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Effect of non-invasive brain stimulation on lower limb function in patients after stroke: A PRISMA-compliant systematic review and meta-analysis

[1]Xueyi Ni, [2]Liru Cui, [3]Ruixia Bi, [1]Jinghua Qian

[1]School of sports medicine and rehabilitation, Beijing Sport University, No. 48 Xinxi Road, Haidian District, Beijing, China; [2]Rehabilitation Center, Beijing Rehabilitation Hospital of Capital Medical University, Beijing; [3]Department of Physical Therapy, Beijing Xiaotangshan Hospital, Beijing, China.

Abstract

Background: In recent years, it is reported that non-invasive brain stimulation [including transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS)] could improve lower limb function in patients after stroke. However, some studies showed no effect. In the present study, we aimed to make a meta-analysis to assess effect of non-invasive brain stimulation on lower limb function in patients after stroke. *Methods:* Studies exploring the effect of tDCS or rTMS on lower limb function in patients after stroke were searched on the PubMed, Web of Science, EMBASE, Medline, Google Scholar before March 2021. Meta-analysis was made to summarize results of these studies. *Results:* The present study showed significantly better walking speed, mobility and muscle strength increase effect in tDCS group compared to sham tDCS group [walking speed: standard mean difference (SMD) = 1.14, 95% CI = 0.48 to 1.80, $I^2 = 74.0\%$, p value for Q test < 0.001; mobility: SMD = 0.79, 95% CI = 0.21 to 1.36, $I^2 = 53.8\%$, p value for Q test = 0.043; muscle strength: SMD = 2.79, 95% CI = 0.61 to 4.98, $I^2 = 93.9\%$, p value for Q test < 0.001]. In addition, meta-analysis showed significantly better walking speed, balance and motor function increase effect in rTMS group compared to sham rTMS group [walking speed: SMD = 3.31, 95% CI = 1.38 to 5.24, $I^2 = 92.1\%$, p value for Q test < 0.001; balance: SMD = 3.54, 95% CI = 1.45 to 5.63, $I^2 = 95.4\%$, p value for Q test < 0.001; motor function: SMD = 1.65, 95% CI = 0.53 to 2.76, $I^2 = 90.3\%$, p value for Q test < 0.001].
Conclusions: This meta-analysis suggested that non-invasive brain stimulation improved lower limb function in patients after stroke. More large scale, blinded RCTs were necessary to confirm the effect of rTMS and tDCS on lower limb function in patients after stroke.

Keywords: Lower limb, repetitive transcranial magnetic stimulation, stroke, transcranial direct current stimulation.

INTRODUCTION

In the early stage of stroke, only approximately 20% to 30% of stroke patients showed preserved lower limb function.[1] Even after spontaneous recovery, 50% of stroke patients with lower limb dysfunction still cannot walk independently.[2] Rehabilitation of independent walking became one of the most important targets for rehabilitation in most stroke patients. Up to now, the effect of most lower limb rehabilitation strategies for stroke, such as electromyography biofeedback, water-based exercise, transcutaneous electrical nerve stimulation, virtual reality, on stroke is uncertain.[3] According to previous studies, brain stimulation could affect brain plasticity and might be valuable for the treatment of lower limb dysfunction of stroke.[4] In the recent decades, two safe, well-known, commonly used, non-invasive brain stimulation (NIBS) techniques, including transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), were widely used in rehabilitation of stroke. Increasing evidence showed that tDCS over the motor cortex, could improve walking speed and balance function in patients after stroke.[5] In addition, it is reported that repetitive TMS

Address correspondence to: Jinghua Qian, School of sports medicine and rehabilitation, Beijing Sport University, No. 48 Xinxi Road, Haidian District, 102211, Beijing, China. Tel: +86-010-83052977, E-mail: JinghuaQian891273@126.com

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(rTMS) could improve walking speed and balance function in patients after stroke.[6] However, some studies showed no effect.[7,8] In the present study, we aimed to make a meta-analysis to assess effect of non-invasive brain stimulation (including tDCS and rTMS) on lower limb function in patients after stroke.

METHODS

Search strategy

On the basis of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline [9], a meta-analysis was used to explore the effect of non-invasive brain stimulation on lower limb function in patients after stroke. We searched for articles before March 2021 in the following databases: PubMed, Web of Science, Medline, EMBASE, Google Scholar. The following key words: ("transcranial direct current stimulation" OR "tDCS" OR "transcranial magnetic stimulation" OR "TMS") AND ("lower limb") AND ("stroke") were used.

Inclusion criteria and exclusion criteria

The present study included randomized controlled trials (RCTs) and crossover trails exploring effects of tDCS or rTMS on lower limb function in patients after stroke. Included studies should provide data regarding the comparison of pre- and post- treatment scores of walking speed, walking endurance, mobility, balance function, muscle strength and motor function of lower limb in patients after stroke. We excluded studies according to the exclusion criteria as follows: (1) studies which did not focus on non-invasive brain stimulation and lower limb function in patients after stroke; (2) reviews, meta-analyses and case studies. After that, full texts were read to exclude articles which did not provide sufficient information of pre- and post-treatment scores of walking speed, walking endurance, mobility, balance function, muscle strength or motor function of lower limb in patients after stroke.

Data collection

Data were extracted as follows: authors and publication year, research location, numbers of cases and controls, mean ages of cases and controls, gender, research type, interventions, treatment location, stimulation intensity of tDCS or frequency of rTMS, treatment intensity and time of poststroke.

Meta-analysis

Meta-analysis was conducted using STATA 12.0 software. The mean values and standard deviation (SD) of reduction or increase rate of walking speed, walking endurance, mobility, balance function, muscle strength and motor function of lower limb in patients after stroke were obtained or calculated from the included studies. The standard mean difference (SMD) and 95% confidence intervals (CI) were computed as the effect size. We assessed heterogeneity between studies with Cochran Q test and inconsistency index (I^2) method. We used a fixed effects model when the heterogeneity was low ($I^2 < 50\%$ or *p* value of Q test > 0.05). Inversely, a random effects model was used when the heterogeneity was high ($I^2 \geq 50\%$ or *p* value of Q test ≤ 0.05). In addition, meta-regression analyses were conducted to explore source of the heterogeneity. Subgroup analyses (for different frequencies of rTMS) were conducted to explore the effect of frequency of rTMS on heterogeneities between studies. The stability of the meta-analysis was evaluated by removing 1 individual study each time. Moreover, Begg's test, Egger's test and funnel plots were used to assess publication bias.

RESULTS

Search results

Figure 1 showed the selection procedures. Supplementary Tables 1 and 2 showed study characteristics of included studies. Finally, the present study included 16 and 12 articles for tDCS[5,7,10-23] and rTMS[6,8,24-33], respectively. Studies for tDCS included 10 RCTs (including 110 patients after stroke given tDCS and 110 patients given sham tDCS over motor cortex) and 6 crossover trails (including 102 patients after stroke). In addition, studies for rTMS included 8 RCTs (including 130 patients after stroke given rTMS and 112 patients given sham rTMS over motor cortex) and 4 crossover trails (including 77 patients after stroke).

Meta-analysis results and systematic review

Effects of tDCS on lower limb function in patients after stroke

There were 7 studies included for effect of tDCS over the motor cortex on walking speed in patients after stroke. Meta-analysis showed significantly better walking speed increase effect in tDCS group compared to sham tDCS group with a

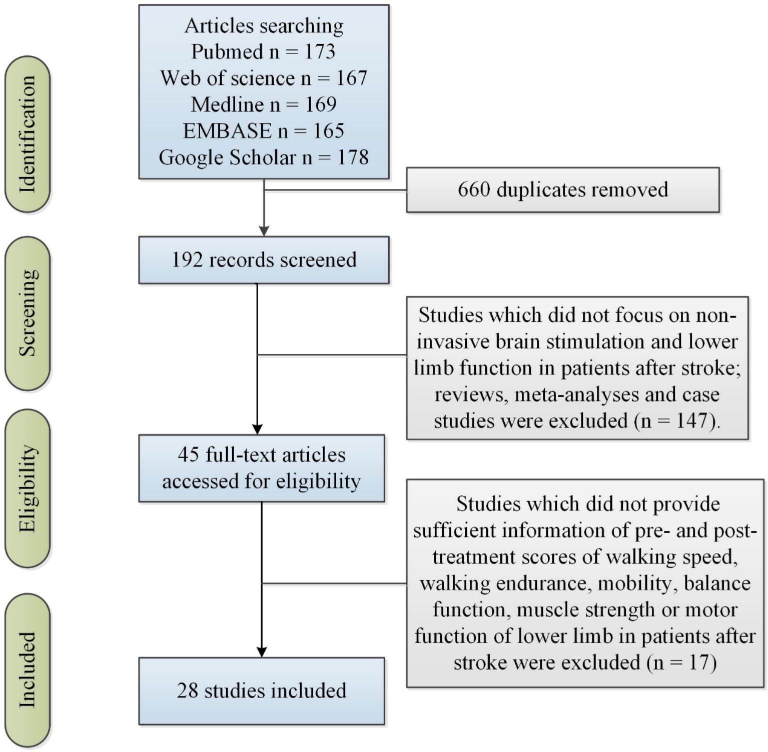

Figure 1. Characteristics of studies included in the meta-analysis.

random effect model (SMD = 1.14, 95% CI = 0.48 to 1.80, I^2 = 74.0%, *p* value for Q test < 0.001, Figure 2. A). 3 studies were included for effect of tDCS over the motor cortex on walking endurance in patients after stroke. Meta-analysis showed no significant difference in walking endurance effect in tDCS group compared to sham tDCS group with a random effect model (SMD = -0.14, 95% CI = -1.45 to 1.16, I^2 = 79.5%, *p* value for Q test = 0.008, Figure 2. B). Seven studies were included for effect of tDCS over the motor cortex on mobility in patients after stroke. Meta-analysis showed significantly better mobility increase effect in tDCS group compared to sham tDCS group with a random effect model (SMD = 0.79, 95% CI = 0.21 to 1.36, I^2 = 53.8%, *p* value for Q test = 0.043, Figure 2. C). 5 studies were included for effect of tDCS over the motor cortex on balance in patients after stroke. Meta-analysis showed no significant difference in balance increase effect in tDCS group compared to sham tDCS group with a random effect model (SMD = 0.51, 95% CI = -0.39 to 1.41, I^2 = 83.7%, *p* value for Q test < 0.001, Figure 2. D). Five studies were included for effect of tDCS over the motor cortex on muscle strength in patients after stroke. Meta-analysis showed significantly better muscle strength increase effect in tDCS group compared to sham tDCS group with a random effect model (SMD = 2.79, 95% CI = 0.61 to 4.98, I^2 = 93.9%, *p* value for Q test < 0.001, figure 2. E). Four studies were included for effect of tDCS over the motor cortex on motor function in patients after stroke. Meta-analysis showed no significant difference in motor function increase effect in tDCS group compared to sham tDCS group with a random effect model (SMD = 0.67, 95% CI = -0.80 to 2.15, I^2 = 89.6%, *p* value for Q test < 0.001, figure 2. F). Additionally, meta-regression analysis showed that ages, gender, stimulation intensity and disease durations were not responsible for heterogeneity across studies regarding effects of tDCS on walking speed, mobility, balance, muscle strength and motor function in patients after stroke (Supplementary Table 3). In the present study, sensitivity analyses showed no changes in the direction of effect when any one study was excluded for all meta-analyses (see Supplementary Figure 1). Begg's test, Egger's tests and funnel plots showed no significant risks of publication bias for meta-analyses of effects of tDCS on walking speed, walking endurance, mobility, balance, muscle strength and motor function in patients after stroke (see Supplementary Table 4 and Supplementary Figure 2).

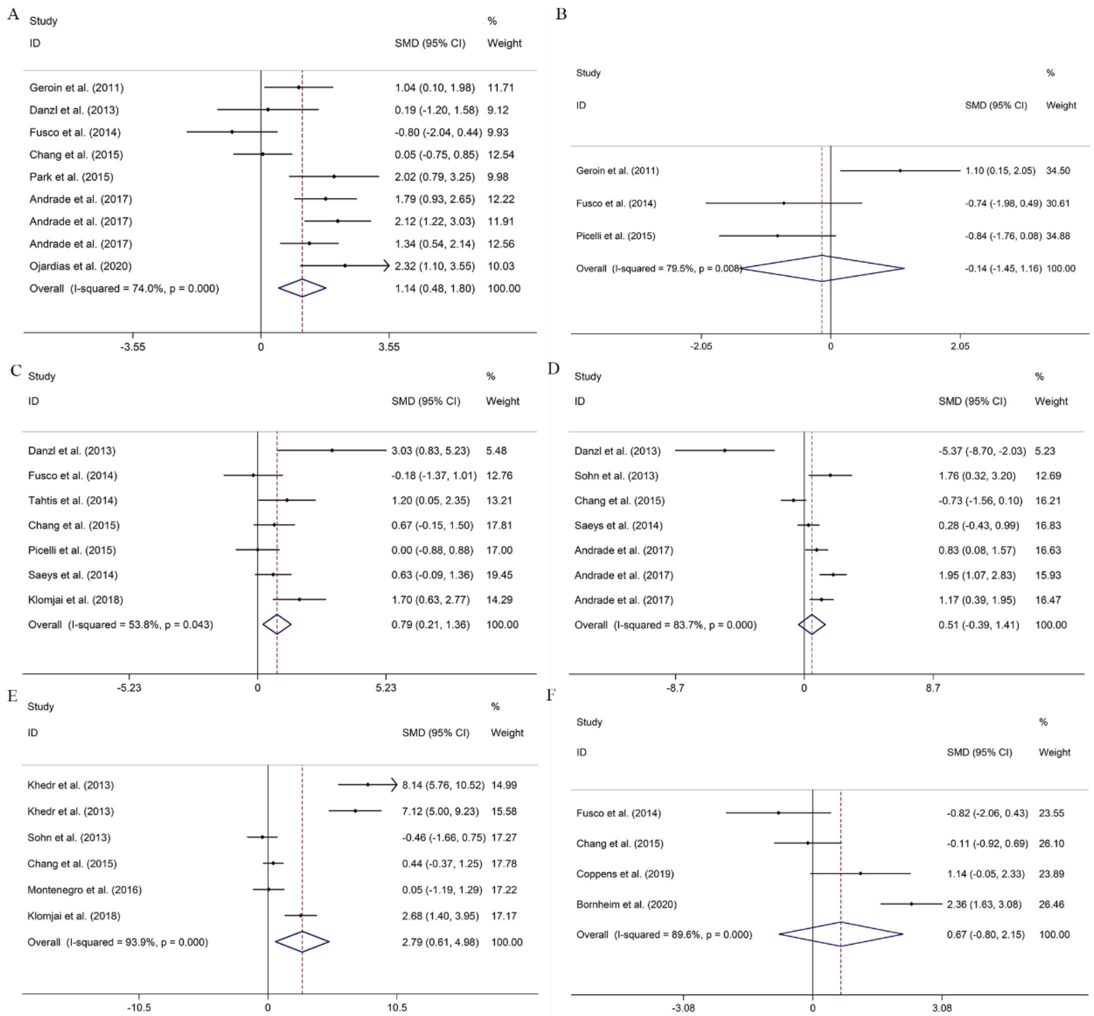

Figure 2. Forest plot regarding effects of tDCS on walking speed (A), walking endurance (B), mobility (C), balance (D), muscle strength (E) and motor function (F) in patients after stroke. Abbreviation: tDCS, transcranial direct current stimulation.

Effects of rTMS on lower limb function in patients after stroke

There were 6 studies included for effect of rTMS over the motor cortex on walking speed in patients after stroke. Meta-analysis showed significantly better walking speed increase effect in rTMS group compared to sham rTMS group with a random effect model (SMD = 3.31, 95% CI = 1.38 to 5.24, I^2 = 92.1%, *p* value for Q test < 0.001, figure 3. A). Subgroup study showed that HF-rTMS showed significantly better walking speed increase effect compared to sham rTMS group (SMD = 4.80, 95% CI = 2.97 to 6.63, I^2 = 71.4%, *p* value for Q test = 0.015; Supplementary Figure 3. A). Five studies were included for effect of rTMS over the motor cortex on balance in patients after stroke. Meta-analysis showed significantly better balance increase effect in rTMS group compared to sham rTMS group with a random effect model (SMD = 3.54, 95% CI = 1.45 to 5.63, I^2 = 95.4%, *p* value for Q test < 0.001, Figure 3. B). Subgroup study showed that LF-rTMS showed significantly better balance increase effect compared to sham rTMS group (SMD = 2.01, 95% CI = 0.28 to 3.73, I^2 = 93.1%, *p* value for Q test < 0.001; Supplementary Figure 3. B). Eight studies were included for effect of rTMS over the motor cortex on motor function in patients after stroke. Meta-analysis showed significantly better motor function increase effect in rTMS group compared to sham rTMS group with a random effect model (SMD = 1.65, 95% CI = 0.53 to 2.76, I^2 = 90.3%, *p* value for Q test < 0.001, Figure 3. C). Subgroup study showed that LF-rTMS showed significantly

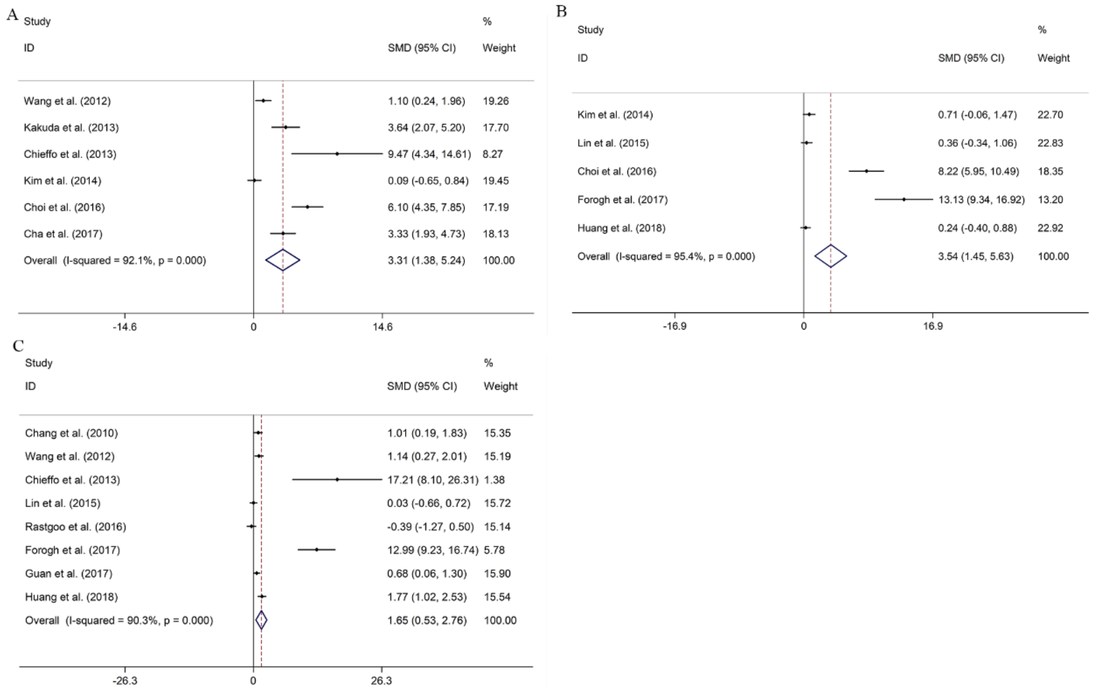

Figure 3. Forest plot regarding effects of rTMS on walking speed (A), balance (B) and motor function (C) in patients after stroke. Abbreviation: rTMS, repetitive transcranial magnetic stimulation.

better motor function increase effect compared to sham rTMS group, whereas no significant difference in motor function increase effect was showed between HF-rTMS group and sham rTMS group (LF-rTMS: SMD = 1.94, 95% CI = 0.30 to 3.58, $I^2 = 93.2\%$, *p* value for Q test < 0.001; HF-rTMS: SMD = 1.39, 95% CI = -0.34 to 3.12, $I^2 = 84.4\%$, *p* value for Q test = 0.002; Supplementary Figure 3. C). Additionally, meta-regression analysis showed that ages, gender, stimulation intensity and disease durations were not responsible for heterogeneity across studies regarding effects of rTMS on walking speed, balance and motor function in patients after stroke (Supplementary Table 5). In the present study, sensitivity analyses showed no changes in the direction of effect when any one study was excluded for all meta-analyses (see Supplementary Figure 4). Begg's test, Egger's tests and funnel plots showed no significant risks of publication bias for meta-analyses of effects of rTMS on walking speed, balance and motor function in patients after stroke (see Supplementary Table 6 and Supplementary Figure 5).

DISCUSSION

The present study showed significantly better walking speed, mobility and muscle strength increase effect in tDCS group compared to sham tDCS group. In addition, meta-analysis showed significantly better walking speed, balance and motor function increase effect in rTMS group compared to sham rTMS group.

The present study showed better walking speed, mobility and muscle strength increase effect in tDCS group compared to sham tDCS group, whereas no significant difference was showed in walking endurance, balance and motor function effect in tDCS group compared to sham tDCS group in stroke. A recent meta-analysis showed statistically significant effects in favour of tDCS for mobility and muscle strength, but no significant effects were found for improving walking speed, walking endurance and balance function.[34] The present study is an updated study for the previous study. Additionally, the present study computed the mean values and SD of reduction or increase rate from baseline to follow-up time of lower limb function, whereas the previous meta-analysis computed the mean values and SD of lower limb function at the follow-up time. The computation of reduction or increase rate is more scientific. Another meta-analysis including 4 trails examined the effects of tDCS on lower limb function after stroke and showed no statistical significance associated with lower extremity function (SMD 0.2, 95% CI: -1.26 to 1.67).[35] Thus, more well-designed, larger sample sized RCTs were essential for the investigation of effect of tDCS on lower limb function in stroke patients. In addition, the present study showed that ages, gender, stimulation intensity and disease durations were not responsible on heterogeneity across studies regarding effects of tDCS on walking speed, mobility, balance, muscle strength and motor function in patients after stroke. Bornheim *et al*.[22] indicated that if tDCS was applied in the acute stages of stroke, functional recovery is improved. Danzl *et al*.[11] indicated that tDCS has the potential to enhance the effectiveness of gait training in chronic stroke. Results of these studies and meta-regression analysis suggested the significant effect of tDCS on lower limb function in both acute and chronic stroke.

In addition, the present meta-analysis indicated significantly better walking speed, balance and motor function increase effect in rTMS group compared to sham rTMS group. A recent meta-analysis indicated the effects of rTMS on lower limb function especially on motor function in patients poststroke.[36] The present study is also an updated study for the previous study.[36] The previous meta-analysis computed the mean values and SD of lower limb function at the follow-up time. But our study computed the mean values and SD of reduction or increase rate from baseline to follow-up time of lower limb function. Additionally, the study aimed to explore the effect of rTMS frequency on heterogeneity across studies. Previous studies supported that rTMS works by modulating cortical excitability. HF-rTMS (> 1Hz) facilitates cortical excitability, whereas LF- rTMS (≤ 1Hz) inhibits cortical excitability.[37] Subgroup study showed that HF-rTMS showed significantly better walking speed increase effect compared to sham rTMS group. Subgroup study showed that LF-rTMS showed significantly better balance and motor function increase effect compared to sham rTMS group. The meta-analysis supported that rTMS with different frequency is effective for different limb function. Thus, individualized strategy with rTMS is essential for stroke patients. In addition, the present meta-regression analysis showed that ages, gender, stimulation intensity and disease durations were not responsible for heterogeneity across studies regarding effects of rTMS on walking speed, balance and motor function in patients after stroke. Guan *et al*.[32] showed that rTMS facilitates motor recovery of acute stroke patients. Chang *et al*.[24] showed positive long-term effects of HF-rTMS on motor recovery during the subacute period of stroke. Choi *et al*.[6] indicated that HF-rTMS improves balance function in the chronic stroke patients. Thus, rTMS could be used in different periods of stroke.

Some limitations were showed in the study. Firstly, the number of included studies was limited to explore the effect of rTMS on the walking endurance, mobility and muscle strength in patients after stroke. Secondly, the number of included studies was limited to explore the sources of heterogeneities across studies regarding the effect of tDCS on walking endurance in patients after stroke.

In conclusion, the present meta-analysis suggested that non-invasive brain stimulation improved lower limb function in patients after stroke. More large scale, blinded RCTs were essential to explore the effect of rTMS and tDCS on lower limb function in patients after stroke.

DISCLOSURE

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Conflict of interest: None

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