Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 435 (2008) 56–59
Neuroscience Letters
www.elsevier.com/locate/neulet

Primary motor cortex activation by transcranial direct current stimulation in the human brain

Yong Hyun Kwon [a], Myoung-Hwan Ko [b], Sang Ho Ahn [c], Yun-Hee Kim [d], Jun Chan Song [e], Chu-Hee Lee [f], Min Cheol Chang [c], Sung Ho Jang [c,*]

[a] *Department of Physical Therapy, Yeungnam College of Science and Technology, Republic of Korea*
[b] *Department of Physical Medicine and Rehabilitation, Research Institute of Clinical Medicine, Chonbuk National University Medical School, Republic of Korea*
[c] *Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, 317-1, Daemyungdong, Namku, Taegu, 705-717, Republic of Korea*
[d] *Department of Physical Medicine and Rehabilitation, Sungkyunkwan University School of Medicine, Republic of Korea*
[e] *Department of Physical Therapy, Kyungbuk College, Republic of Korea*
[f] *Department of Biochemistry and Molecular Biology, College of Medicine, Yeungnam University, Republic of Korea*

Received 2 November 2007; received in revised form 14 January 2008; accepted 4 February 2008

Abstract

Transcranial direct current stimulation (tDCS) can modulate motor cortex excitability in the human brain. We attempted to demonstrate the cortical stimulation effect of tDCS on the primary motor cortex (M1) using functional MRI (fMRI). An fMRI study was performed for 11 right-handed healthy subjects at 1.5 T. Anodal tDCS was applied to the scalp over the central knob of the M1 in the left hemisphere. A constant current with an intensity of 1.0 mA was applied. The total fMRI paradigm consisted of three sessions with a 5-min resting period between each session. Each session consisted of five successive phases (resting–tDCS–tDCS–tDCS–tDCS), and each of the phases was performed for 21 s. Our findings revealed that no cortical activation was detected in any of the stimulation phases except the fourth tDCS phase. In the result of group analysis for the fourth tDCS phase, the average map indicated that the central knob of the left primary motor cortex was activated. In addition, there were activations on the left supplementary motor cortex and the right posterior parietal cortex. We demonstrated that tDCS has a direct stimulation effect on the underlying cortex. It seems that tDCS is a useful modality for stimulating a target cortical region.

Keywords: tDCS; Transcranial direct current stimulation; Functional MRI; Motor cortex

The investigation of the stimulation effect on the brain is important in relation to scientific brain rehabilitation. Recently, many investigators showed that the neural cells of the cerebral cortex could be manipulated by non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) [7,9–11,13,16–18]. tDCS continuously applies a weak direct current between two electrodes positioned on the scalp [11,14]. The stimulation effect can vary according to the polarity of the electrodes. Anodal stimulation increases cortical excitability, while cathodal stimulation decreases it. It is well known that tDCS can modulate motor cortex excitability in normal subjects [9,10,13,16–18]. Moreover, recent studies demonstrated that tDCS can improve motor function in hemiparetic patients with stroke [2,4,6]. These studies have been conducted using behavioral testing, TMS study, and functional neuroimaging [2,4,6,9–11,13,16–18]. However, there have been no reports of the use of functional neuroimaging to demonstrate the direct effect of tDCS on the underlying cortex.

In the current study, we hypothesized that the anodal stimulation of tDCS has the direct stimulating effect on the underlying ipsilateral primary motor cortex (M1) and eventually will increase the neural activity of the underlying M1. Therefore, we attempted to demonstrate a direct effect of tDCS on the underlying M1 in normal subjects using functional MRI (fMRI).

Eleven right-handed healthy subjects (men: 9, mean age: 26.55 ± 1.86) without neurological or psychiatric history were

* Corresponding author. Tel.: +82 53 620 3269; fax: +82 53 620 3269.
E-mail addresses: strokerehab@hanmail.net, belado@med.yu.ac.kr (S.H. Jang).

0304-3940/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2008.02.012

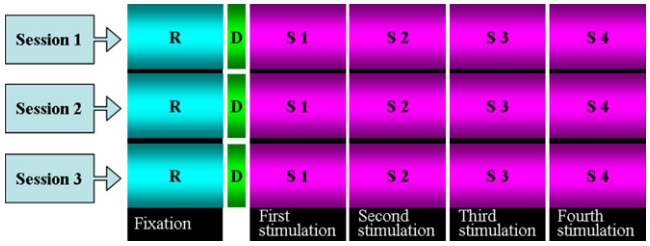

Fig. 1. The paradigm of functional MRI scanning. The total functional MRI paradigm consisted of three sessions with a 5-min resting period between each of the sessions. Each session consisted of five successive phases (resting-transcranial direct current stimulation (tDCS)–tDCS–tDCS–tDCS). Each of the phases was performed for 21 s.

enrolled in this study. We excluded subjects who had participated in any experiment that stimulated the brain such as TMS or tDCS within the year before the study. All subjects understood the purpose of this study, and provided written, informed consent prior to participation in this experiment. This study was approved by the institutional review board of Yeungman university hospital, Daegu, Korea.

Subjects put in a supine position with their eyes closed, and their head, trunk, and arms were immobilized firmly to prevent motion artifacts. Direct current was delivered by a battery-driven constant DC current stimulator (Phoresor® II Auto Model PM850, IOMED, US) with a pair of electrodes (EL508, Biopac system INC, US) and lead (LEAD108, Biopac system INC, US). The electrodes and lead were manufactured to be compatible with a magnetic field. The diameter of the anodal electrode was 3 cm (7.07 cm^2), and that of the cathodal electrode was 6 cm (28.26 cm^2). We used the small anodal electrode to give focal stimulation to underlying cortex. The anodal electrode was placed on the precentral knob of the primary motor cortex (M1) in the left hemisphere; this is the neural center of hand motor function [19]. For determining the exact location of the central knob, the optimal scalp site (motor hot spot where the excitatory threshold was the lowest, latency was the shortest, and average amplitude was the largest) for the resting abductor digiti minimi muscle was determined using TMS over the left cortex. The cathodal electrode was positioned over the supraorbital area in the right hemisphere. A constant current with an intensity of 1.0 mA was applied, with ramp up during the dummy phase (prior to the first tDCS phase) and ramp down after the termination of the fourth tDCS phase for several seconds.

The total fMRI paradigm consisted of three sessions with a 5-min resting recess between each session (Fig. 1). Each session consisted of five successive phases (no stimulation–tDCS–tDCS–tDCS–tDCS). During the no stimulation, no electrical stimulation was provided for 21 s as a control phase. Each subsequent stimulations was performed for 21 s, resulting in the subject receiving tDCS for 84 s at each session. Prior to the first tDCS phase, a 6.2-s dummy phase was conducted to provide time for the manipulation of the stimulator and to eliminate the effect of unstable stimulations in the early phase. Finally, to test regionally-specific condition effects for each of the four stimulation phases, we subtracted the resting phase from each of the four stimulation phases (Fig. 1).

The blood oxygenation level-dependent (BOLD) fMRI measurement, which employs the echo planar imaging (EPI) technique, was performed using a 1.5 T MR scanner (Gyroscan Intera System, Phillips, Germany) with a standard head coil. For the 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 (FOV) of 210 mm, parallel to the bicommissure line of the anterior commissure-posterior commissure. The EPI-BOLD images were acquired over the same 20 axial sections, producing a total of 3000 images for each subject. Imaging parameters consisted of TR/TE = 2.1 s/50 ms, FOV = 210 mm, matrix size = 64 × 64, and slice thickness = 5 mm.

fMRI data analysis was accomplished using SPM2 software (Wellcome Department of Cognitive Neurology, UK) running under MATLAB environment (The Mathworks, USA). The functional data of each participant were motion-corrected. All images were realigned and co-registered. The images were smoothed with an 8-mm isotropic Gaussian kernel. Statistical parametric maps were obtained, and voxels were considered significant at an uncorrected $p < 0.001$. Activations were based on the extent of five voxels. For group analysis of the normal group, images related to the amplitude of the hemodynamic response were entered into one-sample *t*-test random effects analyses, and were registered to the standard stereotaxic space of Talairach coordinates to create statistical parametric maps documenting the group average. Regions of interest were drawn around the primary motor cortex (M1), primary sensory cortex, premotor cortex, supplementary motor area (SMA), and posterior parietal cortex. M1 was defined as the region of the cortex that included the posterior half of the precentral gyrus (including the anterior bank of the central sulcus), and S1 was defined as the postcentral gyrus. The premotor cortex included the anterior half of the precentral gyrus, as well as the anterior bank of the precentral sulcus. SMA was limited to the cortex on the medial wall of the hemisphere, extending from the top of the brain to the depth of the cingulate sulcus, including the dorsal bank of the cingulate sulcus; the posterior boundary was located halfway between the extension of the central and precentral sulci onto the medial surface, and the anterior boundary was defined by the vertical line drawn from the anterior commissure [3].

Our findings revealed that no cortical activation was detected in any of stimulation phases except the fourth tDCS phase. Fig. 2 shows the result of group analysis for the cortical activation induced by the fourth tDCS phase. The average map indicates that the central knob of the left M1 was activated, and the peak voxel size was 12 at $x = -22$, $y = -28$, $z = 56$. In addition, the left SMA was activated, and the peak voxel size was 41 at $x = -4$, $y = -20$, $z = 56$. In the right hemisphere, the posterior parietal cortex was activated, and the peak voxel size was 23 at $x = 42$, $y = -54$, $z = 56$.

Eight of subjects (72.7%) felt the current as a slight itching (three subjects) or slight tingling sensation (five subjects). The rest of the subjects (27.3%) were not sensible of the current at both electrodes. Also, no adverse symptoms related with tDCS were observed.

In the current study, we found out that three areas (the central knob of M1 below the anode, the ipsilateral SMA to the anode,

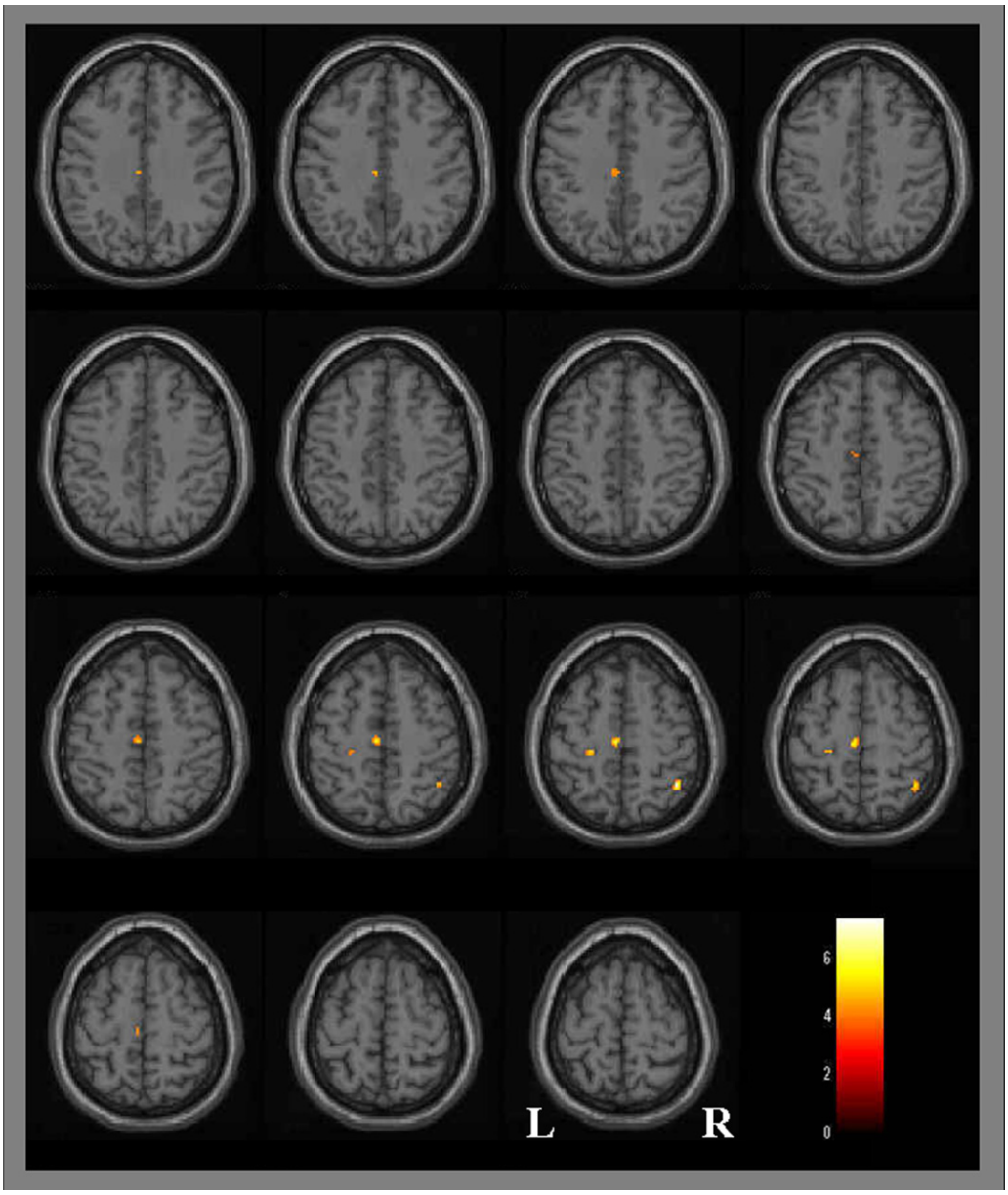

Fig. 2. The average cortical map induced by the fourth transcranial direct current stimulation during functional MRI scanning. Activations occurred on the central knob of the left primary motor cortex, the left supplementary motor cortex, and the right posterior parietal cortex (All brain scan images display a series of slices with a 2-mm gap. The color bar at the right corner indicates the *p*-value for each pixel showing significant activation).

the contralateral posterior parietal cortex to the anode) were activated by the fourth phase tDCS. It appears that the activation of the central knob of M1 could be ascribed to the direct stimulation effect of tDCS, and SMA and posterior parietal cortex activation were associated with sensory stimulation and attention [8], respectively. The inability to clarify whether these activations were ascribed to the cathodal tDCS is one of the limitations of this study.

It is not clear why there no activation occurred during the first, second, and third phases of tDCS. We assume that the stimulation was not intense and long enough to induce fMRI activation at these phases. However, due to the after-effects of the first, second, and third phase stimulations, the excitability of the precentral knob rose enough to show activation on fMRI during the fourth phase tDCS. Previous studies indicated that tDCS causes weak stimulation and the after-effect can last at least 3 min, and support our assumption [5,9,11,16,17]. We think that the fact that the voxel size of the precentral knob was smaller than those of SMA and the posterior parietal cortex provides additional evidence that the intensity of tDCS stimulation was weak.

Many studies have demonstrated the effects of tDCS on the motor cortex of the human brain [9,10,13,16–18]. Most of these studies have used the behavior test and/or TMS studies as assessment tools for the changes of the motor cortex. Thus far, two functional studies like this study have been reported [1,10]. In 2001, Baudewig et al. tried to demonstrate that anodal tDCS (1 mA, 5-min stimulation) applied on the scalp corresponding to the hand motor cortex could change the fMRI activation result-

ing from hand movements before and after anodal stimulation [1]. However, they failed to demonstrate a change in the activation of the hand area of the primary motor cortex. The other recent study was conducted by Lang et al. using PET in 2005 [10]. They demonstrated that the left M1, right frontal pole, right primary sensorimotor cortex, and posterior brain regions were activated by hand movements after anodal stimulation (1 mA, 10-min stimulation) on the left M1 scalp. However, this study also estimated changes of fMRI findings through hand movements before and after tDCS stimulation. Therefore, as far as we know, this is the first functional neuroimaging study to demonstrate the direct cortical effect of tDCS.

It is well known that tDCS is safe. Some researchers have suggested safety guidelines for tDCS used on the human brain [11–13,15]. In the current study, we were obliged to use a smaller electrode than that recommended or those used in previous studies [11–13,15], because we had to use an electrode that was compatible with the MRI machine. No adverse symptoms related with tDCS were observed in the current study. We think that there are two possible reasons for this observed safety. The first possibility is that the tDCS stimulation period for each session was very short (84 s) compared with those of previous studies [2,9,10,17]. The other possibility is that this electrode is safe for use on the human brain. Some studies also reported that there had been no safety problem although they had used the smaller electrode than the safety guideline [1,6,18]. However, further studies to assess the safety of tDCS should be conducted. In the current study, we demonstrated that tDCS can safely stimulate the underlying cortical target region. This means that tDCS could be the modality with which to manipulate the cortical excitability. In addition, tDCS has several advantageous points in terms of its clinical use (simple, safe, and non-expensive) [5,11]. Therefore, it can be developed as a useful therapeutic modality to facilitate brain plasticity. Further studies should be focused on the optimal stimulation conditions to manipulate the cortex.

Future studies should also clarify the relationship between cortical activation and brain plasticity. This study has several limitations in that it was not performed along with (1) behavioral tests and/or TMS study, (2) sham stimulation, and (3) attention control for the subjects. Therefore, further studies that use these combinations of behavioral tests and/or TMS study, sham stimulation, and attention control for the subjects are needed.

In conclusion, we demonstrated that tDCS had a direct stimulation effect on the underlying M1, by using fMRI. It seems that tDCS is a useful modality for stimulation of a target cortical region.

Acknowledgement

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST) (No. M10642120004-06N4212-00410).

References

[1] J. Baudewig, M.A. Nitsche, W. Paulus, J. Frahm, Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation, Magn. Reson. Med. 45 (2001) 196–201.

[2] P.S. Boggio, A. Nunes, S.P. Rigonatti, M.A. Nitsche, A. Pascual-Leone, F. Fregni, Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients, Restor. Neurol. Neurosci. 25 (2007) 123–129.

[3] S.C. Cramer, G. Nelles, J.D. Schaechter, J.D. Kaplan, S.P. Finklestein, B.R. Rosen, A functional MRI study of three motor tasks in the evaluation of stroke recovery, Neurorehabil. Neural. Repair 15 (2001) 1–8.

[4] F. Fregni, P.S. Boggio, C.G. Mansur, T. Wagner, M.J. Ferreira, M.C. Lima, S.P. Rigonatti, M.A. Marcolin, S.D. Freedman, M.A. Nitsche, A. Pascual-Leone, Transcranial direct current stimulation of the unaffected hemisphere in stroke patients, Neuroreport 16 (2005) 1551–1555.

[5] M. Hauck, U. Baumgartner, E. Hille, S. Hille, J. Lorenz, M. Quante, Evidence for early activation of primary motor cortex and SMA after electrical lower limb stimulation using EEG source reconstruction, Brain Res. 1125 (2006) 17–25.

[6] F. Hummel, P. Celnik, P. Giraux, A. Floel, W.H. Wu, C. Gerloff, L.G. Cohen, Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke, Brain 128 (2005) 490–499.

[7] F.C. Hummel, L.G. Cohen, Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? Lancet Neurol. 5 (2006) 708–712.

[8] Y.H. Kim, D.R. Gitelman, A.C. Nobre, T.B. Parrish, K.S. LaBar, M.M. Mesulam, The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry, NeuroImage 9 (1999) 269–277.

[9] N. Lang, H.R. Siebner, D. Ernst, M.A. Nitsche, W. Paulus, R.N. Lemon, J.C. Rothwell, Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects, Biol. Psychiatry 56 (2004) 634–639.

[10] N. Lang, H.R. Siebner, N.S. Ward, L. Lee, M.A. Nitsche, W. Paulus, J.C. Rothwell, R.N. Lemon, R.S. Frackowiak, How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur. J. Neurosci. 22 (2005) 495–504.

[11] M.A. Nitsche, D. Liebetanz, A. Antal, N. Lang, F. Tergau, W. Paulus, Modulation of cortical excitability by weak direct current stimulation–technical, safety and functional aspects, Suppl. Clin. Neurophysiol. 56 (2003) 255–276.

[12] M.A. Nitsche, D. Liebetanz, N. Lang, A. Antal, F. Tergau, W. Paulus, Safety criteria for transcranial direct current stimulation (tDCS) in humans, Clin. Neurophysiol. 114 (2003) 2220–2222 (Author reply 2222–2223).

[13] M.A. Nitsche, W. Paulus, Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation, J. Physiol. 527 (Pt 3) (2000) 633–639.

[14] W. Paulus, Transcranial direct current stimulation (tDCS), Suppl. Clin. Neurophysiol. 56 (2003) 249–254.

[15] A. Priori, Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability, Clin. Neurophysiol. 114 (2003) 589–595.

[16] A. Quartarone, F. Morgante, S. Bagnato, V. Rizzo, A. Sant'Angelo, E. Aiello, E. Reggio, F. Battaglia, C. Messina, P. Girlanda, Long lasting effects of transcranial direct current stimulation on motor imagery, Neuroreport 15 (2004) 1287–1291.

[17] H.R. Siebner, N. Lang, V. Rizzo, M.A. Nitsche, W. Paulus, R.N. Lemon, J.C. Rothwell, Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex, J. Neurosci. 24 (2004) 3379–3385.

[18] B.W. Vines, D.G. Nair, G. Schlaug, Contralateral and ipsilateral motor effects after transcranial direct current stimulation, Neuroreport 17 (2006) 671–674.

[19] T.A. Yousry, U.D. Schmid, H. Alkadhi, D. Schmidt, A. Peraud, A. Buettner, P. Winkler, Localization of the motor hand area to a knob on the precentral gyrus. A new landmark, Brain 120 (Pt 1) (1997) 141–157.