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Onsite-effects of dual-hemisphere *versus* conventional single-hemisphere transcranial direct current stimulation

A functional MRI study☆

Yong Hyun Kwon[1], Sung Ho Jang[2]

1 *Department of Physical Therapy, Yeungnam College of Science & Technology, Daegu 705-703, Republic of Korea*
2 *Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Daegu 705-717, Republic of Korea*

Abstract
We performed functional MRI examinations in six right-handed healthy subjects. During functional MRI scanning, transcranial direct current stimulation was delivered with the anode over the right primary sensorimotor cortex and the cathode over the left primary sensorimotor cortex using dual-hemispheric transcranial direct current stimulation. This was compared to a cathode over the left supraorbital area using conventional single-hemispheric transcranial direct current stimulation. Voxel counts and blood oxygenation level-dependent signal intensities in the right primary sensorimotor cortex regions were estimated and compared between the two transcranial direct current stimulation conditions. Our results showed that dual-hemispheric transcranial direct current stimulation induced greater cortical activities than single-hemispheric transcranial direct current stimulation. These findings suggest that dual-hemispheric transcranial direct current stimulation may provide more effective cortical stimulation than single-hemispheric transcranial direct current stimulation.

Key Words
transcranial direct current stimulation; dual-hemispheric stimulation; cortical activation; functional MRI; primary sensorimotor cortex; neuroimaging; regeneration; neural regeneration

Research Highlights
(1) We compared cortical activation during dual-hemispheric transcranial direct current stimulation and single-hemispheric transcranial direct current stimulation.
(2) During functional MRI scanning, for the dual-hemispheric transcranial direct current stimulation, the anode was placed over the right primary sensorimotor cortex, and the cathode was placed over the left primary sensorimotor cortex, whereas the cathode was placed over the right supraorbital area for conventional single-hemispheric transcranial direct current stimulation.
(3) Dual-hemispheric transcranial direct current stimulation more stongly enhanced higher cortical activity than conventional single-hemispheric transcranial direct current stimulation, as indexed by higher voxel counts and blood oxygenation level-dependent signal intensities.
(4) Dual-hemispheric transcranial direct current stimulation may be more effective for cortical stimulation than single-hemispheric transcranial direct current stimulation.

Abbreviations
SM1, Primary sensorimotor cortex; BOLD, blood oxygenation level-dependent

Yong Hyun Kwon☆, Ph.D., Assistant professor, Department of Physical Therapy, Yeungnam College of Science & Technology, Daegu 705-703, Republic of Korea

Corresponding author: Sung Ho Jang, M.D., Professor, Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, 317-1, Daemyung 5-dong, Namgu, Daegu 705-717, Republic of Korea
strokerehab@hanmail.net

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INTRODUCTION

Transcranial direct current stimulation can alter human brain functions noninvasively by modulating the excitability of targeted cortical neurons. This functional modulation could be mediated by the alteration of neural membrane potentials and N-methyl-D-aspartate receptor potential efficacy[1-3]. During transcranial direct current stimulation, a weak direct current is continuously applied over the scalp through an anodal and a cathodal electrode[4-5]. It has been well established that the two polarities have different neurophysiologic properties[1, 5-6]. For example, anodal currents increase cortical excitability, whereas cathodal currents decrease cortical excitability. Numerous previous studies have demonstrated that transcranial direct current stimulation can modulate cognitive and motor functions associated with targeted brain areas in normal subjects and patients with a brain lesion[7-11].

In transcranial direct current stimulation electrode applications, the anode is used as the active electrode to facilitate the targeted cortex[5, 7], whereas the cathode is applied on the supraorbital area of the opposite hemisphere as a reference electrode, without affecting the target cortex. Although the neurophysiologic properties of each of the two polarities are different, both the anodal and cathodal current can facilitate motor and cognitive functions of homologous cortical areas in the non-dominant hemisphere[12-14]. In this regard, in a recent study, the two currents were applied simultaneously to enhance dominant cortical function using the inter-hemispheric connectivity-driven effect of transcranial direct current stimulation. Specifically, anodal transcranial direct current stimulation was applied on the dominant cortical area and cathodal transcranial direct current stimulation on the non-dominant homologous cortical area (dual-hemispheric transcranial direct current stimulation)[15].

Recently, the effects of transcranial direct current stimulation on various brain functions have been demonstrated in several studies using functional MRI and positron emission tomography[16-20]. Therefore, the fact that anodal current in single-hemispheric transcranial direct current stimulation can induce activation of the underlying targeted cortex has been well established[16-18]. However, no functional neuroimaging study has been conducted to investigate cortical activation by dual-hemispheric transcranial direct current stimulation. In the present study, we compared cortical activation during dual-hemispheric transcranial direct current stimulation and single-hemispheric transcranial direct current stimulation using functional MRI.

RESULTS

Quantitative analysis and general description of subjects

Of the nine healthy subjects recruited for this study, three subjects were excluded because cortical activation on the primary sensorimotor cortex (SM1) was not detected during dual-hemispheric transcranial direct current stimulation (one subject) or single-hemispheric transcranial direct current stimulation (two subjects). Consequently, six subjects were included in the final functional MRI analysis. The baseline data of each subject is shown in Table 1. None of the subjects complained of any adverse symptoms or signs during or after stimulation, except a slight itching sensation under the electrodes.

Voxel counts and blood oxygenation level-dependent (BOLD) signal intensity on the underlying SM1 in dual-hemispheric transcranial direct current stimulation and single-hemispheric transcranial direct current stimulation

The voxel counts and BOLD signal intensities in the right SM1 during dual-hemispheric transcranial direct current stimulation were significantly higher than those induced by single-hemispheric transcranial direct current stimulation ($P < 0.05$; Table 1).

Table 1 Functional MRI activation on the primary sensorimotor cortex during dual-hemispheric transcranial direct current stimulation (tDCS) and single-hemispheric tDCS in healthy subjects

Subject	Sex	Age (year)	Dual-hemispheric tDCS		Single-hemispheric tDCS	
			Voxel count	BOLD signal intensity	Voxel count	BOLD signal intensity
1	M	22	223	3.85	188	3.93
2	M	24	235	3.83	101	3.97
3	M	23	366	6.63	27	3.47
4	M	22	189	4.31	57	3.23
5	M	21	192	3.67	48	3.32
6	F	22	76	3.65	80	3.57
mean±SD		22.33±1.03	213.50±85.41	4.32±1.05	83.50±52.27	3.58±0.28

In each of the regional activation clusters, voxel counts and BOLD signal intensities were analyzed in reference to Talairach coordinates. M: Male; F: female; BOLD: blood oxygenation level-dependent.

DISCUSSION

In the present study, we found cortical activation in the SM1 during both dual- and single-hemispheric transcranial direct current stimulation and both voxel counts and BOLD signal intensities during dual-hemispheric transcranial direct current stimulation. These results suggest that dual-hemispheric transcranial direct current stimulation has an effect similar to conventional single-hemispheric transcranial direct current stimulation with respect to the activation of targeted cortex and that dual-hemispheric transcranial direct current stimulation is more effective than conventional single-hemispheric transcranial direct current stimulation in this respect. However, in three subjects, the cortical activation in the SM1 was not observed during dual- or single-hemispheric transcranial direct current stimulation. This is consistent with a previous study, in which a functional MRI BOLD signal changes induced by on-site transcranial direct current stimulation were not always detected[17]. This phenomenon may be due to individual anatomical differences (*e.g.*, thickness of connective tissue over epidermis and sweat duct resistivity) or electrode parameters (*e.g.*, hydration and resistivity)[21-23]. Several previous neuroimaging studies have demonstrated that the functional MRI BOLD signals are induced by the direct ongoing-effect of transcranial direct current stimulation [16-18]. To the best of our knowledge, the first study designed to investigate the onsite-effect of transcranial direct current stimulation during concurrent functional MRI scanning was conducted by Kwon *et al* [16], and it indicated that cortical activity was induced in the SM1 by anodal transcranial direct current stimulation. In their second transcranial direct current stimulation experiment using functional MRI, it was found that cortical activity in the SM1 was induced after 1 minute of direct current application to the target neurons, and that this activity was maintained with some fluctuations[17]. These prior neuroimaging studies supported our finding that functional MRI BOLD signal changes were induced by the ongoing effect of transcranial direct current stimulation. In addition to the onsite effect of transcranial direct current stimulation, the concurrent application of transcranial direct current stimulation and motor tasks caused an increase in cortical target neuron activity after transcranial direct current stimulation[20, 24-25]. A possible neurophysiologic mechanism underlying these findings is that anodal stimulation can induce changes in the neural excitability of underlying target neural cells in the human brain. Accordingly, we believe that dual-hemispheric direct current stimulation is sufficient to lead to activation of cortical neurons in the resting state.

The present findings showed that dual-hemispheric transcranial direct current stimulation induced higher cortical activities than conventional single-hemispheric transcranial direct current stimulation. This outcome is supported by several prior studies that investigated improvements in behavioral functions induced by the dual-hemispheric and single-hemispheric-connectivity transcranial direct current stimulation effects during or after single-hemispheric stimulation[25-29]. Vines *et al* [15] reported that dual-hemispheric transcranial direct current stimulation, using the simultaneous application of cathodal transcranial direct current stimulation over the dominant motor cortex and anodal transcranial direct current stimulation over the non-dominant motor cortex, improved motor skills of the non-dominant hand in a motor sequencing task significantly more than the single-hemispheric stimulation. In addition, according to prior studies that addressed hemispheric modulation[14, 30], cathodal transcranial direct current stimulation applied over a unilateral hemisphere had a facilitative effect on the ipsilateral upper limb, but an inhibitory effect on the contralateral upper limb. In contrast, anodal transcranial direct current stimulation had the opposite effect. Moreover, Sparing *et al* [13] reported that the inhibitory effects of cathodal transcranial direct current stimulation over the unlesioned posterior parietal cortex and the facilitative effects of anodal transcranial direct current stimulation over the lesioned posterior parietal cortex reduced visuospatial neglect following stroke. These converging evidences may be explained by inter-hemispheric interactions *via* transcallosal inhibition. In the healthy brain, neural activity in homologous areas of both hemispheres was functionally coupled and equally balanced because of mutual inhibitory control *via* transcallosal connections[26]. Therefore, dual-hemispheric transcranial direct current stimulation may have produced greater cortical activity because the cortical excitability was decreased by cathodal transcranial direct current stimulation over the left SM1, which reduced inhibitory inter-hemispheric control of the homologous right SM1. This disinhibitory control in the left homologous area engendered cortical activity in the right SM1 induced by anodal transcranial direct current stimulation over the right SM1. Consequently, we speculate that our observations resulted from onsite transcranial direct current stimulation modulation of inhibitory inter-hemispheric projects.

In conclusion, we found that simultaneous application of anodal transcranial direct current stimulation over the target brain area with cathodal transcranial direct current stimulation over the same brain area in the opposite hemisphere provides a more effective means of activating the underlying target cortex than conventional single-hemispheric transcranial direct current stimulation.

These findings provide a means of more effectively increasing cortical excitability in the underlying motor cortex by transcranial direct current stimulation in the human brain. Nevertheless, we acknowledge that this study has limitations. For example, we focused on the effects of anodal transcranial direct current stimulation in the dominant hemisphere. The small sample size makes generalizations difficult, and no behavioral assessment was performed. Furthermore, the transcranial direct current stimulation was applied for a relatively short time because of mechanical restrictions of the MR equipment. Accordingly, we suggest that future large-scale studies that include neurobehavioral assessments are necessary to fully ascertain the onsite effects of dual-hemispheric stimulation in dominant and non-dominant hemispheres.

SUBJECTS AND METHODS

Design

A non-randomized, concurrent controlled study.

Time and setting

This study was performed in the functional MRI room of Yeungnam University Medical Center, Yeungnam University, Republic of Korea, from August 2011 to November 2011.

Subjects

Nine healthy subjects, including five males and four females, with a mean age of 22.22 ± 0.87 years old, were included in this study. These subjects denied having an abnormal neurological or psychiatric history. All subjects were confirmed to be right-handed by the modified Edinburg Handedness Inventory[27]. None of the subjects had ever participated in a brain stimulation experiment using, for example, transcranial direct current stimulation or transcranial magnetic stimulation. All subjects understood the purpose of this study and provided written informed consent in accordance with the ethical standards of the *Declaration of Helsinki*.

Methods

Application of transcranial direct current stimulation

Direct current was provided *via* a battery-driven constant direct current stimulator (NeuroConn GmbH, Ilmenau, Germany) located outside the MRI room. Current was delivered to the scalp using a pair of electrodes (EL508, Biopac System INC, US) and leads (LEAD108, Biopac System INC, Goleta, CA, USA) designed for use in a magnetic field. MRI compatible electrodes were placed on a water-soaked sponge (5 cm × 7 cm), which was in direct contact with the scalp. The 10/20 international electroencephalographic system, in which M1 corresponds to C3 or C4 in both hemispheres respectively, was used for electrode placement. For the dual-hemispheric transcranial direct current stimulation, the center of anodal electrode was placed over C3 of the SM1 in the left hemisphere, whereas one of the cathodal electrodes was placed over C4 of the SM1 in the right hemisphere. For conventional single-hemispheric transcranial direct current stimulation, the center of the anodal electrode was placed over C3 of the SM1 in the left hemisphere, whereas one of the cathodal electrodes was placed over the supraorbital area in the right hemisphere (Figure 1). The C3 and C4 areas are well known as the neural representational areas of hand motor function[28].

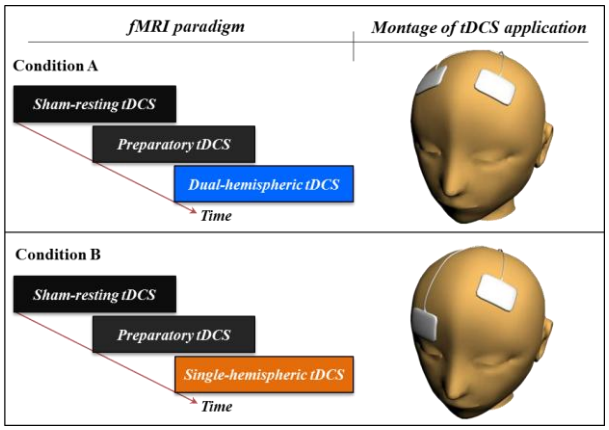

Figure 1 The schema of the experimental design and transcranial direct current stimulation (tDCS) application.

The functional MRI (fMRI) scanning was performed as a block design with a sham-resting phase, preparatory phase, and a stimulation phase. All subjects underwent conditions A and B with a 5-minute rest period between the conditions to allow for the elimination of the effects of the previous tDCS.

The orders of the conditions were evenly counterbalanced in each of subjects to control for order effects in a repeated measures design. For the dual-hemispheric tDCS, the anodal electrode was placed over the primary sensorimoter cortex (SM1) in the right hemisphere, whereas the cathodal electrode was placed over the SM1 in the left hemisphere.

For conventional single-hemispheric tDCS, the anodal electrode was placed over the SM1 in the left hemisphere, whereas the cathodal electrode was placed over the supraorbital area in the right hemisphere.

Experimental paradigm for transcranial direct current stimulation and functional MRI

The subjects were placed in a supine position with their eyes closed, and wore headphones for hearing protection. To prevent motion artifacts during functional MRI scans, movements of the head, trunk, and arms were restricted. The functional MRI paradigm consisted of two conditions (A and B) and was composed of a sham-resting phase, preparatory phase, and a

transcranial direct current stimulation phase. Condition A was scanned in the following order: the sham-resting phase – the preparatory phase – the dual-hemispheric transcranial direct current stimulation phase. Condition B scanned in the following order: the sham-resting phase – the preparatory phase – the single-hemispheric transcranial direct current stimulation phase. All subjects underwent conditions A and B with a 5-minute rest period between the conditions to allow for the elimination of the effects of the previous transcranial direct current stimulation. The orders of the conditions were evenly counterbalanced in each subject to control for order effects in a repeated measure design, such as habituation and learning of the motor task, and to offset any remaining effects of the transcranial direct current stimulation. These factors have been well established in prior studies[7, 29, 31].

The functional MRI paradigm was conducted as a block design with a sham-resting phase, preparatory phase, and a stimulation phase. The sham-resting transcranial direct current stimulation phase lasted for 60 seconds, and served as the control phase for subtraction functional MRI analysis. The preparatory transcranial direct current stimulation cycle of 60 seconds was composed of a preparation period to reach the output of a stable direct current, and the data obtained were excluded from the final data analysis. Transcranial direct current stimulation stimulations included dual- and single-hemispheric transcranial direct current stimulation that lasted over 60 seconds each. The preparatory and stimulation phases were applied at a constant current of 1.0 mA for 2 minutes, with a ramp-up and down over the initial and final 3 seconds of the 60 second stimulation period, respectively. Finally, the sham-resting phase lasted 1 minute and included transcranial direct current stimulation at a current density of 0.029 mA/cm^2 for 2 minutes during the preparatory and stimulation phases. All subjects were instructed to notify our inspector when they felt any adverse effects such as headaches and nausea. In our experiments, the subjects did not complain of any adverse effects, with the exception of a mild itching sensation under the electrodes. Finally, to test region-specific effects for the stimulation phase, we subtracted the sham-rest phase from each of the transcranial direct current stimulation phases, including dual- and single-hemispheric transcranial direct current stimulation.

Functional MRI analysis

BOLD functional MRI and Echo Planar Imaging (EPI) technique were performed using a 1.5T MR scanner (Gyroscan Intera System, Phillips, Germany) with a standard head coil. For anatomic base images, 20 axial, 5-mm thick, T1-weighted, spin echo images were obtained with a matrix size of 256 × 205 and a field of view of 210 mm parallel to the bicommissural line of the anterior commissure-posterior commissure. EPI-BOLD images were acquired over identical 20 axial sections and 310 images per subject (including 10 dummy images) were produced. The imaging parameters used were: repetition time/echo time, 2.0 seconds/50 ms, field of view = 210 mm, matrix size = 64 × 64, and slice thickness = 5 mm. Functional MRI data analysis was performed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) running under the MATLAB environment (The Mathworks, USA). Functional data for each participant were motion-corrected. All images were realigned and normalized, and smoothed with an 8-mm isotropic Gaussian kernel. Statistical parametric maps were obtained, and voxels were considered significant at an uncorrected $P < 0.001$ or family wise error $P < 0.05$, depending on the individual threshold of direct current stimulation. We adopted the optimal significance P value that best depicted the cortical effect of transcranial direct current stimulation, and applied the same P value to the dual- and single-hemispheric transcranial direct current stimulation. Activations were defined as regions of five voxels. Regions of interest were drawn around the SM1 and right frontal areas. The SM1 regions of interest included the precentral and postcentral gyri centered on the precentral knob. Voxel counts were used to estimate the amount of cortical activation in response to transcranial direct current stimulation, because they reliably reflect cortical activations and changes in cerebral blood flow[32-33].

Statistical analysis

To compare voxel counts and BOLD signal intensities between dual-hemispheric transcranial direct current stimulation and single-hemispheric transcranial direct current stimulation, we analyzed these dependent variables using the Mann-Whitney test. Statistical analysis was conducted using PASW 18.0 software (SPSS, Chicago, IL, USA), and statistical significance was accepted at P values of < 0.05.

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Conflicts of interest: None declared.

Ethical approval: The study protocol was approved by the Institutional Review Board of Yeungnam University Hospital, Republic of Korea.

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