J. Phys. Ther. Sci.
23: 65–69, 2011

The Temporal Change of Cortical Activation Induced by the Ongoing Effects of Transcranial Direct Current Stimulation

YONG HYUN KWON, PT, PhD[1)], KI SEOK NAM, PT, MS[1)], MI YOUNG LEE, PT, PhD[2)], JI WON PARK, PT, PhD[3)], SUNG HO JANG, MD[4)]

[1)]*Department of Physical Therapy, Yeungnam College of Science & Technology*
[2)]*Department of Physical Therapy, College of Health and Therapy, Daegu Haany University*
[3)]*Department of Physical Therapy, College of Health Science, Catholic University of Daegu*
[4)]*Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University: 317–1, Daemyung 5-Dong, Namgu, Daegu, 705-717 Republic of Korea.*
TEL: +82 53-620-3269, FAX: +82 53-629-5048, E-mail: strokerehab@hanmail.net

Abstract. [Purpose] The aim of this study was to determine when cortical activation of targeted neurons is induced by the ongoing effects of anodal transcranial direct current stimulation (tDCS), and how temporal change is processed, using functional magnetic resonance image (fMRI). [Subjects and Methods] Eleven healthy right-handed subjects were recruited. Functional MRI was performed for five consecutive 1-minute phases (control, tDCS1, tDCS2, tDCS3, tDCS4). During four tDCS phases, direct current with 1.0 mA was delivered to the hand knob of the precentral gyrus, and the resting phase served as a control session. [Results] Our findings show that cortical neurons below the anodal tDCS were activated from the second through the fourth tDCS phase. However, there was no activation in the first tDCS phase. In addition, the amount of cortical activation (peak voxels) tended to fluctuate from the second phase through fourth phases. [Conclusion] We demonstrated that the a continuous effect of tDCS was induced after 1 minute since the direct current is injected to target neurons. The effect was maintained during the application tDCS, although it fluctuated.
Key words: Transcranial direct current stimulation, Temporal changes; Cortical activation, Functional MRI

(This article was submitted Jun. 9, 2010, and was accepted Jul. 12, 2010)

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a noninvasive technique for stimulating targeted brain regions which delivers a weak direct current through two electrodes attached to the scalp[1–3)]. Depending on the polarity of the current, neural activity of the underlying cortical tissues is temporarily modulated[1,4,5)]. For example, an anodal electrode increases cortical excitability, whereas a cathodal electrode has the opposite effect. Exploiting this property of polarity, tDCS has been used to enhance or reduce a variety of brain functions via direct modulation of the excitability of sensoriomotor, frontal, temporal, and visual cortices[6–10)]. Numerous studies have established the changes in behavioral functions induced during or after tDCS[9,11–14)].

The study of tDCS in conjunction with neuroimaging methods is a promising approach in the field of neuroscience, because it contributes to the body of scientific knowledge concerning neurophysiologic effects in the brain, along with changes in behavioral function. With the development of functional neuroimaging techniques such as functional magnetic resonance image (fMRI) and positron emission tomography (PET), a few studies have demonstrated direct effects on the underlying cortical target neuron during or following tDCS[14–17)]. However, no studies have investigated how temporal changes in cortical activation of the target neurons are processed during the delivery of direct current, even though an ongoing direct effect of tDCS on the underlying cortical region has been demonstrated via fMRI[14)]. Therefore, we sought to determine when the activation of targeted cortical neurons below anodal tDCS is induced, and how the temporal change is processed in conjunction with the ongoing effect of tDCS, via fMRI.

SUBJECTS AND METHODS

Eleven healthy subjects without neurological or psychiatric history (5 men, mean age: 22.60 ± 2.97 years; 6 female, mean age: 22.33 ± 3.27 years) participated in this experiment. All subjects were right-handed as determined by the modified Edinburgh Handedness Inventory[18)]. The subjects understood the purpose of this study, and gave their prior written, informed consent to participation. This

protocol was approved by the Institutional Review Board of Yeungnam University Hospital, and was in accordance with the ethical standards of the Declaration of Helsinki.

Subjects were placed in a supine position with their eyes closed. To prevent motion artifacts during fMRI scanning, movements of the head, trunk, and arms were prohibited. Direct current was generated by a battery-driven constant DC current stimulator (NeuroConn GmbH, Ilmenau, Germany) outside the MRI room. Current was delivered to the scalp of the subjects, using a pair of electrodes (EL508, Biopac System INC, US) and leads (LEAD108, Biopac System INC, US) manufactured for compatibility with a magnetic field. The MRI compatible electrodes, which were pre-gelled with a 1 cm diameter circular contact area on a 38 cm diameter backing, were placed on a water-soaked sponge (5 × 7 cm) in contact with the scalp. The center of the anodal electrode was placed above the precentral knob of the precentral gyrus in the dominant hemisphere. This area is well known as the neural representational area of hand motor function[19]. To confirm the exact location of the central knob, the optimal scalp site for the left cortex was determined by transcranial magnetic stimulation (TMS). TMS was performed using a Magstim 200 magnetic stimulator with a 70 mm butterfly coil. A cloth marked with 1 cm spacing and Cz-referenced to the intersection of the midsagittal and interaural lines was placed on the scalp. Magnetic stimulation was performed at the level of the excitatory threshold (ET) output plus 20%. The MEPs were obtained from both abductor digiti minimi in a relaxed state. Each site was stimulated three times at 1 cm intervals, which established the shortest latency and the average of the peak-to-peak amplitudes. The site where the ET was lowest, latency was shortest, and average amplitude was largest was chosen as the optimal scalp site. The cathode was positioned over the supraorbital area in the right hemisphere. We applied current at a density of 0.029 mA/cm^2, which has been used in previous studies proven safe for prevention of tissue damage[20,21]. tDCS was applied at a constant current with an intensity of 1.0 mA for four minutes, with ramp up current (3 seconds) in the dummy phase (prior to the first tDCS phase) and ramp down current (3 seconds) after termination of the forth tDCS phase.

fMRI was conducted consecutively for one resting phase and four tDCS phases. Each phase included three successive cycles of 60 seconds. No tDCS was delivered during the resting phase which served as the sham control session. The direct current was delivered for 4 minutes during the four tDCS phases. Immediately after the resting phase, a 10-second dummy cycle was inserted to provide time for manipulation of the stimulator and to eliminate the effect of unstable stimulation in the early phase including the ramp up current. Consequently, fMRI scanning was performed for 310 seconds: one resting phase (60 seconds), one dummy cycle (10 second), and four tDCS phases (240 seconds). Finally, to test regionally-specific condition effects for each of the four tDCS phases, we subtracted the resting phase from each of the four tDCS phases.

Blood oxygenation level-dependent (BOLD) fMRI measurements, which employed the 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 (FOV) of 210 mm, parallel to the bicommissure line of the anterior commissure-posterior commissure.

EPI-BOLD images were acquired over the 20 identical axial sections, producing a total of 310 images for each subject, including 10 dummy images. Imaging parameters consisted of TR/TE = 2.0 sec/50 msec, FOV = 210 mm, matrix size = 64 × 64, and slice thickness = 5 mm. fMRI data analysis was performed using SPM2 software (Wellcome Department of Cognitive Neurology, UK) running under the MATLAB environment (The Mathworks, USA). Functional data of each participant were motion-corrected. All images were realigned and normalized. 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 regions of five voxels. For group analysis of the normal group, images associated with the amplitude of the hemodynamic response were entered into one-sample t-test random effects analysis, and registered to the standard stereotaxic space of Talairach coordinates for the creation of statistical parametric maps documenting the group average. The differences in brain activation between the two tasks were compared by a random effect group analysis (uncorrected $p<0.001$). Regions of interest were drawn around the primary sensoriomotor cortex (SM1), supplementary motor area (SMA), and premotor cortex (PMC). The SM1 includes the precentral and postcentral gyrus centered on the precentral knob. The PMC extends horizontally from the precentral sulcus to the rostral limit, which lies halfway between the central sulcus and the anterior-most extent of the brain and between the sylvian fissure and the SMA. The SMA, which is located anterior to the leg somatotopy of the primary motor cortex, extends from the brain vertex to the cingulate sulcus. We conducted voxel counts to estimate the amount of cortical activation in response to tDCS, because these are reliable indicators that reflect cortical activation and changes in cerebral blood flow[22,23].

RESULTS

fMRI data from two of eleven subjects were not completely acquired, due to surplus electrical impedance between the scalp and electrodes during fMRI scanning. Ultimately, a total of nine subjects, all but two subjects, were analyzed for a group-averaged map. Fig. 1 dispalys the results of group analysis of cortical activation induced by anodal tDCS from the first through the fourth phases. The results of the group analysis show that cortical neurons below the anodal tDCS were activated from the second through the fourth phases, while no activation was observed in the first phase. According to the results for the second phase of eight subjects (subject 7 showed no cortical activation), the average map revealed that the ipsilateral

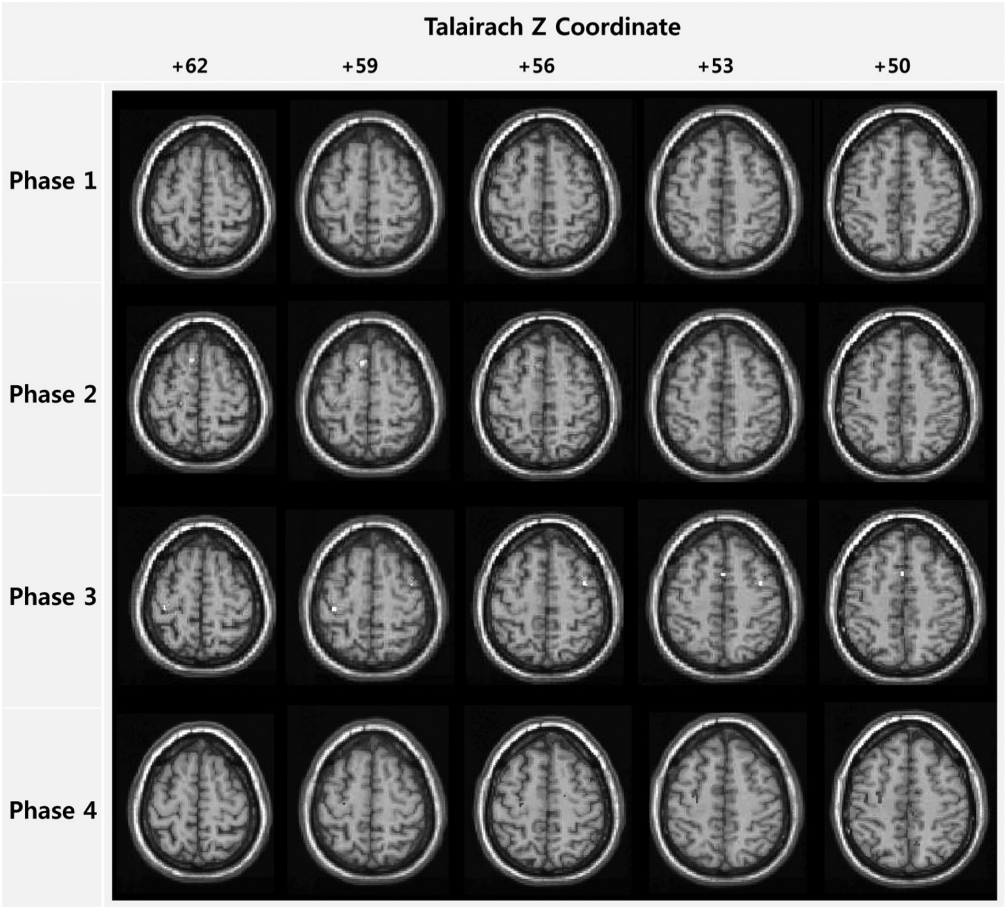

Fig. 1. Average cortical map according to group analysis of functional MRI in four consecutive phases in which the direct current was applied to the underlying precentral knob. All brain scan images display a series of slices with a 3-mm gap.

SM1 (left hemisphere) was activated, and the peak voxel, 34, was located at x=–30, y=–26, z=60. In addition, the ipsilateral PMA was activated (peak voxel 9). Group analysis of the third phase of seven subjects (subjects 4 and 6 omitted) indicated that the ipsilateral SM1was activated, and the peak voxel, 6, was located at x=–36, y=–28, z=62. Additionally, the contralateral PMA was activated (8 peak voxels). In results of the group analysis of seven subjects (subject 5 and 7 omitted) in the fourth phase, the ipsilateral SM1 was activated, and the peak voxel was, 60, was located at x=–26, y=–22, z=64. The contralateral PMA was also activated (peak voxel 6).

DISCUSSION

In the present study, we found that SM1 below the anode was activated from the second through the fourth phases when the anodal tDCS, centered on the precentral knob, was applied during the four consecutive tDCS phases; however, no cortical neurons were activated during the first tDCS phase. The five consecutive phases consisted of one resting control phase and four tDCS phases (the first through the fourth phase); each tDCS phase was one minute long. Therefore, we believe that the ongoing effect of tDCS is induced and maintained after one minute when direct current is applied to the target neurons. In addition, cortical activations were observed in ipsilateral or contralateral PMA. Activations in PMA appear to be related to the connectivity-driven effect of tDCS and the synergistic facilitation of the neural cell near the center of the electrode [11,14,16]. Cortical activation in the regions of interest may be attributable to the BOLD fMRI detected depolarization of the targeted neurons which were driven by cortical excitability changes during the application of tDCS. Previous studies suggested that tDCS may lead to modifications of the neuronal resting membrane potential and to changes in the spontaneous discharge rate[24,25]. It is well established that such neural activity occurs in conjunction with energy metabolism[26,27]. Therefore, we believe that the hemodynamic signal changes could reflect the energetically expensive, synaptic activity induced by the ongoing effect of tDCS.

Individual data showed variations among subjects. Activation of target neurons was not always observed in all phases. This may be attributable to individual differences in electrical conditions such as skin impedance, temperature, etc. Previous electrophysiology studies have suggested that variation of current density is caused by anatomical

parameters (e.g., thickness of the stratum corneum lying on top of the epidermis, sweat duct resistivity) and electrode parameters (e.g. hydration, resistivity)[28–30]. Individual differences in anatomical parameters are well known[29,30]. Further, the number of peak voxels varied among the three consecutive phases (the second to the fourth phase), in which the amount of cortical activation tended to decrease and increase from the second to the fourth phases. Previous neurophysiologic studies have proposed that cortical activity depends upon the balance between excitatory and inhibitory influences[31,32]. Therefore, we believe that such changes in voxel count during the three phases might be due to variations of facilitation and inhibition in the human brain. In contrast, we assume that the direct current was either not sufficiently intense or long enough to reach the excitatory threshold of the targeted cortical neurons due to the electrical instability of the initial current; thus, there was no activation in the first phase[14].

Several previous studies have demonstrated that the ongoing effects of tDCS have induced improvements of motor and cognitive brain function such as motor skill acquisition, motor planning, force endurance, and attention[8,12,33–35]. However, studies that have demonstrated the ongoing effect of tDCS using functional neuroimaging techniques have been rare, thus far. To the best of our knowledge, our previous study, which was conducted in 2008, was the first fMRI study to demonstrate that target cortical neurons on SM1 were activated during delivery of anodal tDCS. Therefore, it is obvious that tDCS has a direct ongoing effect on the underlying targeted cortex in fMRI. However, there were some differences in the experimental conditions of these two studies. The fMRI paradigm of the previous study was not designed for investigation of temporal changes in cortical activation induced by anodal tDCS; however, it was designed to investigate the presence of cortical activation by the anodal tDCS. The fMRI paradigm of our previous study was designed as three repeated sessions consisting of five successive phases (control phase (no stimulation) - tDCS phase 1- tDCS phase 2 - tDCS phase 3 - tDCS phase[4]), with a 5-minute resting period between each session. To perform the subtraction analysis for each of the four tDCS phases, the sum images of the same tDCS phases extracted from each of the three sessions was subtracted from that of the control phase of each session. Therefore, it may be difficult to prove that the lasting tDCS effect was completely eliminated during the five minute resting phase between the three consecutive phases. Moreover, the question of whether or not successive tDCS could maintain the excitatory threshold of target neurons, even after cortical activation emerged, was not evaluated.

Recent tDCS studies have attempted to discover optimal electrical parameters for optimal stimulative conditions of targeted cortical neurons[36–39]. In particular, guidelines for applications have been presented for providing effective current and stimulation positions for maintaining peak current density[36,38]. Therefore, we believe that our findings will provide clinicians with useful information on temporal changes of cortical activation induced by tDCS. However, our study was limited by a small sample size and a short total fMRI scanning time (4 minutes) due to the mechanical restrictions of the MR equipment. Further studies are required to establish a protocol for tDCS application for effective stimulation of the underlying targeted neurons, such as the optimal density and duration of direct current.

ACKNOWLEDGEMENT

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (2009-0064682).

REFERENCES

1) Paulus W: Transcranial direct current stimulation (tDCS). Suppl Clin Neurophysiol, 2003, 56: 249–254.
2) Nitsche MA, Liebetanz D, Antal A, et al.: Modulation of cortical excitability by weak direct current stimulation –technical, safety and functional aspects. Suppl Clin Neurophysiol, 2003, 56: 255–276.
3) Priori A, Berardelli A, Rona S, et al.: Polarization of the human motor cortex through the scalp. Neuroreport, 1998, 9: 2257–2260.
4) Sparing R, Thimm M, Hesse MD, et al.: Bidirectional alterations of interhemispheric parietal balance by non-invasive cortical stimulation. Brain, 2009.
5) Priori A: Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. Clin Neurophysiol, 2003, 114: 589–595.
6) Tanaka S, Hanakawa T, Honda M, et al.: Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. Exp Brain Res, 2009, 196: 459–465.
7) Antal A, Nitsche MA, Paulus W: Transcranial direct current stimulation and the visual cortex. Brain Res Bull, 2006, 68: 459–463.
8) Stone DB, Tesche CD: Transcranial direct current stimulation modulates shifts in global/local attention. Neuroreport, 2009, 20: 1115–1119.
9) Ohn SH, Park CI, Yoo WK, et al.: Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. Neuroreport, 2008, 19: 43–47.
10) Nowak DA, Grefkes C, Dafotakis M, et al.: Effects of low-frequency repetitive transcranial magnetic stimulation of the contralesional primary motor cortex on movement kinematics and neural activity in subcortical stroke. Arch Neurol, 2008, 65: 741–747.
11) Boros K, Poreisz C, Munchau A, et al.: Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. Eur J Neurosci, 2008, 27: 1292–1300.
12) Dockery CA, Hueckel-Weng R, Birbaumer N, et al.: Enhancement of planning ability by transcranial direct current stimulation. J Neurosci, 2009, 29: 7271–7277.
13) Hunter T, Sacco P, Nitsche MA, et al.: Modulation of internal model formation during force field-induced motor learning by anodal transcranial direct current stimulation of primary motor cortex. J Physiol, 2009, 587: 2949–2961.
14) Kwon YH, Ko MH, Ahn SH, et al.: Primary motor cortex activation by transcranial direct current stimulation in the human brain. Neurosci Lett, 2008, 435: 56–59.
15) Baudewig J, Nitsche MA, Paulus W, et al.: Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. Magn Reson Med, 2001, 45: 196–201.
16) Jang SH, Ahn SH, Byun WM, et al.: The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. Neurosci Lett, 2009, 460: 117–120.
17) Lang N, Siebner HR, Ward NS, et al.: How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? Eur J Neurosci, 2005, 22: 495–504.
18) Oldfield RC: The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 1971, 9: 97–113.
19) Yousry TA, Schmid UD, Alkadhi H, et al.: Localization of the motor hand area to a knob on the precentral gyrus. A new landmark. Brain, 1997, 120 (Pt 1): 141–157.
20) Boggio PS, Castro LO, Savagim EA, et al.: Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. Neurosci Lett, 2006, 404: 232–236.

21) Hummel F, Cohen LG: Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair, 2005, 19: 14–19.
22) Ugurbil K, Ogawa S, Kim S, et al.: Imaging brain activity using nuclear spins. Amsterdam: IOS Press, 1999, pp. 261–310.
23) Waldvogel D, van Gelderen P, Immisch I, et al.: The variability of serial fMRI data: correlation between a visual and a motor task. Neuroreport, 2000, 11: 3843–3847.
24) Nitsche MA, Paulus W: Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol, 2000, 527 (Pt 3): 633–639.
25) Samii A, Wassermann EM, Ikoma K, et al.: Characterization of postexercise facilitation and depression of motor evoked potentials to transcranial magnetic stimulation. Neurology, 1996, 46: 1376–1382.
26) Logothetis NK, Pauls J, Augath M, et al.: Neurophysiological investigation of the basis of the fMRI signal. Nature, 2001, 412: 150–157.
27) Magistretti PJ, Pellerin L, Rothman DL, et al.: Energy on demand. Science, 1999, 283: 496–497.
28) Sha N, Kenney LP, Heller BW, et al.: A finite element model to identify electrode influence on current distribution in the skin. Artif Organs, 2008, 32: 639–643.
29) Doheny EP, Caulfield BM, Minogue CM, et al.: The effect of subcutaneous fat thickness on the efficacy of transcutaneous electrical stimulation. Conf Proc IEEE Eng Med Biol Soc, 2008, 2008: 5684–5687.
30) Birlea SI, Birlea NM, Breen PP, et al.: Identifying changes in human skin electrical properties due to long-term NeuroMuscular Electrical Stimulation. Conf Proc IEEE Eng Med Biol Soc, 2008, 2008: 326–329.
31) Chen R: Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res, 2004, 154: 1–10.
32) Orth M, Snijders AH, Rothwell JC: The variability of intracortical inhibition and facilitation. Clin Neurophysiol, 2003, 114: 2362–2369.
33) Reis J, Schambra HM, Cohen LG, et al.: Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. Proc Natl Acad Sci USA, 2009, 106: 1590–1595.
34) Cogiamanian F, Marceglia S, Ardolino G, et al.: Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas. Eur J Neurosci, 2007, 26: 242–249.
35) Iyer MB, Mattu U, Grafman J, et al.: Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology, 2005, 64: 872–875.
36) Miranda PC, Faria P, Hallett M: What does the ratio of injected current to electrode area tell us about current density in the brain during tDCS? Clin Neurophysiol, 2009, 120: 1183–1187.
37) Bikson M, Datta A, Elwassif M: Establishing safety limits for transcranial direct current stimulation. Clin Neurophysiol, 2009, 120: 1033–1034.
38) Im CH, Jung HH, Choi JD, et al.: Determination of optimal electrode positions for transcranial direct current stimulation (tDCS). Phys Med Biol, 2008, 53: N219–N225.
39) Poreisz C, Boros K, Antal A, et al.: Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull, 2007, 72: 208–214.