

# Non-invasive cortical stimulation improves post-stroke attention decline

Eun Kyoung Kang<sup>a</sup>, Min Jae Baek<sup>b</sup>, SangYun Kim<sup>b,c</sup> and Nam-Jong Paik<sup>a,b,d,\*</sup>

<sup>a</sup>Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

<sup>b</sup>Clinical Neuroscience Center, Seoul National University Bundang Hospital, Seongnam, South Korea

<sup>c</sup>Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea

<sup>d</sup>Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, South Korea

**Abstract.** *Purpose:* Attention decline after stroke is common and hampers the rehabilitation process, and non-invasive transcranial direct current stimulation (tDCS) has the potential to elicit behavioral changes by modulating cortical excitability. The authors tested the hypothesis that a single session of non-invasive cortical stimulation with excitatory anodal tDCS applied to the left dorsolateral prefrontal cortex (DLPFC) can improve attention in stroke patients.

*Methods:* Ten patients with post-stroke cognitive decline (MMSE  $\leq$  25) and 10 age-matched healthy controls participated in this double blind, sham-controlled, crossover study involving the administration of real (2 mA for 20 min) or sham stimulation (2 mA for 1 min) to the left DLPFC. Attention was measured using a computerized Go/No-Go test before and after intervention. Improvements in accuracy and speed after stimulation relative to baseline were compared for real and sham stimulations.

*Results:* In healthy controls, no significant improvement in Go/No-Go test was observed after either real or sham stimulation. However, in stroke patients, tDCS led to a significant improvement in response accuracy at 1 hour post-stimulation relative to baseline, and this improvement was maintained until 3 hours post-stimulation ( $P < 0.05$ ), whereas sham stimulation did not lead to a significant improvement in response accuracy ( $P > 0.05$ ). Changes in reaction times were comparable for the two stimulations ( $P > 0.05$ ).

*Conclusion:* Non invasive anodal tDCS applied to the left DLPFC was found to improve attention versus sham stimulation in stroke patients, which suggests that non-invasive cortical intervention could potentially be used during rehabilitative training to improve attention.

**Keywords:** Attention, cognition, stroke, cortical stimulation, tDCS

## 1. Introduction

Attention decline after stroke is common and hampers the rehabilitation process, reduces physical function recovery, and increases dependence on others during the activities of daily life (McDowd et al., 2003). Furthermore, this problem persists despite pharmacotherapeutic and cognitive rehabilitative ef-

forts (Coulthard et al., 2006). Accordingly, more effective interventions are required to improve attention after stroke.

Recently, transcranial direct current stimulation (tDCS), a form of non-invasive cortical stimulation, which modulates cortical excitability at stimulated sites, has been investigated to determine whether it can facilitate motor (Hummel et al., 2005) and language (Monti et al., 2008) recovery in stroke patients. Furthermore, tDCS has been reported to enhance working memory and attention by stimulating the dorsolateral prefrontal cortex (DLPFC) in healthy subjects (Fregni et al., 2005), and in patients with Parkinson's disease (Boggio et al., 2006).

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\*Corresponding author: Nam-Jong Paik, MD, PhD, Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital 300 Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do, 463-707, South Korea. Tel.: +82 31 787 7731; Fax: +82 31 712 3913; E-mail: njpaik@snu.ac.kr.

Table 1  
Patient data

| Patient' No.  | Sex | Age (years)    | Type of stroke (Brain lesion)  | Days after onset  | MMSE           | 1st Session |
|---------------|-----|----------------|--|-------------------|----------------|-------------|
| 1             | F   | 75             | Infarction (Right corona radiata)  | 23                | 19             | Sham        |
| 2             | F   | 66             | Infarction (Both PVWM, right parietal lobe)                              | 3875              | 20             | Real        |
| 3             | M   | 48             | Infarction (Right fronto-parietal lobes, basal ganglia)                  | 1234              | 21             | Sham        |
| 4             | M   | 74             | Infarction (Left fronto-parieto-temporal lobes)                          | 47                | 22             | Real        |
| 5             | M   | 67             | Infarction (Both PVWM, left pons)  | 26                | 25             | Sham        |
| 6             | M   | 71             | Hemorrhage (Right thalamus)  | 77                | 19             | Real        |
| 7             | F   | 84             | Infarction (Right corona radiata)  | 27                | 18             | Sham        |
| 8             | M   | 76             | Hemorrhage (Right basal ganglia)   | 50                | 23             | Real        |
| 9             | M   | 69             | Infarction (Right fronto-occipital lobes, basal ganglia, corona radiata) | 34                | 24             | Sham        |
| 10            | F   | 69             | Hemorrhage (Right basal ganglia)   | 48                | 18             | Real        |
| Mean $\pm$ SE |     | 69.9 $\pm$ 3.0 |  | 544.1 $\pm$ 388.6 | 20.9 $\pm$ 0.8 |             |

F: female, M: male, MMSE: mini-mental state examination, PVWM: periventricular white matter.

Therefore, we tested the hypothesis that a single session of non-invasive cortical stimulation, in the form of excitatory anodal tDCS applied to the left DLPFC, improves attention in stroke patients.

## 2. Method

### 2.1. Subjects

Ten patients (four females) aged 48 to 84 years with post-stroke cognitive decline (MMSE  $\leq$  25) and 10 age-matched healthy control subjects participated in this study (Table 1). We excluded patients with a cerebellar or brainstem lesion, and those with a metallic foreign body implant, a pacemaker, an artificial cochlear, a history of seizure, or an unstable medical condition, and those who were unable to perform the outcome tasks. Patients who were taking Na<sup>+</sup> or Ca<sup>++</sup> channel blockers, such as carbamazepine or NMDA receptor antagonists like dextromethorphan, were also excluded. Medications unassociated with the study taken by patients were maintained throughout the experiment.

The experimental protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital and written informed consent was obtained from all subjects.

### 2.2. Experimental design

After being familiarized with the experimental setting, each of the 10 patients underwent a counter balanced crossover session of anodal tDCS (2 mA for 20 minutes) or sham stimulation (2 mA for 1 minute) separated by an interval of at least 2 days. Session orders were randomized, that is, 5 subjects underwent

the sham session first and the other 5 underwent tDCS first.

At tDCS sessions, the current was slowly increased to 2 mA from the onset of stimulation and applied for 20 min, whereas at sham stimulation sessions the current was slowly increased to 2 mA over 1 min and then slowly tapered down to 0. This procedure has been demonstrated to prevent patients differentiating real and sham stimulation (Gandiga et al., 2006; Hummel et al., 2005).

tDCS (Phoresor<sup>®</sup> II PM850; IOMED<sup>®</sup> Inc., Salt Lake City, Utah) or sham stimulation was delivered through two 25 cm<sup>2</sup> sponge electrodes with an anode positioned over F3 as defined by the international 10–20 EEG system (F3 corresponds to the left DLPFC), and a cathode positioned over the contralateral supra-orbital region. An identical experimental method was applied to the 10 healthy control subjects. Both patients and the investigator that carried out the behavioral measurements were unaware of the type of intervention, because tDCS and sham were administered by another investigator who did not participate in the behavioral task or data analysis.

### 2.3. Outcome measurements

Regarding the Go/No-Go test, numbers of correct responses and reaction times at baseline (Pre), immediately after stimulation (Post1), and at 1 hour (Post2), and 3 hours post-stimulation (Post3) were recorded. Go/No-Go test involved the presentation of the figures “1” or “2” randomly 30 times using Superlab pro v.4.0 software (Cedrus Corporation, San Pedro, CA). One of these figures was presented in the center of a computer screen for 3000 ms, and subjects were instructed to press a right-side blue key as quickly as possible with

Table 2  
Mean attention, perception of fatigue, task difficulty, and sleep quality levels during night prior to testing (rated using numeric 0~10 rating scales; 0 = lowest level, 10 = highest level)

|                | tDCS      |           | Sham      |           | ANOVA <sub>RM</sub>         |                     |                             |
|----------------|-----------|-----------|-----------|-----------|-----------------------------|---------------------|-----------------------------|
|                | Before    | After     | Before    | After     | Intervention effect P value | Time effect P value | Intervention × time P value |
| Attention      | 5.7 ± 2.3 | 4.5 ± 0.9 | 4.4 ± 2.8 | 4.1 ± 2.7 | 0.342                       | 0.101               | 0.324                       |
| Fatigue        | 4.7 ± 1.9 | 3.9 ± 2.0 | 3.7 ± 2.7 | 3.1 ± 2.8 | 0.262                       | 0.163               | 0.811                       |
| Difficulty*    | –         | 3.0 ± 1.9 | –         | 4.0 ± 2.9 | 0.229                       | –                   | –                           |
| Sleep quality* | 5.2 ± 2.8 | –         | 5.1 ± 2.9 | –         | 0.910                       | –                   | –                           |

\*Group task difficulties and sleep qualities were compared using the paired t test.

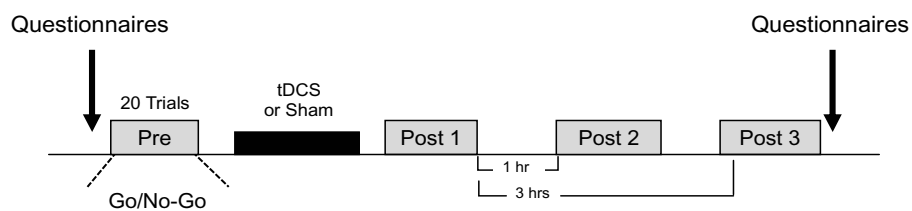


Fig. 1. Experimental design.

the non-paretic hand (the dominant hand for healthy controls) when the figure “1” was shown, but not to press any key when the figure “2” was shown.

Before and after each session, subjects described their subjective attention levels, perceptions of fatigue, task difficulty, and sleep quality during the previous night using a numeric rating scale (range 0~10; 0 = lowest, 10 = highest) (Fig. 1).

Statistical analysis was performed using repeated measures ANOVA (ANOVA<sub>RM</sub>) with “INTERVENTION” (tDCS versus Sham) and “TIME” (Pre, Post1, Post2, Post3) as within subject factors. LSD correction for multiple comparisons was performed conditioned on significant p-values ( $P < 0.05$ ). All values are presented as means ± standard errors (SE).

### 3. Results

#### 3.1. Effects of non-invasive cortical stimulation on Go/No-Go test results in healthy control subjects

In the healthy control group (age = 69.3 ± 2.8 years; MMSE = 29.2 ± 0.2), ANOVA<sub>RM</sub> showed that INTERVENTION<sub>tDCS,Sham</sub>, TIME<sub>Pre,Post1,Post2,Post3</sub>, or INTERVENTION<sub>tDCS,Sham</sub> × TIME<sub>Pre,Post1,Post2,Post3</sub> had no effect on the number of correct responses or on reaction time as determined by the Go/No-Go test ( $P > 0.05$ ; Fig. 2-A).

#### 3.2. Effects of non-invasive cortical stimulation on Go/No-Go test results in stroke patients

In the patient group (age = 69.9 ± 3.0 years; MMSE = 20.9 ± 0.8), numbers of correct responses (control 29.9 ± 0.1 versus patients 23.4 ± 2.1;  $P = 0.006$ ) was significantly decreased and reaction times (control 682.2 ± 49.3 ms versus patients 1267.6 ± 97.3 ms;  $P < 0.001$ ) lengthened respectively, versus the 10 age-matched healthy control group, indicating that attention was lower in the patient group.

ANOVA<sub>RM</sub> revealed that INTERVENTION<sub>tDCS,Sham</sub>, TIME<sub>Before,After</sub>, or INTERVENTION<sub>tDCS,Sham</sub> × TIME<sub>Before,After</sub> had no effect on subjective ratings of attention and fatigue ( $P > 0.05$ ). Furthermore, the paired t test found no difference between sham and real intervention sessions in terms of task difficulty or sleep quality during the previous night, indicating that gross psychophysical conditions during tDCS and Sham administration were comparable ( $P > 0.05$ ; Table 2).

According to Go/No-Go test results, baseline mean correct response numbers (tDCS 23.4 ± 2.1 versus Sham 26.1 ± 1.9, paired t-test  $P = 0.15$ ) and reaction times (tDCS 1267.6 ± 97.3 ms versus Sham 1097.0 ± 94.2 ms,  $P = 0.15$ ) were comparable for tDCS and Sham administration.

ANOVA<sub>RM</sub> revealed a significant INTERVENTION<sub>tDCS,Sham</sub> × TIME<sub>Pre,Post1,Post2,Post3</sub> effect [ $F = 3.11$ ;  $P = 0.043$ ], but no significant INTERVENTION<sub>tDCS,Sham</sub> [ $F = 0.01$ ;  $P = 0.92$ ] or TIME<sub>Pre,Post1,</sub>

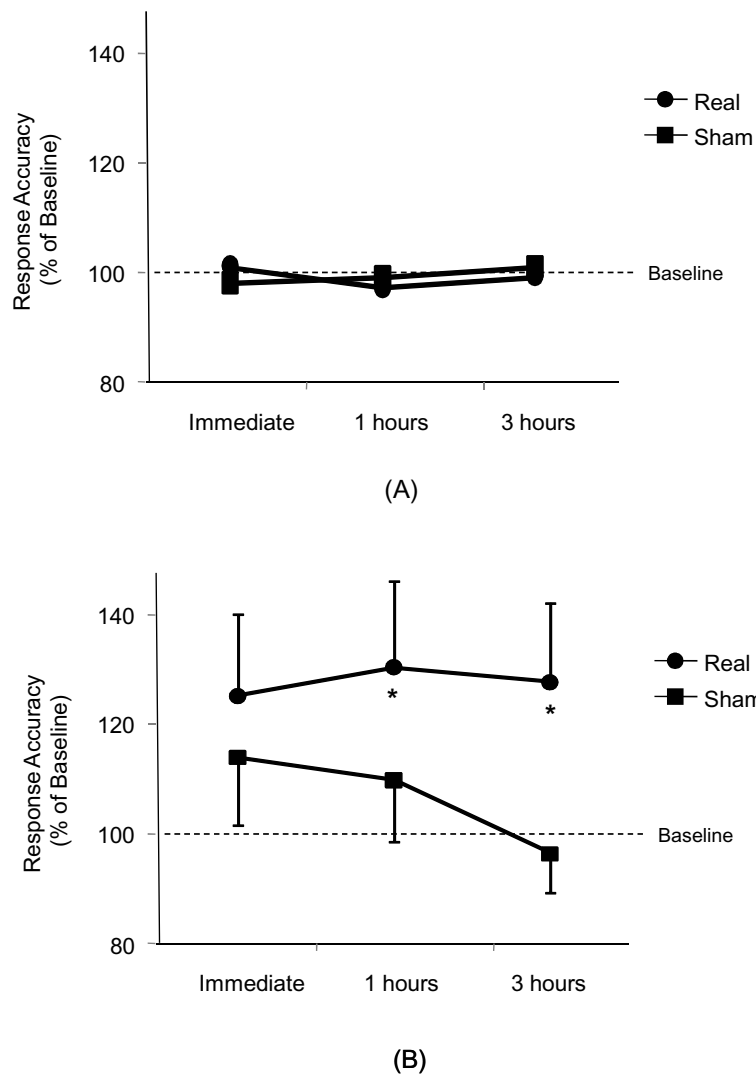


Fig. 2. Graph showing the effects of anodal tDCS on percentage change in Go/No-Go test accuracy relative to baseline (dotted line, 100%). (A) No improvement was observed in healthy controls after either tDCS or sham stimulation. (B) Note that tDCS (asterisk) but not Sham resulted in a response accuracy improvement relative to baseline at 1 hour and 3 hours post-stimulation in stroke patients. Values represent means  $\pm$  SE \* $P < 0.05$ .

Post2,Post3 [F = 2.18;  $P = 0.11$ ] effect on numbers of correct responses. Post hoc testing showed that tDCS induced to a significant improvement in response accuracy at 1 hour post-stimulation relative to baseline (from Pre  $23.4 \pm 2.1$  to Post2  $27.6 \pm 1.0$ ;  $P = 0.024$ ; Fig. 2-B), and this improvement was maintained until 3 hours post-stimulation (Post3  $27.2 \pm 0.7$ ;  $P = 0.041$ ; Fig. 2-B, asterisk), whereas sham stimulation did not lead to significant improvement in response accuracy (from Pre  $26.1 \pm 1.9$  to Post2  $26.8 \pm 0.8$ ;  $P = 0.702$  and to Post3  $24.1 \pm 1.4$ ;  $P = 0.276$ ; Fig. 2-B).

However, ANOVA<sub>RM</sub> revealed no significant effect of INTERVENTION<sub>tDCS,Sham</sub> [F = 0.01;  $P = 0.941$ ],

TIME<sub>Pre,Post1,Post2,Post3</sub> [F = 0.78;  $P = 0.514$ ] or INTERVENTION<sub>tDCS,Sham</sub>  $\times$  TIME<sub>Pre,Post1,Post2,Post3</sub> [F = 1.36;  $P = 0.28$ ] on reaction time.

Regarding the effect of order of stimulation (tDCS first *versus* sham first), ANOVA<sub>RM</sub> showed no significant effect of ORDER<sub>tDCS,Sham</sub> [F = 0.50;  $P = 0.497$ ], TIME<sub>Pre,Post1,Post2,Post3</sub> [F = 2.18;  $P = 0.113$ ], or ORDER<sub>tDCS,Sham</sub>  $\times$  TIME<sub>Pre,Post1,Post2,Post3</sub> [F = 0.70;  $P = 0.563$ ] on numbers of correct responses, and no significant effect of ORDER<sub>DCS,Sham</sub> [F = 1.65;  $P = 0.231$ ], TIME<sub>Pre,Post1,Post2,Post3</sub> [F = 0.783;  $P = 0.514$ ], or ORDER<sub>tDCS,Sham</sub>  $\times$  TIME<sub>Pre,Post1,Post2,Post3</sub> [F =

1.204;  $P = 0.327$ ] on reaction times, indicating that improvements in numbers of correct responses after tDCS session were not caused by order of stimulation.

#### 4. Discussion

The main finding of this double blind, sham controlled, cross-over study was that a single session of anodal tDCS applied to the left DLPFC improved attention versus sham stimulation in stroke patients.

Cognitive impairments, such as, memory, orientation, and attention deficit frequently occur after stroke, though sometimes, attentional deficit is the only cognitive impairment apparent (Tatemichi et al., 1994). Sustaining attention is prerequisite of motor relearning (McNevin et al., 2000), which is essentially the mechanism of functional recovery after stroke (Hikosaka et al., 2002). The traditional neurocognitive approaches (Coulthard et al., 2006) used to improve attention in stroke patients often result in incomplete resolution, and thus, more effective adjuvant strategies that enhance the effects of neurocognitive training are needed.

tDCS can non-invasively modulate the excitability of targeted brain regions, e.g., anodal stimulation increases, whereas cathodal stimulation decreases cortical excitability (Nitsche and Paulus, 2000). Furthermore, this technique is easily administered in parallel with cognitive rehabilitative training (Gandiga et al., 2006). Recently, tDCS was reported to improve motor (Hummel et al., 2005) and language function (Monti et al., 2008) in stroke patients, and in the cognitive domain, it has been reported that a single session of anodal tDCS applied to the left DLPFC improves working memory task results in healthy subjects (Fregni et al., 2005) and in idiopathic Parkinson's disease (Boggio et al., 2006).

Based on these reports, we hypothesized that a single session of anodal tDCS applied to the left DLPFC would improve attention in stroke patients. We chose the Go/No-Go test because it is known to provide sensitive measures of attention with high test-retest reliability (Aranda et al., 2001).

The DLPFC plays a crucial role during working memory and attention tasks (D'Esposito et al., 1998). It receives somatosensory and visual input information from the parietal heteromodal association cortex regarding peripheral vision, motion, spatial orientation, and tactile sensations from the trunk and extremities, and projects to subcortical monoaminergic and cholinergic sources (Devinsky and D'Esposito, 2004). Accordingly, the DLPFC influences global behaviors,

such as, attention and arousal, and any lesion disrupting this network is likely result in an attention or arousal deficit.

In the present study, we found that the application of tDCS to left DLPFC improved Go/No-Go test accuracy in stroke patients, although it did not lead to statistically significant acute (Post1 in the present study) improvements. We speculate that this lack of an acute improvement, which has been found in other studies (Kuo et al., 2008; Nitsche et al., 2003) was due to a limited sample size, the adoption of different behavioral outcome measures, the different natures of populations studied, or to the application of tDCS before the task rather than during the task.

It is notable that comparable subjective ratings of attention levels, perceptions of fatigue, task difficulties, and sleep qualities during previous nights (as determined using numeric rating scales between sessions), and no changes in reaction times argues against the notion that the observed maintenance of accuracy was the result of a non specific effect of tDCS.

It should be noted that we did not monitor mood in this study, and because a depressed mood is common after stroke and might interfere with performance, we cannot rule out the possibility that indirect effects of tDCS reduced this depression, and thus, improved attention during the behavioral task. Furthermore, no extracephalic electrode montage was used in the present study (Priori et al., 2008), and therefore, we also cannot exclude the possibility that the observed beneficial effects were due to placing the cathode on skin overlying the right supraorbital region, which corresponds to the right prefrontal cortex.

In conclusion, noninvasive anodal tDCS applied to left the DLPFC was found to improve attention as compared with sham stimulation, which suggests that tDCS could be used during cognitive or motor rehabilitative training to improve attention.

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