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The enhanced cortical activation induced by transcranial direct current stimulation during hand movements

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ABSTRACT

The aim of this study is to evaluate whether tDCS applied on the primary motor cortex (M1) in company with hand movements could enhance cortical activation, using functional MRI (fMRI). Twelve right-handed normal subjects were recruited. Real tDCS and sham tDCS with hand movements were applied during fMRI scanning. Subjects performed grasp-release hand movements at a metronome-guided frequency of 1 Hz, while direct current with 1.0 mA was delivered to the primary motor cortex. The averaged cortical map and the intensity index were compared between real tDCS with hand movements and sham tDCS with hand movements. Our result showed that cortical activation on the primary sensorimotor cortex was observed under both of two conditions; real tDCS with hand movements and sham tDCS with hand movements. Voxel count and peak intensity were 365.10 ± 227.23 and 5.66 ± 1.97, respectively, in the left primary sensorimotor cortex during real tDCS with right hand movements; in contrast, those were 182.20 ± 117.88 and 4.12 ± 0.88, respectively, during sham tDCS with right hand movements. Significant differences in voxel count and peak intensity were observed between real tDCS and sham tDCS ($p < 0.05$). We found that anodal tDCS application during motor task enhanced cortical activation on the underlying targeted motor cortex, compared with the same motor task without tDCS. Therefore, it seemed that tDCS induced more cortical activity and modulated brain function when concurrently applied with motor task.

Clarification of the relationship between external stimuli and brain response is an important topic in neurorehabilitation, because repeated facilitation by external stimuli can induce brain plasticity [18]. Neurostimulation modalities have been developed for modulation of cortical function in the human brain [2,4,13,21,22]. Transcranial direct current stimulation (tDCS) is a recently re-introduced technique for stimulation of cortical neurons by delivery of weak currents through the skull, which leads to changes in polarity-dependent excitability [9,26]. For example, excitability of cortical neurons is increased by anodal tDCS, whereas it is decreased by cathodal tDCS. A number of studies have demonstrated that application of tDCS upon the motor cortex could enhance motor performance in terms of strength, fatigue resistance of the targeted muscle, or higher motor function, such as visuo-motor coordination [6,9,11,15,17,30]. These behavioral results are described by an ongoing or long lasting tDCS effect [4,7,15,27]. Recent functional neuroimaging studies have demonstrated increased cortical excitability of the motor cortex during or after delivery of tDCS [1,19,21]. However, very little is known about changes in cortical activation when tDCS is combined with other neurorehabilitative modalities.

Since the development of functional neuroimaging techniques, many studies of cortical activation by external stimuli have been reported [1,3,5,7,10,16,19,20,24]. These include voluntary movement, somatosensory stimulation, electrical stimulation, or magnetic stimulation. Among the various external stimuli for cortical activation, voluntary movement has been used as an essential modality for neurorehabilitation. In the current study, we attempted to investigate whether anodal tDCS applied concurrently with hand movements could increase cortical activation of the primary sensormotor cortex (SM1).

Twelve subjects without neurological or psychiatric history (men: 5, mean age: 21.50 ± 2.64) were recruited. All subjects were right-handed, as verified by the modified Edinburgh Handedness Inventory [28]. All of the patients understood the purpose of this study, and gave their written, informed consent for participation in this experiment. The procedures were approved by the Institutional Review Board of Yeungnam University Hospital, which was in accordance with the ethical standards of the Declaration of Helsinki.

Direct current was generated by a battery-driven constant DC current stimulator (NeuroConn GmbH, Ilmenau, Germany) from

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outside the MRI room. Current was delivered to the scalp of the subject, using a pair of electrodes (EL508, Biopac System INC, US) and lead (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 cm × 7 cm) in contact with the scalp. The water-soaked sponge to directly contact with the skin was used for adjusting the electrical density for safety guideline and preventing a heating event caused by absorption of MRI radiofrequency power. No adverse symptoms related with tDCS were observed in the current study. 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 [33]. 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 resting motor threshold output plus 20%. 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. Latency was shortest at the site where the resting motor threshold was lowest, and the largest average amplitude was chosen as the optimal scalp site. The cathodal electrode 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 for prevention of tissue damage; this current density has been proven safe in previous studies [3,14].

Subjects were placed in a supine position with their eyes closed. To prevent motion artifacts during fMRI scanning, movement of the head, trunk, and arms was restricted. The fMRI paradigm consisted of two conditions (condition A and condition B), which had three alternative phases, respectively, including the real tDCS motor phase, the sham tDCS motor phase, and the resting phase. Condition A was scanned in the following order; the sham tDCS motor phase – the resting phase – the real tDCS motor phase, and condition B proceeded as follows; the real tDCS motor phase – the resting phase – the sham tDCS phase. The two conditions were evenly counterbalanced in each of the subjects, in order to control order effects in a repeated measure, such as habituation and learning of the motor task in fMRI, and to offset the lasting effect of tDCS. These factors have been well established in prior studies [12,23,25]. BOLD signal was acquired during delivery of tDCS in the real tDCS and sham tDCS motor phases. The resting phase without fMRI scanning was provided for elimination of the long lasting effect of tDCS and the motor task habituation performed in the prior phase during a period of approximately 5 min. The real tDCS motor phase was composed of three consecutive cycles, including control cycle (no tDCS and motor action for 63 s), preparatory tDCS cycle (preparation without tDCS and motor action for 63 s), and tDCS cycle (tDCS with motor action for 63 s). The real tDCS phase was applied at a constant current with an intensity of 1.0 mA for 2 min, with a ramp up current (3 s) prior to the initial stimulation and ramp down current (3 s) after termination of the final tDCS phase. The preparatory tDCS cycle without motor performance included a preparation period for induction of cortical excitability in the tDCS with motor performance cycle, and was then excluded in the final data analysis. The sham tDCS phase consisted of two consecutive cycles, including a control (no tDCS and motor action for 63 s) and a sham tDCS cycle (no tDCS with motor action for 63 s). All of the subjects were instructed that they would feel senseless or a mild itching sensation under the electrodes, depending on the variability of individuals, who were blinded to tDCS conditions. Therefore, subjects in the sham phase believed that they were receiving tDCS in all procedures, without delivery of real tDCS. For the motor task paradigm, all of the subjects performed grasp-release hand movements at a metronome-guided frequency of 1 Hz. Finally, in order to test region-specific condition effects for each of the stimulation phases, we subtracted the control cycle from the real tDCS or the sham tDCS phase with the motor performance cycle.

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 identical 20 axial sections, producing a total of 310 images for each subject, including 10 dummy images. Imaging parameters consisted of TR/TE = 2.0 s/50 ms, FOV = 210 mm, matrix size = 64 × 64, and slice thickness = 5 mm. fMRI data analysis was accomplished using SPM8 software (Wellcome Department of Cognitive Neurology, UK) running under a MATLAB environment (The Mathworks, USA). Functional data for 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 the 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 creation of statistical parametric maps documenting the group average. Differences in brain activation between the two tasks were compared by a random effect group analysis (uncorrected $p < 0.001$). Based on the group averaged images, regions of interest were drawn around the SM1, supplementary motor area (SMA), and premotor cortex (PMC). The SM1 includes the precentral and postcentral gyruses 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 sensoriomotor cortex, extends from the brain vertex to the cingulate sulcus. Voxel counts are reliable indicators that reflect cortical activation and changes in cerebral blood flow; therefore, we conducted voxel counts in order to estimate the amount of cortical activation in response to tDCS [31,32].

An independent t-test was conducted for comparison of differences in voxel size and peak intensity in the SM1 during the real tDCS phase with those during the sham tDCS phase. Statistical analyses were performed using SPSS software (version 17.0). Statistical significance was set at $p < 0.05$.

Table 1 indicates the amount of activation clusters in the primary motor cortex during real tDCS with hand movements and sham tDCS with hand movements. Fig. 1 shows the average maps obtained by group analysis of functional echo planar imaging in each of the regional activation clusters. As a result, real tDCS with hand movement induced more cortical activation in terms of the voxel count and peak intensity, than sham tDCS with hand movement. Significant differences in voxel count and peak intensity were observed between real tDCS and sham tDCS ($p < 0.05$).

In the current study, we investigated whether simultaneous application of tDCS on the SM1 with hand movements could increase cortical activation, compared to hand movements without tDCS. We found that tDCS application during hand movements enhanced cortical activity, compared with the same motor task