Effect of non-invasive brain stimulation on motor function after spinal cord injury: a systematic review and meta-analysis

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Systematic Review

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Abstract

Background: In recent years, non-invasive brain stimulation (NIBS) has often been used for therapeutic effects on motor functions. However, there is no clear evidence for the efficacy of NIBS in populations with spinal cord injury (SCI). This study aims to conduct a meta-analysis to summarize the existing evidence on the effectiveness and safety of NIBS for motor dysfunction after a spinal cord injury to obtain new insights.

Methods: Two investigators systematically screened English articles from PubMed, MEDLINE, Embase, and Cochrane Library for eligible randomized and prospective controlled trials regarding the effects of NIBS in motor function recovery after SCI. Studies with at least three sessions of NIBS were included. We assessed the methodological quality of selected studies as described in the evidence-based Cochrane Collaboration' tool. A meta-analysis of the motor function was performed by pooling the standardized mean difference (SMD) with 95% confidence intervals (CI).

Results: A total of 14 studies involving 225 patients were included. Nine studies used repetitive transcranial magnetic stimulation (rTMS) and 5 studies used transcranial direct current stimulation (tDCS). The meta-analysis showed that NIBS could improve the lower extremity strength (SMD = 0.58, 95% CI= 0.02 to 1.14, P = 0.004), balance (SMD = 0.64, 95% CI= 0.05 to 1.24, P= 0.03) and decrees the spasticity (SMD = -0.64, 95% CI=-1.20 to-0.03, P =0.04); while functional mobility of the NIBS group was not statistically significant than that of the control group (upper extremity strength: P=0.07; spasticity: P=0.12). The motor function of upper extremity strength in the NIBS group did not reach statistical significance when compared with the sham group. Only one patient reported seizures occurred during stimulation; no other serious adverse events were reported.

Conclusion: NIBS appears to have a positive effect on motor function of the lower extremity in SCI patients. However, the marginal p-value and a high heterogeneity suggest that these results should be interpreted with caution. Further high-quality clinical trials are needed to support or refute the use and optimize the stimulation parameters of NIBS in clinical practice.

Introduction

Spinal cord injury (SCI) refers to the damage and severe loss of neurons in the spinal cord [1], which results in altered sensory, motor, or autonomic function and affects a patient's psychological, and social well-being [2]. Since spinal cord injury is incomplete in most cases, increasing the connectivity of descending corticospinal pathway [3] and the neuroplasticity of neurons in the motor cortex to the spinal cord can play a critical role in restoring motor function [4]. However, spontaneous recovery after spinal cord injury is variable and limited, and standard pharmacological and rehabilitative approaches have been reported to promote recovery of motor function, but the overall effect remains limited and shows a considerable individual variation [5]. In addition, some emerging therapies such as stem cell transplantation [6] and exosome therapy [7] have been reported to have a certain restorative effect on the nerves, but most of these therapies are invasive and most are still in the animal testing stage, limiting their clinical application.

In recent years, non-invasive brain stimulation (NIBS), including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), has received extensive attention. NIBS mainly regulates the excitability of the cerebral cortex through electric fields or magnetic fields, which has the advantage of being a non-invasive and easy operation [8]. In the TMS, the time-varying magnetic field acts on the cerebral cortex to produce induced current and affects brain metabolism in specific brain networks. In general, high-frequency stimulation (5 Hz or higher) increases cortical excitability, while low-frequency stimulation (1 Hz or below) decreases cortical excitability [9]. Furthermore, a model form of rTMS called theta-burst stimulation (TBS) consisting of 3 pulses of 50Hz and repeating at 5 Hz to reach a total number of 600 pulses, also has been extensively used [9]. The tDCS uses a weak direct current to modulate the activity of neurons in the cerebral cortex [8]. Anodal tDCS increases the excitability of the cortex whereas cathodal tDCS decreases it[9].

There has been an increasing interest in investigating the potential of NIBS in improving motor function after SCI. Despite some studies that have shown positive effects of NIBS on motor function after SCI [10, 11] others have failed to provide evidence of obvious therapeutic effects compared with the control group [11-14]. In addition, several high-quality randomized controlled trials (RCTs) have been published in the last few years [15]. The transience of single-session effects of NIBS suggests that multiple sessions may be needed to induce persistent effects [16, 17], the aim of this review is therefore to quantitatively investigate the effectiveness and update the evidence of NIBS on motor dysfunction by evaluating all RCTs with multiple sessions involving people with SCI.

Methods

A preplanned protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022319400) by the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [18]. Furthermore, our review is described based on the
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19].

Search strategy

Randomized control trials were identified by searching MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and the clinical trials registry and database of the U.S. National Institutes of Health (ClinicalTrials.gov) on December 10, 2021. We put no restrictions on the year of publication in our search. Only studies published in English with the full text available were included. The following keywords were searched: spinal cord injuries, non-invasive brain stimulation, NIBS, Transcranial Direct Current Stimulation, tDCS, Transcranial Magnetic Stimulation, and TMS. When appropriate, database filters were used to refine the search strategy. Search strategies were developed for each database using both free-text terms and the controlled vocabulary (MeSH and Emtree). The PubMed search strategy is illustrated in Additional file 1. A manual search was also conducted from the reference lists of previous systematic reviews to identify additional relevant studies.

Selection criteria

The study participants included patients with motor dysfunction after SCI, meeting the diagnostic criteria for spinal cord injury (International standards for neurological classification of spinal cord injury, revised 2019). The intervention included NIBS (minimum 3 sessions with stimulation), including tDCS and rTMS. Studies evaluating the effect to recover motor function with sham NIBS as a comparator. Studies were excluded if they were review studies, basic experiments, a summary of meetings, book chapters, case reports, full text is not available, unpublished, or duplicate literature, including a sample with mixed neurologic conditions (neuropathic pain, neurogenic bladder, and so on).

Study selection

First, two reviewers (JMC and XLL) independently screened all records based on the titles and abstracts. Second, the full texts were screened to determine the final study. All duplicate documents were removed by using the Endnote X8. The full text of all relevant studies was subsequently retrieved and further examined carefully. The reviewers attempted consensus to establish which studies fulfilled the eligibility criteria. Any disagreements were resolved by discussion with a third independent reviewer (YY).

Data extraction

Two reviewers independently conducted data extraction using a predefined data extraction form. Disagreements were resolved through discussion or, if required, adjudication by a third reviewer. The following variables were extracted from studies: (1) the general characteristics extracted consisted of authors, year of publication, (2) study designs, (3) sample characteristics included sample size, age, duration, SCI degree, level, etc., (4) intervention measures and control protocol type, (5) outcomes of motor function, (6) adverse effects. The mean scores and SD of the outcomes before and after the interventions were extracted, as well as the mean change scores and SD for meta-analyses. If the data reported in articles could not be used for data pooling, the authors of the articles were contacted for requesting the necessary data. Otherwise, the publications with unavailable data were removed.

Methodological quality assessment

The quality of the included studies was evaluated according to the RevMan 5.4 software (Cochrane Collaboration, Oxford, United Kingdom). All included studies were evaluated by seven domains: (1) how random sequences generate (2) allocation concealment (3) blinding of participants (4) binding of outcome assessment (5) inadequate outcome data (6) whether selecting to report outcome (7) other possible bias. According to Cochrane Collaboration's tool for assessing the Risk of Bias [8, 18], each domain was classified as a high, low, or unclear risk of bias. Studies with a low risk of bias in three or more domains were suggested as trials of a moderate to high methodological quality [8]. Usually, tests for funnel plot asymmetry are performed only when at least 10 studies are included in a meta-analysis [18]. Although 14 studies were included in this analysis, when sorted by outcomes, each outcome contained fewer than 10 studies. Thus, publication bias in these trials could not be assessed by graphical analysis of the funnel plot [18].

Outcome indicators

Data were divided into several meta-analyses to identify possible NBIS effects. The primary outcome measurements of functional level, extremity strength, mobility, spasticity, and balance of each study were extracted (see Table 1). When multiple outcome measurements were reported without indication of a primary outcome, a representative measurement in the area of SCI research was chosen based on its validity and reliability [20]. We pooled the data as change values for all outcomes, if available. If not, they were estimated from the final and baseline values. Outcome measurements chosen by these criteria are summarized in Table 1. The extremity strength was measured by the American Spinal Injuries Association (ASIA) impairment scale Upper Extremity Motor Score (UEMS), Lower Extremity Motor Score (LEMS), and Jebsen Taylor hand function test (JTHFT). The mobility was measured as the 10m walking test (10MWT), 6-minute walking test (6MWT), and timed
up and go test (TUG) respectively. The spasticity was measured using the upper/ lower Modified Ashworth Scale (MAS) and Hmax/Mmax amplitude ratio (H/M). Body balance was measured Berg Balance Test (BBT). Data from crossover studies were considered taking into account the two periods of the study to warrant a correct analysis of crossover studies and avoid biased results[18].

**Statistical Analysis**

Meta-analyses were performed using RevMan version 5.4 software. To combine the outcomes in our meta-analysis, the standardized mean difference (SMD) with 95% confidence intervals (CI) was calculated with random-effects model weighting as the pooled effect size. And P <0.05 was considered statistically significant. The statistical heterogeneity between the studies was assessed by Cochran's Q test and quantified with the I² statistic (I² ≥ 50% indicated substantial heterogeneity) [21]. To identify the sources of heterogeneity, sensitivity analysis was conducted with STATA 16.0 software.

**Results**

**Identification of studies**

A PRISMA flowchart of the search strategy, study selection, and exclusions by stage of the systematic review is shown in Fig. 1. Searches of the databases identified 853 studies. The manual search screening through the reference lists identified 3 studies. After duplicates removal, 634 potentially relevant studies were screened by title and abstract. Subsequently, the full texts of the remaining 93 studies were assessed. A total of 14 studies met our inclusion criteria and were described in qualitative analysis (Fig. 1). All studies were published in English. Four trials were conducted in Spain, 4 in the U.S.A, 1 in the UK, 1 in Finland, 1 in Denmark, and 2 in Austria.

**Study selection and characteristics**

Characteristics of studies are summarized in Table 1, and Table2 and summarized below. All of the included controlled studies were RCTs. Eight trials compared parallel intervention groups [10-13, 15, 22-24] and 6 studies [25-30] used a crossover design. The test groups all received NIBS, and patients in the control group received the sham stimulation. In addition, 2 studies combined physical therapy [10, 27], 5 combined robot training [11, 12, 15, 23, 24], 1 combined peripheral nerve stimulation[22], 1 combined massed practice[13], 1 combined antispastic medication [30]. In terms of the stimulation pattern of TMS, all but one [22] of the remaining studies used excitability stimulation patterns. All articles involving tDCS used anodal stimulation. The frequency of treatment ranged from three [24, 27] to four[22], five[10-13, 15, 23, 26, 28-30] or seven[25] times per week. The duration of treatment ranges from 3[25] to 36 [24] sessions. The treatment intensity (in terms of session duration) ranged from 200s [26, 29] to 30 min[13] and the treatment time did not differ between the control and experimental groups. Due to considerable heterogeneity in study designs about follow-up, the first assessment available post-intervention was chosen as a follow-up. The data were sorted and analyzed based on outcome to provide an overview of the effects of NIBS on each of the categories: 5 studies used results from UEMS[10, 12, 23, 25, 26] and 2 used JTHFF [11, 27] on the upper extremity strength, 5 used LEMS[10, 12, 23, 25, 26] on the lower extremity strength, 2 used UMAS[22, 26], 7 used LMAS [15, 22, 23, 25, 28-30] and 3 used H/M ratio[28-30] on spasticity, 3 used BBT[15, 24, 25] on body balance, 4 used 10MWT [10, 15, 24, 25], 3 used 6MWT[10, 15, 24] and 4 used TUG [15, 24] on mobility. Thus, the results of these clinical trials were pooled in different meta-analyses.

A total of 225 participants were pooled in the meta-analyses and the demographic characteristics are shown in Table1. The number of participants in each study ranged from 5[22] to 43[15]. The pooled sample was predominantly males (73.78%) with a mean (SD) of 44.31 (15.08) years of age and 2.77 (5.32) years of the duration of post-injury. All included studies provided information on the level of spinal cord injury and baseline severity according to the ASIA. The number of patients with the injury level cervical was 128 (56.89%) of the sample, whereas thoracic was 92 (40.89%) and lumbar was 5 (2.22%). Complete SCI at A level of impairment in ASIA was present only in 1 patient, and incomplete SCI at B level was in 5(2.22%), level C in 115 (51.11%), and level D in 104 (46.22%) of these patients.

**Adverse effects**

Among 14 included studies, 8 reported no obvious adverse effects [12, 13, 22, 24-26, 28, 29]. One study has reported that 1 patient experienced a seizure during TMS stimulation [10]. Five studies have reported minor adverse effects [11, 15, 23, 27, 30], such as tingling, itching, skin redness, sleepiness, facial muscle contraction, or headache, which were observed also in the sham group.

**Quality**

Figure 2 presents the review authors judgments about each risk of bias domain and percentages of risks across all included studies. 8 studies (57.14%)[12, 13, 22, 23, 25, 28-30] reported adequate random sequence generation and 3 (21.43%) [10, 11, 15] hid the allocation
scheme, all presented blinding of participants and personnel, 13 (92.86%) presented blinding of outcome assessment and all described a low risk for attrition, showing a low risk of bias. Therefore, all of the included studies presented moderate to high methodological quality.

**Effects of interventions**

**Extremity strength**

In the NIBS group, lower extremity strength measured by LEMS was greater than that in the sham groups (SMD=0.58, 95% CI=0.02 to 1.14, \(P =0.04, \text{I}^2=52\%\)) (Fig. 3a). No greater improvements in the upper extremity strength were observed in the NIBS groups compared to the sham groups (SMD =0.4, 95% CI= -0.03 to 0.83; \(P=0.07, \text{I}^2 =0\%\)) (Fig. 3a).

**Balance**

Significantly greater improvements by BBT were observed in the NIBS groups compared to the sham groups (SMD =0.64, 95% CI= 0.05 to 1.24, \(P =0.03, \text{I}^2 =0\%\)) (Fig. 3b).

**Spasticity**

The changes of spasticity in upper limbs assessed by UMAS were not more significant in the NIBS groups than in sham groups (SMD= -1.25, 95% CI= -2.83 to 0.34, \(P=0.12, \text{I}^2 =62\%\)) (Fig. 4a). In the NIBS groups, significant changes in lower limbs assessed by LMAS were observed than in the sham groups (SMD= -0.61, 95% CI= -1.20 to -0.03, \(P=0.04, \text{I}^2 =64\%\)) (Fig. 4a). However, the overall changes in spasticity of lower limb measured by H/M ratio were similar in the sham groups and sham groups (SMD= -0.95, 95% CI= -2.64 to 0.73, \(P=0.27, \text{I}^2 =86\%\)) (Fig. 4b).

**Mobility**

Mobility was similar in the NIBS groups and sham groups, which was evaluated by the gait distance of 6MWT (SMD= -0.17, 95% CI= -0.68 to 0.34; \(P=0.51, \text{I}^2 =63\%\)) (Fig. 5a), the speed of 10MWT (SMD= 0.85, 95% CI= -0.07 to 1.76; \(P=0.07, \text{I}^2 =14\%\)) (Fig. 5b), time-to-complete the 10MWT (SMD= -0.35, 95% CI= -0.88 to 0.18; \(P=0.19, \text{I}^2 =0\%\)) (Fig. 5c), and TUG (SMD= 0.01, 95% CI= -0.51 to 0.52, \(P =0.98, \text{I}^2 =16\%\)) (Fig. 5d).

**Sensitivity analysis results**

Sensitivity analysis revealed that the heterogeneity across subgroups did not change after excluding any one study, suggesting the source of the heterogeneity was multifaceted. The results are shown in Additional file 2.

**Discussion**

As a new neuromodulation technique, NIBS has been reviewed in improving motor function after SCI [3, 17]. The present systematic review and meta-analysis evaluate the effect and summarize the safety profiles of NIBS. The data for participants demonstrate evidence that NIBS has positive effects on strength and spasticity of lower extremities, and balance.

From a motor control perspective, damage to spinal tracts disturbs the information transmission from the brain to the spinal cord and results in maladaptive reorganization of the entire neuraxis that contributes to motor dysfunction[17]. At the spinal level, maladaptive reorganization of spinal circuits leads to spasticity, due in part to the loss of descending control of inhibitory spinal circuits[31]. Clinically, injuries are divided to be (neurologically) complete or incomplete, depending on the presence or absence of neurological functions below the segmental level of injury. Numerous histological analyses and electrophysiologic studies have demonstrated that most patients diagnosed with complete SCI with loss of all neurological functions below the injury have residual physiological or anatomical continuity of Central nervous system tracts across the lesion. These remainder provide a fertile ground for the NIBS, which is concerned with establishing central axonal regeneration and reestablishing physiological reconnections[32].

NIBS is applied over the motor cortex in SCI patients to take advantage of neuroplasticity to activate the residual axon and establish functional connectivity in the corticospinal tract. Some clinical studies have shown the ultimate therapeutic effect is produced by strengthening transmission in the nervous system, excitation, inhibition, or modulation of neuronal [33]. In addition, several studies in animal models of SCI have also shown the benefits of NIBS. One study showed that following injury, NIBS can enhance spontaneous collateral or regenerative sprouting of corticospinal tracts, as well as produce motor recovery corresponding to increased axonal growth[34]. Another study showed that tDCS can increase the expression of a brain-derived neurotrophic factor in mouse cortical slices, which can promote changes in synaptic plasticity[35]. The study by Poirrier et al. showed that after 8 weeks of treatment with 10Hz rTMS, a significant positive correlation between the final motor function of SCI in animal models and grey matter density of serotonergic fibers in the spinal segment just
caudal to the lesion [36]. The studies by Cao et al. reported that rTMS could alleviate the spasticity and promote the motor function following SCI might be related to the up-regulated to varying degrees of GABA receptors[37] and potassium-chloride cotransporter-2 protein[38]. However, the study by Poirier et al suggested mechanism that rTMS is beneficial in low thoracic lesions because it activates the central locomotor generator[39].

In the meta-analysis, the motor cortex was selected as a stimulation site in all studies and the NIBS showed a significant effect on the lower extremity strength and balance. However, there was no greater improvement in functional mobility in the NIBS group compared to the sham group. In addition, high heterogeneity was observed in LEMS and 6MWT. Previous studies have shown that NIBS targeting lower extremity motor regions can activate spinal circuits that contribute to walking. However, evidence for the value of NIBS to improve lower extremity function in SCI is limited [17]. In the present study, most of the participants in the analyses were older, and in the chronic stage, which may also be associated with a low improvement rate of functional mobility [4]. It should be noted that we did not account for the difference in demographic and clinical indices in calculations of the efficacy, which, in turn, could also affect the obtained results. Furthermore, the results found in the mobility analysis may have been influenced by the small number of participants in the primary studies, which is associated with low statistical power and therefore a high probability of type II error [40].

Our present meta-analysis showed that NIBS had a significant benefit in spasticity of lower limbs evaluated by LMAS, this was consistent with the review performed by Korzhova et al. [41]. However, despite previous studies that have associated the spasticity of the lower extremity with the results of some neurophysiological examinations such as F-waves [33], H reflex, and H/M ratio [22], the H/M ratio in our results failed to show significant change after the NIBS sessions. The results found in the H/M ratio analysis may have been affected by the smaller number of studies (only 3 studies included). Another, no less important, cause of large heterogeneity in the NIBS effect on spasticity, which was found in the studies, is the use of different stimulation protocols (frequency, total number of stimuli, stimulation intensity). For example, several TMS studies demonstrated a good effect of theta bursts with a total frequency of 5 Hz in patients [29]. In other studies of TMS, the effect was also observed for high-frequency stimulation [28, 30]. Therefore, these differences indicated the potential value and research ability of NIBS in spasticity post-SCI.

Although a few clinical trials have shown a positive effect of NIBS on upper extremity motor function in SCI patients, the present study did not find conclusive results of UMAS and UEMS to support the notion. In this line, these findings are consistent with the aforementioned studies by Lu et al. and Mateo et al. [42, 43]. The insufficient evidence might be explained by several factors. First, unlike motor dysfunction of the lower extremity which can occur in the cervical, thoracic, and lumbar levels of SCI, motor dysfunction of the upper extremity only occurs in patients with cervical levels with relatively low incidence. Second, most the patients with cervical SCI have severe secondary complications, leading to poorer adherence to trial training specifications [42, 43]. Third, unilateral hemisphere stimulation may not be the most efficacious approach for improving upper extremity function in SCI, because the motor dysfunction of the upper extremity after SCI is typically bilateral [17]. Four, arm and hand function are a complex issue both in spinal cord injury and non-spinal cord injury patients with tetraplegia, including a wide variety of highly acyclic movements that are not easily objectively measurable [42, 44].

Overall, our results are important for the emerging field of NIBS on motor recovery of lower limbs after SCI and support previous evidence suggesting. Additionally, the present systematic review provides important information for future studies designed to address aspects of motor rehabilitation using NIBS as a rehabilitation tool for individuals after SCI. However, our results are limited to the short-term effects of NIBS, as the included studies did not assess long-term follow-up. Future original research should consider this aspect.

This review found that some studies reported mild adverse events. The most concerning adverse event was a seizure after rTMS [4]. No major adverse events were observed in the current review, and no studies reported deterioration in motor function after NIBS. To establish the routine use of NIBS for SCI, it is necessary to develop a method to identify the lowest risk stimulation parameters. Therefore, it is suggested that more clinical evidence is needed in the future to regard the relationship between safety and stimulation parameters to improve the effectiveness of treatment.

**Limitation**

Some limitations in the present study should be pointed out. First, the methodologic quality of all included trials was either low or good, and the study designs differed considerably. Moreover, eligibility criteria, random sequence generation, and allocation concealment were commonly heterogeneous or not clearly stated in the articles. The risk of bias within these trial areas is represented in the final risk of bias graph. The power of the findings and their implication for clinical practice are thereby diminished. Second, we only included English-language articles, which may cause bias owing to missing some published studies in this area in another language. Third, while tDCS and TMS are different types of stimulation with different working mechanisms, our findings indicate that they might trigger comparable effects on motor function. However, we were unable to perform sub-analyses to clarify different types of NIBS techniques and different stimulation parameters due to the small number of studies extracted and variability in stimulation parameters reported, thus limiting our understanding of the
positive changes in motor function promoted by NIBS. Fourth, functional neuroimaging and neurophysiological markers are likely needed to facilitate a more precise application of NIBS in SCI of motor dysfunction. The last, it remains unclear whether time post-injury, lesion level, and type of injury are significant variables affecting NIBS results. These factors should be considered in the formation of homogeneous samples to observe whether these factors are predictors of better motor responses after NIBS.

**Conclusion**

From the concept of rehabilitation aimed at improving neuroplasticity, NIBS may be a promising complementary treatment when used in conjunction with conventional therapies or training to enhance motor function in patients with SCI. We conclude that there is the initial evidence of the efficacy of NIBS in improving motor dysfunction in the lower extremities of SCI patients and encourage further high-quality research in this field.

**Abbreviations**

NIBS: non-invasive brain stimulation; SCI: spinal cord injury; SMD: standardized mean difference; CI: confidence intervals; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; TBS: theta-burst stimulation; RCTs: randomized controlled trials; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD: standard deviation; ASIA: American Spinal Injuries Association; UEMS: Upper Extremity Motor Score; LEMS: Lower Extremity Motor Score; JTHFT: Jebsen Taylor hand function test; 10MWT: 10m walking test; 6MWT: 6-minute walking test; TUG: timed up and go test; MAS: Modified Ashworth Scale; H/M: Hmax/Mmax amplitude ratio; BBT: Body balance was measured Berg Balance Test.

**Declarations**

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**Authors’ contributions**

Study objective: JMC, JWX. Literature search: JMC, XLL. Data extraction: JMC, XLL.

Methodological quality assessment: JMC, XLL, YY. Critical review and approval of manuscript: JMC, XLL, YY, SMX, JWX. All authors have read and approved the final manuscript.

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**Availability of data and material**

The datasets supporting the conclusions of this article are included within the article.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

All authors have approved this manuscript for publication. This manuscript has not previously been published and is not pending publication elsewhere.

**Competing interests**

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**References**


Tables

Table 1. Study characteristics, design, methodological aspects, and function outcomes measures used in the NIBS studies.
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Country</th>
<th>Design</th>
<th>Sample</th>
<th>Participants</th>
<th>Mean (SD)</th>
<th>Relevant outcome Measures (meta-analysis)</th>
<th>Follow-up</th>
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<tr>
<td>Tolmacheva et al. 2017</td>
<td>Finland</td>
<td>Parallel Randomized Double-blind Sham-controlled</td>
<td>n=5</td>
<td>ASIA Scale (A/B/C/D): B1C3D1 Level of injury (C/T/L): C5 Gender (male): 4</td>
<td>Age (years): 47.8 (12.85) Duration (months): 51.8 (25.88)</td>
<td>Spasticity = UMAS, LMAS Timing: 0, 4week</td>
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<td>Gomes-Osman et al. 2015</td>
<td>USA</td>
<td>Crossover Double-blind Randomized Sham-controlled</td>
<td>n=11</td>
<td>ASIA Scale (A/B/C/D): C5D6 Level of injury (C/T/L): C11 Gender (male): 1 Aetiology: Traumatic 11</td>
<td>Age (years): 46.7 (12) Duration (years): 6.6 (8.2)</td>
<td>Extremity strength = JTHFT Timing; before and after the intervention</td>
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<tr>
<td>Krogh et al. 2022</td>
<td>Denmark</td>
<td>Double-blind, Randomized Sham-controlled</td>
<td>n=19 (10/9)</td>
<td>ASIA Scale (A/B/C/D); Exp = A1C3D6; Con = C2D7; Level of injury (C/T/L): Exp = C5T4L1; Con = C6T1L2; Gender (male): Exp = 8; Con = 7 Aetiology:</td>
<td>Age (years): Exp = 57.1 (8.3); Con = 51.8 (12.1) Duration (days): Exp = 91.3 (40.8); Con = 87.3 (69.5)</td>
<td>Extremity strength = LEMS Mobility function = 6MWT, 10MWT Balance = TUG Timing: 0, 4week</td>
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<td>Kumru et al. 2016</td>
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<td>Randomized</td>
<td>Double-blind</td>
<td></td>
<td>24 (12/12)</td>
<td>C12D3</td>
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</tbody>
</table>

Note: The table above summarizes data from various studies comparing different intervention strategies for traumatic and non-traumatic injuries.
<table>
<thead>
<tr>
<th>Raithatha et al.</th>
<th>USA</th>
<th>Randomized, Double-blind</th>
<th>n=15 (9/6)</th>
<th>Age (years):</th>
<th>Mobility function=10MWT, 6MWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-controlled</td>
<td></td>
<td></td>
<td></td>
<td>Exp=40.56(12.24); Con=58.0 (5.36)</td>
<td>Balance = TUG, BBT</td>
</tr>
<tr>
<td>Level of injury (C/T/L):</td>
<td></td>
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<td></td>
<td>Exp=8(8.43); Con=7.67(15.36)</td>
<td>Timing;0, 12week</td>
</tr>
<tr>
<td>Exp=C7D1B1; Con=C4D2</td>
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<td>Level of injury (C/T/L):</td>
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</tr>
<tr>
<td>Exp=C4T4L1; Con=C5L1</td>
<td></td>
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<td>Gender (male):</td>
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<tr>
<td>Exp=5; Con=5</td>
<td></td>
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<td>Aetiology:</td>
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<tr>
<td>traumatic 15</td>
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<table>
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<tr>
<th>Simis et al.</th>
<th>USA</th>
<th>Parallel Randomized Double-blind</th>
<th>n=43(21/22)</th>
<th>Age (years):</th>
<th>Mobility function=10MWT, 6MWT</th>
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<tbody>
<tr>
<td>Sham-controlled</td>
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<td></td>
<td></td>
<td>Exp=31(14.82); Con=41 (15.56)</td>
<td>Spasticity=LMAS</td>
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<td>Level of injury (C/T/L):</td>
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<td>Exp=16(13.33); Con=15.5(11.85)</td>
<td>Balance = TUG, BBT</td>
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<tr>
<td>Exp=C4T17; Con=C11T11</td>
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<td>Gender (male):</td>
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<tr>
<td>Exp=17; Con=15</td>
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<td>Aetiology:</td>
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<td>traumatic 19; non-traumatic 2</td>
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<td>traumatic 18; non-traumatic 4</td>
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<table>
<thead>
<tr>
<th>Yozbatiran et al.</th>
<th>USA</th>
<th>Randomized Double-blind</th>
<th>n=8(4/4)</th>
<th>Age (years):</th>
<th>Extremity strength=JTHFT</th>
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<tbody>
<tr>
<td>Sham-controlled</td>
<td></td>
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<td></td>
<td>Exp=49.7(5.40); Con=55.7(2.90)</td>
<td>Timing;0, 2week</td>
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<tr>
<td>Level of injury (C/T/L):</td>
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<td>Exp=25.2(10.4); Con=141.2(48.2)</td>
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<td>Exp=C1D3; Con=C2D2</td>
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<tr>
<td>Gender (male):</td>
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<tr>
<td>Exp=4; Con=3</td>
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<table>
<thead>
<tr>
<th>Aetiology: -</th>
<th>Age (years): 53.3(4.1)</th>
<th>Extremity strength=UEMS</th>
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</thead>
<tbody>
<tr>
<td>Potter-Baker et al. 2017</td>
<td>n=8</td>
<td>Timing;0, 2week</td>
</tr>
<tr>
<td>Longitudinal Randomized, Double-blinded Sham-controlled</td>
<td>Age (years): 53.3(4.1)</td>
<td>Extremity strength=UEMS</td>
</tr>
<tr>
<td>USA</td>
<td>ASIA Scale (A/B/C/D): B2D6</td>
<td>Duration (months):</td>
</tr>
<tr>
<td></td>
<td>Level of injury(C/T/L): C8</td>
<td>Exp=54.4(30.8); Con=164(153.6)</td>
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<tr>
<td></td>
<td>Gender(male):8</td>
<td>Extremity strength=UEMS</td>
</tr>
<tr>
<td></td>
<td>Etiology: traumatic</td>
<td>Timing;0, 2week</td>
</tr>
<tr>
<td></td>
<td>ASIA Scale: American Spinal Injury Association motor score and class; Level of injury: C, Cervical, T, thoracic, L, lumbar; Con: control group; Exp: experimental group; LEMS: ASIA lower extremity motor score; UEMS: ASIA upper extremities motor score; MAS: Modified Ashworth Scale; TUG, timed up and go test; JTHFT: Jebsen-Taylor Hand Function Test; BBT: Berg Balance Test; 10MWT: 10-m walk test; 6MWT: 6-min walk test.</td>
<td>Extremity strength=UEMS</td>
</tr>
</tbody>
</table>

Table 2. Detailed NIBS setting and number/frequency of sessions used in each included study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation type</th>
<th>Session(n)</th>
<th>Stimulation site</th>
<th>Parameter</th>
<th>Adverse effects (n)</th>
</tr>
</thead>
</table>
| Tolmacheva et al. 2017                    | Exp= Active TMS+PNS  
Con= Sham TMS+PNS                                     | 16         | Arm primary motor cortex       | 0.2Hz, 20 min, 100% RMT during 4 weeks                                                              | -                   |
| Benito et al. 2012                        | Exp= Active rTMS+Rehabilitation therapy  
Con= Sham rTMS+Rehabilitation therapy                  | 15         | Leg motor area                 | 20 Hz for 2 s bursts, intertrain intervals of 28 s, over 20 min, 90% RMT, 1800 pulses/session, 15 days | -                   |
| Gharooni et al. 2018                      | Exp= Active iTBS  
Con= Sham iTBS                                        | 10         | Primary motor cortex           | 50 Hz for 3 stimuli, 80% RMT, 600 pulses/session in 200 s for 2 weeks                               | -                   |
| Gomes-Osman et al. 2015                   | Exp= Active TMS+ RTP  
Con= Sham TMS+RTP                                          | 3          | Corticomotor hand region       | 10 Hz, 80% RMT, 800 pulses/session, 3 days/session for 1 week                                       | Transient Headache: 3 |
| Krogh et al. 2022                         | Exp= Active rTMS+ LL-RT classes + LL-PT classes  
Con= Sham rTMS+ LL-RT classes + LL-PT classes             | 20         | Leg primary motor cortex       | 20 Hz, 100% RMT, 1800 pulses/session, over 22 min/day, 5 days/session for 4 weeks                  | Seizure: 1          |
| Kumru et al. 2016                         | Exp= Active TMS+ Lokomat training  
Con= Sham TMS+ Lokomat training                           | 20         | Motor area                     | 20 Hz for 2 s duration bursts, 90% RMT, 1800 pulses/session over 20 min, 5 days/session for 4 weeks | Facial muscle contraction: 8  
Mild headache: 1       |
| Nardone et al. 2014                       | Exp= Active TMS  
Con= Sham TMS                                        | 5          | Primary motor cortex           | 20 Hz for 2 s long bursts, 90% RMT, 1600 pulses/session over 20 min, 5 days/session for 1 week       | -                   |
| Nardone et al. 2017                       | Exp= Active TMS  
Con= Sham TMS                                        | 10         | Leg area of dominant primary motor cortex | 50 Hz, 80% AMT, 600 pulses/session  
iTBS: 3 pulses of 50 Hz repeated at 5 Hz for total of 600 stimuli (200 s), 5 days/session for 2 weeks | -                   |
| Kumru et al. 2010                         | Exp= Active TMS+ Antispastic medication  
Con= Sham TMS+ Antispastic medication                    | 5          | Primary motor cortex           | 20 Hz for 2 s duration bursts, 90% RMT, 1600 pulses/session over 20 minutes, 5 days/session for 1 week | Twitching facial muscles: 3 |
| Kumru et al. 2016                         | Exp= anodal DC + Lokomat training  
Con= Sham tDCS+ Lokomat training                          | 20         | Anode= leg motor cortex        | 2 mA× 20 min/day, 5 days/session for 4 weeks                                                        | -                   |
| Raithatha et al. 2016                     | Exp= anode tDCS+ Lokomat training  
Con= Sham tDCS+ Lokomat training                          | 36         | Lower extremity motor cortex   | 2 mA× 20 min/day, 3 days/session for 12 weeks, current density of 0.08 mA/cm²                     | -                   |
| Simis et al. 2021                         | Exp= Active TMS+ Lokomat training  
Con= Sham TMS+ Lokomat training                          | 30         | Primary motor cortex           | 2 mA× 20 min/day, 3 days/session for 10 weeks (outpatients group) or 5 days/session for 6 weeks (inpatients group) | Tingling and itching |
| Yozbatiran et al. 2016                    | Exp= anodal tDCS+ exoskeleton robot-assisted arm training | 10         | Primary motor cortex           | 2 mA× 20 min/day, 5 days/session for 2 week, current density of 0.0571 mA/cm²                     | Tingling, skin redness, and sleepiness |
27 Potter-Baker et al. 2017

Con= Sham tDCS+ exoskeleton robot-assisted arm training

Exp= anodal tDCS+ massed practice

10 Primary motor cortex 2mA×30min/day, 5days/week for 2 weeks.

Con= Sham tDCS+ massed practice

rTMS: repetitive transcranial magnetic stimulation; RMT: resting motor threshold; Con: control group; Exp: experimental group; iTBS: intermittent Theta-burst stimulation; tDCS: transcranial direct current stimulation; PNS: Peripheral nerve stimulation; RTP: repetitive task practice; LL-RT: lower limb resistance training; LL-PT: lower limb physical therapy

Figures

Identification of studies via databases and registers

Records identified from:
- Databases (n = 853)
- Other sources (n = 3)

Records removed before screening:
- Duplicate records removed (n = 222)
- Records marked as ineligible by automation tools (n = 0)
- Records removed for other reasons (n = 0)

Records screened by title and abstract (n = 634)

Reports sought for retrieval (n = 95)

Reports assessed for eligibility (n = 93)

Full-text articles excluded (n = 78):
- Non-RCT (n = 2)
- Clinical trials with incomplete data (n = 44)
- Investigate measure by NIBS only (n = 14)
- Retracted article (n = 1)

Studies included in quantitative synthesis (n = 14)

Figure 1

Flow of studies through the review Study selection and characteristics
Figure 2

Cochrane risk of bias assessment of the included studies. (a) Risk of bias graph; (b) Risk of bias summary.
### Figure 3

Weighted mean difference (95% CI) of the effect of NIBS compared with sham on (a) lower extremity strength by pooling data from 5 trials (LEMS) and upper extremity strength by pooling data from 5 trials (UEMS and JTHFF) in people with SCI; (b) Balance from 2 tails.

#### a

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NIBS Mean</th>
<th>NIBS SD</th>
<th>NIBS Total</th>
<th>Sham Mean</th>
<th>Sham SD</th>
<th>Sham Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Gharooni et al. 2018</td>
<td>3.3</td>
<td>14.34</td>
<td>10</td>
<td>3.5</td>
<td>14.65</td>
<td>10</td>
<td>10.8%</td>
<td>-0.01 [-0.89, 0.86]</td>
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<tr>
<td>Gomes-Osman et al. 2015</td>
<td>45</td>
<td>52</td>
<td>11</td>
<td>29</td>
<td>68</td>
<td>11</td>
<td>11.5%</td>
<td>0.25 [-0.59, 1.09]</td>
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<tr>
<td>Kumru et al. 2016(2)</td>
<td>2.81</td>
<td>3.12</td>
<td>15</td>
<td>0.56</td>
<td>0.81</td>
<td>16</td>
<td>13.4%</td>
<td>0.96 [0.23, 1.73]</td>
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</tr>
<tr>
<td>Potter-Baker et al. 2017</td>
<td>12.21</td>
<td>7.99</td>
<td>3</td>
<td>11.28</td>
<td>6.92</td>
<td>3</td>
<td>4.0%</td>
<td>0.10 [-1.50, 1.70]</td>
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</tr>
<tr>
<td>Yozbatiran et al. 2016</td>
<td>0.96</td>
<td>11</td>
<td>4</td>
<td>0.06</td>
<td>0.26</td>
<td>4</td>
<td>5.2%</td>
<td>0.10 [-1.29, 1.49]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td>0.40 [-0.03, 0.83]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 4 (P = 0.47); I² = 0%</td>
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<td></td>
<td>Test for overall effect: Z = 1.83 (P = 0.07)</td>
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</table>

- Lower extremity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NIBS Mean</th>
<th>NIBS SD</th>
<th>NIBS Total</th>
<th>Sham Mean</th>
<th>Sham SD</th>
<th>Sham Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tr>
<td>Benito et al. 2012</td>
<td>4.8</td>
<td>3.36</td>
<td>10</td>
<td>1.3</td>
<td>2.49</td>
<td>10</td>
<td>9.4%</td>
<td>1.13 [0.17, 2.09]</td>
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<tr>
<td>Gharooni et al. 2018</td>
<td>5.2</td>
<td>15.89</td>
<td>10</td>
<td>5.1</td>
<td>13.87</td>
<td>10</td>
<td>10.8%</td>
<td>0.01 [-0.87, 0.88]</td>
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<tr>
<td>Krogh et al. 2022</td>
<td>12.5</td>
<td>14.96</td>
<td>10</td>
<td>-3</td>
<td>12.24</td>
<td>9</td>
<td>9.2%</td>
<td>1.08 [0.10, 2.06]</td>
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<tr>
<td>Kumru et al. 2016(1)</td>
<td>3.4</td>
<td>4.4</td>
<td>12</td>
<td>4.1</td>
<td>3.2</td>
<td>12</td>
<td>12.3%</td>
<td>-0.18 [-0.98, 0.63]</td>
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<tr>
<td>Kumru et al. 2016(2)</td>
<td>8.51</td>
<td>6.34</td>
<td>15</td>
<td>3.55</td>
<td>3.31</td>
<td>16</td>
<td>13.4%</td>
<td>0.96 [0.21, 1.71]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>0.58 [0.02, 1.14]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.21; Chi² = 8.32, df = 4 (P = 0.08); I² = 52%</td>
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<td>Test for overall effect: Z = 2.03 (P = 0.04)</td>
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</table>

- Total (95% CI)

<p>| | | | | | | | | | |</p>
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<td></td>
<td>0.48 [0.14, 0.82]</td>
</tr>
</tbody>
</table>

- Heterogeneity: Tau² = 0.08; Chi² = 12.17, df = 9 (P = 0.20); I² = 26%

Test for overall effect: Z = 2.79 (P = 0.005)

Test for subrouous differences: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%

#### b

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NIBS Mean</th>
<th>NIBS SD</th>
<th>NIBS Total</th>
<th>Sham Mean</th>
<th>Sham SD</th>
<th>Sham Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
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<tbody>
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<tr>
<td>Ratithatha et al. 2016</td>
<td>7</td>
<td>3.6</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>12.0%</td>
<td>0.22 [-1.49, 1.93]</td>
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<tr>
<td>Sinis et al. 2021</td>
<td>27</td>
<td>31.64</td>
<td>20</td>
<td>6.5</td>
<td>25.56</td>
<td>21</td>
<td>88.0%</td>
<td>0.70 [0.07, 1.33]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td>0.64 [0.05, 1.24]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%</td>
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<td></td>
<td>Test for overall effect: Z = 2.12 (P = 0.03)</td>
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</tr>
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</table>
Figure 4

Weighted mean difference (95% CI) of the effect of NIBS compared with sham on (a) upper extremity spasticity by pooling data from 2 trials (UMAS) and lower extremity strength by pooling data from 7 trails (LMAS) in people with SCI; (b) H/M ratio from 3 tails.
Figure 5

Weighted mean difference (95% CI) of the effect of NIBS compared with sham on mobility by pooling data from (a) 3 trials of 6MWT, (b) 2 trails of 10MWT in speed, (c) 2 trails of 10MWT in time-to-complete, (d) 4 trails of TUG.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- **Supplementarymaterial1.docx**
- **Supplementarymaterial2.pdf**