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# Is transcranial direct current stimulation a potential method for improving response inhibition?☆

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## Abstract

Inhibitory control of movement in motor learning requires the ability to suppress an inappropriate action, a skill needed to stop a planned or ongoing motor response in response to changes in a variety of environments. This study used a stop-signal task to determine whether transcranial direct-current stimulation over the pre-supplementary motor area alters the reaction time in motor inhibition. Forty healthy subjects were recruited for this study and were randomly assigned to either the transcranial direct-current stimulation condition or a sham-transcranial direct-current stimulation condition. All subjects consecutively performed the stop-signal task before, during, and after the delivery of anodal transcranial direct-current stimulation over the pre-supplementary motor area (pre-transcranial direct-current stimulation phase, transcranial direct-current stimulation phase, and post-transcranial direct-current stimulation phase). Compared to the sham condition, there were significant reductions in the stop-signal processing times during and after transcranial direct-current stimulation, and change times were significantly greater in the transcranial direct-current stimulation condition. There was no significant change in go processing-times during or after transcranial direct-current stimulation in either condition. Anodal transcranial direct-current stimulation was feasibly coupled to an interactive improvement in inhibitory control. This coupling led to a decrease in the stop-signal process time required for the appropriate responses between motor execution and inhibition. However, there was no transcranial direct-current stimulation effect on the no-signal reaction time during the stop-signal task. Transcranial direct-current stimulation can adjust certain behaviors, and it could be a useful clinical intervention for patients who have difficulties with response inhibition.

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## Key Words

neural regeneration; neurorehabilitation; transcranial direct current stimulation; pre-supplementary motor area; stop-signal task; response inhibition; inhibitory control; motor learning; behavioral modification; grants-supported paper; neuroregeneration

## Research Highlights

- (1) Anodal transcranial direct-current stimulation over the pre-supplementary motor area altered the motor-inhibition reaction time during the stop-signal task.
- (2) Performance on the stop-signal task during and after anodal transcranial direct-current stimulation applied to the pre-supplementary motor area caused a significant reduction in the stop-signal reaction time required for the appropriate responses between motor execution and inhibition.
- (3) Transcranial direct-current stimulation could be a useful clinical intervention for patients with difficulty in response inhibition.

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## INTRODUCTION

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Executive control of movement in motor learning involves the ability to stop inappropriate actions, impulsive behaviors, or negative feedback. These cognitive processes attached to motor execution and inhibition allow appropriate responses that meet complicated task demands and adapt to changing environments. Many studies have investigated the underlying cognitive and neural mechanisms of response inhibition in executive control<sup>[1-3]</sup>.

Motor inhibition is associated with the inferior frontal gyrus, prefrontal areas, and the fronto-basal ganglia network<sup>[4-7]</sup>. In particular, volitional suppression is associated with increased pre-supplementary motor area activity<sup>[8-10]</sup>. The pre-supplementary motor area is involved in initiating self-paced actions and mediating response inhibition that is required for voluntary muscle relaxation<sup>[11-12]</sup>. Moreover, pre-supplementary motor area lesions can lead to selective deficits in response inhibition when actions compete. Neuroimaging studies have shown that increased pre-supplementary motor area activation reflects adjusting and monitoring response strategies that balance opposing task demands<sup>[13-16]</sup>. This increased activation influences the stop-movement process and appears to be especially crucial for cancelling responses<sup>[1, 9, 15]</sup>. Thus, response inhibition is improved through facilitation of the functional connections between the pre-supplementary motor area and basal ganglia, which is known as a braking system for superiority responses prior to initiation of a planned action.

The stop-signal task is commonly used to evaluate the extent of a voluntary stop movement, and to measure reaction times and performance errors in both motor execution and inhibition<sup>[17-19]</sup>. This task is a strong experimental paradigm for examining the abortion of an incipient response, and is based on the race model of response inhibition<sup>[20-21]</sup>. Participants initiate a response on each trial, and they must then try to abort the response when a stop-signal occurs. Many previous studies have revealed that successfully aborting a movement is associated with pre-supplementary motor area activation, which, in the stop-signal task, needs to be higher during response inhibition than during normal motor execution<sup>[7-9]</sup>. Thus, the pre-supplementary motor area facilitates corticospinal excitability during action reprogramming through the repeated performance of the stop-signal task.

Among the non-invasive neurostimulation techniques that are used to manipulate cortical excitability, transcranial direct current stimulation has recently been used in neurorehabilitation<sup>[22-27]</sup>. In the stimulation of cortical tissue by transcranial direct-current stimulation, the excitability of cortical neurons is increased by anode, whereas it is decreased by cathode. Recently, functional neuroimaging studies have demonstrated that cortical excitability of the motor cortex increased during and after transcranial direct-current stimulation<sup>[23-24]</sup>. Moreover, several studies have demonstrated that applying transcranial direct-current stimulation to motor cortex, especially the primary motor cortex (M1), enhances motor performance in terms of visuo-motor coordination<sup>[22, 26-27]</sup>. However, very little is known about the influence transcranial direct-current stimulation has on the pre-supplementary motor area, which is related to executive control of the stopping process. Further, there have not been any published reports regarding how response times in motor learning for both initiating and aborting movements change due to repeatedly stopping planned movements following transcranial direct-current stimulation.

We therefore attempted to demonstrate whether anodal transcranial direct-current stimulation applied to the pre-supplementary motor area concurrently with motor acquisition of the repeated stop-signal task could decrease the temporal response times for both the initiating and aborting processes.

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## RESULTS

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### Quantitative analysis of subjects

Forty healthy subjects without any neurological or psychiatric history were recruited in this study. An equal number of subjects were randomly assigned to either the transcranial direct-current stimulation condition or sham-transcranial direct-current stimulation condition in which no stimulation was delivered. All subjects consecutively performed a stop-signal task in three phases: before, during, and after the delivery of anodal transcranial direct-current stimulation (or no delivery) over the pre-supplementary motor area. All subjects were included in the final analysis.

### Transcranial direct current stimulation over the pre-supplementary motor area improved inhibitory control

The transcranial direct-current stimulation and sham-transcranial direct-current stimulation groups did

not differ in gender (males: 20, females: 20) or age ( $23.0 \pm 1.8$  years).

Table 1 displays the stop-signal reaction time and the no-signal reaction time for each condition in the test phases. Univariate analysis showed a large main effect of condition ( $P < 0.05$ ), test phase ( $P < 0.05$ ), and condition-by-test interaction ( $P < 0.05$ ) for the stop-signal reaction time, suggesting it was significantly reduced in the transcranial direct-current stimulation condition compared to the sham condition. In contrast, no main effects of condition ( $P > 0.05$ ), test phase ( $P > 0.05$ ), or a condition-by-test interaction ( $P > 0.05$ ) for the no-signal reaction time were observed, suggesting that no-signal reaction time was similar under the two conditions.

## DISCUSSION

Here, we found that anodal transcranial direct-current stimulation applied to the pre-supplementary motor area during and after the performance of the stop-signal task caused a significant reduction in stop processing-times, but not in go processing-times. Further, no significant changes in stop and go processing-times were observed under sham conditions. These results imply that application of transcranial direct-current stimulation over the pre-supplementary motor area led to a decrease in stop processing-times required for the appropriate inhibitory motor responses. Thus, we believe that reduction in the stop-signal reaction time may be attributed to the effect of direct stimulation during or after delivery of the transcranial direct-current stimulation over the pre-supplementary motor area as motor skill learning progressed.

These behavioral changes are related to pre-supplementary motor area cortical excitability during or after delivery of the transcranial direct-current stimulation that contributes to response inhibition by

monitoring performance or adjusting behavior<sup>[13, 15, 28]</sup>. Previous studies have revealed that the pre-supplementary motor area might be necessary for inhibiting competing motor plans when opposing tasks result in response conflict<sup>[7-8, 29-30]</sup>. Additionally, previous studies have reported a relative reduction in corticomotor excitability when aborting a planned action compared to action initiation, the latter of which might be mediated by fronto-basal ganglia circuits for inhibitory control<sup>[4-6]</sup>. Thus, we assume that transcranial direct-current stimulation applied to pre-supplementary motor area can especially affect motor inhibition when stop and go actions compete. Our findings show that a decline in the stop-action response time was in line with previous stop-signal task experimental findings, which reinforced the selection between the inhibition and the execution in the response competition<sup>[7-8, 31]</sup>. Combined transcranial direct-current stimulation that enhances learning of the stopping process might therefore be more effective than task alone, and this is ascribed to the effect of the transcranial direct current stimulation.

Previous studies have also demonstrated behavioral changes in response inhibition and executive control that are influenced by automatic processing through task goals that can be primed<sup>[2, 32]</sup>. They reported that goal-directed actions could be started and guided to completion automatically by information in the task environment. It appears that executive controls, such as response inhibition, can be triggered by both top-down and bottom-up control, which reduces the need for selection of goal-directed action. Reports also indicate that the efficiency of response inhibition improves in concert with reductions in the preparation for action before stop signals, and this improvement can reduce the demand of response inhibition during the stopping process<sup>[3, 33-34]</sup>. Accordingly, reductions in the stop-signal reaction time correspond to increased preparation, which suggests a close connection and prominent role of the pre-supplementary motor area during performance of the stop-signal task.

Table 1 Changes in response time from visual stimuli among the stop-signal task test phases in healthy subjects

	Pre-SMA tDCS condition			Sham-tDCS condition			Test	Condition	Interaction (test x condition)
	Before	During	After	Before	During	After			
NSRT (ms)	891.0±85.6	920.6±105.5	911.4±126.8	885.3±99.5	907.5±116.1	888.5±128.6	0.119	0.461	0.643
SSRT (ms)	387.4±58.0	321.7±47.0	311.2±43.3	385.9±43.3	349.0±42.0	336.8±39.8	0.000 <sup>a</sup>	0.016 <sup>a</sup>	0.047 <sup>a</sup>

All data are reported as mean  $\pm$  SD. Superscript "a" indicates the use of two-way repeated measures analysis of variance and significance at the  $P < 0.05$  level. Pre-SMA: Pre-supplementary motor area; NSRT; no-signal reaction time; SSRT; stop-signal reaction time.

Previous neuroimaging results have determined that response inhibition elicits activity in multiple brain regions, including the pre-supplementary motor area, inferior frontal gyrus, and subthalamic nucleus<sup>[35-37]</sup>. Increased activation in the right inferior frontal gyrus influenced stopping but not initiating, and it appears to be especially crucial for cancelling responses. Moreover, in patients with pre-supplementary motor area lesions, response inhibition is impaired and is correlated with the stop-signal reaction time but not with the go-response time<sup>[14, 38]</sup>. Our study showed that after either transcranial direct-current stimulation or motor training alone, only the stop-signal reaction time decreased, while the go-response time did not change. These findings imply that under conditions of increased response competition, stimulation of the pre-supplementary motor area and goal priming for action canceling may delay the preparation for an executive trigger or do not reduce the speed of the 'go' process once triggered.

The pre-supplementary motor area is thought to modulate response strategies between the inhibition and the execution. It plays an important role in an effort to balance the opposing demands of the stop and go tasks. Here, we found that applying transcranial direct-current stimulation to the pre-supplementary motor area improved the ability to stop the motor response as indexed by a faster stop-signal reaction time. Such findings have been supported by several behavioral studies, suggesting that inhibitory control can be modulated by polarity-specified effects during the application of non-invasive neurostimulation<sup>[26, 29, 39]</sup>. Moreover, according to prior transcranial magnetic stimulation studies based on changes in the right inferior frontal gyrus and supplementary motor complex during the stopping process, voluntarily cancelling an action is an active process, which likely suppresses excitability throughout the entire motor system<sup>[40-41]</sup>. Thus, the transcranial direct-current stimulation applied to specific brain regions could adjust behaviors after conflicts or errors in responses inhibition. Additionally, it could be a useful clinical intervention for patients who have difficulties with response inhibition. The most important limitation of this study is that we did not estimate the magnitude of the activation within inhibition-related brain regions using functional neuroimaging techniques. Thus, further neuroimaging studies will be required to provide more details regarding the behavioral and neural interactions between response-selection mechanisms and inhibition.

This study provides strong evidence that anodal transcranial direct-current stimulation over the pre-supplementary motor area reduces stop-signal reaction time. The results support the idea that anodal transcranial direct-current stimulation enhances voluntary abortion of movement. In addition, transcranial direct-current stimulation appears to be an effective means to modulate appropriate responses between motor execution and inhibition.

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## MATERIALS AND METHODS

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### Design

A sham-controlled transcranial direct-current stimulation experiment with repeated measurements.

### Time and setting

This study was performed at the Functional Training Room, Department of Physical Therapy, Yeungnam College of Science & Technology, Republic of Korea, from May 2012 to July 2012.

### Subjects

Healthy subjects were recruited in this study by posting notices in Yeungnam College and Yeungnam University hospital. Subjects had no previous exposure to other sequence-learning studies or experiments that use external stimulation of the cerebral cortex, such as transcranial magnetic stimulation or transcranial direct-current stimulation. All subjects were right-handed, as verified by a handedness questionnaire using the modified Edinburgh Handedness Inventory<sup>[42]</sup>. All subjects gave their written informed consent prior to this experiment, which was in accordance with the ethical standards of the *Declaration of Helsinki*<sup>[43]</sup>. All subjects were randomly assigned to either the transcranial direct-current stimulation or the sham-transcranial direct-current stimulation condition.

### Methods

#### Stop-signal task

The stop-signal task consisted of Go (75% of trials) and Stop (25% of trials) trials, which were performed on a computer using stimulus-presentation software (STOP-IT, Universiteit Gent, Belgium) and four arrow response-keys (left, right, up, or down). During Go trials, a square (■), circle (●), diamond (◆), or triangle (▲) stimulus was randomly displayed on the monitor. For Stop trials, a stop-signal (x) was presented on top of the shape following a delay (the stop-signal delay). The stop-signal delay was initially set at 250 ms and was

continually adjusted following a tracking procedure to obtain a stopping accuracy of 0.50. This was manipulated by adjusting the delay time<sup>[44]</sup>. If the subject successfully stopped the button press during a Stop trial, the next Stop trial became more difficult by increasing the stop-signal delay by 50 ms. If the subject failed to stop the button press, the next Stop trial was made easier by decreasing the stop-signal delay by 50 ms. The stop-signal reaction time, which represented the latency of the stopping process, was estimated by subtracting the mean stop-signal delay from the mean correct reaction time during the Go trials (no-signal reaction time). The analyzing program (ANALYZE-IT, Universiteit Gent, Belgium) allowed experimenters to estimate the stop-signal reaction time for each subject and calculate the means for all dependent variables of interest<sup>[23]</sup>.

### **Transcranial direct current stimulation**

The direct current was delivered by a battery-driven constant DC current stimulator (Phoresor II Auto Model PM 850, IOMED, USA) with a pair of water-soaked sponge electrodes (5 cm × 7 cm). The center of the anodal electrode was placed over the right pre-supplementary motor area, and the cathodal electrode was placed over the left cheek of the subject. The 10/20 international electroencephalographic system was used for electrode placement, in which the pre-supplementary motor area corresponds to a position 4 cm anterior to the electrode position Cz in both hemispheres<sup>[45-47]</sup>. This area is known to represent conflict resolution or monitoring.

### **Outcome measures and test procedure**

Before starting the stop-signal task, all subjects were seated in front of a table with the left hand on the response key. The stop-signal task consisted of one block of 132 trials (Go trials: 99, Stop trials: 33). All subjects performed the stop-signal task within the transcranial direct-current stimulation test paradigm during three consecutive phases: pre-transcranial direct-current stimulation, transcranial direct-current stimulation, and post-transcranial direct-current stimulation. All subjects performed the stop-signal task without transcranial direct-current stimulation. In the transcranial direct-current stimulation phase, stimulation started 5 minutes before the onset of the stop-signal task to insure that task began under proper stimulation. The post-transcranial direct-current stimulation phase began immediately after the end of the transcranial direct-current stimulation phase. In total, current was applied for 10 minutes at 1mA based on the safety criteria proposed by Nitsche *et al*<sup>[48]</sup>. All subjects

felt the current as a mild itching sensation under the electrodes at stimulation onset, or did not report any sensation. For the sham-transcranial direct-current stimulation condition, electrodes were placed in identical positions without delivering any current during the task. Thus, the subjects felt the initial itching sensation, but received no current for the rest of the procedures.

### **Task paradigms**

All subjects were instructed to press the correct button as quickly as possible during the Go trials, but not to press any button during the Stop trials. A fixation cross was shown on the monitor for a null (baseline) period until the start of the next trial. The stimulus remained on the monitor until subjects responded, or until 1250 ms had elapsed. The default inter-stimulus interval was 2 000 ms and was independent of reaction time. Each trial began with a presentation of the fixation cross, which was replaced by the Go trial stimulus after 250 ms. Each stimulus shape was paired with a single correct response key (square, circle, diamond, and triangle with left-, right-, up- and down-arrow keys, respectively). If either a button press occurred prior to the presentation of the Go trial, or the subject pressed the wrong button in response to the figure, the trial was excluded from analysis.

### **Statistical analysis**

Demographic data, such as gender and age, were analyzed by an independent *t*-test. The following variables were estimated or calculated: the mean stop-signal delay, the stop-signal reaction time, and the no-signal reaction time. Analysis of the stop-signal reaction time was calculated by subtracting the mean stop-signal delay from the untrimmed mean reaction time. The mean raw reaction time for all no-signal trials was first calculated (*i.e.*, mean correct reaction time), and the mean stop-signal delay was then subtracted from this value. Therefore, all data and two dependent variables, including the no-signal reaction time and the stop-signal reaction time, were analyzed. The effects during and post transcranial direct-current stimulation were determined using a two-way analysis of variance (conditions: transcranial direct-current stimulation, sham-transcranial direct-current stimulation; conditions × test: pre-transcranial direct-current stimulation, transcranial direct-current stimulation, post-transcranial direct-current stimulation) with repeated measures of the two dependent variables, the stop-signal reaction time and the no-signal reaction time. All data are reported as mean ± SD. All statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Statistical

significance was set at  $P < 0.05$ .

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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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