Exploring Non-invasive Brain Stimulation Effects on Physical Outcomes in People With Parkinson's Disease: An Umbrella Evidence Mapping Review With Meta-analyses

This is the Published version of the following publication

Exploring Non-invasive Brain Stimulation Effects on Physical Outcomes in People With Parkinson's Disease: An Umbrella Evidence Mapping Review With Meta-analyses

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Abstract

Background. Non-invasive brain stimulation (NIBS) is sometimes used alongside medication to alleviate motor symptoms in people with Parkinson's disease (PD). However, the evidence supporting NIBS's effectiveness for improving motor function in PD patients is uncertain. *Objective.* This umbrella review aims to synthesize recent systematic reviews and meta-analyses that have evaluated the effectiveness of NIBS in improving motor function in people with PD, with a key focus being to examine the quality of the evidence presented. *Methods.* The review protocol was registered in PROSPERO (CRD42022380544) and conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The search strategy was guided by the Population, Intervention, Comparison, and Outcome framework, focusing on individuals with idiopathic PD (Hoehn and Yahr stages 1-4). The review included studies comparing various NIBS techniques (eg, repetitive transcranial magnetic stimulation and transcranial direct current stimulation) to sham or alternative treatments, targeting motor and cognitive regions. Six databases were searched up to June 2024. Methodological quality was assessed using Assessment of Multiple Systematic Reviews 2 (AMSTAR2), and random-effects meta-analyses were performed to pool standardized mean differences (SMDs). *Results.* The final analysis included 31 meta-analyses and 10 systematic reviews. Overall, the reviews were rated as moderate quality (54% average for AMSTAR2). NIBS showed a small-to-moderate effect on motor function (Unified Parkinson's Disease Rating Scale-Section III scores; SMD = −0.80), functional mobility (gait speed and timed-up-and-go; SMD = −0.39), and freezing of gait (SMD = −0.58), but no significant effect on balance. *Conclusion.* NIBS offers small-to-moderate benefits for motor symptoms and functional movement in PD, though it does not significantly impact balance. Practitioners should consider the variety of techniques and treatment parameters before application.

Keywords

brain stimulation, physical, motor, mobility

Background

Parkinson's disease (PD) affects between 1% and 3% of the older adult population worldwide and is the second most common neurodegenerative disease behind Alzheimer's.[1,2] Compared to healthy age-matched counterparts, people with PD have a significantly higher mortality rate.[3] While pharmacotherapies (eg, Levodopa) may improve quality of life and some motor functions, certain dopamine-resistant motor symptoms progressively worsen over time (ie, postural instability and gait difficulties [PIGD]) and is of continuing concern. Specifically, individuals with PD that have the PIGD subtype are at an increased risk of falls and freezing of gait (FoG) episodes compared to those with the

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tremor-dominant PD subtype.[4] Hence, there is a need for non-pharmacotherapeutic interventions that alleviate PIGD symptoms and decrease falls and FoG risk.

Non-invasive brain stimulation (NIBS) includes the use of transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), or transcranial magnetic stimulation (TMS) to modulate cortical excitability. Detailed discussion of the physiological impacts of these techniques has been described elsewhere,[5-7] but in brief, tDCS applies a direct weak electrical current (typically between 1 and 2 mA) to underlying, adjacent cortical tissue and relies on polarity-specific membrane potential alterations. The electrical current applied via tDCS therefore aims to shift the resting membrane potential state toward either depolarization or hyperpolarization depending on the site being targeted.[5] On the other hand, the electrical current applied via tACS enhances the spontaneous oscillatory activity of cortical neurons, and at certain frequency bands can alter cortical excitability both during and post stimulation.[8] Similarly, tRNS potentially modulates cortical excitability by using low-intensity biphasic alternating current.[9] In contrast to these direct current approaches though, TMS passes a brief electrical current through magnetic coils, causing a changing magnetic field that penetrates the scalp resulting in neuromodulation of cortical neurons in proximity to the stimulation site. Stimulation intensities typically range from 80% to 120% of motor threshold,[10] with intensities greater than motor threshold triggering action potentials in cortical neurons.[11]

Independent of the mode, NIBS is relatively easy to administer, cost effective, and can be applied with few side effects provided the correct treatment guidelines are adhered to.[12] As such, the use of NIBS, and in particular tDCS and rTMS, has become a tenable clinical treatment option for numerous neurodegenerative and neuropsychiatric populations.[13-16] In individuals with PD for example, NIBS has received widespread attention as an adjuvant therapy used concurrently alongside other treatments such as exercise training or medication, or as a standalone tool, in an attempt to restore neurological and physical function[17-20] and reduce FoG episodes.[21] However, there are notable inter- and intra-individual variability in NIBS outcomes,[22] as well as considerable PD study and population heterogeneity.[20,23] Therefore, questions about the effectiveness of NIBS as a physical rehabilitative tool for people with PD remain.

Recently, there has been a growing number of systematic reviews and meta-analyses focussed on the use of NIBS to improve physical outcomes in people with PD, often with conflicting findings. Therefore, the primary aim of this umbrella review is to summarize and map the overarching NIBS evidence on its effectiveness for improving physical outcomes in people with PD.

Materials and Methods

The protocol was published in June 2024[24] and was registered a priori in the International Registry PROSPERO (ID: CRD42022380544). We followed the Joanna Briggs Institute reviewer's manual[25] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] Additionally, we employed the Population, Intervention, Comparison, and Outcomes (PICO) framework to guide our search strategy and inclusion/exclusion criteria.

We included reviews of studies with individuals diagnosed with idiopathic PD based on the Movement Disorder Society Clinical Diagnostic Criteria for PD (MDS-PD Criteria),[27] regardless of sex, with participants ranging from stage 1 (unilateral involvement only) to stage 4 (severe disability, but still able to walk and stand unassisted) according to the Hoehn and Yahr (H&Y)[28] scale (*Population*). We considered reviews of studies where NIBS was applied for either a single session or more, targeting the primary motor cortex (M1), dorsolateral prefrontal cortex (DLPFC), dorsal premotor cortex, cerebellum, or supplementary motor area (SMA; *Intervention*). We included reviews of studies that compared NIBS techniques as standalone therapies or in combination with exercise training or medication, with comparisons made against sham stimulation, no treatment (ie, regular care), or alternative treatments such as exercise only without sham stimulation (*Comparison*). Each of the reviews needed to examine the effect of NIBS on physical outcomes in people with PD (*Outcome measure*).

Inclusion Criteria

We included systematic reviews and meta-analyses of randomized and clinical controlled studies published from 2013 onwards that compared various forms of NIBS techniques, with no treatment, exercise, or sham stimulation in people with PD. Selecting reviews from the past decade was chosen to avoid overlap and overrepresentation of single studies. Included systematic reviews (with and without meta-analysis) focused on populations that (1) had a clinical diagnosis of PD established via the MDS-PD criteria and (2) had stages 1 to 4 H&Y disease severity.[28] No exclusions were applied based on the presence of co-morbidities. Given the wide scope of physical outcomes, we separated the physical outcome measures across systematic reviews into (1) motor function (ie, Unified Parkinson's Disease Rating Scale [UPDRS]-Section III scores), (2) functional movement (ie, gait speed, or dynamic balance like timed-up-and-go [TUG]), and (3) static balance or postural control measures. A fourth outcome of disease severity (using the FoG questionnaire [FoG-Q]) was also examined.

Exclusion Criteria

We excluded all systematic reviews (with and without meta-analyses) of randomized controlled trials or other experimental studies that were published before November 2013 (ie, past 10 years of evidence), or were not written in English. For articles where the full-text was unavailable following an online search, attempts were made to contact the authors directly to retrieve the full-text copy. Articles were excluded if the authors could not be contacted or if they could not provide the full-text copy of the article.

Data Sources and Search Strategy

Six separate databases were searched: PubMed/MEDLINE, PEDro, Scopus, CINHL, EBSCO (ie, PsychInfo, PsychTherapy, and SPORTDiscus), and Cochrane Library, for systematic reviews (with or without meta-analyses) that were written in English up to June 2024. Various arrangements of the keywords in "Parkinson's disease" AND "noninvasive brain stimulation or transcranial*" AND "physical function or strength or walking or gait" was used within the title and/or abstract searches. Where a filter was absent, the key words in "systematic review," "meta-analysis," or "practice guidelines" was also used within the title and/or abstract searches. A full list of MeSH terms and Boolean operators used for the searches can be found in Supplemental Table 1. In addition, the reference lists of each of the included reviews were manually checked to retrieve articles that were not covered by the database searches.

Methodological Quality

Methodological quality were recorded using the Joanna Briggs Institute critical appraisal checklist for Systematic Reviews and Research Syntheses.[29] Two members of the research team (SJO and CL) screened the titles and abstracts of the studies and extracted the data using an online systematic screening tool (Covidence). Any conflicts in screening were resolved by a third member of the research team (DMH). The methodological quality of the included reviews was assessed using the Assessment of Multiple Systematic Reviews 2 (AMSTAR2) instrument, which provides an empirical evaluation of their methodological rigor. The AMSTAR2 instrument uses a scoring system that ranges from 0 to 16, with higher scores indicating better quality.[30] It includes 16 items that assess various aspects of systematic reviews and meta-analyses, such as the thoroughness of the search strategy and the evaluation of publication bias. Each item is scored dichotomously as either 0 or 1. Based on the AMSTAR2 scores, reviews are categorized as high quality (satisfying at least 80% of the items), moderate quality (satisfying between 40% and 79% of the items), or low quality (satisfying less than 40% of the items).[30,31] To ensure consistency, all extracted review information and quality rankings were compared among raters (DMH and NT) to establish inter-rater reliability.

Meta-analysis

We performed random-effects pooled meta-analyses using the included effect sizes for studies reporting standardized mean difference (SMD). By pooling the SMD's and applying 95% confidence intervals (CIs) weighted for sample size, we derived an aggregated effect size that encompassed all the reviews.[32] The estimated SMD's were interpreted using the description presented by Hopkins et al[33]; an SMD of >4.0 = an extremely large clinical effect; between 2.0 and 4.0 = a very large effect; 1.2 to 1.9 = a large effect; 0.6 to 1.1 = a moderate effect; 0.2 to 0.59 = a small effect; and 0.0 to 0.19 = a trivial effect. Heterogeneity among the reviews was assessed using the I^2 statistic, which quantifies the degree of variability between study results (<25% = negligible; 25%-50% = low; 50% to 75% = moderate to high; >75% = very high).[34] Additionally, we assessed publication bias using the Egger test, a statistical method that evaluates the presence of bias in the reporting of study outcomes.[35]

When the results from meta-analyses were reported as mean difference (MD) or weighted MD (WMD), they were re-expressed as SMD. As a form of sensitivity analysis, we conducted a separate meta-analysis including these studies to ensure that conversion to SMD did not influence the overall results. If necessary, CIs and standard error (SE) where converted to standard deviation (SD) using the formulas recommended by the Cochrane Handbook for Systematic Reviews of Interventions version 6.2[36]:

$$SD = \sqrt{(N)} * (\text{upper limit} - \text{lower limit}) / 3.92$$

OR

$$SD = \sqrt{(N)} * SE$$

Where N is the number of participants (sample size), and upper and lower bound limits refer to the 95% CI's, respectively.

Analysis of Degree of Overlap in Studies

Citation matrices were generated to determine overlap in studies across reviews, while the corrected covered areas (CCAs) were also calculated (CCA = 0%-5%, slight; 6%-10%, moderate; 11%-15%, high; and >15%, very high overlap)[37] to assess the impact of overlap in reviews on the findings of this umbrella review.
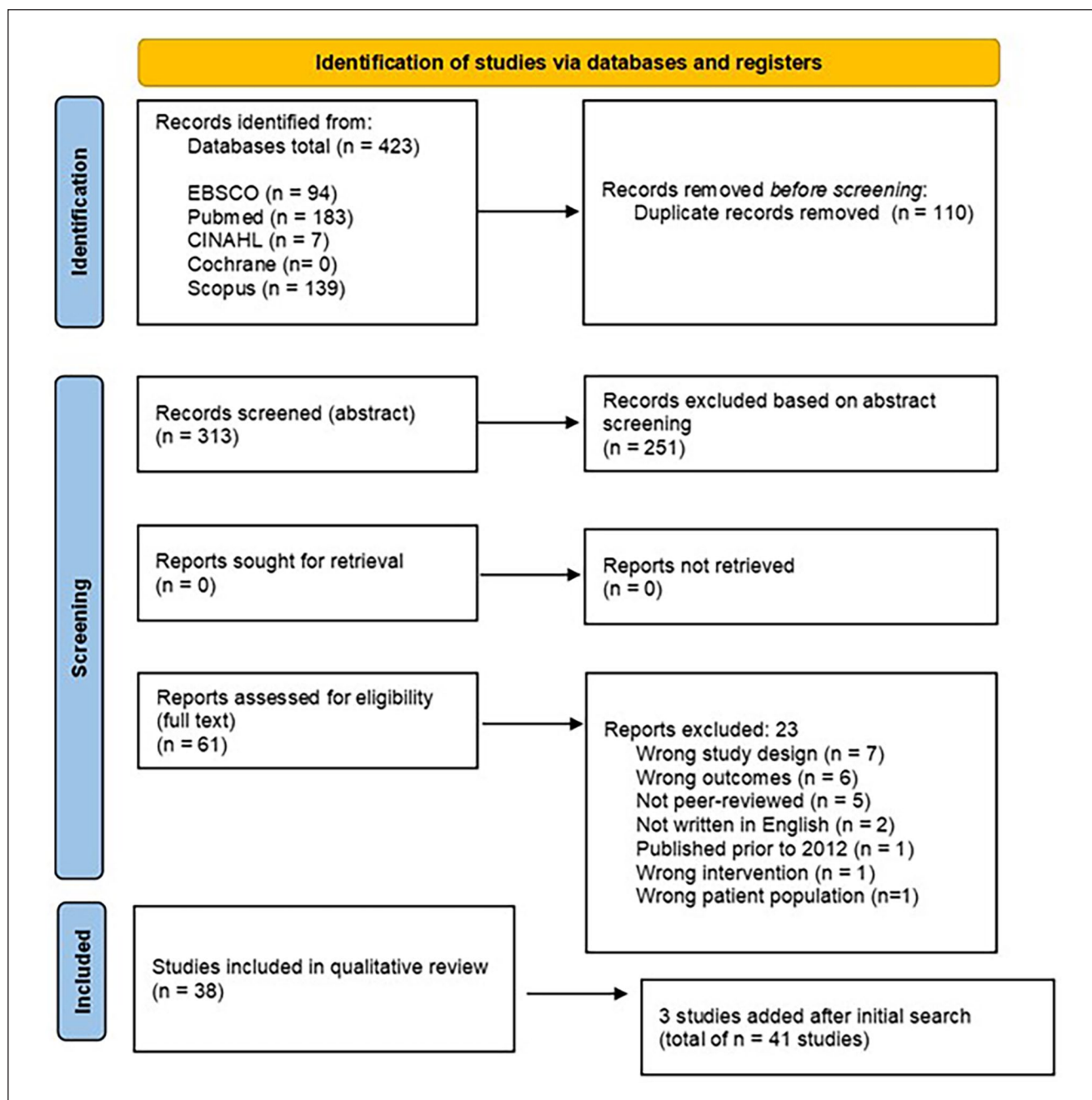
Figure I. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of review.

Results

Search Results

A comprehensive search of 6 databases yielded a total of 61 reviews that were potentially eligible for inclusion in this umbrella review. After careful examination, 18 reviews were excluded as they did not meet the predefined eligibility criteria (Figure 1). The reasons for exclusion varied and are listed in Supplemental Table 2. This left a total of 38 reviews that were deemed eligible and included in this umbrella review for further analysis. Three additional studies published in 2022,[38] 2023,[39] and in 2024[40] were included subsequent to the initial search and screening process, owing to their relevance to our research objectives (n=41 reviews in total included). Of these included reviews, 31 were systematic review with meta-analysis, 10 were either systematic or scoping reviews only (without meta-analysis).

Summary of the Included Reviews

The number of studies included in each review ranged from 7 to 33 (Table 1) and the number of participants ranged from 40 to 1596. NIBS techniques mainly included rTMS only (19 studies, 46%), tDCS only (13 studies, 32%), or mix of rTMS and tDCS (8 studies, 20%), with 1 study investigating galvanic vestibular stimulation. Of the meta-analyses, the more common physical outcomes included assessing the effects of NIBS on motor disability (measured via the UPDRS-III; 18 studies, 58%), functional mobility including gait speed and TUG tests (11 studies, 35%) and balance (6 studies, 19%). Nine meta-analyses examined the effects of NIBS alone versus sham stimulation, while 18 meta-analyses examined the effects of NIBS versus a control group. The stimulation parameters and sites varied considerably across the reviews (Supplemental Table 3).

Methodological Quality and Quality of Evidence

There was a moderate level of agreement between reviewer scores for the AMSTAR2 ($\kappa=.75$). For the AMSTAR2, the average score across all the included reviews was 8.7 out of 16 (54%), and so the average quality of the reviews was rated as moderate. A total of 12 out of the 41 reviews were rated as low quality, and only 4 reviews were rated as high quality.[40-43] Many reviews failed to include a comprehensive list of excluded studies (item 7, 88%) and half of the reviews (54%) did not discuss the likely impact of publication bias on their results (item 12). This involves reviews failing to perform a sensitivity analysis to determine how many missing "null" studies would be needed to invalidate the results they obtained. Only 39% of reviews designed their research questions and inclusion criteria using the components of PICO (item 1), and 37% stated that their search methodology was designed a priori and pre-registered (item 2). Also, 63% of the reviews did not report the sources of funding of the individual studies that were included within their results (item 10; Figure 2).

NIBS Effects

Motor Function (UPDRS-III). Our review included 18 meta-analyses that examined the effects of NIBS on motor function (UPDRS-Section III) in people with PD, irrespective of co-morbidities. About 13 of these meta-analyses reported SMD's, and our pooled results indicated that NIBS had a moderate positive effect on UPDRS-III scores (SMD=−0.80; 95% CI −1.37 to −0.23; n=7043; $P=.006$; $I^2=98.47\%$; Figure 3). This result was unaffected when including studies which reported MD instead of SMD (SMD=−0.73, 95% CI −1.23 to −0.23; n=7106; $P=.004$; $I^2=97.7\%$). In addition, when 1 study was removed due to separating groups into "on" versus "off" medication,[44] there was still a moderate positive effect on UPDRS-III scores (SMD=−0.89; 95% CI −1.55 to −0.24; n=6884; $P=.007$; $I^2=98.71\%$).

Our review included 2 meta-analyses that examined the effects of NIBS on motor function of people with PD with clinical depression. Due to the wide variety of outcomes used to assess clinical depression, which included instruments such as the Hamilton Rating Scale for Depression, the Montgomery-Åsberg Depression Rating Scale, and the Beck Depression Inventory, we opted not to pool the results. Qin et al[45] proposed that the motor benefits after treatment with high frequency (HF)-rTMS might be better than sham-rTMS (MD=−2.80, 95% CI −5.45 to −0.15), and this was also supported by Chen et al[46] who reported that rTMS could alleviate motor symptoms of people with PD with clinical depression (WMD=−2.617, 95% CI −4.183, −1.051).

Functional Mobility: Gait Speed and TUG. Our review included 17 meta-analyses that examined the effects of NIBS on functional movement in people with PD. Of these, 11 meta-analyses reported SMD's. Our pooled results indicated that NIBS had a small positive effect on functional mobility (SMD=−0.39, 95% CI −0.51 to −0.28; n=4852; $P<.001$; $I^2=51.4\%$; Figure 4), which was unaffected when including studies for which MD was reported instead of SMD (SMD=−0.35, 95% CI −0.46 to −0.24; n=5509; $P<.001$; $I^2=52.2\%$). When 1 study was removed due to separating groups into "on" versus "off" medication,[44] there was still a small positive effect on functional mobility (SMD=−0.35, 95% CI −0.47 to −0.24; n=4693; $P<.001$; $I^2=57.1\%$).

Two sub-analyses were performed separating gait speed from TUG results. Nine studies examined the effects of NIBS on gait speed only in people with PD and reported SMD's. The pooled results revealed that NIBS had a small positive effect on gait speed (SMD=−0.43, 95% CI −0.61 to −0.25, $P<.001$; n=2239; $I^2=50.2\%$; Supplemental Figure 1). This result was not different when 1 study was removed due to separating groups into "on" versus "off" medication[44] (SMD=−0.44, 95% CI −0.65 to −0.24, $P<.001$; n=2080; $I^2=55.8\%$). In addition, another 9 studies examined the effects of NIBS on TUG performance only in people with PD. The pooled results also revealed that NIBS had a small positive effect on TUG scores (SMD=−0.36, 95% CI −0.58 to −0.13, $P=.002$; n=3189; $I^2=77.1\%$; Supplemental Figure 2).

Freezing of Gait. Our review included 5 meta-analyses that examined the effects of NIBS on FoG in people with PD. Our pooled results indicated that NIBS had a moderate and significant positive effect on reducing FoG (SMD=−0.58, 95% CI −0.91 to −0.26, $P<.001$; n=1183; $I^2=78.3\%$; Figure 5).

Table 1. Summary of the Characteristics and Main Findings of the Included Reviews.

Systematic review + meta-analysis	N. studies incl[a] (total participants)	Sample characteristics[b]	Stim type	Main findings
Mahmud et al. 2022	5 (n = 40)	Age 37-67 years Severity H&Y: 2-4 Disease length 4-11 years	GVS	Balance and postural control (incl sway path, sway velocity, and postural angles) ↑
Zanjani et al. 2015	11 (n = 246)	Age Grand mean = 63 years Severity AverAge H&Y: 2.3 Disease length NR	rTMS	**Short term** UPDRS-III ↑ **Long term (1 month)** UPDRS-III ↔
Chou et al. 2015	20 (n = 470)	Age 63.6 ± 8.2 years Severity H&Y: 1-5 Disease length 5-16 years	rTMS	Motor symptoms ↑ (both off and on) Note: HFr-TMS over M1 and LFrTMS over frontal regions beneficial
Zhu et al. 2015	8 (n = 319)	Age 61-69 years Severity UPDRS-III: 11.7-45.0 Disease length 5-17 years	rTMS	UPDRS-III ↑
C-L Xie et al. 2015	8 (n = 312)	Age 57-67 years Severity NR Disease length NR	rTMS	UPDRS-III ↑
Chung & Mak 2016	22 (n = 555)	Age NR Severity H&Y: 1-4 NR (6) Disease length NR	rTMS	**Short term** Upper limb function ↑ Walking performance ↑ UPDRS-III ↑ (larger effect in off) **Long term** Walking performance ↑ UPDRS-III ↑
Shukla et al. 2016	21 (n = 573)	Age 57-69 years Severity H&Y: 2.0-3.4 Disease length 4-16 years	rTMS	UPDRS-III ↑
Hai-jiao 2018	7 (n = 181)	Age 59-69 years Severity NR Disease length Unclear	rTMS	UPDRS-III ↔

Table 1. (continued)

Systematic review + meta-analysis	N. studies incl[a] (total participants)	Sample characteristics[b]	Stim type	Main findings
Qin et al. 2018	9 (n = 332)	*Age* 59-69 years *Severity* NR *Disease length* NR	rTMS	UPDRS-III ↑
Yang et al. 2018	23 (n = 646)	*Age* 56-70 years *Severity* H&Y: 1-4 *Disease length* 3-17 years	rTMS	UPDRS-III ↑ (on/off)
Y-J Xie et al. 2020	14 (n = 298)	*Age* Grand mean 63 ± 10 *Severity* H&Y 1-5 *Disease length* 3-12 years	rTMS	Walking time ↑ (on) Freezing of gait ↔ TUG ↔
S Li et al. 2020	28 (n = 838)	*Age* 57-70 years *Severity* NR *Disease length* 3-17 years	rTMS	UPDRS-III ↑
Chen et al. 2021	12 (n = 511)	*Age* 58-67 years *Severity* NR *Disease length* 4.9-8 years	rTMS	**Short term** Motor symptoms ↑ **Long term** Motor symptoms ↔
Cheng et al. 2022	8 (n = 189)	*Age* 60-75 years *Severity* H&Y: 1-3 *Disease length* 1.8-10.4 years	rTMS	UPDRS-III ↔ (on) UPDRS-III ↑ (off) Gait speed ↑ (off) Upper limb movement (on and off) ↔
Zhou et al. 2022	15 (n = 323)	*Age* 60-72 years *Severity* H&Y: 1-5 *Disease length* 4-14 years	rTMS	**Short term** TUG ↑ Walking performance (incl. speed and time of 10-25 m walk test, and 6 minute distance covered) ↑ **Long term** TUG ↑ Walking performance ↑
Zhang et al. 2022	14 (n = 469)	*Age* 60-69 years *Severity* H&Y: 1.8-3.5 *Disease length* 5-16 years	rTMS	UPDRS-III (incl. MDS-UPDRS-III) ↑

(continued)

Table 1. (continued)

Systematic review + meta-analysis	N₀ studies incl[a] (total participants)	Sample characteristics[b]	Stim type	Main findings
Deng et al. 2022	16 (n=419)	*Age* 59-75 years; *Severity* H&Y: 2-3.1; *Disease length* 2.5-12	rTMS	**Short term** Gait ↑; Walking speed ↑; TUG ↑; **Long term** Gait/walking ↑; TUG ↑
Hvingelby et al. 2022	148 (n=92)	*Age* 59-69 years; *Severity* NR; *Disease length* Unclear	rTMS	**HFr-TMS** Walking speed ↑; Freezing of gait ↑
Li et al. 2022	32 (n=1048)	*Age* 57-72 years; *Severity* H&Y: 1-3.5; *Disease length* 3-17	rTMS	General motor symptoms ↑ (on); UPDRS-III ↑ (on); Walking time ↑ (on); TUG ↑ (on); FOG ↑ (on); LID ↑ (on)
Kim et al. 2019	7 (n=102)	*Age* 64-74 years; *Severity* NR; *Disease length* 4.3-10.3 months	rTMS Mixed	Freezing of gait ↑; UPDRS-III ↔; Note: outcomes greater when stimulation over M1 compared to frontal cortex
Elsner et al. 2016	6 (n=137)	*Age* 59-75 years; *Severity* H&Y: 2-3.1; *Disease length* 2.5-12	tDCS	UPDRS-III ↑; Gait ↔
Lee et al. 2019	18 (n=325)	*Age* 57-72 years; *Severity* UPDRS-III: 11.2-47.7; *Disease length* 5-17 years	tDCS	**Short term (<24 hours)** Functional movements ↑ (incl. TUG, 10m walk time, gait speed); **Long term (≥4 weeks)** Functional movements ↔ (on)
Nascimento et al. 2021	5 (n=117)	*Age* 61-67 years; *Severity* H&Y: 1-3; *Disease length* 6-8 years	tDCS	Gait (incl. speed, step length, cadence) ↔
Liu et al. 2021	21 (n=736 with PD)	*Age* 54-77 years; *Severity* 10.9-47.7; *Disease length* 1-11 years	tDCS	UPDRS-III ↔; TUG ↔; Balance ↔; Gait (incl. velocity, cadence, stride length, stride width) ↔

(continued)

Table 1. (continued)

Systematic review + meta-analysis	No. studies incl[a] (total participants)	Sample characteristics[b]	Stim type	Main findings
Krogh et al. 2022	6 (n=102)	*Age* 64-74years *Severity* NR *Disease length* 4.3-10.3 months	tDCS rTMS	Freezing of gait ↑ Gait speed ↔ TUG ↑
De Oliveira et al. 2022	10 (n=236)	*Age* 58-74years *Severity* H&Y: 1.3-2.8 *Disease length* 4.3-12.3	tDCS	UPDRS-III ↔ TUG/gait speed ↔ BBS ↔
Leuk et al. 2022	32 (n=526 healthy and n=216 with PD)	*Age* 58-78years *Severity* NR *Disease length* NR	tDCS	Upper limb motor learning ↑ (incl. but not limited to SRTT, Funnel task, Writing, Finger tapping, precision grip, pegboard)
Berretta et al. 2022	10 (n=276)	*Age* 62-79years *Severity* NR *Disease length* NR	tDCS	Balance and postural control (mixed static and dynamic balance tests) ↑
X Zhang et al. 2023	32 (n=1586)	*Age* 60-69years *Severity* H&Y: 1.8-3.5 *Disease length* 5-16years	tDCS rTMS	UPDRS-III scores ↑ Walking-related variables improved: step width ↑, cadence ↑, and 6MWT ↑. Subgroup analyses showed significant improvements in UPDRS-III scores (rTMS: ↑; tDCS: ↑) and TUG time (rTMS: ↑; tDCS: ↑). Note: rTMS was more effective than tDCS in improving UPDRS-III scores and TUG time.
Nguyen et al. 2024	23 (n=569)	*Age* 50-79years *Severity* H&Y: 1-4 *Disease length* 1-18years	tDCS	Gait (incl. cadence and stride time) ↑ Gait (incl. speed, stride length, freezing of gait, and walk time) ↔ Balance (incl. TUG) ↑ Balance (incl. BBS, DGI) ↔
Goodwill 2017	33 (n=137)	*Age* Mean: 64years *Severity* H&Y: 13/24 >3 *Disease length* Mean: 8years	tDCS /tACS rTMS	**rTMS** UPDRS-III ↑ Gait ↑ Hand movements ↔ **tDCS/tACS** UPDRS-III ↔ Gait ↑ Hand movements ↔

Table 1. (continued)

| Systematic review	No	Sample characteristics	Stim type	Main findings
Xia et al. 2022	4 (n=101)	Age NR / Severity NR / Disease length NR	rTMS	Motor function (incl. walk time, pegboard, ball test, tremor, dyskinesia) ↑
Broeder et al. 2015	9 (n=NR)	Age 61-72years / Severity H&Y 1-4 / Disease length 7-13.2years	tDCS	UPDRS-III ↑↔ / Gait and TUG ↑↔ / Hand movements ↑↔
Beretta et al. 2020	17 (n=NR)	Age 56.7-79years / Severity UPDRS-III: 10.9-47.7 / Disease length 4.4-9.4years	tDCS	UPDRS-III ↑↔ / Gait/Freezing of gait ↑↔ / Upper limb function ↑↔
Fregni et al. 2020	23 (n=NR)	Age NR / Severity NR / Disease length NR	tDCS	UPDRS-III ↑↔ / Walking/Gait ↑↔ / TUG ↑↔ / Freezing of gait ↑ / Balance ↑
Simpson & Mak 2020	10 (n=195)	Age 58-74years / Severity H&Y: 1.6-2.5 / Disease length 6-12years	tDCS	UPDRS-III ↑ / Upper limb motor tasks (incl. sequence speed and performance, force, and finger tapping) ↑
Pol et al. 2021	18 (n=342)	Age 62-72years / Severity H&Y: 1.3-2.8 / Disease length 4-11 years	tDCS	MI or SMA / Gait (incl. but not limited to 10m walk, TUG, cadence, and velocity) ↑
Madrid & Benninger 2021	92 (n=2080)	Age NR / Severity NR / Disease length NR	tDCS/tACS rTMS	**HF rTMS over MI** / UPDRS-III ↑ / Gait ↔ / HF rTMS over DLPFC / UPDRS-III ↔ / Combined HFr-TMS over MI + DLPFC / UPDRS-III ↔ / LF rTMS over SMA / UPDRS-III ↔ / tDCS over MI / UPDRS-III ↑ / tDCS over MI + DLPFC / Gait ↑

(continued)

Table 1. (continued)

Systematic review	No	Sample characteristics	Stim type	Main findings
Delgado-Alvarado et al. 2019	6 (n = NR for NIBS)	Age 62–78 years Severity NR Disease length NR	tDCS rTMS	**Short term** tDCS over MI Freezing of gait ↑ TUG ↑ rTMS Freezing of gait ↑ ↔ **Long term** tDCS Freezing of gait ↑ (on) rTMS Freezing of gait ↑↔
Da Silva et al. 2021 (scoping review)	12 (n = NR)	Age 53–73 years Severity NR Disease length NR	tDCS rTMS	UPDRS-III ↑ ↔ Gait ↑ ↔
Fujikawa et al. 2022	32 (n = NR)	Age NR Severity NR Disease length NR	tDCS rTMS	**rTMS** UPDRS-III ↑ Freezing of gait ↑ **tDCS** UPDRS-III ↑ Gait ↑ ↔ Freezing of gait ↑ TUG ↑ BBS ↑

Abbreviations: NR, not reported; H&Y, Hoehn and Yahr scale; UPDRS-III, Unified Parkinson's Disease Rating Scale–Section III; MI, primary motor cortex; SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; TUG, timed up and go; BBS, Berg Balance Scale; DGI, dynamic gait index; tDCS, transcranial direct current stimulation; LID, levodopa induced dyskinesia; SRTT, serial reaction time task; 6MWT, 6-minute walk test; rTMS, repetitive transcranial magnetic stimulation; HF, high frequency; LF, low frequency; tACS, transcranial alternating current stimulation; TES, electrical stimulation; tRNS, random noise stimulation; GVS, galvanic vestibular stimulation.
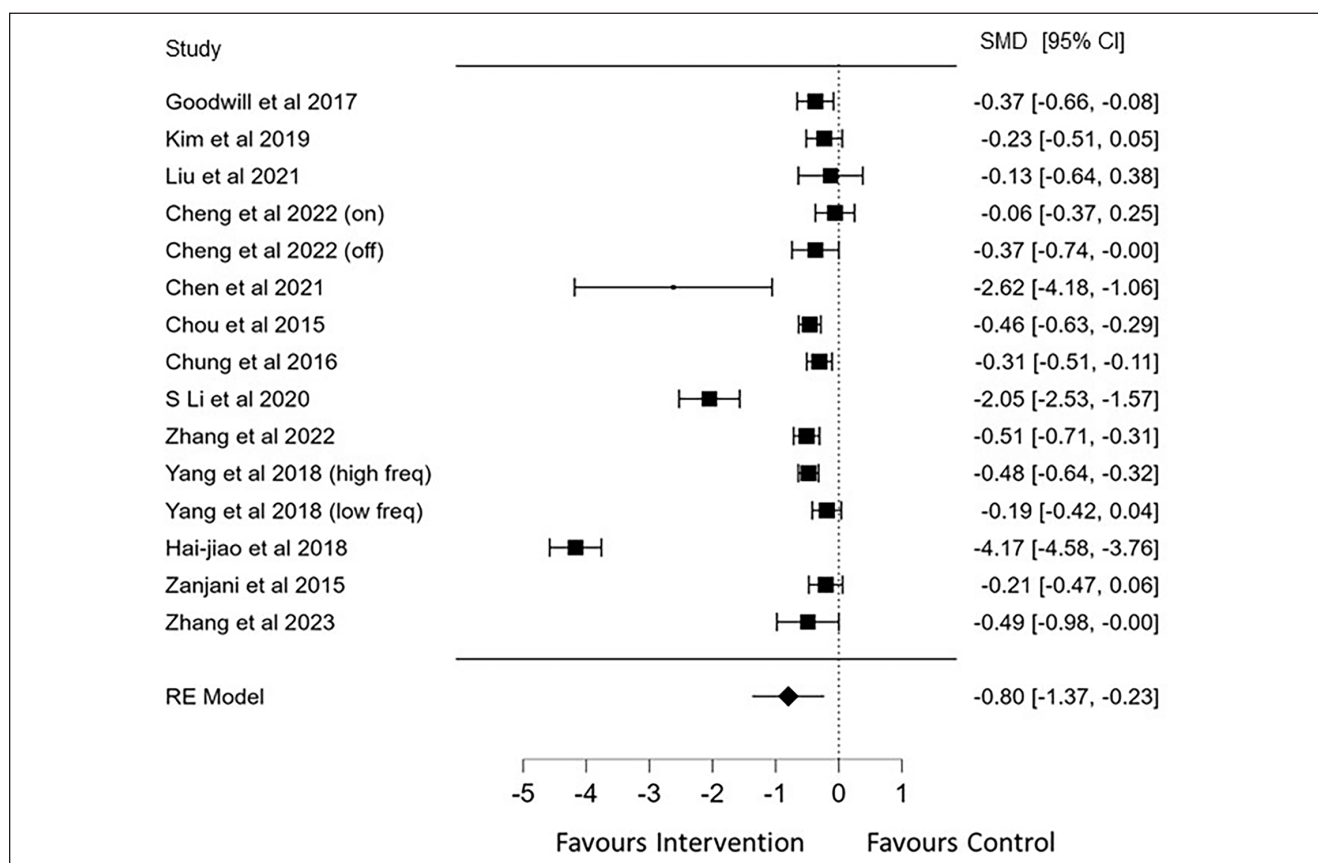
On/off = on medication or off medication. ↑ is improved, ↔ is no change, ↓ is got worse. Some of the systematic reviews are listed as both ↑↔ where they have included different studies that reported either increases or no change for the same outcome measure.

[a]The total number of studies and participants was reported. For studies including other neurological diseases other than Parkinson's disease, we specifically reported the number of Parkinson's disease studies and participants.

[b]Age, severity, and disease duration was provided as a range due to the large variations in reporting methods.
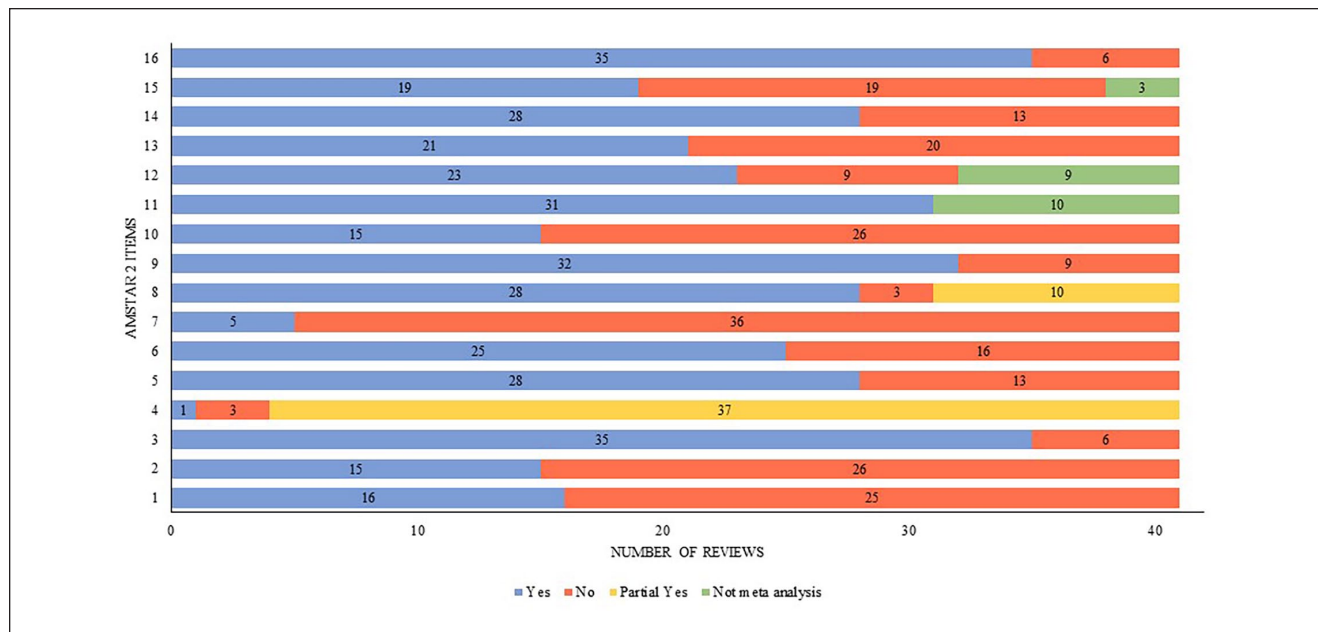
**Figure 2.** Quality assessment (AMSTAR2).

Figure 3. Pooled meta-analysis of the effects of non-invasive brain stimulation on Unified Parkinson's disease Rating Scale (UPDRS) motor function (section III) scores.
Abbreviations: On, on medication; Off, off medication; high freq, high frequency transcranial magnetic stimulation (TMS); low freq, low frequency TMS; RE, random effects.
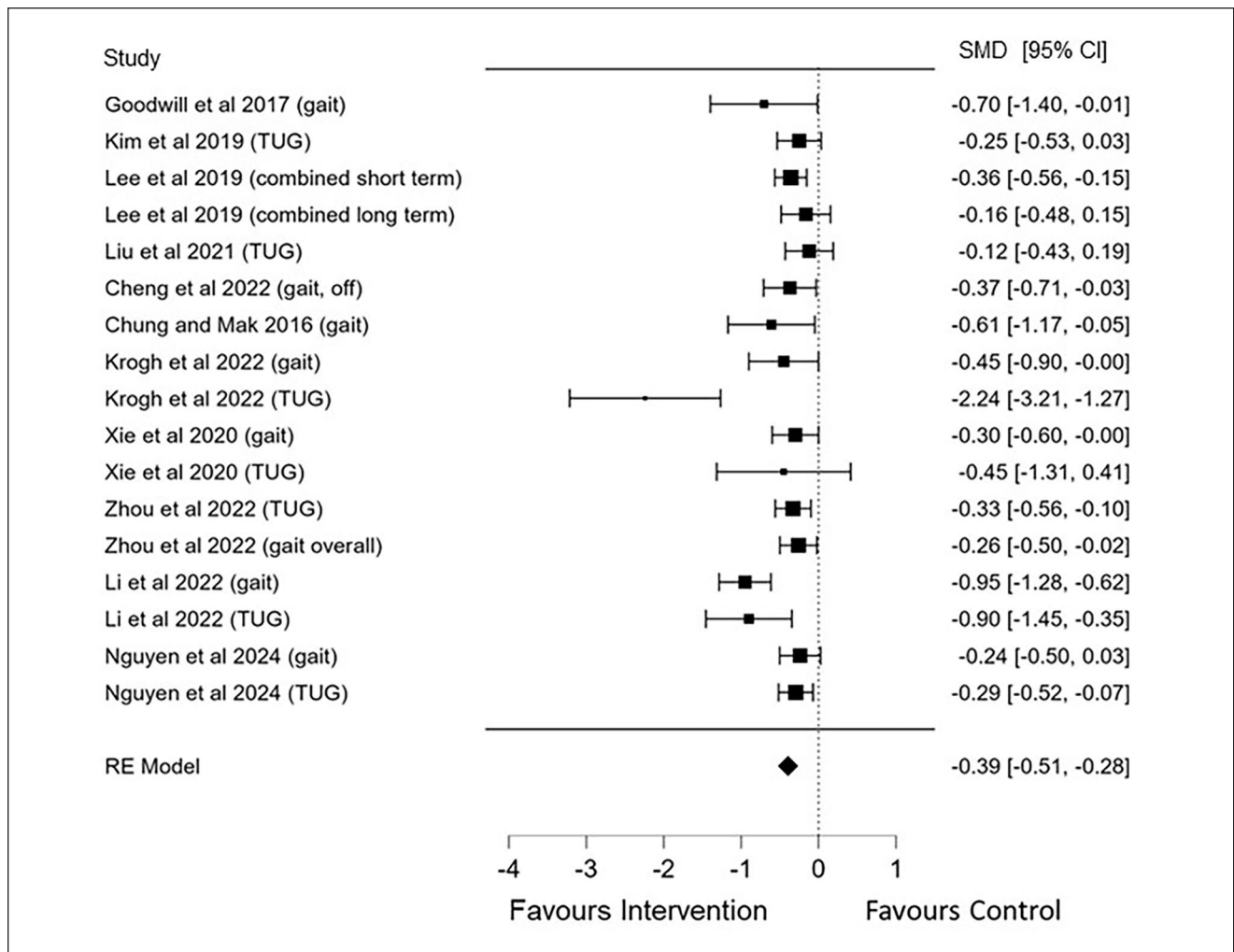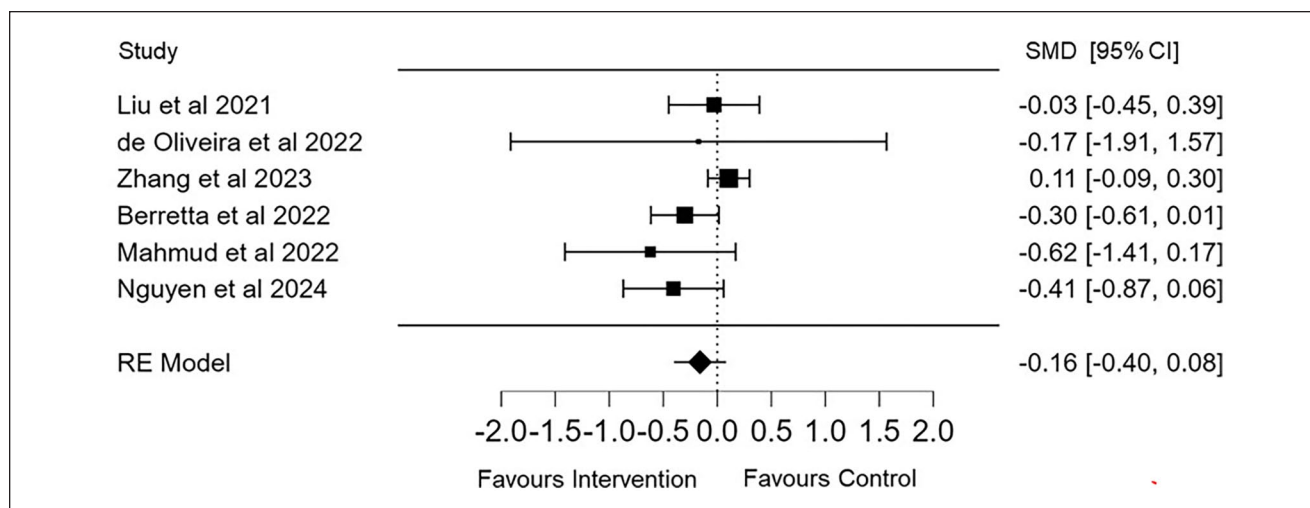
Figure 4. Pooled meta-analysis of the effects of non-invasive brain stimulation on functional mobility.
Abbreviations: Off, off medication; TUG, timed-up-and-go; gait, gait speed; RE, random effects.
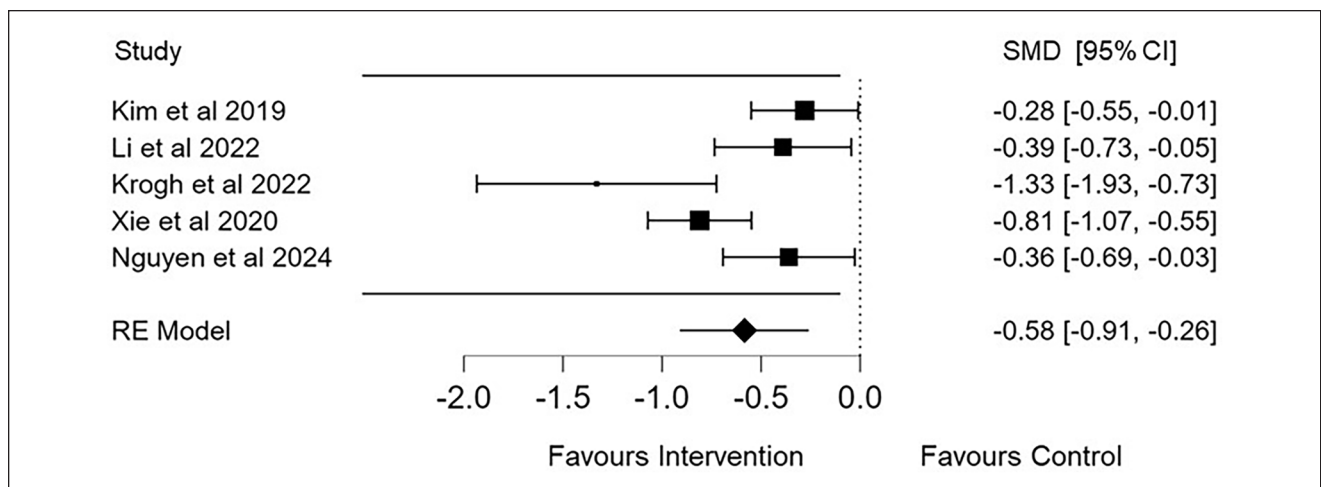
Figure 5. Pooled meta-analysis of the effects of non-invasive brain stimulation on freezing of gait (FoG) scores.
Abbreviation: RE: random effects.

Figure 6. Pooled meta-analysis of the effects of non-invasive brain stimulation on balance.
Abbreviation: RE: random effects.

Static Balance/Postural Control Measures. Our review included 6 meta-analyses that examined the effects of NIBS on static balance/postural control outcomes in people with PD. Five meta-analyses used the Berg Balance Scale (BBS) as the primary balance outcome (1 combined BBS with dynamic posturography[47]) and 1 explored dynamic posturography (ie, body sway) in isolation.[38] Pooled results indicated that NIBS had no effect on static balance/postural control outcomes (SMD=−0.16, 95% CI −0.40 to 0.08, P=.196; n=1175; I^2=47.6; Figure 6).

As part of our sensitivity analysis, we examined the funnel and Q–Q plots for outcomes with very high heterogeneity (>75%), including UPDRS-III ($I2$=98.47%), TUG sub-analysis ($I2$=77.1%), and FoG ($I2$=78.3%) outcomes. For UPDRS-III, 3 studies were excluded based on visual inspection of the funnel and Q–Q plots, as well as a high likelihood of bias.[46,48,49] After their removal, a small but significant effect remained (SMD=−0.37, 95% CI=−0.45 to −0.28, P<.001), and heterogeneity was substantially reduced ($I2$=23.93%; Egger's test P=.118). For the TUG outcome, 1 study was removed following the same approach [41]. A small but significant positive effect of NIBS on TUG scores was still observed (SMD=−0.24, 95% CI=−0.33 to −0.14, P<.001), with heterogeneity effectively eliminated ($I2$=0.02%; Egger's test P=.143). Lastly, for FoG, removing the same study[41] resulted in a moderate and significant positive effect on FoG scores (SMD=−0.50, 95% CI=−0.83 to −0.17, P=.003), although heterogeneity dropped slightly from very high to high ($I2$=74.15%; Egger's test P=.661).

Degree of Overlap

Overall, there were 161 primary studies that were examined across the 41 reviews included in this umbrella review. The CCA across all the included reviews was 6.58%, suggesting moderate overlap of primary studies (Supplemental Figure 3). For the reviews focussing on motor function (UPDRS-III) specifically, the CCA was 2.16%, suggesting slight overlap of primary studies (Supplemental Figure 4). For the reviews focussing on functional movement, including TUG and gait speed assessments, the CCA was 1.81%, suggesting a slight overlap of primary studies (Supplemental Figure 5). Due to the limited number of reviews focussing on specific balance and FoG outcomes, the CCA for these groups of reviews also suggest a slight overlap in primary studies (Supplemental Figures 6 and 7).
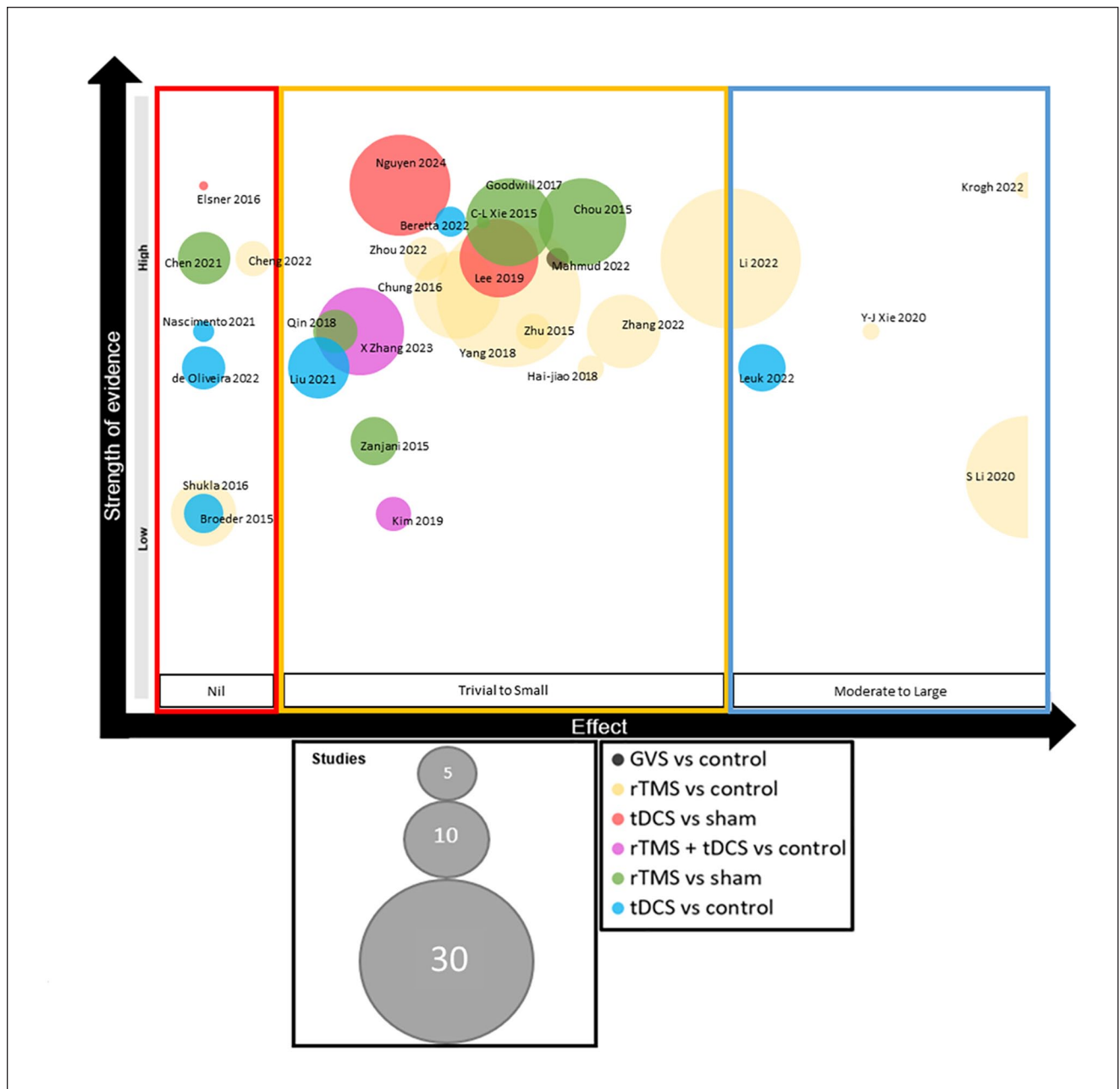
Evidence Map

A visual bubble plot of the meta-analyses included in this umbrella review was designed, based on previous maps[50] and in-line with our published methodology.[24] Generally, most meta-analysis rated as high-quality reported a trivial to small positive effect of NIBS on motor outcomes in people with PD (Figure 7).

Discussion

Methodological Quality of Reviews

This umbrella review is the first to consolidate and evaluate the quality of evidence from NIBS systematic reviews and meta-analyses in PD. The average methodological quality score using AMSTAR2 for the included reviews was "moderate," with various inconsistencies present in the rigor and reporting standards. The updated PRISMA 2020 guidelines revised several reporting elements to enhance clarity in systematic reviews, including requiring authors to report on data preparation, synthesis, heterogeneity and sensitivity

Figure 7. Evidence visual map synthesis. The meta-analyses are grouped into 3 categories on the *x*-axis, depending on the effect of the interventions for their primary outcome ("nil," "trivial to small," and "moderate to large"). Along the *y*-axis, studies are ranked based on the AMSTAR 2 score. The bubble size represents the number of studies included in each review. The bubble color represents the type of noninvasive brain stimulation explored, and if the comparison was a control or sham stimulation.
Abbreviations: GVS, galvanic vestibular stimulation; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

analyses, and citing excluded studies and explaining reasons for exclusion.[26] Our findings reveal that half of the reviews did not address how publication bias may have impacted the findings (54%), and many reviews failed to provide a comprehensive list of excluded studies (88%). Thus, at a minimum, future reviews should aim to incorporate these methodological approaches to improve quality

and ensure compliance with all items outlined in the PRISMA 2020 guidelines.

Despite the combined corrected coverage area for the included reviews being moderate at 6.58%, only slight overlap was observed across the motor outcomes when analyzed separately, with ranges between 1.8% and 2.2%. This suggests a sufficient spread of primary studies, along

with considerable complexity and diversity among the reviews, indicating that the evidence can be trusted for various motor outcomes in PD. This finding is not unexpected, as we exclusively included reviews published in the past 10 years (from 2013 onward) to minimize overlap in primary studies. It also implies that over the past decade reviews are becoming increasingly targeted in addressing specific questions related to NIBS and motor outcomes for PD.

A broader critique of the meta-analyses included within our review is that the various methodological approaches used to analyze trial data likely lead to diverse and often non-standardized effects. Using pooled standard deviation of change scores, post-intervention scores, or pre- and post-intervention scores, when conducting a meta-analysis can often result in biased and difficult-to-interpret results.[51] Whilst it is difficult to determine which statistical approaches were used by the meta-analyses included herein, authors who wish to perform future meta-analysis on the effects of NIBS techniques on physical function in PD should consider alternative approaches like using log transformation of factor effects, and using minimum clinically important differences for standardization after meta-analysis.[51]

NIBS on Motor Function and Functional Movement

Our results suggests that NIBS can benefit motor function in PD. This aligns with previous work suggesting that various modes of NIBS may enhance motor cortex excitability and facilitate motor performance in PD.[18,43,44,52-55] In our review, NIBS also exhibited a small yet significant positive effect on functional movement, including gait speed and TUG performance. This finding is particularly relevant as gait difficulties significantly impair quality of life[56] and increase falls risk in people with PD.[4] When applied to the motor or prefrontal cortex, NIBS (especially rTMS and tDCS) can modulate the release of dopamine in the caudate nucleus[57] and putamen,[58] and their cortico-striatal projections[59] which may, at least partially, explain the short term effects of NIBS on motor function and functional movement in PD.

In our review, NIBS demonstrated small to moderate significant effects on UPDRS-III scores, suggesting that NIBS may enhance overall motor function in PD. This finding aligns with evidence-based guidelines on the therapeutic use of NIBS.[60,61] However, it is important to determine whether this effect reaches the minimal clinically meaningful difference threshold. Moderate to large clinically important differences in UPDRS-III scores lies between −5.2 and −10.8 points difference from baseline scores.[62] Comparing to a previous example,[63] our result translates to a moderate

clinically important difference. Individual differences in pathophysiology likely influence NIBS treatment outcomes, and so future studies should aim to determine optimal stimulation protocols for various clinical subtypes and symptoms. Tailoring NIBS therapies to address specific symptoms may result in greater, and more clinically meaningful, improvements in motor function.

As PD progresses, balance while standing, walking with a narrow base, and turning actions become more unstable.[64-67] As such, NIBS has commonly been proposed as an effective treatment option to attenuate the postural instability experienced by people with PD.[38,47,68] However, our review showed that NIBS had a non-significant trivial effect on static balance and postural control outcomes. Zhang et al[39] suggested that there was no effect of NIBS (ie, both rTMS and tDCS) on balance (measured via the BBS; MD = 1.39; 95% CI −1.13 to 3.91; P = .28), which is akin to the findings of Nguyen et al[40] (SMD = 0.406; 95% CI −0.059 to 0.87; P = .087). In contrast, other meta-analyses have reported significant improvements in balance and dynamic posturography following tDCS applied over the M1 (SMD = −0.30; −0.61 to 0.01; P = .07)[47] and following GVS (SMD = 0.16; 0.01 to 0.31; P < .05).[38] These discrepancies may result from variations in stimulation methods, differences in the location and frequency of treatments, and differences between study cohorts. In addition, the complexity of postural instability in PD, which involves multiple neural pathways and sensorimotor integration processes,[69,70] may also be difficult to treat using a single stimulation paradigm/location. It must also be acknowledged that the heterogeneity in study designs and balance assessment methods used across the reviews could also account for these mixed results.

FoG episodes are debilitating for people with PD, often resulting in poor quality of life for the patient and their carer.[71] Our review demonstrated that NIBS had a moderate positive effect on reducing FoG. However, some careful consideration is needed when interpreting our results. Firstly, we included 5 meta-analyses that explored the effects of NIBS on FoG, using the FoG questionnaire. Of these, 1 meta-analysis included just 2 randomized trials with low sample sizes in their analysis[41] and showed a large and significant effect in favor of rTMS for improving FoG (N = 38 real and 20 sham patients; SMD = −1.33; −1.94 to 0.73; P < .0001). Another meta-analysis included 4 randomized trials, and showed no effect of rTMS improving FoG (N = 45 real and 45 sham patients; SMD = −0.81; −1.68 to 0.06; P = .07).[72] Given the heterogeneity in findings, it remains uncertain whether NIBS is effective in the treatment of FoG at this time, despite our positive results. Further clinical trials, with larger samples, and more homogenized techniques for stimulation location, dosage, and follow-up are needed.

Additional Considerations

Exploring NIBS timing, location, dosage, and effectiveness across different PD stages is crucial, yet we were unable to assess this for several reasons. First, to our knowledge, no studies have directly compared NIBS in early onset versus advanced PD. Second, prospective studies typically include a range of PD severities in a treatment/comparison group. A suggestion for future research is to include multi-arm trials where the same treatment is delivered across groups ranging from mild to severe disease.

The interaction between NIBS and PD medications is another crucial consideration that has been poorly investigated. To date, only 1 meta-analysis has explored the effects of NIBS during "on" versus "off" therapy[44] and so it is currently unclear if NIBS effectiveness is influenced by the medication state. Cheng et al[44] among 6 studies (n = 159 patients) found that rTMS applied over the SMA could significantly improve the UPDRS-III score for PD patients in the "off," not in the "on," medicine state ("off" medication SMD = −0.37, 95% CI −0.65 to −0.09, $P < .01$; "on" medication SMD = −0.06, 95% CI −0.37 to 0.25; $P = .69$).

A limitation of the meta-analyses included in this review is that most studies either combine data from populations "on" and "off" medication or focus solely on patients in the "on" medication state. Additionally, these reviews often pool outcomes from patients taking a combination of medications, such as Levodopa, dopamine agonists, catechol-*O*-methyltransferase inhibitors, and anticholinergics. Consequently, further primary research is needed to better assess the effects of NIBS when used alongside combination medications, and to compare its efficacy in the "on" versus "off" medication states for improving motor outcomes. This research is crucial because certain symptoms, such as FoG, do not respond well to dopamine-based treatments, suggesting that NIBS could offer potential benefits. Moreover, dopamine medications can lead to side effects like dyskinesia and neuropsychiatric issues, which may make higher doses intolerable.[73] Investigating the use of NIBS with lower medication doses could help reduce these side effects while maintaining motor improvements, but this needs thorough exploration before any therapeutic recommendations can be made.

To our knowledge there has been 3 network meta-analysis exploring the relative effectiveness of different NIBS modes and brain sites on motor outcomes in people with PD.[74-76] These were excluded from our pooled results due to the difficulty of unpacking analyses to make direct pairwise comparisons. Nevertheless, the results of these network meta-analyses warrant discussion. Across all network meta-analyses, high-frequency TMS consistently improved UPDRS-III scores in the short term compared to sham,[74-76] with effectiveness observed across multiple brain sites (SMA, DLPFC, prefrontal cortex, and M1).[74] In addition, the surface under the cumulative ranking curve value, which

is often used to rank the treatment outcome scores, suggested that high-frequency repetitiveTMS (HFr-TMS) had the highest probability of being effective in enhancing motor outcomes in the short-term (values of between 77%[75] and 95.1%[74]) or dual-mode therapy with HFr-TMS and tDCS (88.5%).[76] However, some limitations warrant caution when interpreting these findings. These include the low number of studies investigating NIBS techniques other than HFr-TMS and the scarcity of direct comparisons between different NIBS modes across various brain sites in people with PD.

Strengths and Limitations

The strengths of this umbrella review include, first and foremost, successfully achieving our primary goal of evaluating and summarizing the scope and quality of systematic reviews that report the effects of NIBS on physical function in PD. We achieved this by thoroughly reviewing the literature to: (1) map the evidence using a novel bubble plot for visual inspection, (2) assess the quality of the included reviews using the AMSTAR2 scale, and (3) analyze the number of primary studies to determine the degree of overlap between reviews. Additionally, we extracted results from 31 meta-analyses and conducted an aggregate meta-analysis focused on motor function, mobility, FoG, and balance. This approach provides a more comprehensive and robust overview of the latest NIBS evidence on physical outcomes in PD.

Though we followed standardized criteria for conducting this review and reporting the findings, there are certain limitations which should be acknowledged. For instance, even though we performed a comprehensive search of multiple databases, we might have missed potential reviews by limiting the search to English-language studies. However, Cochrane recommendations are unclear about including only English-language studies and do not indicate that this would likely bias the review results. In addition, we relied on the meta-analyses results reported in the included reviews and did not extract or verify data from the original studies, or re-run a meta-analysis based on original data, as this was beyond the scope of this umbrella review.

Conclusion

This umbrella review includes 31 meta-analyses (41 reviews in total) involving 14 253 participants. While the overall quality of the systematic reviews needs improvement, NIBS therapy shows potential benefits for motor function (UPDRS-Section III) and functional mobility (TUG and gait speed) in PD patients, along with some positive effects on reducing FoG. However, the effects on static balance and postural control are limited. To strengthen recommendations, future primary clinical studies should focus on determining optimal NIBS parameters, including

stimulation intensity, frequency, and duration, as well as effective combinations with pharmacotherapy and exercise. More rigorous systematic reviews and meta-analyses that follow the PRISMA 2020 reporting criteria are essential to establish precise guidelines for the "optimal dose" and "location" of NIBS therapy in PD.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525-535. doi:10.1016/S1474-4422(06)70471-9
2. Hirsch L, Jette N, Frolkis A, Steeves T, Pringsheim T. The incidence of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2016;46(4):292-300.
3. Poortvliet PC, Gluch A, Silburn PA, Mellick GD. The Queensland Parkinson's project: an overview of 20 years of mortality from Parkinson's disease. *J Mov Disord*. 2021;14(1):34-41. doi:10.14802/jmd.20034
4. Pelicioni PH, Menant JC, Latt MD, Lord SR. Falls in Parkinson's disease subtypes: risk factors, locations and circumstances. *Int J Environ Res Public Health*. 2019;16(12):2216.
5. Polania R, Kuo M-F, Nitsche MA. Physiology of transcranial direct and alternating current stimulation. In: Brunoni AR, Nitsche MA, Loo CK, eds. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management*. Springer International Publishing; 2021:29-47.
6. Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci*. 2018;21(2):174-187.
7. Stagg CJ, Nitsche MA. Physiological basis of transcranial direct current stimulation. *The Neuroscientist*. 2011;17(1):37-53. doi:10.1177/1073858410386614
8. Kuo M-F, Polanía R, Nitsche M. Physiology of transcranial direct and alternating current stimulation. In: Brunoni A, Nitsche M, Loo C, eds. *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management*. Springer International Publishing; 2016:29-46.
9. Antal A, Herrmann CS. Transcranial alternating current and random noise stimulation: possible mechanisms. *Neural Plasticity*. 2016;2016:3616807.
10. Turi Z, Lenz M, Paulus W, Mittner M, Vlachos A. Selecting stimulation intensity in repetitive transcranial magnetic stimulation studies: a systematic review between 1991 and 2020. *Eur J Neurosci*. 2021;53(10):3404-3415. doi:10.1111/ejn.15195
11. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med*. 2015;58(4):208-213. doi:10.1016/j.rehab.2015.05.005
12. Fried PJ, Santarnecchi E, Antal A, et al. Training in the practice of noninvasive brain stimulation: recommendations from an IFCN committee. *Clin Neurophysiol*. 2021;132(3):819-837. doi:10.1016/j.clinph.2020.11.018
13. Kesikburun S. Non-invasive brain stimulation in rehabilitation. *Turk J Phys Med Rehabil*. 2022;68(1):1-8. doi:10.5606/tftrd.2022.10608
14. Veldema J, Gharabaghi A. Non-invasive brain stimulation for improving gait, balance, and lower limbs motor function in stroke. *J NeuroEng Rehabil*. 2022;19(1):1-24.
15. He J, Tang Y, Lin J, Faulkner G, Tsang HWH, Chan SHW. Non-invasive brain stimulation combined with psychosocial intervention for depression: a systematic review and meta-analysis. *BMC Psychiatry*. 2022;22(1):273. doi:10.1186/s12888-022-03843-0
16. Fitzgerald PB, Gill S, Hussain S, et al. The place of non-invasive brain stimulation in the RANZCP clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry*. 2021;55(4):349-354.
17. Zheng H-B, Liu B, Shen J, Xie F, Ji Q-M, Zhu X-Y. Non-invasive brain stimulation for treating psychiatric symptoms in Parkinson's disease: a systematic review

and meta-analysis. *J Clin Neurosci*. 2022;106:83-90. doi:10.1016/j.jocn.2022.10.013

18. Wenjie Z, Bin D, Fen X, et al. Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: a systematic review and meta-analysis of randomised controlled trials. *EClinicalMedicine* 2022;52:101589.

19. Cosentino G, Todisco M, Blandini F. Noninvasive neuromodulation in Parkinson's disease: neuroplasticity implication and therapeutic perspectives. *Handb Clin Neurol*. 2022;184:185-198. doi:10.1016/b978-0-12-819410-2.00010-2

20. Madrid J, Benninger DH. Non-invasive brain stimulation for Parkinson's disease: clinical evidence, latest concepts and future goals: a systematic review. *J Neurosci Methods*. 2021;347:108957. doi:10.1016/j.jneumeth.2020.108957

21. Potvin-Desrochers A, Paquette C. Potential non-invasive brain stimulation targets to alleviate freezing of gait in Parkinson's disease. *Neuroscience*. 2021;468:366-376. doi:10.1016/j.neuroscience.2021.05.037

22. Castrillon G, Sollmann N, Kurcyus K, Razi A, Krieg SM, Riedl V. The physiological effects of noninvasive brain stimulation fundamentally differ across the human cortex. *Sci Adv*. 2020;6(5):eaay2739.

23. Terranova C, Rizzo V, Cacciola A, et al. Is there a future for non-invasive brain stimulation as a therapeutic tool? *Front Neurol*. 2018;9:1146. doi:10.3389/fneur.2018.01146

24. Harris DM, O'Bryan SJ, Latella C. Non-invasive brain stimulation as treatment for motor impairment in people with Parkinson's disease: protocol for an umbrella review. *PLoS ONE*. 2024;19(6):e0304717. doi:10.1371/journal.pone.0304717

25. Aromataris E, Fernandez RS, Godfrey C, Holly C, Khalil H, Tungpunkom P. *Methodology for JBI Umbrella Reviews*. University of Wollongong; 2014.

26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10(1):89. doi:10.1186/s13643-021-01626-4

27. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*. 2015;30(12):1591-1601.

28. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations the Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Mov Disord*. 2004;19(9):1020-1028.

29. Porritt K, Gomersall J, Lockwood C. JBI's systematic reviews: study selection and critical appraisal. *Am J Nurs*. 2014;114(6):47-52.

30. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol*. 2009;62(10):1013-1020.

31. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7(1):1-7.

32. Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ*. 2009;181(8):488-493.

33. Hopkins W, Marshall S, Batterham A, Hanin J. Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sports Exerc*. 2009;41(1):3.

34. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.

35. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

36. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Wiley; 2008.

37. Hennessy EA, Johnson BT. Examining overlap of included studies in meta-reviews: guidance for using the corrected covered area index. *Res Synth Methods*. 2020;11(1):134-145. doi:10.1002/jrsm.1390

38. Mahmud M, Hadi Z, Prendergast M, et al. The effect of galvanic vestibular stimulation on postural balance in Parkinson's disease: a systematic review and meta-analysis. *J Neurol Sci*. 2022;442:120414. doi:10.1016/j.jns.2022.120414

39. Zhang X, Jing F, Liu Ya, et al. Effects of non-invasive brain stimulation on walking and balance ability in Parkinson's patients: a systematic review and meta-analysis. *Front Aging Neurosci*. 2023;14:1065126.

40. Nguyen TXD, Mai PT, Chang Y-J, Hsieh T-H. Effects of transcranial direct current stimulation alone and in combination with rehabilitation therapies on gait and balance among individuals with Parkinson's disease: a systematic review and meta-analysis. *J NeuroEng Rehabil*. 2024;21(1):27. doi:10.1186/s12984-024-01311-2

41. Krogh S, Jønsson AB, Aagaard P, Kasch H. Efficacy of repetitive transcranial magnetic stimulation for improving lower limb function in individuals with neurological disorders: a systematic review and meta-analysis of randomized sham-controlled trials. Journal of rehabilitation medicine. *J Rehabil Med*. 2022:54:jrm00256.

42. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for idiopathic Parkinson's disease. *Cochrane Database Syst Rev*. 2016;7:CD010916. doi:10.1002/14651858.CD010916.pub2

43. Deng S, Dong Z, Pan L, et al. Effects of repetitive transcranial magnetic stimulation on gait disorders and cognitive dysfunction in Parkinson's disease: a systematic review with meta-analysis. *Brain Behav*. 2022;12(8):e2697.doi:10.1002/brb3.2697

44. Cheng B, Zhao W, Sun L, et al. Effect of theta burst stimulation-patterned rTMS on motor and nonmotor dysfunction of Parkinson's disease: a systematic review and metaanalysis. *Front Neurol*. 2022;12:762100. doi:10.3389/fneur.2021.762100

45. Qin B, Chen H, Gao W, et al. Effectiveness of high-frequency repetitive transcranial magnetic stimulation in patients with depression and Parkinson's disease: a meta-analysis of randomized, controlled clinical trialsd. *Neuropsychiatr Dis Treat*. 2018;14:273-284. doi:10.2147/NDT.S156695

46. Chen J, He P, Zhang Y, et al. Non-pharmacological treatment for Parkinson disease patients with depression: a meta-analysis of repetitive transcranial magnetic stimulation and cognitive-

behavioral treatment. *Int J Neurosci*. 2021;131(4):411-424. doi:10.1080/00207454.2020.1744591

47. Beretta VS, Santos PCR, Orcioli-Silva D, Zampier VC, Vitório R, Gobbi LTB. Transcranial direct current stimulation for balance rehabilitation in neurological disorders: a systematic review and meta-analysis. *Ageing Res Rev*. 2022;81:101736. doi:10.1016/j.arr.2022.101736

48. Hai-jiao W, Ge T, Li-na Z, et al. The efficacy of repetitive transcranial magnetic stimulation for Parkinson disease patients with depression. *Int J Neurosci*. 2020;130(1):19-27. doi:10.1080/00207454.2018.1495632

49. Li R, He Y, Qin W, et al. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson's disease: a meta-analysis. *Neurorehabil Neural Repair*. 2022;36(7):395-404. doi:10.1177/15459683221095034

50. Miake-Lye IM, Hempel S, Shanman R, Shekelle PG. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Syst Rev*. 2016;5(1):28. doi:10.1186/s13643-016-0204-x

51. Hopkins WG, Rowlands DS. Standardization and other approaches to meta-analyze differences in means. *Stat Med*. 2024;43(16):3092-3108. doi:10.1002/sim.10114

52. de Oliveira PCA, de Araújo TAB, Machado DGdS, et al. Transcranial direct current stimulation on parkinson's disease: systematic review and meta-analysis. *Front Neurol*. 2022;12:794784.

53. Paloma Cristina Alves de O, Thiago Anderson Brito de A, Daniel Gomes da Silva M, et al. Transcranial direct current stimulation on parkinson's disease: systematic review and meta-analysis. *Front Neurol*. 2022;12:794784.

54. Shan D, Zhimei D, Liya P, et al. Effects of repetitive transcranial magnetic stimulation on gait disorders and cognitive dysfunction in Parkinson's disease: a systematic review with meta-analysis. *Brain Behav*. 2022;12:e2697.

55. Ni R, Yuan Y, Yang L, et al. Novel non-invasive transcranial electrical stimulation for Parkinson's disease. *Front Aging Neurosci*. 2022;14:880897. doi:10.3389/fnagi.2022.880897

56. Wu Y, Guo XY, Wei QQ, et al. Non-motor symptoms and quality of life in tremor dominant vs postural instability gait disorder Parkinson's disease patients. *Acta Neurol Scand*. 2016;133(5):330-337.

57. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*. 2001;21(15):RC157.

58. Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain*. 2003;126(12):2609-2615.

59. Cho SS, Strafella AP. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. *PLoS ONE*. 2009;4(8):e6725. doi:10.1371/journal.pone.0006725

60. Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol*. 2020;131(2):474-528. doi:10.1016/j.clinph.2019.11.002

61. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087

62. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol*. 2010;67(1):64-70. doi:10.1001/archneurol.2009.295

63. Zhang W, Deng B, Xie F, et al. Efficacy of repetitive transcranial magnetic stimulation in Parkinson's disease: a systematic review and meta-analysis of randomised controlled trials. *eClinicalMed*. 2022;52:101589. doi:10.1016/j.eclinm.2022.101589

64. Kawami Y, Nikaido Y, Nose S, et al. Mediolateral postural control during gait in Parkinson's disease. *Prog Rehabil Med*. 2022;7:20220048.

65. Lazarotto L, Bobbo GZ, Siega J, et al. Static and dynamic postural control: comparison between community old adults and people with Parkinson's disease. *Physiother Res Int*. 2020;25(3):e1844.

66. Doná F, Aquino C, Gazzola JM, et al. Changes in postural control in patients with Parkinson's disease: a posturographic study. *Physiotherapy*. 2016;102(3):272-279.

67. van Wegen EE, van Emmerik RE, Wagenaar RC, Ellis T. Stability boundaries and lateral postural control in parkinson's disease. *Motor Control*. 2001;5(3):254-269.

68. Ghosh S. Improvement of gait and balance by non-invasive brain stimulation: its use in rehabilitation. *Expert Rev Neurother*. 2019;19(2):133-144. doi:10.1080/14737175.2019.1564042

69. Park J-H, Kang Y-J, Horak FB. What is wrong with balance in Parkinson's disease? *J Move Disord*. 2015;8(3):109.

70. Rinalduzzi S, Trompetto C, Marinelli L, et al. Balance dysfunction in Parkinson's disease. *BioMed Res Int*. 2015;2015(1):434683.

71. Cronin P, Collins LM, Sullivan AM. Impacts of gait freeze on quality of life in Parkinson's disease, from the perspectives of patients and their carers. *Ir J Med Sci*. 2024;193(4):2041-2050.

72. Xie Y-J, Gao Q, He C-Q, Bian R. Effect of repetitive transcranial magnetic stimulation on gait and freezing of gait in Parkinson disease: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2020;101(1):130-140. doi:10.1016/j.apmr.2019.07.013

73. Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, Montastruc JL. Limitations of current Parkinson's disease therapy. *Ann Neurol*. 2003;53(S3):S3-S15.

74. Wang Y, Ding Y, Guo C. Assessment of noninvasive brain stimulation interventions in Parkinson's disease: a systematic review and network meta-analysis. *Sci Rep*. 2024;14(1):14219. doi:10.1038/s41598-024-64196-0

75. Qiu Y, Yin Z, Wang M, et al. Motor function improvement and acceptability of non-invasive brain stimulation in patients with Parkinson's disease: a Bayesian network analysis. *Front Neurosci*. 2023;17:1212640. doi:10.3389/fnins.2023.1212640

76. Liu X, Li L, Liu Y. Comparative motor effectiveness of non-invasive brain stimulation techniques in patients with Parkinson's disease: a network meta-analysis. *Medicine (Baltimore)*. 2023;102(39):e34960. doi:10.1097/md.0000000000034960