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Non-Invasive Brain Stimulation Improves Paretic Limb Force Production: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Non-invasive brain stimulation (NIBS) facilitates motor improvements post stroke. Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are representative NIBS techniques frequently used in stroke motor rehabilitation. Our primary question is: Do these two techniques improve force production capability in paretic limbs?
Objective: The current systematic review and meta-analysis investigated the effects of tDCS and rTMS on paretic limb force production in stroke survivors.
Methods: Our comprehensive search identified 23 studies that reported changes in force production following tDCS or rTMS interventions. Each used random assignment and a sham control group. The 23 qualified studies in our meta-analysis generated 29 comparisons: 14 tDCS and 15 rTMS comparisons.
Results: Random effects models indicated improvements in paretic limb force after tDCS and rTMS rehabilitation. We found positive effects on force production in the two sets of stimulation protocols: (a) increasing cortical activity in the ipsilesional hemisphere and (b) decreasing cortical activity in the contralesional hemisphere. Moreover, across acute, subacute, and chronic phases, tDCS and rTMS improved force production.
Conclusion: Cumulative meta-analytic results revealed that tDCS and rTMS rehabilitation protocols successfully improved paretic limb force production capabilities.

Introduction

Hemiparesis is a common motor deficit post stroke. The affected side of the upper and lower extremities interferes with both unilateral and bilateral movements [1,2]. Typically, an inability to generate and modulate force production in paretic limbs causes movement control impairments such as compromised motor coordination, excessive movement variability, and motor dysfunctions evaluated by clinical assessments [3–5]. After experiencing a stroke, patients frequently show less magnitude of force production when executing actions on their paretic limb in comparison to their non-paretic limbs [6,7]. This post stroke weakness may be attributed to impaired muscles (e.g., decreased motor unit firing rate and motor unit recruitment) [8,9] or altered brain activation patterns [10].

Conventional rehabilitation protocols (e.g., bimanual movement training, robotic training, or power training) focusing on the recovery of affected muscles reveal evidence of robust force production improvements [1,11–15]. These rehabilitation protocols facilitate improved muscle properties and motor control [16,17]. Moreover, Harris and colleagues reported that increased paretic limb strength was significantly correlated with improvements in activities of daily living [18]. In line with these findings, stroke researchers continue to search for optimal rehabilitation protocols that effectively improve impaired muscle strength contributing to motor recovery in stroke survivors.

A highly popular avenue of stroke motor rehabilitation focuses on non-invasive brain stimulation (NIBS) techniques. Two common NIBS techniques used as stroke rehabilitation protocols are: (a) tDCS (transcranial direct current stimulation) and (b) rTMS (repetitive transcranial magnetic stimulation). Potential mechanisms underlying these NIBS techniques indicate that tDCS or rTMS may modulate cortical excitability in specific areas of the brain by delivering low electrical current to the scalp, and this altered functional activity

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in targeted regions appears to contribute to motor rehabilitation [19]. For stroke patients, the interhemispheric competition model assumes that the ipsilesional hemisphere may be double-disabled because of ipsilateral damage and/or greater interhemispheric inhibition from the contralesional hemisphere. Moreover, balancing asymmetrical brain activation between M1 (i.e., primary motor cortex) of the two hemispheres contributes to restoring motor functions in paretic limbs [20,21]. Despite the debate surrounding the interhemispheric competition model (e.g., inter-individual variability issue) [22,23], many rehabilitation protocols using tDCS or rTMS are prevalent: (a) anodal tDCS or high frequency rTMS (>1 Hz) on M1 of the ipsilesional hemisphere for increasing cortical excitability, (b) cathodal tDCS or low frequency rTMS (≤1 Hz) on M1 of the contralesional hemisphere for decreasing cortical excitability, and (c) bilateral tDCS (anodal tDCS + cathodal tDCS) or rTMS (high frequency rTMS + low frequency rTMS) on M1 of both hemispheres [19,20,24].

Previous meta-analysis studies reported that balanced cortical activity between M1 of the hemispheres following tDCS or rTMS protocols may contribute to motor improvements in paretic limbs (e.g., various clinical assessments or activities of daily living) [25–28]. However, Chhatbar and Feng pointed out that these meta-analytic findings are still susceptible to inconsistency in outcome measures as well as selection criteria [29]. Consequently, the methodological heterogeneity across individual studies may result in overestimated or underestimated standardized effect sizes [23,30,31]. To overcome and minimize these heterogeneity issues in previous meta-analysis studies, we conducted a systematic review and comprehensive meta-analysis by investigating the effects of NIBS on common outcome measures, paretic limb force production in stroke patients. Further, our meta-analysis only included studies that used random assignment and a sham control group – two methodological techniques that increased the quality of our meta-analysis [31,32]. Indeed, integrative findings from tDCS and rTMS interventions would vastly increase our understanding of the NIBS effects on stroke motor recovery and potential recovery mechanisms by including a higher number of qualified comparisons while decreasing publication bias [31].

Thus, the current systematic review and meta-analysis addressed three leading questions: (a) Do tDCS and rTMS interventions improve paretic limb forces in stroke survivors? (b) Do paretic limb forces post stroke increase after one of three sets of stimulation protocols: anodal tDCS or high frequency (>1 Hz) rTMS on the ipsilesional hemisphere; cathodal tDCS stimulation or low frequency (≤1 Hz) rTMS on the contralesional hemisphere; or bilateral stimulation? and (c) Do tDCS and rTMS protocols assist in recovering paretic limb forces at each post stroke stage: acute, subacute, or chronic?

Materials and methods

Literature search and study selection

Based on suggestions of The PRISMA statement [33], we performed a systematic review and meta-analysis. The computerized literature searches focused on stroke studies that reported the effect of tDCS or rTMS on force produced by paretic limbs (literature search period: June 2015–February 2016). We did not limit the type of publications considered. Our comprehensive search included refereed studies, conference proceedings, and negative result studies. We systematically searched studies using three data bases: (a) PubMed, (b) ISI's Web of Knowledge, and (c) Cochrane Database of Systematic Reviews. Seven keywords included: (a) stroke, (b) cerebrovascular accident, (c) brain infarct, (d) transcranial direct current stimulation (tDCS), (e) repetitive transcranial magnetic stimulation (rTMS), (f) strength, and (g) force.

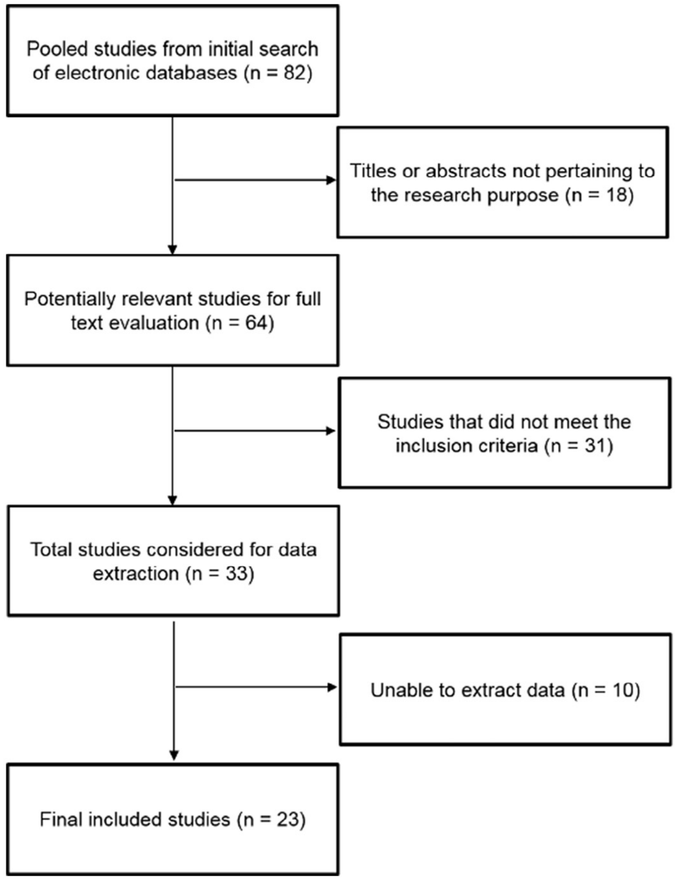

Figure 1. Flow chart for study selection.

Fig. 1 displays the selection algorithm and numbers of included and excluded studies. All titles, abstracts, and text were dually and independently reviewed by the authors based on the inclusion and exclusion criteria to minimize bias. Inclusion criteria for this meta-analysis included: (a) quantitative evaluation of tDCS or rTMS effects on paretic limb forces, (b) a between-group comparison: active tDCS (i.e., anodal, cathodal, and bilateral) or rTMS (i.e., low frequency: ≤ 1 Hz, high frequency: > 1 Hz, and bilateral) stimulation versus sham control stimulation, and (c) a within-group comparison: pretest versus posttest. We excluded studies that failed to report both random assignment and a sham control group. Based on these criteria, 82 potential publications were initially identified. Substantially reviewing these articles revealed 59 studies for exclusion: (a) 18 review articles, (b) 21 studies without force production outcome measures, (c) three case studies, (d) 10 studies that failed to report statistical information, (e) one bimanual force production study, and (f) six no sham control studies. The remaining 23 studies qualified for the meta-analysis [34–56].

The 23 qualified studies involved 11 tDCS studies and 12 rTMS studies. For the 11 tDCS studies, eight reported one comparison out of three tDCS protocols (i.e., anodal, cathodal, or bilateral stimulation; $8 \times 1 = 8$ comparisons), whereas three studies reported both anodal and cathodal stimulation comparisons ($3 \times 2 = 6$ comparisons). Thus, 14 comparisons in the tDCS studies were included in our meta-analyses: (a) anodal stimulation on M1 of ipsilesional hemisphere: nine comparisons, (b) cathodal stimulation on M1 of contralesional hemisphere: three comparisons, and (c) bilateral (anodal + cathodal) stimulation: two comparisons.

The 12 rTMS studies involved nine studies that reported one comparison out of two rTMS protocols (i.e., low or high frequency;