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Special Review

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A Literature Review on Optimal Stimulation Parameters of Transcranial Direct Current Stimulation for Motor Recovery After Stroke

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Soo Ho Lee, Yeun Jie Yoo

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Correspondence to
Yeun Jie Yoo
Department of Rehabilitation Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea.
Email: yeunjie@catholic.ac.kr

HIGHLIGHTS

- Bihemispheric transcranial direct current stimulation (tDCS) may be more effective for motor recovery than unihemispheric.
- tDCS intensity and duration exhibit nonlinear effects on corticospinal excitability.
- Proper electrode size ensures effective modulation of target electrical activity.

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Yeun Jie Yoo
Department of Rehabilitation Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, 93 Jungbu-daero, Paldal-gu, Suwon 16247, Korea.
Email: yeunjie@catholic.ac.kr

ORCID iDs
Soo Ho Lee
https://orcid.org/0009-0007-2897-9942
Yeun Jie Yoo
https://orcid.org/0000-0003-1323-4503

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Conflict of Interest
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ABSTRACT

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique with potential in stroke rehabilitation by modulating cortical excitability. However, the optimal parameters, including electrode placement, current intensity, stimulation duration, and electrode size, remain poorly understood, and the interactions among these factors contribute to mixed results in motor recovery post-stroke. This review explores the various stimulation parameters and their impact on enhancing corticospinal excitability (CSE) and motor function recovery. Different electrode placement (montages), such as anodal, cathodal, and bi-hemispheric stimulation, have demonstrated varying effectiveness in restoring motor function. Bihemispheric stimulation demonstrated a larger effect size compared to other unihemispheric (anodal or cathodal) stimulation; however, its relative superiority remains inconclusive. Inter-individual anatomical variations, such as skull thickness, lesion location, and cortical atrophy, can affect tDCS outcomes, highlighting the need for personalized electrode placement guided by computational modeling based on brain imaging. Furthermore, stimulation intensity, typically 1–2 mA, exhibited nonlinear effects on CSE, contrasting with the dose-response relationships observed in earlier studies. Stimulation duration is also critical, with evidence suggesting that prolonged stimulation may reverse excitability-enhancing effects beyond a certain threshold. While smaller electrodes enhance focality, an appropriately sized electrode is necessary to effectively modulate electrical activity in the target region, with evidence suggesting a dose-response relationship between electrode size and motor recovery. Overall, the interplay among these parameters underscores the need for personalized and optimized tDCS protocols to achieve consistent motor recovery in stroke patients. Future research should focus on refining these parameters to maximize the therapeutic benefits of tDCS.

Keywords: Transcranial Direct Current Stimulation; Motor Recovery; Stimulation Parameters

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation technique that delivers a low-voltage direct electrical current through electrodes placed on the scalp to

modulate neuronal activity of targeted brain regions. Typically, anodal stimulation is applied to increase cortical excitability in nearby brain regions, while cathodal stimulation is used to decrease the excitability. Compared to repetitive transcranial stimulation (rTMS), tDCS is inexpensive, easy to administer, and portable, making it a promising adjunctive therapy for stroke rehabilitation.

In stroke patients, cortical stimulation via tDCS and rTMS is currently guided by the 'interhemispheric competition model' [1]. This model suggests that, under normal conditions, the two cerebral hemispheres maintain balanced interhemispheric inhibition through the corpus callosum. Following a stroke, however, this balance is disrupted, with increased inhibitory signals from the contralesional hemisphere exerting a 'double disabling' effect on motor function in the lesioned hemisphere [2]. Previous clinical studies have thus been conducted to address interhemispheric imbalance in order to enhance neuronal plasticity, ultimately promoting motor recovery [3].

The efficacy of tDCS in stroke patients may be influenced by several stimulation parameters, including 1) electrode placement (montage), 2) current intensity, 3) stimulation duration, and 4) electrode size. One challenge in applying tDCS in clinical practice is the considerable variation in the parameters used across previous studies, which makes it difficult to determine the most effective settings. Although the optimal stimulation parameters for enhancing motor recovery remain largely unknown, this article reviews the published studies on each of these parameters.

ELECTRODE PLACEMENT (MONTAGE)

Based on the interhemispheric competition model described above, three montages are generally used for enhancing corticospinal excitability (CSE) in the lesioned primary motor cortex (M1):

1) Anodal stimulation: Anodal stimulation is applied to the ipsilesional M1, and cathodal stimulation is applied to the contralesional supraorbital region to increase the excitability of the lesioned motor cortex.
2) Cathodal stimulation: Cathodal stimulation is applied to the contralesional M1, while anodal stimulation is applied to the ipsilesional supraorbital region to decrease the excitability of the contralesional motor cortex.
3) Bi-hemispheric stimulation: Anodal stimulation is applied to the ipsilesional M1, and cathodal stimulation is applied to the contralesional M1 to restore interhemispheric balance.

In a meta-analysis examining the effects of tDCS on upper-limb function post-stroke, Van Hoornweder et al. [4] found that all stimulation types resulted in significant improvements. However, bihemispheric stimulation was associated with a slightly larger effect size compared to other stimulation types: anodal stimulation (standardized mean difference [SMD], 0.52; 95% confidence interval [CI], −0.04, 1.07; p = 0.033; I^2 = 72%), cathodal stimulation (SMD, 0.64; 95% CI, −0.05, 1.33; p = 0.003; I^2 = 0%), and bihemispheric stimulation (SMD, 0.84; 95% CI, −0.06, 1.74; p = 0.027; I^2 = 78%). Chhatbar et al. [5] conducted a meta-analysis of studies that used the Fugl-Meyer Assessment (FMA) for upper extremity function as the sole outcome measure. They found that the bihemispheric montage was associated with superior recovery compared to anodal or cathodal montages: anodal stimulation (SMD, 0.21; 95% CI, −0.72, 1.14;

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p = 0.65; I^2 = 71%), cathodal stimulation (SMD, 0.43; 95% CI, −0.23, 1.08; p = 0.20; I^2 = 45%), and bihemispheric stimulation (SMD, 1.30; 95% CI, −0.14, 2.75; p = 0.08; I^2 = 81%). In a recent randomized controlled study comparing bihemispheric stimulation, anodal stimulation, and sham stimulation in 35 subacute ischemic stroke patients, both stimulation protocols resulted in significant improvements in the FMA for upper and lower extremities compared to the sham group. However, no significant difference was observed between the two stimulation protocols [6]. The relative superiority of bihemispheric stimulation over unihemispheric (anodal or cathodal) stimulation for motor recovery remains inconclusive.

Another important consideration in tDCS montage is inter-individual anatomical variation, which may contribute to the variability of tDCS effects. Variations in skull and scalp thickness, lesion location and size, and the degree of cortical atrophy can significantly influence the distribution and intensity of the electric field. Therefore, an optimized approach that leverages computational brain modeling, guided by individual brain imaging for electrode placement, may yield a more accurate and personalized montage for targeting specific brain regions than the conventional 10–20 electroencephalogram system-based approach [7].

CURRENT INTENSITY

The current intensity of tDCS is typically applied within a range of 1 to 2 mA. Chhatbar et al. [8] demonstrated that a higher intensity of 4 mA, delivered through a 35 cm^2 electrode over a 30-minute period, was safe and well-tolerated in stroke patients. Early studies have suggested a dose-response relationship between anodal tDCS intensity and the enhancement of CSE, as well as improvements in FMA for upper extremity function [8,9]. Recent findings have revealed mixed results regarding this dose-response relationship. Jamil et al. [10] investigated CSE, measured by motor evoked potential (MEP) amplitudes, in healthy participants following anodal and cathodal tDCS at varying intensities—sham, 0.5, 1.0, 1.5, and 2.0 mA—applied to the left M1 for 15 minutes each. For anodal stimulation, all intensities produced a significant increase in CSE; however, the pattern of the facilitatory effect followed a U-shape as intensity increased. Both 0.5 and 2.0 mA resulted in the highest effects. In contrast, cathodal stimulation at lower intensities (0.5 and 1.0 mA) led to a decrease in excitability, while intensities above 1.0 mA did not reduce CSE. These findings suggest that for anodal stimulation, there is no linear, intensity-dependent increase in excitability enhancement, which is consistent with several previous studies [11,12]. For cathodal stimulation, increasing intensity does not lead to a stronger reduction in excitability, and other study reported that 20 minutes of 2.0 mA cathodal stimulation shifted cortical plasticity from inhibition to facilitation [13]. The underlying mechanism of this phenomenon remains unclear. tDCS is believed to induce calcium-dependent plasticity at glutamatergic synapses, likely modulated by a reduction in GABAergic activity. A higher intracellular calcium influx promotes long-term potentiation (LTP), while a lower influx rate leads to long-term depression (LTD). The nonlinear effects of tDCS are supposed to arise between the known plasticity zones, where the respective calcium concentrations may not lead to a clearly directed form of plasticity [14].

STIMULATION DURATION

Early studies observed a linear increase in CSE with longer durations of anodal tDCS, specifically up to 13 minutes [9,15]. However, recent research challenges this assumption.

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Vignaud et al. [16] found that while 20 minutes of anodal tDCS at both 1 mA and 2 mA significantly enhanced CSE regardless of the intensity, 30 minutes of anodal tDCS had no effect on modulation of CSE, as measured by paired-pulse TMS. Similarly, Hassanzahraee et al. [17] reported that with 1 mA anodal tDCS, increasing the stimulation duration in 2-minutes intervals from 22 to 30 minutes revealed a threshold effect; specifically, the excitability-enhancing effect was reversed with stimulation durations ≥ 26 minutes, as measured through MEP. The authors further examined the intensity threshold for CSE as measured by MEP, by applying four current intensities—0.3, 0.7, 1.0, and 1.5 mA—with a fixed stimulation duration of 26 minutes [18]. They observed a reversal of the excitability-enhancing effect at intensities of 1.0 mA or greater. This finding appears inconsistent with the results of Jamil et al. [10], who reported that the highest CSE was achieved at 2.0 mA when anodal tDCS was applied for 20 minutes. These observations suggest that the threshold may not be fixed and that a more complex interaction likely exists between the applied tDCS parameters in modulating cortical excitability. This phenomenon can be understood through the Bienenstock-Cooper-Munro (BCM) rule, a theoretical model of homeostatic plasticity [19]. According to the BCM rule, the threshold for synaptic plasticity dynamically shifts in response to prior neural activity, whether inhibitory or excitatory, to prevent excessive excitation or inhibition. Consequently, when initial stimulation facilitates synaptic activity (LTP), this shift would adjust the threshold to favor synaptic inhibition (LTD) for the remainder of the stimulation period, thereby maintaining balance in CSE [20].

ELECTRODE SIZE

Unlike rTMS, which provides focal stimulation, tDCS delivers current across a broader area, influenced by both the electrode size and the electric field distribution between the two electrodes. While smaller anode sizes enhance focality, a limitation of tDCS is its low spatial resolution of the current [21]. Therefore, the electrode must be adequately sized to effectively modulate the electrical activity in the target region. Chhatbar et al. [5] demonstrated a dose-response relationship between electrode size and improvements in the FMA of upper extremity. Similarly, Ho et al. [22] found that a 5 × 7 cm^2 electrode produced higher electric fields at the motor hotspot compared to a 4 × 4 cm^2 electrode. When considering the perilesional reorganization and role of the motor network in stroke recovery, this broad distribution of the electrical field may positively contribute to neuroplasticity [23,24]. However, if the low spatial resolution of tDCS can be addressed through an optimized montage guided by brain imaging-based computational modeling, as described earlier in the article, it may be possible to identify an electrode size that modulates CSE more focally and efficiently.

CONCLUSION

In this review, we summarize factors influencing the modulation of neuronal excitability by tDCS, including electrode placement, current intensity and duration, and electrode size. The optimal parameters for tDCS remain inadequately defined, and the complex interactions among the various stimulation parameters likely contribute to the inconsistent findings observed in post-stroke motor recovery. Therefore, future research should prioritize the careful optimization of stimulation parameters to more effectively confirm and enhance the therapeutic effects of tDCS.

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