● RESEARCH ARTICLE

Is effect of transcranial direct current stimulation on visuomotor coordination dependent on task difficulty?

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Abstract

Transcranial direct current stimulation (tDCS), an emerging technique for non-invasive brain stimulation, is increasingly used to induce changes in cortical excitability and modulate motor behavior, especially for upper limbs. The purpose of this study was to investigate the effects of tDCS of the primary motor cortex on visuomotor coordination based on three levels of task difficulty in healthy subjects. Thirty-eight healthy participants underwent real tDCS or sham tDCS. Using a single-blind, sham-controlled crossover design, tDCS was applied to the primary motor cortex. For real tDCS conditions, tDCS intensity was 1 mA while stimulation was applied for 15 minutes. For the sham tDCS, electrodes were placed in the same position, but the stimulator was turned off after 5 seconds. Visuomotor tracking task, consisting of three levels (levels 1, 2, 3) of difficulty with higher level indicating greater difficulty, was performed before and after tDCS application. At level 2, real tDCS of the primary motor cortex improved the accurate index compared to the sham tDCS. However, at levels 1 and 3, the accurate index was not significantly increased after real tDCS compared to the sham tDCS. These findings suggest that tasks of moderate difficulty may improve visuomotor coordination in healthy subjects when tDCS is applied compared with easier or more difficult tasks.

Key Words: neural regeneration; transcranial direct current stimulation; visuomotor coordination; task difficulty; primary motor area; motor learning; neural regeneration

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Introduction

Transcranial direct current stimulation (tDCS) is an emerging technique for non-invasive brain stimulation that allows the modulation of cortical excitability, resulting in changes in brain function (Reis et al., 2008). The advantages of tDCS over transcranial magnetic stimulation (TMS), an alternative non-invasive brain stimulation technique, are that it is relatively inexpensive, simple to use, and easily transportable (Clancy et al., 2014). In particular, tDCS delivers low-intensity current to the brain, thereby facilitating (anodal stimulation) or inhibiting (cathodal stimulation) spontaneous neuronal activity; neurophysiological long-lasting effects of a single tDCS session can outlast the stimulation period by up to 90 minutes (Nitsche et al., 2003; Stagg and Nitsche, 2011). Neuronal segments orientated toward the stimulation anode have been shown to hyperpolarize, and concomitantly the segments oriented toward the cathode depolarize (Radman et al., 2009a). Clinical brain stimulation modalities, and associated therapeutic outcomes, may depend specifically on subthreshold (*e.g.*, tDCS) and suprathreshold (*e.g.*, TMS) neuronal effects (Wagner et al., 2007). In response to the unique electric fields, cortical neuron morphology relative to electric fields and cortical cell types are factors in determining sensitivity to subthreshold and suprathreshold brain stimulation (Radman et al., 2009a, b). A small direct current, typically 1–2 mA, is then applied and has been shown to influence the spontaneous activity of cortical neurons (Clancy et al., 2014).

In the motor domain, tDCS has been effectively used to enhance motor performance in healthy and brain-damaged individuals (Convento et al., 2014). Motor learning has been consistently shown to be associated with a large-scale cortical network that includes areas such as the primary motor area (M1), premotor and supplementary motor areas, basal ganglia, and cerebellum (Ungerleider et al., 2002; Quartarone et al., 2004; Reis and Fritsch, 2011). Several studies have shown that this technique may modulate cortical excitability in the human motor cortex (Di Lazzaro et al., 2004; Kwon et al.,

2008) and visual cortex (Antal et al., 2004a; Sparing et al., 2009), mediate beneficial effects on motor learning (Bolognini et al., 2009; Hunter et al., 2009) and visuomotor coordination tasks (Antal et al., 2004b, c), as well as have clinical applications (Arul-Anandam and Loo, 2009; Ferrucci et al., 2009). Especially, tDCS of the M1 can improve different motor functions, including motor execution (Antal et al., 2004c; Boggio et al., 2006), motor learning, and adaptation (Hunter et al., 2009; Stagg and Nitsche, 2011), consolidation of motor learning, and motor imagery.

Recently, several studies have reported that the percentage of correct movements increases in the early phase after tDCS of cortical areas compared to non-stimulation conditions, resulting in behavioral improvement at the beginning of the practice process (Antal et al., 2008). The chosen task is a visuomotor tracking paradigm, which offers a well-defined practice curve and can be modulated by tDCS of the M1 (Antal et al., 2004b). It is already well known that tDCS enhances cortical activation and motor performance by recruiting additional cortical neurons. However, there has been no study on the effects of task difficulty level on visuomotor coordination when tDCS is applied. Therefore, in this study, we investigated the effects of tDCS of the M1 on visuomotor coordination based on three levels of difficulty in healthy individuals.

Subjects and Methods

Subjects
A total of 38 healthy volunteers, 27 females and 11 males, aged 21.8 ± 1.4 years, were recruited from Yeungnam University College, Republic of Korea into this study *via* advertisement. These participants were subjected to real tDCS (*n* = 19) or sham tDCS (*n* = 19). Prior to participation, all subjects underwent a neurological examination to screen for any exclusion criteria regarding the use of non-invasive brain stimulation, such as taking any medication. All subjects were right-handed, according to the modified Edinburg Handedness Inventory (Oldfield, 1971) (mean score 87.46 ± 19.62). All subjects provided written informed consent prior to the experiment, and the study was approved by the Institutional Review Board of Yeungnam University Hospital (YUHS-40-14-032) in accordance with the ethical standards of the *Declaration of Helsinki*.

Test procedure
This study was designed as a single-blind, sham-controlled, and randomized crossover trial. All subjects were seated in front of a table with their left hands on the table and performed a tracking task comprising three levels of task difficulty. The level of task difficulty was dependent on velocity and was presented as various amplitudes from 1.5–3 Hz (level 1: 80 rpm, level 2: 120 rpm and level 3: 160 rpm). The task order was presented randomly and counter-balanced across all subjects according to stimulation condition. Depending on the individual, all subjects felt the current as a mild itching sensation or not at all under the electrodes during the initial stages of stimulation, and subjects were blinded to

stimulation conditions. For active conditions, tDCS intensity was 1mA while stimulation was applied for 15 minutes, in accordance with current safety data. For the sham control, electrodes were placed in the same position, but the stimulator was turned off after 5 seconds, as described previously. This ensured that participants could feel an itching sensation at the beginning of tDCS while no effective stimulation was delivered, thereby allowing successful blinding for real versus sham stimulations. The three-level tracking task test was performed before and after tDCS motor phase.

Transcranial direct current stimulation
A simple and constant current stimulator (Phoresor II Auto Model PM 850, IOMED, US) was used to deliver a direct current of 1 mA for 15 minutes with rubber surface electrodes (5 cm × 7 cm) housed in saline-soaked sponges. For stimulation of the primary motor area (M1), the anodal electrode was placed over C3 or C4 (according to the 10/20 electroencephalography system) in the right hemisphere while the reference electrode was placed over the supraorbital area in the left hemisphere. This area is well known as the neural representational area of hand motor function. All participants tolerated tDCS well, and no adverse effects related to the application of tDCS were observed or reported.

Tracking task
The tracking task was produced by metacarpal phalangeal joint extension and flexion movement. Participants were seated with their right elbows flexed on a table and used their left hands to hold a custom-made rotator machine with a built-in potentiometer. For the tracking task, the subjects were instructed to track the red target sine wave displayed on the computer screen for 15 seconds as accurately as possible. The response sine wave made by each subject was displayed as a black solid line, which was tracked up as the metacarpal phalangeal joint was extended and tracked down as the metacarpal phalangeal joint was flexed. For the tracking task, accuracy of tracking performance in each of the three trials was calculated as an accuracy index (AI). AI = 100(P–E)/P.

P value was the magnitude of the target pattern of each subject, measured as the root mean square (RMS) value between the sine wave and the vertical line at the up and down apexes. E value was calculated as the RMS error between the target and the response sine wave. The magnitude of P is based on the scale of the vertical axis, which is each subject's range of wrist motion. Therefore, the AI is normalized to each subject's own range of motion and takes into account any differences in excursion of the tracking target among subjects. The maximal score is 100. Negative scores occur when the response line is so distant from target that it falls on the opposite side of the midline.

Statistical analysis
Demographic data, such as gender and age, were analyzed using an independent *t*-test. The pre- and after-effects of tDCS were determined using two-way analysis of variance (factors: real-tDCS, sham-tDCS, factors × test: pre-tDCS,

Table 1 Mean and standard deviation (SD) of the accurate index (AI) depending on three levels of tracking task difficulty

	Real tDCS		Sham tDCS				
	Before	After	Before	After	Test (F)	Condition (F)	Interaction (F)
Level 1	8.09±0.70	8.92±0.3	8.26±0.64	8.77±0.68	0.000(26.148)	0.967(0.002)	0.223(1.539)
Level 2*	7.87±0.95	8.74±0.42	8.32±0.59	8.54±0.85	0.000(21.996)	0.548(0.369)	0.008(2.033)
Level 3	7.80±0.82	8.57± 0.55	8.21±0.60	8.64±0.65	0.001(33.906)	0.210(1.630)	0.115(2.604)

*$P < 0.05$, *vs.* sham tDCS. Tracking task test was performed before and after tDCS motor phase. Level 1: 80 rpm, level 2: 120 rpm and level 3:160 rpm. tDCS: Transcranial direct current stimulation.

post-tDCS) with repeated measures of the three dependent variables (levels 1, 2, and 3). All statistical analyses were performed using PAWS 18.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was used as the criterion for statistical significance.

Results

General data of participants
The mean age of the real tDCS group (5 males and 12 females) and sham tDCS group (6 males and 13 females) was 21.89 ± 0.87 years and 21.63± 1.67 years. There was no significant difference in distribution of sex between real tDCS and sham tDCS groups.

tDCS improved visuomotor coordination ability
Table 1 indicates the pre-test and post-test of the AI depending on three levels of task difficulty for each group. Univariate analysis reveals significant difference in levels of task difficulty. At level 2, univariate analysis shows a large main effect of time ($F = 21.996$, $P < 0.001$) and group-by-time interaction ($F = 7.970$, $P < 0.008$), suggesting that AI was increased in the tDCS condition compared to the sham tDCS condition. However, at levels 1 and 3, univariate analysis showed only a large main effect of time ($F = 26.148$, $P < 0.001$, $F = 6.822$, $P < 0.001$, respectively).

Discussion
In the current study, we attempted to determine whether or not the effects of tDCS on visuomotor coordination depend on the level of task difficulty in healthy subjects. Examinations were performed to evaluate three levels of task difficulty using a tracking task with various velocities. Only at level 2, the tDCS group significantly increased the AI compared with the sham tDCS group. Consequently, we observed improvement of visuomotor coordination only at moderate task difficulty after tDCS of the M1.

At level 2 task difficulty, our observation of increased motor performance after tDCS is consistent with previous reports using similar paradigms for the upper limb (Reis et al., 2009; Stagg and Nitsche, 2011). Possible mechanisms behind the effects of tDCS can be based on two main factors. First, motor learning is typically accompanied by activity-dependent modifications of synapses inducing Hebbian plasticity in the form of long term potentiation-like or long term depression-like changes within cortical neurons (Abbott and Nelson, 2000; Muellbacher et al., 2002). Neuronal circuits involved with hand tracking were likely active or at a heightened state before and during performance of the motor task. Hence, it is possible that these were more accessible to the membrane-shifting properties of tDCS thereby shaping synaptic plasticity and resulting in improved motor performance and learning. On the contrary, moderate changes in background excitability may reduce the threshold at which synapses are strengthened, thus enabling pre-activated synapses in cortical networks to be engaged more easily and produce a stronger, more enhanced output during execution of the task (Antal et al., 2008). These results indicate that application of anodal tDCS enhanced visuomotor coordination compared with the sham tDCS group.

Secondly, increased visuomotor coordination can be attributed to peripheral afferent feedback associated with a task and the effect of multiple cortical areas projecting into the motor cortex. Changes in afferent feedback from fingers and intrinsic muscles have been shown to influence patterns of cortical activity associated with tracking tasks (Doemges and Rack, 1992). Further, given that multiple cortical areas contribute to the control of movement, the increased AI may reflect greater inputs from other areas projecting into the motor cortex during performance of the task (Pearce and Kidgell, 2009). Combined with previous findings, the results of this study indicate that increasing the precision of a movement task can elevate cortical excitability due to the greater motor demand of the more precise task (Classen et al., 1998; Hasegawa et al., 2001). In our study, the level 2 task (moderate level) increased cortical excitability compared to level 1task when tDCS was applied.

Typically with more difficult tasks, task lateralization may be efficient when easier targets are presented, whereas bilateral activation may improve the brain's resolving power with difficulty to discriminate targets. In addition, higher motor task difficulty is associated with enhanced premotor cortex activation according to several studies (Catalan et al., 1998; Haaland et al., 2004). In the level 3 task, there was no significant difference in AI between real tDCS and sham tDCS. These results indicate that the difficulty level of the task was influenced by alternative brain activity. Finally, the findings suggest that complex reasoning can be understood in terms of adaptive activation of large-scale brain networks.

The clinical implication of our findings is that moderate task difficulty may be useful to improve visuomotor coordination in healthy subjects when tDCS is applied compared with easier or more difficult tasks. However, the present study has some limitations. The single-blinded test is the most important limitation of this study, and further studies

involving double-blinded tests are required to avoid unconscious bias. It is possible that fewer effects may reach a statistically significant level if more subjects had been tested. In addition, due to the size of the electrodes and the placement position of the return electrode, the learning improvements cannot be solely attributed to the M1, and it is also likely that motor areas adjacent to the M1 or premotor areas are affected by stimulation, contributing to our results.

Author contributions: *All authors conceived and designed the overall study, performed experiments, analyzed the data, wrote the paper, and approved the final version of the paper.*
Conflicts of interest: *None declared.*

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