Non-Invasive Brain Stimulation Improves Paretic Limb Force Production:

A Systematic Review and Meta-Analysis

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Abstract

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.

Keywords: Meta-analysis; systematic review; transcranial direct current stimulation (tDCS); repetitive transcranial magnetic stimulation (rTMS); stroke; force production

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 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 and our comprehensive search considered 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 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 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].

Insert Figure 1 about here

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; $9 \times 1 = 9$ comparisons) whereas three studies

revealed two comparisons (i.e., low and high frequency: two studies; two high frequency: one study; $3 \times 2 = 6$ comparisons). Thus, the 15 total comparisons in the rTMS studies included: (a) high frequency rTMS on M1 of ipsilesional hemisphere: six comparisons and (b) low frequency rTMS on M1 of contralesional hemisphere: nine comparisons. Overall, our meta-analysis analyzed 29 total comparisons out of the 23 qualified tDCS and rTMS studies.

Motor Outcome Measures

The primary outcome measures for estimating force production in paretic limbs included: (a) pinch force: seven comparisons, (b) grip force: 19 comparisons, (c) elbow flexion torque: one comparison, and (d) knee extension torque: two comparisons.

Meta-analytic techniques

We used the Comprehensive Meta-Analysis software (version 3.0; Englewood, NJ, USA) to calculate and determine meta-analytic findings. We calculated individual effect sizes based on either (a) force differences between the active stimulation and sham control groups at posttest or (b) force change in the active stimulation group from pretest to posttest. In both cases, we confirmed: (a) no significant force difference between active stimulation and sham control groups at pretest and (b) no significant force improvement in the sham control groups from pretest to posttest. Tables 1 and 2 summarize the stroke participants' information as well as tDCS and rTMS intervention parameters. Table 3 displays statistical summary data including force outcome measures, individual weighted effect sizes, confidence intervals, standardized effect size, Q statistic, I^2, T^2, and Egger's regression intercept. In addition, for methodological quality assessment we determined PEDro scores for each study [57].

Insert Tables 1 and 2 about here

Concerning the model selected for analyses, Borenstein and colleagues suggested that a fixed effect meta-analysis assumes that all studies included in the analysis are identical and have a common effect size [31]. In contrast, a random effects meta-analysis posits that effect sizes differ as a function of some causes (e.g., participants or rehabilitation protocols) and no common effect size appears across studies. Indeed, when we include studies from the published literature, the random effects model is more appropriate than the fixed effect model because (a) each study's weight is more balanced and (b) the wider standard error and confidence level of the summary effect. Thus, consistent with these conventional recommendations by a distinguished group of meta-analytic experts [31, 32], we conducted random effects meta-analyses.

Measuring Heterogeneity and Publication Bias

Quantifying heterogeneity between comparisons involved three metrics: (a) Cochran's Q, (b) T^2 (estimate of tau-squared), and (c) Higgins and Green's I^2 [58, 59]. Cochran's Q is a statistical test showing the extent of heterogeneity based on a p-value. Given that the null hypothesis is that the treatments are equally effective, a p-value less than 0.05 indicates heterogeneity between studies. The second heterogeneity test, T^2, is an estimate of variance of the observed effects with weights assigned in a random effects model [31]. A T^2 value greater than 1.0 indicates substantial heterogeneity with greater variance between studies. Finally, I^2 quantifies the percentage of the heterogeneity in the outcome measures used in the meta-analysis. An I^2 value of greater than 50% indicates substantial heterogeneity and findings should be interpreted cautiously.

Further, traditional procedures for estimating publication bias include funnel plots and Egger's regression test [31, 59-63]. Based on three conventional steps, we estimated publication bias by (a) a funnel plot displaying standardized mean differences versus standard error for each

comparison (i.e., symmetry of studies), (b) a corrected funnel plot with imputed values after applying the trim and fill technique (i.e., comparing an original standardized effect size with corrected standardized effect size), and (c) Egger's regression test identifying the relationship between actual effect sizes and standard error values (i.e., precision). A significant intercept (β_0) indicates high publication bias.

<div align="center">

Results

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Standardized Mean Difference Effect

A random effects model meta-analysis on the 29 comparisons revealed a significant overall standardized mean difference effect (effect size: $ES = 0.55$; $SE = 0.07$; 95% CI = 0.41 − 0.69; $p < 0.0001$; $Z = 7.84$). This cumulative effect size value indicates a medium positive effect [31, 64]. Table 3 shows the 40 individual weighted effects for each comparison. Details for calculating an individual effect size are shown in the Supplementary Data Table 2. The effect sizes ranged from -0.57 to 1.51 (Fig. 2). Given that two comparisons were greater than two standard deviations beyond the standardized mean effect size [49, 53], we conducted an initial subsequent analysis after removing the two outliers. This analysis revealed that the standardized effect was still nearly the same medium value ($ES = 0.545$; $SE = 0.072$; 95% CI = 0.405 − 0.685; $p < 0.0001$; $Z = 7.61$) as the original analysis. These findings indicate that the tDCS or rTMS protocols improved paretic limb force production post stroke.

Insert Table 3 and Figure 2 about here

Heterogeneity and Publication Bias

Variability calculations on the 29 comparisons showed low heterogeneity (Q statistic = 27.91, $p = 0.47$; $T^2 = 0.00$; $I^2 = 0.00\%$; see Table 3). An original funnel plot includes a slightly asymmetrical distribution of the effect sizes (white circles) over the comparison studies.

Moreover, imputing only two values (black circles) on the lower, left side of the original funnel plot created a symmetrical distribution [61]. As shown in Figure 3, the trim and fill technique revealed a relatively identical standardized effect size (black diamond) in comparison to the original effect size (white diamond). Further, Egger's regression analysis failed to identify a significant intercept (β_0 = -0.01; p = 0.99) indicating no relationship between the actual effect sizes and standard error (precision). Thus, we are confident in stating that there was minimal publication bias in our 29 comparisons.

Insert Figure 3 about here

Methodological Quality

As shown in the Supplementary Data Table 1, each of the 23 studies included in our meta-analysis used random assignment (18 parallel group design studies and five cross-over designs studies) and a sham control group. The PEDro scores ranged from 5 to 11 (mean = 8.3 and SD = 1.7). A higher score indicates better methodological quality in the study. The calculated mean of PEDro score revealed good overall quality across 23 studies included in this meta-analysis.

Moderator Variable Analyses

tDCS versus rTMS

The first moderator variable analysis determined the contribution of the tDCS and rTMS protocols to paretic limb force production post stroke. This subgroup analysis revealed two significant standardized effect sizes: (a) 14 tDCS comparisons: ES = 0.44; SE = 0.10; 95% CI = 0.25 – 0.64; p < 0.0001; Z = 4.48; T^2 = 0.00; I^2 = 0.00% and (b) 15 rTMS comparisons: ES = 0.66; SE = 0.10; 95% CI = 0.45 – 0.86; p < 0.0001; Z = 6.35; T^2 = 0.01; I^2 = 6.47%. These

findings indicate that both tDCS and rTMS protocols facilitated force production capabilities post stroke.

Stimulation Protocols

A second moderator variable analysis compared the effect of three sets of stimulation protocols on force production capabilities post stroke: (a) anodal tDCS stimulation or high frequency rTMS on M1 of ipsilesional hemisphere (increasing brain activation), (b) cathodal tDCS stimulation or low frequency rTMS on M1 of contralesional hemisphere (decreasing brain activation), and (c) bilateral (anodal + cathodal) tDCS or bilateral (low: $\leq$ 1 Hz + high: > 1 Hz frequency) rTMS. Fifteen comparisons that used stimulation on the ipsilesional hemisphere revealed a significant standardized $ES = 0.57$ ($SE = 0.09$; 95% CI = 0.38 − 0.75; $p < 0.0001$; Z = 6.01; $I^2 = 0.00\%$; $T^2 = 0.00$). Twelve comparisons that used stimulation on the contralesional hemisphere showed a significant standardized $ES = 0.58$ ($SE = 0.15$; 95% CI = 0.29 − 0.87; $p < 0.0001$; Z = 3.94; $T^2 = 0.11$; $I^2 = 41.85\%$). Given only two comparisons in our meta-analysis used stimulations on bilateral hemispheres, we did not calculate a bilateral stimulation effect size. Together, the tDCS or rTMS protocols on ipsilesional and contralesional hemispheres improved force production in stroke survivors.

Recovery Stages

A third moderator variable analysis focused on the three post stroke recovery stages: acute (< 1 month), subacute (1 month - 6 month), and chronic (> 6 month). This classification is based on conventional and traditional recovery stages [65]. The analysis revealed significant standardized effect sizes for each recovery stage: (a) nine acute comparisons ($ES = 0.69$; $SE = 0.14$; 95% CI = 0.43 − 0.96; $p < 0.0001$; Z = 5.11; $T^2 = 0.00$; $I^2 = 0.00\%$), (b) seven subacute comparisons ($ES = 0.62$; $SE = 0.13$; 95% CI = 0.36 − 0.87; $p < 0.0001$; Z = 4.72; $T^2 = 0.00$; $I^2 = $

0.00%), and (c) 13 chronic comparisons (ES = 0.43; SE = 0.13; 95% CI = 0.18 – 0.68; p = 0.001; Z = 3.40; T^2 = 0.05; I^2 = 26.94%). Positive effects of tDCS or rTMS protocols on force production capabilities on the paretic limb appeared in each of three post stroke recovery stages.

Addressing Potential Confounds: Motor Training, Session Number, and Effect Size

Calculation

We addressed three additional issues that may influence the rehabilitative effects of the two selected NIBS techniques: (a) NIBS combined with motor training (NIBS only versus NIBS with motor training), (b) number of stimulation sessions (single session versus multiple sessions), and (c) method used in calculating individual effect sizes (between-group difference at posttest versus within-group difference from pretest to posttest). Both NIBS only and NIBS combined with motor training conditions revealed significant standardized effect sizes: (a) four NIBS only comparisons (ES = 0.45; SE = 0.18; 95% CI = 0.09 – 0.81; p = 0.014; Z = 2.46; T^2 = 0.05; I^2 = 29.81%) and (b) 24 NIBS combined with motor training (ES = 0.58; SE = 0.08; 95% CI = 0.43 – 0.74; p < 0.0001; Z = 7.36; T^2 = 0.00; I^2 = 0.00%). Nine single session comparisons revealed a significant standardized ES = 0.53 (SE = 0.14; 95% CI = 0.26 – 0.79; p < 0.0001; Z = 3.91; I^2 = 26.00%; T^2 = 0.04). Twenty multi-session comparisons showed a significant standardized ES = 0.57 (SE = 0.09; 95% CI = 0.40 – 0.75; p < 0.0001; Z = 6.46; T^2 = 0.00; I^2 = 0.00%). Moreover, 21 comparisons that reported between-group differences at the posttest revealed a significant standardized ES = 0.55 (SE = 0.09; 95% CI = 0.38 – 0.73; p < 0.0001; Z = 6.18; I^2 = 0.00%; T^2 = 0.00). Eight comparisons that reported within-group differences from pretest to posttest showed a significant standardized ES = 0.56 (SE = 0.13; 95% CI = 0.30 – 0.82; p < 0.0001; Z = 4.17; T^2 = 0.04; I^2 = 26.74%). The effect of NIBS techniques on paretic limb

force was comparable under additional motor training conditions, different number of

stimulation session, and method in calculating individual effect size.

Discussion

The current meta-analysis investigated the effects of two NIBS techniques (i.e., tDCS and

rTMS) on a common motor outcome measure, paretic limb force production in stroke survivors.

All 23 studies included in our meta-analysis used random assignment and a sham control group.

Twenty-nine total comparisons from 23 studies confirmed that both NIBS techniques improved

force production capabilities in stroke survivors. Moderator variable analyses focused on tDCS

versus rTMS comparisons, two sets of stimulation protocols (i.e., increasing cortical excitability

in the ipsilesional hemisphere or decreasing cortical excitability in the contralesional

hemisphere), and three post stroke recovery stages (i.e., acute, subacute, and chronic). Each of

the moderator variable analyses revealed positive effects of tDCS or rTMS protocols on paretic

limb force.

Importantly, treatment effects of two NIBS techniques (i.e., tDCS or rTMS) administered

to 530 stroke individuals revealed positive effects on paretic limb force production as indicated

by a significant medium standardized effect size (0.55). In addition, a moderator variable

analysis on tDCS versus rTMS supported a conclusion that both tDCS (*ES* = 0.44) and rTMS (*ES*

= 0.66) improved capabilities to generate force. Restoring paretic limb force during rehabilitation

is crucial for executing successful movements and improving activities of daily living post stroke

[1, 18, 66]. Given that all 29 comparisons are related to the magnitude of force production (i.e.,

muscle strength), improvements in force production as shown by the current robust meta-

analysis indicate increased muscle strength in the paretic limbs. Thus, cumulative findings

indicate that tDCS and rTMS interventions may facilitate motor rehabilitation including recovery of muscle strength in the paretic limbs.

Two sets of stimulation protocols across tDCS and rTMS revealed positive significant effect sizes. Increasing cortical excitability in the ipsilesional hemisphere (via anodal tDCS and high frequency rTMS) and decreasing cortical excitability in the contralesional hemisphere (via cathodal tDCS and low frequency rTMS) improved paretic limb force production. These findings are interpreted as support for an assumption of the interhemispheric competition theory for stroke motor recovery [20, 21]. That is, balanced cortical activities between hemispheres after NIBS techniques may contribute to motor improvements (e.g., force production capabilities) [67]. Further, these meta-analytic findings were consistent with previous systematic reviews and meta-analyses that reported benefits of the NIBS techniques on stroke motor function assessed by various clinical assessments [25, 26, 28]. Thus, the present findings extended the positive effects of NIBS techniques on stroke motor recovery as indicated by quantifying a common outcome measure, paretic limb force production.

Benefits of the two NIBS techniques on paretic limb force production appeared in each of the three post stroke recovery stages: acute, subacute, and chronic. Although several previous systematic reviews and meta-analyses reported positive effects of NIBS techniques on motor functions for the chronic stage post stroke [27, 68], our findings indicate that tDCS and/or rTMS improved muscle strength in paretic limbs in each of the three recovery stages. One possible interpretation of these findings indicates that the positive effect of NIBS techniques on stroke motor rehabilitation may occur for individuals at the two initial recovery phases (i.e., acute and subacute) post stroke as well as the chronic stage. Stinear and Byblow argued that progress toward motor recovery may be advanced when patients received rehabilitation protocols within

six months post a stroke, during the spontaneous recovery period [69]. Specifically, the effects of

neuromodulation interventions on neural plasticity and reorganization of brain activation

between hemispheres may increase during the spontaneous recovery period in comparison to the

chronic stage [69, 70]. Thus, further studies investigating the different effects of NIBS

techniques based on post stroke recovery stages will be necessary.

Moreover, focusing on force production as a common motor function outcome measure

minimized the level of heterogeneity in the current meta-analysis (Q statistic = 27.91 and p =

0.47; $T^2 = 0.00$; $I^2 = 0.00\%$). Higgins and Green reported that statistical heterogeneity (i.e.,

variability of effect sizes across divergent studies) increases because of diversity in clinical

interventions or methodologies in single studies [59]. That is, comparing findings from different

outcome measures may cause an underestimating or overestimating of treatment effects in a

meta-analysis [23]. However, despite the small amount of heterogeneity across our qualified

studies, the random effects model further minimized the statistical heterogeneity issues

surrounding standardized effect sizes [31]. Together, our random effects model meta-analyses on

paretic limb force production effectively support the conclusion that tDCS or rTMS techniques

shows positive effects on stroke motor rehabilitation while minimizing heterogeneity.

Two limitations are noted. First, the current meta-analysis included either flexor strength

in the upper limbs or extensors strength in the lower limbs that may have different level of

spasticity: more spasticity typically appears in flexors than extensors [71]. Second, given that the

only two lower limb studies were included in this meta-analysis, the positive effects of NIBS

techniques on lower limb strength should be treated with caution.

Although we showed clinically positive effects of tDCS and rTMS on paretic limb force,

high inter-individual variability in response to NIBS techniques has been observed [23]. To

minimize inter-individual variability, developing individualized stimulation intensities is necessary. Priori, Hallett, and Rothwell reported that individualized intensities of tDCS and rTMS may contribute to increasing rehabilitation effects [72]. Indeed, Miranda, Lomarev, and Hallett argued that constant stimulation intensities across individuals who have diverse anatomical brain structures (e.g., scalp and/or skull thickness) may cause different current flows to the brain [73]. A consequence is an increasing inter-individual variabilty and potentially adverse effects (e.g., painful stimulation). However, individualized intensities based on a spherical model of the head (e.g., modeling by scalp and skull thickness) can provide relatively equivalent current flow to each individual, and contribute to minimizing inter-individual variability and painful stimulation [73].

Moreover, increasing interconnectivity between brain regions may be considered to optimize the efficacy of both NIBS techniques. tDCS and rTMS administered on M1 are known to facilitate local changes in M1 as well as distant changes in interconnected brain regions (i.e., premotor cortex and supplementary motor area) [22]. Given that an increased interconnectivity between M1 and other brain regions improved paretic limb functions [74], one promising stroke motor rehabilitation approach would be investigating the effects of anodal tDCS or high frequency rTMS stimulation on multiple motor areas (i.e., M1, premotor cortex, and supplementary motor area) within the ipsilesional hemisphere.

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Competing Interest

None

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Figure Captions

Figure 1. Flow chart for study selection

Figure 2. Meta-analysis forest plot of the effects of tDCS and rTMS on paretic limb force.
Data derived from a random effects model. Each line and tick mark represents an individual effect size (alphabetical order same as Table 3). The red diamond indicates a standardized effect size (0.55). Circles indicate tDCS, squares denote rTMS, and colors indicates phase of recovery (white: acute, blue: subacute, and black: chronic).

Figure 3. Funnel plots of the comparisons for random effects model. The x-axis indicates the standardized difference in means and the y-axis shows the standard error associated with each comparison. The white diamond on the x-axis indicates a standardized effect size with our original 29 comparisons and the black diamond indicates a revised standardized effect size after the trim and fill technique.

Table 1. Participant characteristics

Study	Total N	Mean Age	Gender	TSO (month)	Stroke Type	Affected Hemisphere	Pre-treatment impairment Level	Recovery Stage
Au-Yeung 2014 [34]	10	62.6	10 M	99.6	8 I, 2 H	5 L, 5 R	UE-FMA = 58.3 / 66	Chronic
Avenanti 2012 [44]	30	63.2	14 F, 16 M	31.5	20 I, 10 H	14 L, 16 R	MRC = 72-76 / 100	Chronic
Bolognini 2011 [56]	14	46.7	9 F, 5 M	35.2	12 I, 2 H	8 L, 6 R	UE-FMA = 26.0 / 66	Chronic
Cha 2014 [35]	20	58.8	NR	14.2	NR	11 L, 9 R	UE-FMA = 21.6 / 66	Chronic
Cha 2015 [55]	30	63.7	14 F, 16 M	4.0	18 I, 12 H	NR	NR	Subacute
Chang 2010 [45]	28	56.6	11 F, 17 M	1.0	28 I	15 L, 13 R	UE-FMA = 26.2 / 66	Subacute
Conforto 2012 [46]	30	55.8	12 F, 18 M	1.0	30 I	15 L, 15 R	NIHSS = 5.0 / 42	Subacute
Di Lazzaro 2014 [38]	20	64.8	7 F, 13 M	0.1	20 I	12 L, 8 R	NIHSS = 5.9 / 42	Acute
Hummel 2006 [36]	11	57.0	5 F, 6 M	41.8	11 I	NR	ASS = 1.1 / 4	Chronic
Khedr 2009 [47]	36	57.9	17 F, 19 M	0.6	36 I	13 L, 23 R	NIHSS = 13.4 / 42	Acute
Khedr 2009 [48]	26	57.3	16 F, 10 M	0.5	NR	12 L , 14 R	BI = 25.2 / 100	Acute
Khedr 2010 [54]	48	59.5	24 F, 24 M	0.2	48 I	27 L, 21 R	NIHSS = 9.6 / 42	Acute
Khedr 2013 [37]	40	58.3	14 F, 26 M	1.0	40 I	18 L, 22 R	NIHSS = 10.7 / 42	Subacute
Pomeroy 2007 [49]	27	74.8	18 F, 9 M	1.0	27 I	14 L, 13 R	ARAT = 17.5 / 57	Subacute
Rose 2014 [50]	19	64.6	6 F, 13 M	61.7	NR	10 L, 9 R	UE-FMA = 39.2 / 66	Chronic
Sasaki 2013 [51]	29	65.0	9 F, 20 M	0.6	13 I, 16 H	16 L, 13 R	NIHSS = 6.3 / 42	Acute
Sattler 2015 [39]	20	65.2	6 F, 14 M	0.2	20 I	NR	UE-FMA = 48.0 / 66	Acute
Sohn 2013 [40]	11	58.5	2 F, 9 M	2.1	4 I, 7 H	5 L, 6 R	NR	Subacute
Stagg 2012 [41]	13	66.4	3 F, 10 M	40.2	12 I, 1 H	9 L, 4 R	UE-FMA = 43.2 / 66	Chronic

Takeuchi 2005 [52]	20	59.0	5 F, 15 M	27.0	20 I	8 L, 12 R	UE-FMA = 61.8 / 66	Chronic
Takeuchi 2008 [53]	20	62.3	4 F, 16 M	29.9	20 I	7 L, 13 R	UE-FMA = 44.6 / 66	Chronic
Tanaka 2011 [42]	8	59.6	4 F, 4 M	21.1	NR	3 L, 5 R	SIAS (Knee) = 3.8 / 5	Chronic
Viana 2014 [43]	20	55.5	4 F, 16 M	33.5	19 I, 1 H	8 L, 12 R	UE-FMA = 40.3 / 66	Chronic
Total	$N = 530$	$M = 60.6$		$M = 19.5$				
		$SD = 5.4$		$SD = 25.2$				

Abbreviations. ASS: Ashworth Spasticity Score; ARAT: Action Research Arm Test; BI: Barthel Index; F: female; H: hemorrhagic; I: ischemic; L: left; M: male; MRC: Motricity index; NIHSS: National Institutes of Health Stroke Scale; NR: not reported; R: right; SIAS: Stroke Impairment Assessment Set; TSO: Time since Stroke Onset (interval between stroke onset and treatment initiation); UE-FMA: upper extremity Fugl-Meyer assessment

Table 2. Stimulation protocols

Study	Limb	Treatment	Session	Active Stim.	Site	Parameter Setup
Au-Yeung 2014 [34]	UE	tDCS only	1	atDCS, ctDCS	M1^{hand}	1 mA, 35 cm^2, 20 min
Avenanti 2012 [44]	UE	rTMS before PT	10	L-rTMS (1 Hz)	M1^{hand}	90% RMT, 1500 pulses, 25 min
Bolognini 2011 [56]	UE	tDCS during CIMT	10	Bi tDCS	M1^{hand}	2 mA, 35 cm^2, 40 min
Cha 2014 [35]	UE	tDCS after MT	20	atDCS	M1^{hand}	1 mA, 35 cm^2 , 20 min
Cha 2015 [55]	UE	rTMS before MT	20	L-rTMS (1Hz)	M1^{hand}	90% RMT, 1200 pulses, 10 min
Chang 2010 [45]	UE	rTMS before MT	10	H-rTMS (10 Hz)	M1^{hand}	90% RMT, 20 pulses×50 trains, ITI=55 s
Conforto 2012 [46]	UE	rTMS before MT	10	L-rTMS (1 Hz)	M1^{hand}	90% RMT, 1500 pulses, 25 min
Di Lazzaro 2014 [38]	UE	tDCS during CIMT	5	Bi tDCS	M1^{hand}	2 mA, 35 cm^2, 40 min
Hummel 2006 [36]	UE	tDCS only	1	atDCS	M1^{hand}	1 mA, 25 cm^2, 20 min
Khedr 2009 [47]	UE	rTMS^{NR} and MT	5	L-rTMS (1 Hz)	M1^{hand}	100%RMT, 900 pulses, 15 min
				H-rTMS (3 Hz)	M1^{hand}	130%RMT, 30 pulses×30 trains, ITI=2 s
Khedr 2009 [48]	UE	rTMS^{NR} and MT	5	H-rTMS (3 Hz)	M1^{hand}	120%RMT, 300 pulses
Khedr 2010 [54]	UE	rTMS^{NR} and MT	5	H-rTMS (3 Hz)	M1^{hand}	130%RMT, 750 pulses
				H-rTMS (10 Hz)	M1^{hand}	100%RMT, 750 pulses
Khedr 2013 [37]	UE	tDCS before MT	6	atDCS, ctDCS	M1^{hand}	2 mA, 35 cm^2, 25 min
Pomeroy 2007 [49]	UE	VMC / rTMS before MT	8	L-rTMS (1 Hz)	M1^{hand}	120%RMT, 200 pulses
Rose 2014 [50]	UE	rTMS after MT	16	L-rTMS (1 Hz)	M1^{hand}	100%RMT, 1200 pulses
Sasaki 2013 [51]	UE	rTMS^{NR} and MT	5	L-rTMS (1 Hz)	M1^{hand}	90% RMT, 1800 pulses, 30 min

				H-rTMS (10 Hz)	M1 [hand]	90% RMT, 1000 pulses, ITI=50 s
Sattler 2015 [39]	UE	tDCS + rPNS before OT	5	atDCS	M1 [hand]	1.2 mA, 35 cm^2, 13 min
Sohn 2013 [40]	LE	tDCS only	1	atDCS	M1 [leg]	2 mA, 25 cm^2, 10 min
Stagg 2012 [41]	UE	tDCS[NR] and RT	1	atDCS, ctDCS	M1 [hand]	1 mA, 35 cm^2, 20 min
Takeuchi 2005 [52]	UE	rTMS after force practice	1	L-rTMS (1 Hz)	M1 [hand]	90% RMT, 1500 pulses, 25 min
Takeuchi 2008 [53]	UE	rTMS before MT	1	L-rTMS (1 Hz)	M1 [hand]	90% RMT, 1500 pulses, 25 min
Tanaka 2011 [42]	LE	tDCS only	1	atDCS	M1 [leg]	2 mA, 35 cm^2, 10 min
Viana 2014 [43]	UE	tDCS during VRT	15	atDCS	M1 [hand]	2 mA, 35 cm^2, 13 min

Abbreviations. atDCS: anodal transcranial direct current stimulation; Bi: bilateral (anodal + cathodal); ctDCS: cathodal transcranial direct current stimulation; CIMT: constraint-induced movement therapy; H-rTMS: high frequency of repetitive transcranial magnetic stimulation; ITI: intertrain interval; LE: lower extremity; L-rTMS: low frequency of repetitive transcranial magnetic stimulation; M1: primary motor cortex; MT: motor training; NR: timing of stimulation was not reported; OT: occupational therapy; PT: physical therapy; RMT: resting motor threshold; rPNS: repetitive peripheral nerve stimulation; tDCS: transcranial direct current stimulation; RT: response time task; UE: upper extremity; VMC: voluntary muscle contraction; VRT: virtual reality therapy

Note. stimulation site: anodal tDCS or high frequency rTMS on ipsilesional hemisphere; cathodal tDCS or low frequency rTMS on contralesional hemisphere; bilateral tDCS (anodal + cathodal)

Table 3. Meta-analysis force production capabilities results

Study	Outcome Measure	Ctrl / Rx (N)	SMD	95% CI		Relative Weight
Au-Yeung 2014 [34]	Pinch force[*] (pre vs. post-atDCS)	10	0.32	-0.34	0.93	4.7
	Pinch force[*] (pre vs. post-ctDCS)	10	0.32	-0.64	0.60	4.9
Avenanti 2012 [44]	Tip-pinch force[*] (sham vs. L-rTMS at post)	14 / 8	0.47	0.15	2.00	2.2
Bolognini 2011 [56]	Grip force[*] (sham vs. bi tDCS at post)	7 / 7	0.54	-1.23	0.87	1.7
Cha 2014 [35]	Grip force[*] (sham vs. atDCS at post)	10 / 10	0.45	-0.61	1.15	2.4
Cha 2015 [55]	Grip force[*] (sham vs. L-rTMS at post)	15 / 15	0.37	-0.12	1.35	3.5
Chang 2010 [45]	Grip force[NR] (pre vs. post-H-rTMS)	18	0.25	0.01	0.99	7.9
Conforto 2012 [46]	Pinch force[*] (pre vs. post-L-rTMS)	15	0.30	0.22	1.38	5.6
Di Lazzaro 2014 [38]	Grip force[NR] (sham vs. bi tDCS at post)	10 / 10	0.45	-0.68	1.08	2.5
Hummel 2006 [36]	Pinch force[*] (pre vs. post-atDCS)	11	0.32	-0.18	1.05	5.0
Khedr 2009 [47]	Grip force[#] (sham vs. H-rTMS at post)	12 / 12	0.42	-0.19	1.44	2.8
	Grip force[#] (sham vs. L-rTMS at post)	12 / 12	0.44	0.32	2.06	2.5
Khedr 2009 [48]	Grip force[#] (sham vs. H-rTMS at post)	12 / 14	0.40	-0.18	1.39	3.0
Khedr 2010 [54]	Grip force[&] (sham vs. 3 Hz H-rTMS at post)	13 / 12	0.42	0.08	1.72	2.8
	Grip force[&] (sham vs. 10 Hz H-rTMS at post)	13 / 13	0.40	-0.12	1.46	3.0
Khedr 2013 [37]	Grip force[#] (sham vs. atDCS at post)	13 / 14	0.40	0.03	1.60	3.1
	Grip force[#] (sham vs. ctDCS at post)	13 / 13	0.41	0.10	1.72	2.9
Pomeroy 2007 [49]	Elbow flexion torque[*] (sham + VMC vs. L-rTMS + VMC)	7 / 6	0.57	-1.68	0.54	1.5
Rose 2014 [50]	Grip force[*] (sham vs. L-rTMS at post)	10 / 9	0.46	-1.05	0.76	2.3

Study	Measure	N				
Sasaki 2013 [51]	Grip force* (pre vs. post-L-rTMS)	11	0.33	0.02	1.33	4.4
	Grip force* (pre vs. post-H-rTMS)	9	0.38	0.03	1.51	3.4
Sattler 2015 [39]	Grip force* (sham + rPNS vs. atDCS + rPNS at post)	10 / 10	0.46	-0.31	1.48	2.4
Sohn 2013 [40]	Knee extension torque* (sham vs. atDCS at post)	11 / 11	0.33	0.02	1.33	4.4
Stagg 2012 [41]	Grip force* (sham vs. atDCS at post)	13 / 13	0.29	-0.08	1.07	5.7
	Grip force* (sham vs. ctDCS at post)	13 / 13	0.29	-0.08	1.07	5.7
Takeuchi 2005 [52]	Pinch force+ (sham vs. L-rTMS at post)	10 / 10	0.45	-0.55	1.21	2.4
Takeuchi 2008 [53]	Pinch force+ (pre vs. post-L-rTMS)	10	0.46	0.60	2.42	2.3
Tanaka 2011 [42]	Knee extension torque* (sham vs. atDCS at post)	8 / 8	0.47	0.32	2.16	2.2
Viana 2014 [43]	Grip force* (sham vs. atDCS at post)	10 / 10	0.45	-0.85	0.90	2.5

Model	Standardized Effect Size	SE	95% CI	Q statistic	T^2	I^2	Egger's regression (β_0)
Random	0.55	0.07	0.41 – 0.69	27.91 ($p = 0.47$)	0.00	0.00	-0.01 ($p = 0.99$)

Abbreviations. atDCS: anodal transcranial direct current stimulation; bi: bilateral (anodal + cathodal or high + low frequency); CI: confidence interval; ctDCS: cathodal transcranial direct current stimulation; H-rTMS: high frequency of repetitive transcranial magnetic stimulation; L-rTMS: low frequency of repetitive transcranial magnetic stimulation; rPNS: repetitive peripheral nerve stimulation; SE: standard error; VMC: voluntary muscle contraction

Note. force measurement: *dynamometer; +load cell; #Medical Research Council Scale; &Hemispheric Stroke Scale; and NRnot reported