Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory

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The time-dependent effect of transcranial direct current stimulation (tDCS) on working memory was investigated by applying anodal stimulation over the left prefrontal cortex. This single-blind, sham-controlled crossover study recruited I5 healthy participants. A three-back verbal working-memory task was performed before, during, and 30 min after 1mA anodal or sham tDCS. Anodal tDCS, compared with sham stimulation, significantly improved working-memory performance. Accuracy of response was significantly increased after 20 min of tDCS application, and was further enhanced after 30 min of stimulation. This effect was maintained for 30 min after the completion of stimulation. These results suggest that tDCS at 1mA enhances working memory in a time-dependent manner for at least 30 min in healthy participants. *NeuroReport* 19:43–47 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: anodal stimulation, transcranial direct current stimulation, working memory

Introduction

Working memory is used for temporary storage and manipulation of information, and plays a basic role in long-term memory, language, and executive function [1]. Working memory has long been associated with the prefrontal cortex, in which verbal working memory is handled mainly by the left hemisphere and spatial working memory by the right hemisphere [2]. Understandably, memory enhancement is a major field of interest for those involved in cognitive neuroscience and rehabilitation. In addition to pharmacotherapeutic and psychotherapeutic approaches, brain stimulation using magnetic or electrical techniques has recently been investigated as a means of enhancing memory. Transcranial direct current stimulation (tDCS) changes the membrane potential and modulates cerebral excitability [3,4]. In humans, anodal polarization increases the excitabilities of the motor, visual, and prefrontal cortices, to improve motor learning, working memory, and verbal fluency [5–9].

Recently, the effect of tDCS on working memory was investigated using different application methods with variable results. Fregni *et al.* [5] reported that working memory in healthy participants is improved by 10 min of continuous anodal stimulation at 1 mA, using 35-cm²-sized electrodes over the prefrontal cortex, whereas Boggio *et al.* [9] reported that continuous tDCS for 20 min at 2 mA (but not at 1 mA) using the same-sized electrodes improved working memory in patients with Parkinson's disease. Marshall *et al.* [8], however, applied intermittent tDCS for 15 min using smaller electrodes (8-mm diameter) over the bilateral frontal lobes and reported a negative effect on working memory. Therefore, it is conceivable that stimulation methods, intensity and duration, site of stimulation, and size of electrode are all important variables in the effects of tDCS on working memory in healthy participants and in those with brain disease. To our knowledge, no clear consensus has been established on a safe and cognitively enhancing intensity and duration of tDCS.

In this study, we applied 1mA anodal tDCS to the left prefrontal cortex of healthy participants for up to 30 min, and evaluated its cognitive-enhancing effects and the residual effects after tDCS administration. We also investigated participant concentration and fatigue versus application time, to evaluate the potential side effects of tDCS.

Methods

Participants

This study enrolled 15 healthy participants (age 26.5 ± 3.5 years; 5 men, 10 women); they received both anodal and sham tDCS over the left prefrontal cortex. All participants were right-handed, and their mean time spent in full-time education was 15.7 ± 1.0 years. No participant had a history of neuropsychiatric or cardiovascular disease. Written informed content was obtained from all participants before they entered the study, and the study protocol was approved by our local ethics committee.

Experimental protocol

This study was designed as a single-blind, crossover, sham-controlled experiment. All participants participated in both anodal and sham tDCS. The order of stimulation was counterbalanced and randomized across all participants. To minimize carryover effects, the interval between tDCS sessions was 2 weeks.

Initially, the participants were familiarized with the cognitive tasks. Participants practiced the three-back verbal working-memory task until response accuracy reached a plateau. Working-memory assessments were performed before (Baseline), during tDCS at 10 min (T1), at 20 min (T2), at 30 min (T3), and 30 min after tDCS completion (T4) (Fig. 1a). The five task sets and the stimuli presented in each task were randomized to avoid difficulty bias. Participant concentration and fatigue were each recorded using a visual analog scale (i.e. 1 represented 'no concentration or no fatigue' and 10 represented 'highest levels of concentration or fatigue') at the same times as the working-memory assessments.

Cognitive paradigm

To evaluate changes in working memory during and after tDCS, we used a three-back verbal working-memory task that was similar to the one previously described [5,9,10]. Participants were presented with a pseudorandom set of 28 Korean letters. Stimuli were generated using SuperlabPro v. 2.0 software (Cedrus Corporation, San Pedro, California, USA). Each letter was displayed on a computer monitor for 900 ms, followed by a blank screen for 100 ms between stimuli. Participants were required to memorize the letters and to press the space bar on a keyboard with a left finger, if the presented letter was the same as the letter presented three stimuli before (Fig. 1b). The total number of targets was 30, and the total number of foil stimuli was 60. Accuracy (number of correct responses/total targets), error rate (number of incorrect responses/total foils), and response time (interval between target presentation and pressing the space bar) were determined.

Transcranial direct current stimulation application

Direct current was transferred using a pair of saline-soaked surface sponge electrodes (5×5 cm), and was delivered using a constant current stimulator, Phoresor PM850 (IOMED, Salt Lake City, Utah, USA). For anodal stimulation of the left dorsolateral prefrontal cortex, the anode was placed over F3 (according to the 10–20 international system for electroencephalogram electrode placement), and the cathode was placed over the contralateral right supraorbital area. A constant current of 1 mA was applied for 30 min. For sham stimulation, the same electrode placement was used, but the current was applied for 5 s, and was then tapered off
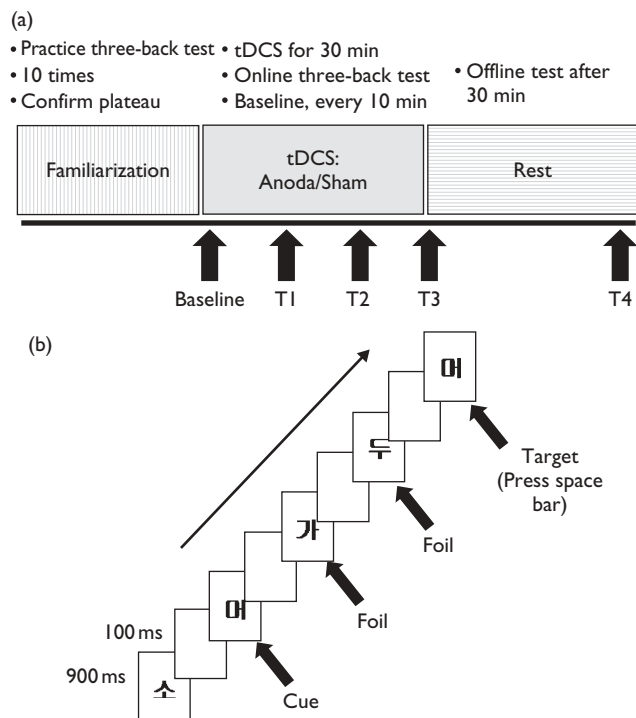

Fig. I (a) Experimental design. For familiarization purposes, participants practiced tasks I0 times, until working memories reached a plateau. Each participant was tested every I0 min during anodal or sham stimulation, and at 30 min after stimulation. Anodal and sham stimulations were randomized for each participant, and the order was counterbalanced across participants. The three-back verbal working-memory test consisted of Korean letters. (b) Participants were required to respond (press a keyboard space bar) if the presented letter was the same as the letter presented three stimuli before.

over 5 s. After the stimulator had been turned off, the electrodes were kept in place for 30 min. This method of sham stimulation has also been used in other tDCS studies [5,11,12].

Data analysis

The primary outcomes of this study were accuracy, error rate, and response time during/after anodal stimulation versus sham stimulation. Analyses were performed using SPSS 13.0 statistical software (Chicago, Illinois, USA). Evaluations performed at different times were analyzed using repeated-measures analysis of variance. Posthoc comparisons were made using Bonferroni-corrected t-tests, to determine whether stimulation time had an effect on the primary outcome. The differences between anodal and sham tDCS at each assessment were analyzed by independent t-tests. Data were reported as means and standard deviations, and significance was accepted at $P < 0.05$.

Results

Accuracy

Accuracies measured at baseline did not differ between the anodal and sham tDCS groups. Accuracies recorded after 20 (T2) and 30 (T3) minutes of stimulation, and at 30 min after completing stimulation (T4), however, differed significantly from those after sham tDCS stimulation. Anodal tDCS induced significantly larger increases in accuracy than sham

Table I Changes in accuracy, error rate, and reaction time induced by tDCS

	Baseline	TI	T2	T3	T4
Accuracy					
Anodal	0.69 ± 0.11	0.72 ± 0.14	0.76 ± 0.13[a,b]	0.80 ± 0.12[a,b,c]	0.79 ± 0.12[a]
Sham	0.66 ± 0.16	0.70 ± 0.13	0.69 ± 0.11	0.69 ± 0.14	0.71 ± 0.13
Error rate					
Anodal	0.05 ± 0.04	0.06 ± 0.04	0.05 ± 0.03	0.05 ± 0.04	0.03 ± 0.03
Sham	0.05 ± 0.05	0.06 ± 0.04	0.05 ± 0.03	0.05 ± 0.04	0.04 ± 0.04
Reaction time (ms)					
Anodal	571.9 ± 52.0	558.9 ± 55.6	533.4 ± 51.0	554.7 ± 58.1	544.6 ± 58.2
Sham	527.4 ± 37.4	548.8 ± 63.3	542.2 ± 49.7	555.0 ± 54.5	544.8 ± 51.4
Concentration					
Anodal	7.0 ± 0.9	6.7 ± 1.0	6.5 ± 1.0	6.8 ± 1.0	6.6 ± 1.2
Sham	7.0 ± 1.3	6.8 ± 1.4	6.8 ± 1.3	6.9 ± 1.3	7.0 ± 1.1
Fatigue					
Anodal	3.9 ± 1.7	3.7 ± 1.6	4.0 ± 1.2	4.1 ± 1.6	4.1 ± 1.7
Sham	3.9 ± 1.2	3.8 ± 1.4	3.8 ± 1.6	4.0 ± 1.4	3.9 ± 1.4

Values are mean ± standard deviation.
[a]Significant at $P < 0.05$ vs. baseline.
[b]Significant at $P < 0.05$ vs. previous test.
[c]Significant at $P < 0.05$ vs. sham.
TI, after 10 min of tDCS; T2, after 20 min of tDCS; T3, after 30 min of tDCS; T4, 30 min after completing tDCS.
tDCS, transcranial direct current stimulation.

stimulation did at these time points ($P < 0.05$), and accuracy at T3 was significantly higher than for sham ($P < 0.05$). Repeated-measures analysis of variance revealed that extended treatment had a significant effect on accuracy (F=5.37; $P < 0.01$, Table 1, Fig. 2a).

Error rate
Error rates measured at T1, T2, T3, and T4 were not significantly different compared with baseline for real or sham tDCS treatments (Table 1, Fig. 2b).

Reaction time
Reaction times measured at T1, T2, T3, and T4 were not significantly different compared with baseline for real or sham tDCS treatments (Table 1, Fig. 2c).

Concentration, fatigue, and side effects
Concentration and fatigue were recorded at T1, T2, T3, and T4, and there was no significant difference between real and sham tDCS (Table 1). All participants successfully completed the experimental procedure, and no participant reported any side effects.

Discussion
The results of this study indicated that anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) enhanced verbal working memory in healthy participants in a time-dependent manner. The accuracy of verbal working-memory tasks increased after 10 min of tDCS application, and this effect was further enhanced by 30 min of stimulation. The accuracies at 30 min of stimulation were significantly different between anodal and sham tDCS. Furthermore, this memory-enhancing effect was maintained at 30 min after discontinuation of tDCS. Error rates, reaction times, concentration, and fatigue did not change significantly during or after intervention. To our knowledge, this is the first study to explore the time-dependent effects of tDCS on cognitive function.

tDCS is known to induce a polarity-dependent excitability shift of stimulated brain areas, which has a modulatory effect on behavioral outcomes [4,13,14]. According to previous studies, the effect of tDCS on brain activity seems to depend on stimulation polarity [4,15]. In particular, anodal tDCS is known to induce neuronal depolarization in the neuronal membrane and to increase local excitability. Therefore, improvements in working memory observed during this study are considered to be due to enhanced local cortical excitability in the left dorsolateral prefrontal cortex. Furthermore, tDCS might have an additional effect on the neuronal network associated with working memory beyond the sites of stimulation, as was demonstrated by a previous neuroimaging study [3].

Recently, many studies on the effects of tDCS on working memory have been conducted in healthy participants and in patients with brain disease [6,7,9,12]. These studies reported diverse behavioral effects that might have been due to different methodologies relating to electrode position, current intensity, duration of application, and diversity of cognitive paradigms employed [5,9,13]. In patients with Parkinson's disease, Boggio et al. [9] used 1 or 2 mA tDCS for 20 min with 35-cm²-sized electrodes, but found that working memory improved only after administration of 2 mA tDCS. Fregni et al. [5,16] demonstrated that 1 mA anodal tDCS over the left DLPFC in healthy participants increased working-memory performance after 10 min of stimulation, and found that the behavioral results depended on the stimulation site and polarity. In contrast, Iyer et al. [6] reported that an intensity of 2 mA (but not of 1 mA) for 20 min improved word generation in healthy participants. The mean age of the participants, however, differed in the above-mentioned studies; participants in Iyer's study [6] were older on average than those in Fregni's study. Importantly, age, education level, and underlying disease might modulate the effects of tDCS. Participants enrolled in this study were healthy and young, and had spent more than 13 years in full-time education, which might explain the positive effects of 1-mA tDCS on cognitive function in our study. Further studies at different intensities would provide more information
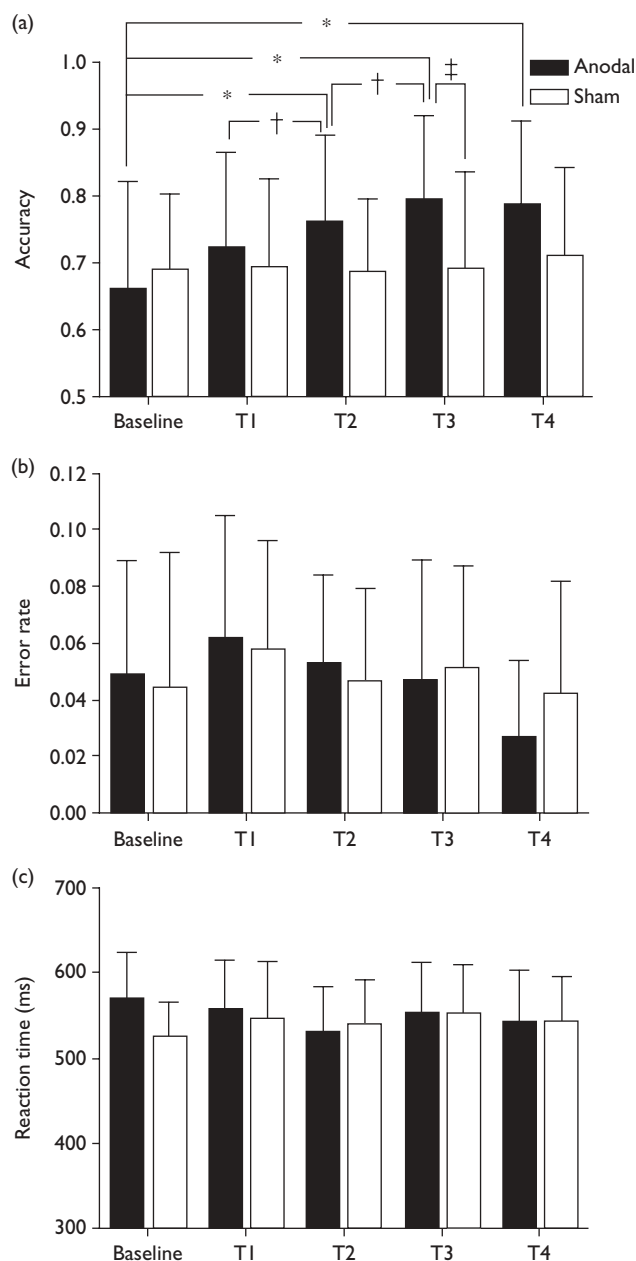
Fig. 2 Changes in accuracy (a), error rate (b), and reaction time (c), induced by transcranial direct current stimulation (tDCS). (a) Accuracy was improved by anodal tDCS. Repeated-measures analysis of variance (ANOVA) showed a significant group × time factor interaction (F=5.37, $P < 0.01$). *Significant at $P < 0.05$ versus baseline. †Significant at $P < 0.05$ versus the previous test. ‡Significant at $P < 0.05$ versus sham. (b) Error rates were not changed by anodal or sham tDCS. (c) Reaction times were not changed by anodal or sham tDCS.

about time-dependent changes in working memory in healthy and diseased participants. In this study, we limited tDCS application to 30 min for safety reasons [6,9,17]. tDCS stimulation, nevertheless, increased working memory in a time-dependent manner, and this effect was maintained at 30 min after stimulation. The residual effects of single and repetitive tDCS remain to be explored in further studies.

The excitability shifts induced by tDCS are comparable with those achieved by repetitive transcranial magnetic stimulation. Repetitive transcranial magnetic stimulation studies have also demonstrated cognitive improvements and modulation of left DLPFC in healthy participants and in patients with clinical depression [18,19] or Parkinson's disease [20]. These two noninvasive brain stimulation methods are, however, dissimilar in terms of their strengths and weaknesses [21,22]. The tDCS device is simple, wearable, battery-powered, and allows participants to perform their daily activities. Although the large electrode limits the focality of the stimulation, it operates at low current densities. Moreover, the large electrode and low current density allow protracted tDCS stimulation to be performed safely over a large area. Therefore, tDCS can present benefits for stimulating the prefrontal cortex for an extended period of time [5]. These unique advantages of tDCS also make it more useful for promoting working memory.

In this study, only the accuracy of the working-memory task was improved, but not error rates or response times. The accuracy of working memory can be mediated by cognitive processes such as encoding, maintenance, selection, and decision-making, which are considered to be crucial functions of the DLPFC. In contrast, error detection might be mediated through coordinated function with other brain areas like the cingulate or temporoparietal cortices [23–25]. Therefore, it might not have been obviously improved by tDCS administration to the DLPFC. Reaction times were also unchanged in this study after tDCS application. Before the experiment, participants attended familiarization sessions until their performances touched a plateau. We were thus able to eliminate the 'learning effect' of the working-memory task. In addition, to exclude the possible influence of the excited motor cortex in the stimulated hemisphere, we instructed participants to perform the tasks with their left hands while the left hemisphere was being stimulated. This might have prevented unwanted effects on reaction time owing to a spread of cortical excitability. Moreover, concentration and fatigue could have confounded the observed cognitive performances. These parameters were, however, no different after anodal and sham stimulation, and were unchanged by tDCS. These findings suggest that concentration and fatigue were not influenced by tDCS, and that they did not affect the results of our study.

Conclusion
In conclusion, we found that anodal tDCS administered to the left DLPFC at 1 mA has a time-dependent, positive impact on working memory, without any noticeable side effects, in healthy participants. Future studies should address the durability of this effect after repeated tDCS sessions.

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