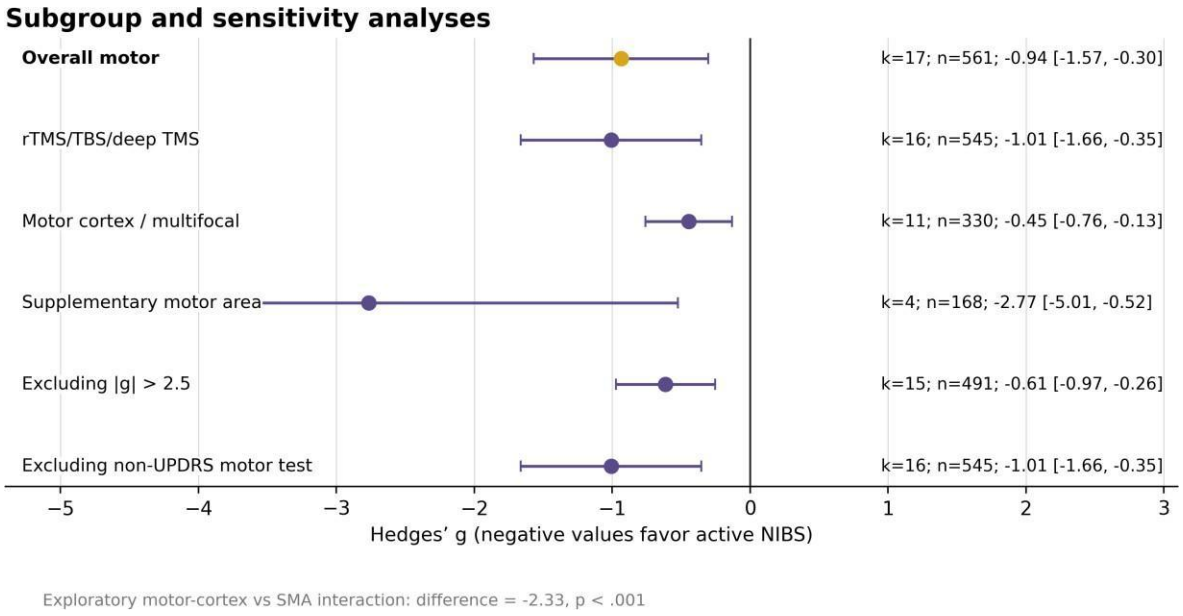

Figure 3. Random-effects subgroup and sensitivity analyses for the motor outcome.

Because subgroup estimates can still be influenced by individual trials, the robustness of the overall motor result was also examined by sequentially omitting each comparison. As shown in Figure 4, the recalculated pooled effects remained on the side favoring active NIBS after every omission, although the confidence intervals remained broad.

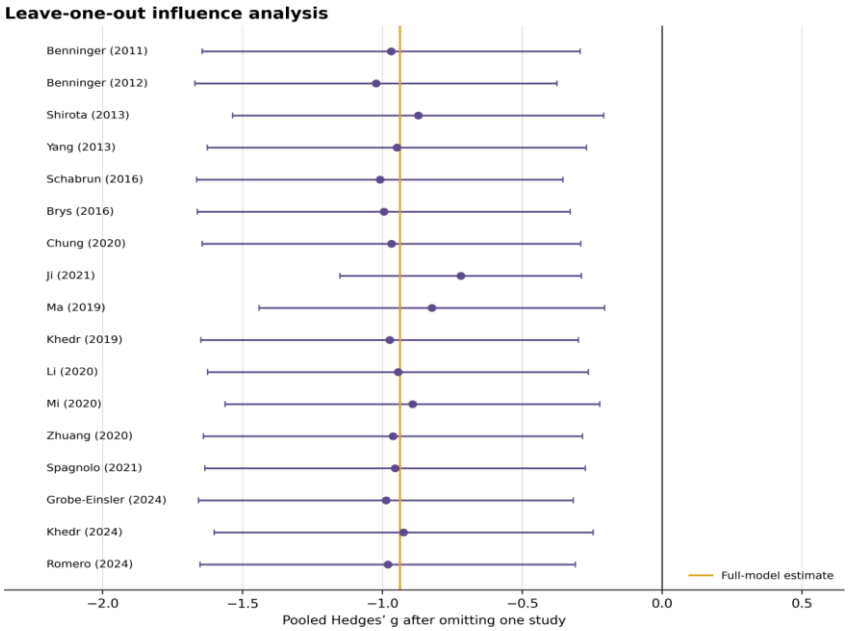

Figure 4. Leave-one-out analysis of the primary motor synthesis.

3.13 Mood Outcome and Small-Study Effects

One trial was performed with 18 participants which offered a valid mood comparison. Although it was standardised to favour active stimulation, the difference was based on one study only, and a pooled mood effect, and the extent of between-study differences, could not be derived. The motor-outcome funnel plot was visually asymmetric, but there is significant heterogeneity which makes interpretation difficult. The existence of statistically significant asymmetry was not revealed by Egger regression (intercept = −3.33, p = .258).

However, this non-significant test should not be taken as evidence that publication or small-study effects were non-existent, given that 17 comparisons were included and there was considerable heterogeneity.

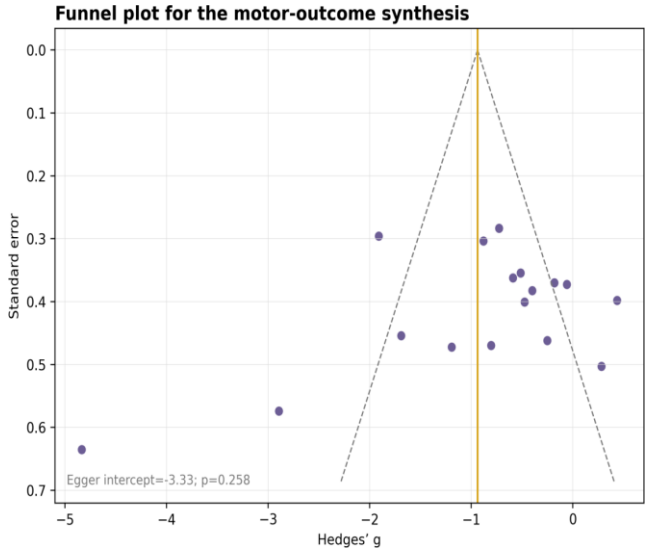

Figure 5. Funnel plot for the primary motor synthesis. The dashed contours indicate approximate 95% pseudo-confidence limits around the random-effects mean.

3.14 Safety

Safety reporting was incomplete, and the numbers were too small for a pooled relative risk estimate. Full arm-level counts for

all adverse events were provided for 3 of 18 trials involving 94 participants; none of these trials had any adverse events in the active or sham arms. In 9 trials (336 participants), the number of serious adverse events was fully reported, also with no events in either group. In 5 trials, complete reporting of withdrawals due to adverse events was done, and there were no withdrawals for either group.

One deep-rTMS trial reported that 39 participants had an actively treated arm, and that there were 7 mild adverse events that were self-limited. Other studies reported transient symptoms (headache, dizziness, tinnitus, discomfort, fatigue) without necessarily specifying the number of participants affected by allocation. Thus, few serious events were documented, and evidence is not sufficient to determine relative safety. The percentage of trials that completed the participant-level reporting for each safety endpoint is shown in Figure 6.

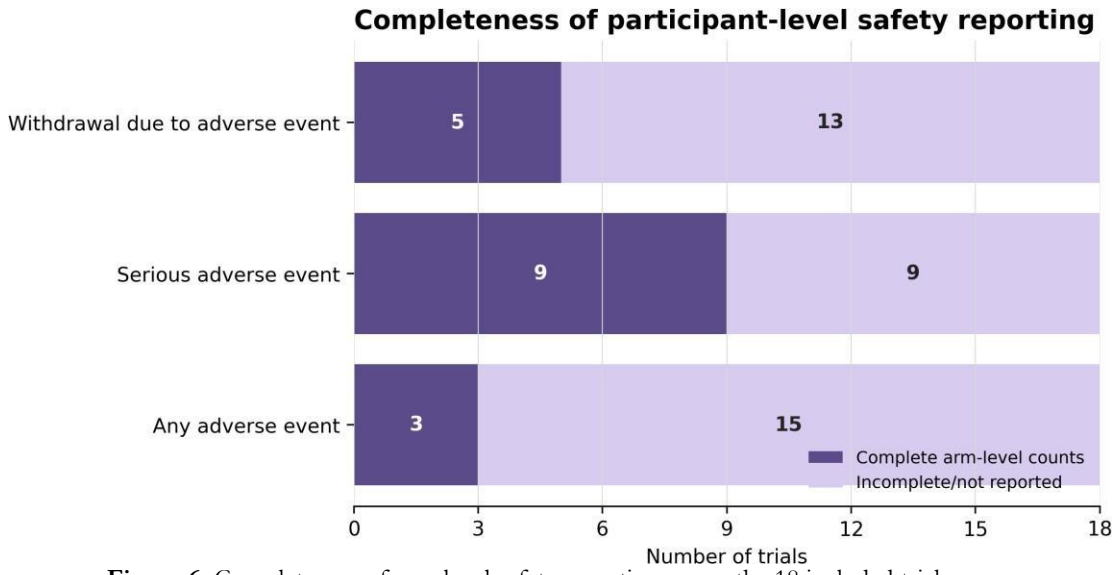

Figure 6. Completeness of arm-level safety reporting across the 18 included trials.

4. DISCUSSION

4.1 Principal Findings

There was a mean immediate post-intervention benefit of active NIBS over sham, with a Hedges' g of −0.94 (95% CI [−1.57, −0.30]) across 17 motor comparisons (561 participants) and was statistically significant at p = .006. This is a large standardized mean effect but with large heterogeneity (I^2 = 83.6%, τ^2 = 1.20; Q[16] = 97.56, p < .001).

This is more important, however, because the 95% prediction interval ranged from −3.36 to 1.49, meaning that a future similar trial may result in a substantial benefit, no effect, or a harmful effect. The main finding is thus not a consistent effect of NIBS, but an average motor gain that is highly variable between protocols and settings and has a short time course.

The primary result was consistent, however, in the expected direction. Restriction to 16 magnetic-stimulation studies yielded g = −1.01 (95% CI [−1.66, −0.35]), the DerSimonian–Laird estimate was −0.92 (95% CI [−1.39, −0.46]), and all leave-one-out estimates remained favorable (range, −1.02 to −0.72). While these convergent analyses mitigate worries that the overall direction originated from an individual tDCS comparison or a single analytical estimator or influential study, they do not dispel concerns regarding effect size.

4.2 Interpretation in Relation to Previous Evidence

The direction of the favorable effect is consistent with the results of randomized-trial syntheses of rTMS for PD (Lu et al., 2026; Zhang et al., 2022) as well as recommended directions of selected motor-cortex protocols (Lefaucheur et al., 2020). However, the overall estimate of −0.94 was more than twice the motor-cortex/multifocal subgroup estimate (11 studies; n = 330; g =

−0.45, 95% CI [−0.76, −0.13]; I^2 = 30.5%). This smaller, but more consistent, sub-population is perhaps more representative

of an average effect that could be reproduced in the future.

Favoring this interpretation, removal of two estimates that had $|g| > 2.5$ resulted in a pooled g of

−0.61 (95% CI [−0.97, −0.26]) with an I^2 of 66.6% ; the result remained statistically significant.

The SMA subgroup generated a much larger estimate (4 studies; n = 168; g = −2.77, 95% CI [−5.01, −0.52]), and the between-target contrast was significant (difference = −2.33, p < .001). However, the value of I^2 was 85.4%, the CI was very wide and the prediction interval included the null. This apparent superiority, however, might be due to extreme estimates or correlated differences in frequency, pulse dose, number of sessions, medication state and quality of trials rather than target alone.

In line with previous reviews, the results suggest that SMA is a suitable clinical target for further head-to-head SMA protocol testing but do not establish it as the best clinical target (Madrid & Benninger, 2021; Zhang et al., 2022).

Data indicated that there was still insufficient evidence to make comparisons of tDCS and mood outcomes. When the only tDCS motor comparison study was removed, the resulting estimate (g

= −1.01) was similar to the overall estimate (g = −0.94), suggesting that the overall motor estimate was not caused by tDCS. This interpretation, which aligns with the mixed or null results seen in the average effects from tDCS reviews (de Oliveira et al., 2021; Duan & Zhang, 2024; Nguyen et al., 2024).

One small comparison found that the mood estimate favoured active stimulation (g = −1.09, 95% CI [−2.11, −0.08]) but this one study does not provide evidence of the replicability of this result. Similarly, the Egger regression of the motor data was not significant (intercept = −3.33, p =.258), and 17 heterogeneous comparisons offered insufficient power to rule out small-study effects.

4.3 Safety and Clinical Implications

In the 336 patients in the 9 trials that reported on the arm-level serious event endpoints, no serious adverse event was reported, and no patients were withdrawn due to any adverse event in the 169 patients in the 5 trials that completely reported the arm-level withdrawal endpoint. These findings are consistent with known safety guidelines for NIBS (Rossi et al., 2021; Antal et al., 2017), although only half of the trials (50.0%) and a quarter (27.8%) reported these endpoints, respectively.

Only 16.7% (3 of 18) of the counts for adverse events were complete. There was one deep-rTMS study with 39 active participants with 7 mild events (17.9%) but no compatible sham count. Thus, a comparative risk ratio was not possible and lack of detection of a major signal should not be taken as evidence of safety equivalence.

NIBS should be considered clinically as a potential complementary tool for dopaminergic therapy, rehabilitation or existing device therapy. The wide prediction interval suggests that benefit varies by protocol and patient. Target, dose, state of medication, co-interventions, accessibility, contraindications and patient priorities should be considered in clinical decisions. The absolute change on UPDRS-III should be added to standardized effects in order to ascertain if the statistical improvements are clinically relevant.

4.4 Strengths and Limitations

Strengths include a prespecified immediate motor outcome, one independent comparison per study, directionally aligned Hedges' g values, REML estimation with Hartung–Knapp confidence limits, prediction intervals and multiple sensitivity analyses. In 17 motor studies, all the leave-one-out estimates were negative (−1.02 to −0.72), providing more confidence in the direction of benefit. The artificial inflation of the safety denominator (Higgins et al., 2024; IntHout et al., 2014) due to preservation of unreported safety cells as missing was avoided.

Several limitations remain. The majority of trials involved a small number of patients, protocols were clinically heterogeneous and the motor synthesis was composed of various magnetic experimental protocols and one tDCS comparison. Immediate post-intervention results are not necessarily useful when determining durability. Because of the sparseness of target groups, the analysis of the effect of prefrontal and cerebellar stimulation was unreliable, and frequency, session dose, medication state and rehabilitation could not be separated from target. The extreme SMA estimates helped to drive heterogeneity; and there were observational contrasts between subgroups across trials.

Power and specificity of funnel plot and Egger analyses were somewhat restricted. Lastly, the definitions of safety were not consistent and reporting did not occur at arm-level. These restrictions decrease the certainty of the pooled effect in spite of its average direction being strong.

4.5 Implications for Future Research

Future trials should be properly powered, prospectively registered and based on consensus reporting of stimulation parameters and medication state, sham credibility, assessor blinding and clinically meaningful motor outcomes. To determine whether target, frequency or dose is responsible for treatment response, direct comparisons between the different types of treatments need to be made. The number of adverse events per arm by participant, serious events, discontinuations, and number exposed to treatment should be reported in studies together with the immediate assessment as well as prespecified follow-up assessments.

Individual-participant-data meta-analysis may be useful to find out whether benefit is modified by baseline severity, duration of illness, age or responsiveness to medications. Until then, target-specific estimates should guide research priorities and should not be used to provide definitive treatment rankings.

5. CONCLUSION

Active NIBS produced a statistically significant average improvement in immediate motor outcomes compared with sham stimulation in adults with PD, and the direction of benefit was robust across several sensitivity analyses. The evidence was dominated by magnetic stimulation and was characterized by substantial heterogeneity and a prediction interval crossing the null. Mood efficacy was supported by only one small study, and incomplete adverse-event reporting precluded comparative safety pooling.

NIBS is therefore a promising short-term adjunct for motor symptoms, but confidence in the size, durability, target specificity, and safety of its effects requires larger, better harmonized, and transparently reported randomized trials.

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